The role of self-blame in major depressive disorder and its impact on social-economical decision making: evidence from neuroimaging and neuroeconomical experiments

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<tr>
<td>ACC</td>
<td>Anterior Cingulate Cortex</td>
</tr>
<tr>
<td>BA</td>
<td>Brodmann Area</td>
</tr>
<tr>
<td>DG</td>
<td>Dictator Game</td>
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<td>IPGQ</td>
<td>Interpersonal Guilt Questionnaire</td>
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<tr>
<td>MADRS</td>
<td>Montgomery Asberg Depression Rating Scale</td>
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<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
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<tr>
<td>OA</td>
<td>Other Agency</td>
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<tr>
<td>OFC</td>
<td>Orbitofrontal Cortex</td>
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<td>PFC</td>
<td>Prefrontal Cortex</td>
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<td>PD</td>
<td>Prisoner's Dilemma</td>
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<tr>
<td>SA</td>
<td>Self Agency</td>
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<td>STR</td>
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<td>TOSCA</td>
<td>Test of Self-Conscious Affect</td>
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<tr>
<td>[sg] ACC</td>
<td>Subgenual Cingulate Cortex</td>
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<tr>
<td>UG</td>
<td>Ultimatum Game</td>
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<tr>
<td>[vm] PFC</td>
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ABSTRACT

The role of self-blame in major depressive disorder and its impact on social-economical decision making: evidence from neuroimaging and neuroeconomical experiments

Erdem Pulcu, The University of Manchester

For the degree of Doctor of Philosophy (Ph.D.)

16 April, 2014

This Ph.D. investigates behavioural and neuroimaging correlates of affective disturbances related to self blaming moral emotions in major depressive disorder (MDD), and their impact on social economical decision making. Guilt is one of the core symptoms of MDD, and there is growing evidence of abnormally elevated shame in MDD especially when patients are symptomatic. In the introduction, behavioural and neuroimaging studies of emotional impairments in MDD and their influence on social economical decision making are reviewed. The third chapter investigated temporal discounting behaviour in current and remitted patients with MDD compared with healthy participants. Temporal discounting relates to the extent to which people consider making financial investments into the future and therefore is an important dimension of social economical decision making and reward valuation over time which is likely to influence people's behavioural preferences. We showed that discounting coefficients for large sized rewards are significantly higher in current MDD and correlate significantly with depressive symptoms, particularly hopelessness about the future. The fourth chapter considers altruism in MDD, as investigated by four different neuroeconomical paradigms relating to different forms of altruistic behaviours. Previous publications theoretically associated MDD with guilt driven pathological hyper altruism. However, behavioural-economical evidence to support this hypothesis is lacking. Using neuroeconomical paradigms, we investigated whether elevated levels of altruistic forms of guilt translate into altruistic behaviour in current and remitted MDD. Furthermore, we investigated whether elevated self blaming feelings may be triggered by receiving unfair offers in the Ultimatum Game. We showed that patients with current MDD made fewer charitable donations, and secondly we showed that elevated levels of guilt may be important for understanding the lack of altruistic punishment behaviour. Taken together, we suggested that the hyper altruism hypothesis should be revised, particularly to exclude altruistic punishment behaviour. Across these different experiments a pattern has emerged showing that patients with remitted MDD behaved significantly more altruistically. This raised the question whether patients with remitted MDD are experiencing altruistic behaviours more socially rewarding. In the next paper/chapter, we aimed to address this issue by using an adapted version of the charitable donations experiment with functional imaging. We showed that there is an abnormal hyperactivation in subgenual cingulate cortex and right striatum for altruistic decisions. The final research paper investigated whether shame relative to guilt has distinct functional neuroanatomy in patients fully remitted from symptoms. Chapter 6 shows that shame is associated with increased response of the right amygdala and the right posterior insula in patients with remitted MDD. We argued that these abnormal activations may be a biomarker of depression vulnerability. In the discussion section, we evaluated the findings of our experiments and discussed their implications from an interdisciplinary perspective, raising new research questions for the future directions of understanding social decision-making in major depression.
DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.
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My sincere gratitude to Rebecca Elliott and Roland Zahn, who allowed me the freedom to make this project my own and who supported me throughout these three long years. Thank you so much for the time and effort you invested in the papers presented in this theses. It was a great pleasure to be working with you both. I would like to thank you Rebecca for all the mentoring and advice you have given me throughout these years and thank you so much for bearing with me when I am complaining about research matters. I learned so much from you and think that there is so much more that I could learn. I think without your support, I would not have been able to complete this work.

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Last but not least, I would like to thank to my family, especially my mother who has given me her unconditional support through the tough times. I think none of this could be possible otherwise. Thank you so much, I am highly grateful!
Major depression is a complex neuropsychiatric disorder with impairments in cognitive, emotional and neurobiological domains. Various aetiological models suggest that a combination of developmental, psychosocial, neurobiological and genetic factors cause major depressive disorder (Kendler et al., 2006, Sjoholm et al., 2009). The key symptoms of major depression are persistent low mood, severe reduction in energy and interest, intense feelings of worthlessness, hopelessness and, in about half of patients, excessive guilt (American Psychiatric Association, 2000). These symptoms are mostly observed cross-culturally (Sartorius et al., 1980).

The World Health Organisation (WHO) suggests that there are 350 million individuals suffering from MDD (World Health Organization, 2001). Independent studies show that prevalence rates are gradually increasing around the world (Joyce et al., 1990, Compton et al., 2006, Klerman et al., 1985). Consequently, WHO considers MDD as the leading cause of disability in the western world (World Health Organization, 2001), and projects that it will be the second leading cause of mortality by 2030; moving up from its present fourth rank (Mathers and Loncar, 2005).

Lifetime prevalence of depressive disorders is estimated at 16% in the UK (Sahakian et al., 2010). The annual costs of mental health disorders reach as high as £ 77 billion in the UK when secondary costs arising from broader impacts, such as reduced work efficiency, are also considered (Beddington et al., 2008). These figures representing the economical and social costs of depression in the Western world, justify the need for continuous, interdisciplinary research, focusing on factors that contribute to vulnerability and as well as factors that promote resilience to major depressive disorder (MDD).

MDD is associated with affective impairments, including abnormalities in processing emotions which are related to self blame. The role of self blaming emotions in depression will be reviewed
more in detail in the next section. Previous experimental studies conducted in healthy participants fairly consistently show that self-blaming emotions (also known as prosocial emotions) promote various forms of altruistic decision making. Affective and prosocial emotion processing impairments observed in MDD may be linked to social decision-making abnormalities which contribute to poor psychosocial functioning observed in symptomatic patients and may remain as trait vulnerability factors even during periods of remission. However, there is no study in the literature which has investigated how affective impairments may contribute to abnormal social decision-making in patients with MDD. Due to the relative paucity of evidence in this domain, the next chapter is written and published as an opinion review, where I aimed to suggest an important relationship between the findings of affective and decision-making studies which focused on social and moral emotion themes that remain unexplored in patients with MDD. This approach is in line with previous research publications and reviews of our research group (e.g., Moll et al., 2005) which have also attempted to highlight the knowledge gap in the literature, and make specific suggestions for paradigms to address key questions.

Throughout the experiments reported by this Ph.D., I took a neuroeconomics approach in designing the paradigms. This preference reflected a personal interest in behavioural economics, and also complemented the expertise of my supervisory team. Neuroeconomical paradigms are well established and well quantified interpersonal decision-making problems using primary and secondary rewards to capture real-life decision-making behaviour in ecologically valid laboratory experiments. There are very few studies using neuroeconomical paradigms in clinical populations with depression (see next section Table 2) and I aimed to address this knowledge gap by investigating social decision-making using these paradigms in MDD. Previous neuroimaging studies in healthy participants suggest that certain social/altruistic decisions lead to
responses in regions of the brain which are also associated with pathophysiology of MDD. Therefore, by conducting experiments in this domain (see Paper 4) I aimed to understand the role of those brain regions during social decision-making in patients with MDD. This approach could potentially reveal important links between neural dysfunction and social decision-making impairments. Previous studies in healthy participants suggest that self blaming moral emotions elicit responses in regions of the brain which are also implicated in social decision-making. On the basis of such overlapping neural circuitry, it is plausible to hypothesise that social decision-making impairments in MDD may arise from abnormal affective processing in interpersonal decision-making challenges. This is because interpersonal decision-making problems which are captured by neuroeconomical paradigms also probe prosocial feelings (e.g., feeling guilty because of an unfair interpersonal exchange). In order to address one aspect of this issue and to understand whether shame activates regions associated with social decision-making, I investigated its functional neuroanatomy. This is one of the key knowledge gaps in the literature and at the time of writing this thesis there were no neuroimaging studies in patient groups. Furthermore, evidence about the functional neuroanatomy of shame (as opposed to guilt) is scarce even in healthy participants. It would be important to provide knowledge about functional neuroanatomy of shame in depression, as it would make a contribution to the understanding of its role in depression pathophysiology. Novel findings related to neuroanatomy of shame may also help improving scientific understanding of these closely related self blaming emotions in major depression and possibly provide evidence to redefine their diagnostic roles in the future.

This Ph.D. thesis consisted of several neuroeconomical and neuroimaging experiments and also used emotion rating and emotion priming designs in order to decipher the influence of self
blaming emotions in social-economical decision making in MDD. These experiments aimed to address the following overarching research questions:

1. Do symptoms of depression influence subjective reward devaluation over time (i.e. temporal discounting)? Does value-based reward devaluation influence individuals' preferences in social decision-making?

2. Do patients with current MDD act altruistically across different domains of altruistic behaviours as proposed by the guilt driven pathological hyper altruism hypothesis? Could increased altruistic preferences be a trait vulnerability feature which is detectable during periods of remission?

3. What may be the role of abnormal self blame in certain types of altruistic behaviours which require blaming others and punishing them for behavioural or moral transgressions?

4. Could social decision-making deficits observed in some patients have neuronal origins in key regions associated with pathophysiology of major depression? Could these be detected during periods of remission?

5. Is it possible to dissociate the functional neuroanatomy of shame from guilt in patients with depression during periods of full remission?

In the next chapter, a literature review is presented as an opinion piece which aims to provide a background for the primary research questions listed above and also to highlight the importance of affective decision-making research in MDD. The subsequent paper investigated reward devaluation over time in MDD. In order to use neuroeconomical paradigms effectively, it was important to understand whether or not different clinical groups perceived monetary rewards over time differently. In order to address this issue, a hypothetical monetary choice task was used
and differences in temporal discounting were investigated. This chapter aimed to address the first overarching research question.

In the fourth chapter, multiple neuroeconomical paradigms were used to investigate altruism in MDD in a systematic manner; looking at interpersonal cooperation, interpersonal fund allocation, altruistic punishment and charitable donation behaviour. Studying charitable donation behaviour in this cohort required developing an ecologically and culturally valid experimental charitable donations paradigm. There have been no experimental studies published by UK research groups using UK charities and therefore it was important to design an experimental charitable donations task. In order to do so, people's perceptions about charitable organisations in England and Wales were assessed, by conducting a pilot study. The primary aim of the pilot study was to address whether being more familiar with the charitable organisations or having stronger affilative feelings to their mission statements increased the likelihood of people deciding to donate. These preferences were investigated in a sample of 95 registered UK charities to inform the design of an ecologically and culturally valid experimental charitable donations paradigm to probe real life financial decision-making mechanisms in behavioural economical experiments presented in this thesis. The key results of the pilot study are presented briefly in the Methods section of Chapter 4.

Altruistic decision-making paradigms also imitate situations in which two individuals interact with each other. In order to understand how depression influences these types of altruistic decisions which involve interactions between two individuals, Prisoner's Dilemma, Dictator Game and the Ultimatum Game paradigms were used. The Prisoner's Dilemma experiment was based on a hypothetical water shortage scenario in which participants interacted with a computer strategy to collect their daily ration of water, the Dictator and the Ultimatum Game made use of
hypothesised currency, and real currency was used in the charitable donations experiment. Previous experiments using the Ultimatum Game in MDD did not show elevated altruistic punishment response, which would conceptually require blaming other individuals for moral/behavioural transgressions. These previous findings raised the question of whether elevated self blame may be responsible for the lack of altruistic punishment behaviour in currently depressed patients. This issue was addressed by conducting an emotion rating experiment following the Ultimatum Game decision-making.

In the following chapter of the Ph.D., a modified version of the experimental charitable donations paradigm was used within a functional neuroimaging setting; in order to investigate whether any functional abnormality exists in fronto-meso-limbic networks which are important for guiding human altruistic decisions. As reviewed previously, patients with MDD have structural and functional abnormalities in these networks, and therefore, it would be important to investigate the function of these networks with a social decision-making paradigm to understand their role in social reward processing.

The final chapter aimed to identify regions associated with shame in major depression relative to guilt, which is one of the core symptoms of MDD. Participants were shown hypothetical positive and negative social scenarios and asked to imagine these situations involving their best friend and to rate how they would feel. In summary, the identified knowledge gap in the literature review section was targeted by these aforementioned behavioural and neuroimaging experiments. The present thesis is written in the alternative/paper publication format allowed by the University of Manchester, and the details of the experimental paradigms are written in the methods section of each research paper and/or in relevant supporting supplementary materials sections. Finally, the implications of the results of these Ph.D. experiments are discussed in an
interdisciplinary manner, raising future research questions which could help advance our understanding of social economical decision-making in MDD.

**Information on Collaboration and Co-Authors:**

The candidate completed the research presented in this thesis in collaboration with a number of other individuals who are recognised as co-authors in published/submitted manuscripts. The candidate’s supervisory team, Dr Rebecca Elliott, Dr Roland Zahn and Prof Bill Deakin contributed to the design of the experiments, recruitment strategy, as well as to the theoretical framing of arguments during the writing up stage of the manuscripts and therefore they are acknowledged as co-authors. The remitted patients were recruited from a larger neuroimaging study of resilience to depression in which Dr Rebecca Elliott is the lead principal investigator. Dr Paula Trotter and Dr Emma Thomas handled screening and recruitment of remitted patients for this ongoing study, as well as data collection in Chapter 3, and therefore they are acknowledged as co-authors in Chapters 3, 4 and 5. Prof. Ian Anderson was the lead clinician and consultant for the recruitment of the symptomatic patient group and therefore he is acknowledged as a co-author on Chapters 3, 4 and 5. Dr Gabriella Juhasz and Prof Barbara Sahakian were principal investigators of the ongoing Resilience to Depression Study and therefore they are acknowledged as co-authors in all chapters which reported data from remitted patients, apart from Chapter 6 where the data belonged to a different cohort of participants. Martyn McFarquhar helped design online survey questionnaires for the preliminary screening of remitted patients and therefore he is acknowledged as a co-author on Chapters 3, 4 and 5. Dr Sophie Green collected the data for Chapter 6, which presents a secondary analysis of this dataset, and therefore she is acknowledged as a co-author on this chapter. Dr Karen Lythe contributed to discussions about the modeling of the data analysis in Chapter 6 and therefore she is acknowledged as a co-author. Dr Jorge Moll
collaborates extensively with the co-supervisor Dr Roland Zahn and his experimental designs were adapted for the present research and therefore he is acknowledged as a co-author on Chapters 5 and 6. All manuscripts have been written by the candidate with input from the members of the supervisory team. All the co-authors had an opportunity to comment on the final version of each manuscript before submitting to the journals. All the co-authors agreed about their roles and their contributions were acknowledged in each manuscript.

Details of the ethics approval for each manuscript are given in the Methods section of each paper.
CHAPTER 2: The role of self-blaming moral emotions in major depression and their impact on social-economical decision making

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Abstract

People with major depressive disorder (MDD) are more prone to experiencing moral emotions related to self-blame, such as guilt and shame. DSM-IV-TR recognises excessive or inappropriate guilt as one of the core symptoms of current MDD, whereas excessive shame is not part of the criteria for MDD. However, previous studies specifically assessing shame suggested its involvement in MDD. In the first part of this review, we will consider literature discussing the role of self-blaming moral emotions in MDD. These self-blaming moral emotions have been purported to influence people when they make social and financial decisions in cognitive studies, particularly those using neuroeconomical paradigms. Such paradigms aim to predict social behaviour in activities of daily living, by using important resource tangibles (especially money) in laboratory conditions. Previous literature suggests that guilt promotes altruistic behaviour via acting out reparative tendencies, whereas shame reduces altruism by means of increasing social and interpersonal distance. In the second part of this review, we will discuss the potential influence of self-blaming moral emotions on overt behaviour in MDD, reviewing clinical and experimental studies in social and financial decision-making, in which guilt and shame were manipulated. This is not a well-established area in the depression literature, however in this opinion paper we will argue that studies of moral emotions and their impact on behavioural decision-making are of potential importance in the clinical field, by linking specific symptoms of a disorder to a behavioural outcome which may lead to stratification of clinical diagnoses in the future.
Introduction
Moral emotions (e.g., guilt, shame, indignation, prosocial forms of pride, gratitude) are discussed as of a critical evolutionary importance (Gintis et al., 2008). It has been suggested that humans acquired the capacity to feel these emotions over the course of evolution to motivate behaviour that is directed towards other people’s or societal needs, thereby promoting social cooperation (Zahn et al., 2012). The relationship between moral emotions and social behaviour has been of interest to philosophers since the Classical periods. More recently the relationship has been considered by clinicians and social psychologists, and moral emotion has become a “hot topic” in neuroscience, with the emergence of “social neuroscience” as a distinct discipline (Ochsner and Lieberman, 2001).

Healthy functioning of a moral emotion system forms the basis of balancing selfish needs with those of other people. Its dysfunction can lead to certain types of psychopathology. For example, lack of moral emotions such as sympathy and guilt has been mentioned among the key personality traits of psychopathic individuals (Haji, 2010, Mahmut et al., 2008, Hare, 1985). By contrast, the experience of self-blaming moral emotions, such as guilt, shame, and self-contempt/disgust can be exaggerated in mood disorders (Zahn et al., 2012). In the case of major depression, guilt is often exaggerated and experienced out of context (Prosen et al., 1983), and is recognised as one of the core symptoms of depression: “feelings of worthlessness or excessive or inappropriate guilt nearly every day (not merely self-reproach or guilt about being sick)” (American Psychiatric Association, 2000).
In the first part of this opinion paper (sections 2 and 3), we will discuss the role of self-blaming moral emotions (guilt and shame) in major depressive disorder. There is emerging evidence for the role of self-contempt/disgust in major depressive disorder (Green et al., 2013), but this is not further reviewed because of the relative paucity of evidence. We will focus on reviewing evidence from behavioural and neuroimaging studies in people with clinical diagnoses of major depression, and will only briefly mention some of the studies in healthy populations with and without symptoms of MDD. It is beyond the scope of this paper to provide an overview of studies of guilt and shame in populations that were not assessed using diagnostic interviews. A recent meta-analysis has addressed this issue and provided evidence for the relationship between guilt, shame and depression in patient populations as well as individuals reporting depressive symptoms (Kim et al., 2011). In the second part (section 4 onwards), we will discuss the impact of these self-blaming moral emotions on decision-making. Considering neuroeconomical studies in clinical, subclinical and healthy populations with mood induction, we will aim to highlight the potential implications of their findings for social-economical decision making in major depression. For the purposes of clarity, the present review will use “major depression” only when referring to studies conducted in people with clinical diagnoses of depression.

Framing the review of this literature as an opinion/prospective review is in line with the approach of our research group (Moll et al., 2005). The other two key reasons for this framing is the limited number of studies which investigated affective processing and decision-making in clinical populations (see Tables 1 and 2, in certain domains there were no previous publications) and secondly often conflicting findings reported even by the same research
group when investigating the same theme in people with depressed mood and those who meet clinical criteria for MDD (for example, (Harle et al., 2010, Harlé and Sanfey, 2007)).

1. General clinical aspects of major depressive disorder

Major depression is a complex disorder with impairments in cognitive, emotional and neurobiological domains. Various aetiological models suggest that a combination of developmental, psychosocial, neurobiological and genetic factors cause major depressive disorder (Kendler et al., 2006, Sjoholm et al., 2009). The key symptoms of major depression are persistent low mood, severe reduction in energy and interest, intense feelings of worthlessness, hopelessness and, not; in about half of the patients, also excessive guilt. These symptoms are observed cross-culturally at a clinically significant level (Sartorius et al., 1980). However, more recent studies suggest that there is significant cultural variation in severity of affective symptoms such as guilt, which is experienced more severely in Western cultures (Jeon et al., 2013). Taken together, these features make depression a leading cause of disability in the western world (Eaton et al., 2008a). Lifetime prevalence of depressive disorders is estimated at 16% in the UK (Sahakian et al., 2010). The annual cost of mental health disorders reach as high as £ 77 billion in the UK when secondary costs arising from broader impacts such as reduced work efficiency are considered (Beddington et al., 2008). These figures, which are representative of the prevalence and social cost of depression throughout the developed world, justify the need for continuous, interdisciplinary research on depression, focusing on factors that constitute vulnerability as well as factors that promote resilience to major depressive disorder (MDD).

2. Self-blaming moral emotions in major depressive disorder
There are several self-conscious moral emotions (e.g., guilt, shame, and prosocial forms of pride, (Tangney, 2002)), and it has been argued that certain of these are selectively enhanced in MDD (Zahn et al., 2012). Guilt and shame can be defined as “self-blaming moral emotions”, as distinct from other moral emotions such as indignation, related to blaming others (other-blaming) or self-praising moral emotions such as pride (Tangney, 2002). Vulnerability to MDD has been associated with elevated levels of self-blaming emotions compared with other-blaming emotions (Green et al., 2013) as predicted by attributional models of major depressive disorder (Abramson et al., 1978).

2.1. The role of guilt in major depressive disorder

Excessive or out of context (inappropriate) guilt has been recognised as one of the distinctive clinical symptoms of MDD, especially of the melancholic subtype (American Psychiatric Association, 2000). In a developmental psychological study in healthy children, it was shown that excessive or inappropriate guilt becomes less normative with age, as children make less predictive errors in explaining cause and effect relationships (Tilghman-Osborne et al., 2012). These authors suggest that excessive or inappropriate guilt becomes exponentially depressotypic with age. A recent meta-analysis showed that levels of guilt on the Hamilton Depression scale were higher in younger adults with current major depression compared with older adults (Hegeman et al., 2012). It is unclear, however, how representative the included studies were of the respective younger and older populations. Another study showed that parental guilt induction was more significant than the influence of parental depressive symptoms on the way children internalised their parent’s problems, which may be an additional vulnerability feature for adult MDD in these high-risk populations (Rakow et al., 2011). The symptom profiles of female patients with recurrent MDD, suggest that worthlessness and excessive guilt are the most
discriminating factors for patients with and without history of suicide attempts (Bi et al., 2012). Other previous studies showed that patients with current MDD have significantly elevated levels of guilt measured on scales which conceptualized guilt in different ways: “delusional” and “affective” (Berrios et al., 1992), “state” and “trait” (Ghatavi et al., 2002) and “survivor” and “omnipotent responsibility” guilt (O'Connor et al., 2002).

A subtype of guilt that has been consistently reported in clinical populations as an exaggerated moral emotion (Blacher, 2000, O'Connor et al., 2002) is “survivor guilt”, associated with perceiving oneself as being better off than others (O'Connor et al., 2000b). Historically, this concept gained clinical recognition during the Korean War, where it was noticed that when grenade explosions claimed multiple lives, the survivors subsequently became vulnerable to severe depression (Blacher, 2000). Similar observations of "post-survival" guilt were also recorded among the survivors of World War II (O'Connor et al., 2000b) and patients undergoing treatment in an intensive care unit following successful organ transplantation (Blacher, 2000). In the post-operative cases mentioned by Blatcher (2000), survivor guilt originates from limited availability of compatible donors helping a limited number of patients to recover, whereas leaving others on the waiting lists. Other forms of combat-related guilt significantly predict MDD diagnosis, especially when it arises from inactions in the face of observations of abusive violence, probably due to violations of one's own moral conduct (Marx et al., 2010). Survivor guilt scores were elevated in people with major depression treated as inpatients and predicted the severity of depression (O'Connor et al., 2002).

Survivor guilt scores might have further predictive value in identifying populations who are vulnerable to future major depressive episodes. One recent study showed that scores for survivor and omnipotent responsibility guilt (defined as taking responsibility for events which may be out
of one's control and feeling guilty about their consequences) were significantly higher in a population of people with MDD fully remitted from symptoms compared with healthy participants (Green et al., 2012b). However, the same sample did not show elevated shame scores. These findings suggest that elevated guilt levels may be a trait vulnerability feature, or alternatively a scar following previous episodes of MDD. This proposal is plausible as recent studies suggest that 25% of remitted patients experience residual guilt (Zajecka et al., 2013), and ability to focus away from affective disturbances during the acute phase of MDD contributes positively to recovery rates (Thompson et al., 2013). Survivor guilt may be an important construct that links research in the area of major depression to post-traumatic stress disorder (PTSD), disorders with a high degree of co-occurrence. Taken together, the studies in this section suggest that MDD is characterised by significantly higher levels of guilt, even when the symptoms are fully remitted.

2.2 The role of shame in major depressive disorder

Whilst considering the role of shame in MDD, it is important to note that despite its proposed significance, exaggerated shame is not considered a diagnostic symptom of MDD (by contrast with guilt). Tangney and colleagues (2007) have investigated the role of shame in predicting depressive symptoms in healthy people using the Test of Self-Conscious and Affect (TOSCA) scale, which assesses indirect manifestations of affect on behaviour (Tangney et al., 2007b). Their research group conceptualized shame with attempts to deny, hide or escape the shame-eliciting situation; as a result leading to interpersonal separation and increased social distance (Tangney et al., 2007b). They showed that shame-proneness accounts for a substantial quantity of variance in depressive symptoms to an extent that this pattern cannot be reduced to an attributional style (Tangney et al., 1992b). However, they found these results in populations with
no clinical diagnosis of depression (Tangney et al., 1996, Tangney et al., 1998). Mild depressive symptoms in healthy populations could be due to a variety of reasons other than major depression suggesting a lack of specificity. Furthermore, although social withdrawal is an important clinical aspect of MDD, it may be more fundamental to other psychiatric disorders such as social phobia or borderline personality disorder (Rusch et al., 2007).

While shame-proneness may not be specific to depression, there is increasing evidence that it is clinically relevant. In clinical populations, it was shown that shame responses in the face of everyday social dilemmas were elevated in current major depression and that shame-proneness as a trait increased the risk of recurrence (Andrews, 1995, Thompson and Berenbaum, 2006). A recent study found a significant relationship between shame responses and severity of depression, and specifically suicidal ideation, more strongly than elevated levels of guilt (Bryan et al., 2013a). The same research group also reported that in military personnel abnormal shame processing interacts with hopelessness which in return increased severity of suicidal ideation (Bryan et al., 2013b). Another study showed that patients with recurrent major depressive episodes have significantly higher levels of shame, compared with those patients who only had a single episode (Andrews and Hunter, 1997). In children, it was shown that increased levels of shame responses predicted the severity of major depression in a population of preschool children as young as three years old (Luby et al., 2009). This finding is particularly important as it could suggest that shame-proneness in children may also be a vulnerability factor for MDD in later life. Similarly, a recent study lends support for this interpretation such that shame proneness was shown to predict the likelihood of having MDD diagnosis in early adolescence and particularly correlating with the severity of depression symptoms in males (Mills et al., 2013). Finally, shame
reactions and self-blame in the face of stressful life events, such as cancer diagnosis, were associated with MDD diagnosis following the onset of cancer (Hill et al., 2011).

A recent meta-analysis, investigated the relationship between guilt, shame and depressive symptoms in patients with MDD, as well as individuals self reporting depressive symptoms (Kim et al., 2011). Kim and colleagues showed that there is a stronger relationship between shame and depressive symptoms relative to the association between a generic form of guilt and depressive symptoms. However, they suggested that the relationship between shame and depressive symptoms was not statistically stronger than the relationship between two maladaptive forms of guilt (i.e. omnipotent responsibility guilt and inappropriate/out of context guilt) and depressive symptoms.

2.3 Relationship between guilt and shame

The self-blaming moral emotions of guilt and shame are closely linked. Previous studies have shown significant correlations between context-dependent moral emotions such as guilt and shame (Tangney et al., 1992a), however these constructs can be theoretically distinguished. It is suggested that this distinction mainly relies on participants’ ability to accurately define these moral emotions separately when they experience them within a social context (Tangney et al., 1996). However, patients with MDD may be impaired in their ability to make this distinction. A recent behavioural study provided participants with handheld devices and probed their feelings in the course of daily activities, using items on the Positive and Negative Affects Scale (PANAS), to assess emotions including guilt and shame (Demiralp et al., 2012). The authors showed that patients with MDD were less able to differentiate between negatively valenced emotions, including both guilt and shame. We consider these findings to be particularly important as they
suggest that symptomatic criteria for guilt established on the basis of consistent patient accounts in clinical interviews may be insensitive to discriminate guilt from shame. It is possible that the current diagnostic criteria make an overgeneral assumption that pathological self-blame in MDD loads onto guilt, whilst underevaluating the role of shame.

The difficulties in classification of guilt and shame into different categories of moral emotions may partially arise from the limitations of methodologies being used for their assessment (as is often done by asking participants how they would feel in a given hypothetical scenario). Attempts to differentiate between these moral emotions aimed at a distinction based on: (a) types of eliciting events, (b) social audience and (c) the extent to which a person attributes the failure, within the context of the eliciting event, to the self or the behaviour (Tangney, 1996). Guilt is conceptualised as a more private experience which is reactive to norm violation, leading to behavioural self-blame. On the other hand, shame is referred to as a more public experience which emerges in a wider range of situations which may lead to characterological self-blame (Tangney, 1996). An association of guilt with behavioural, and shame with characterological self-blame is consistent with Janoff-Bulman’s suggestions of differences between characterological and behavioural self-blame patterns in people with symptomatic subclinical depression (Janoffbulman, 1979). Characterological self-blame is regarded as more depressogenic, as it provides limited space for positive change, whereas self-blame emerging from behavioural violations of one's moral conduct may subside once that behaviour is modified. Two theoretical models supported the characterological versus behavioural self-blame differentiation argument. The revised learned-helplessness model posits that people who suffer from MDD often make internal, stable and global attributions for negative events (Abramson et al., 1978). In an alternative model, Higgins (1987) suggested a differentiation between guilt and
shame based on different patterns of self-discrepancies. Higgins argued that an inability to comply with significant others’ moral standards results in shame, whereas an inability to comply with one’s own moral standards results in guilt (Higgins, 1987b).

On the other hand, recent work by O’Connor and colleagues provides evidence against the general association of guilt-proneness with behavioural self-blame by identifying characterological forms of empathy-based guilt (O’Connor et al., 1997, O’Connor et al., 2002, O’Connor et al., 1999). Using the Interpersonal Guilt Questionnaire (IGQ-67, (O’Connor et al., 1997)), which captures characterological forms of empathy-based guilt, they showed elevated scores in symptomatic MDD (O’Connor et al., 2002). Although, empathy-based guilt may be maladaptive for an individual with regard to group competition, it is argued that altruistic individuals with high empathy-based guilt may have provided survival advantages in the competition between groups in our evolutionary history (O’Connor et al., 2012, O’Connor et al., 2000b, Wilson and Wilson, 2007). Empathy-based guilt as measured on the IGQ-67 were associated with depressive symptoms and this association remained even when controlling for levels of shame as measured on Tangney et al.’s scale (O’Connor et al., 1999).

2.4 Functional neuroanatomy of guilt and shame

In this section we will consider social cognitive neuroscience studies investigating the functional neuroanatomy of guilt and shame, and discuss whether these emotions can be distinguished based on their functional neuroanatomy.

Shin and colleagues (2000) used an autobiographical episodic memory paradigm with positron emission tomography (PET) in order to measure regional cerebral blood flow (rCBF) during guilt-related imagery. In this study, participants rated stimuli in the guilt condition as evoking
shame to an extent which was not significantly different than post-scanning guilt ratings, pointing to difficulties teasing apart guilt and shame experimentally (Shin et al., 2000). The authors showed that guilt relative to a neutral condition led to rCBF increase in dorsal anterior cingulate gyrus (BA32) and anterior insula; whilst leading to decreased rCBF in posterior insula. A functional magnetic resonance imaging (fMRI) study conducted in healthy participants showed that guilt-specific stimuli were associated with significantly increased activation in left posterior superior temporal sulcus (STS) and medial frontopolar cortex (Takahashi et al., 2004). Furthermore, Takahashi and colleagues explored the differences in neural response between guilt and embarrassment (an affective state closely related to shame). They found that embarrassment activated the right anterior temporal lobe and hippocampus bilaterally, compared with guilt. More recent studies concerning the neural response to shame-specific stimuli have been somewhat inconclusive. Wagner and colleagues (2011) showed that compared with guilt, shame-specific stimuli were not associated with selective activations. In another study, it was shown that in post-scanning ratings, embarrassment and shame were the second and third most highly descriptive emotions in defining stimuli designed to evoke guilt, as previously suggested by the findings of Shin et al 2000 (Morey et al., 2012a). Firstly, these authors showed that people felt significantly more guilt when their actions affected others rather than themselves. Secondly, they suggested that activation in ventrolateral regions of the prefrontal cortex correlated significantly with post-scanning guilt ratings for actions affecting other individuals. However, they did not provide co-variation analyses with shame ratings and consequently did not discuss the extent to which this activation may be due to shame or embarrassment. Basile and colleagues (2010) investigated neurobiological substrates of two other subtypes of guilt: deontological guilt (emerging from violations of one's own moral conduct) and altruistic (i.e. survivor) guilt. Pairing
different guilt scripts with Ekman's emotional faces in an event-related fMRI design, they showed that deontological guilt activated dorsal and ventral regions of the anterior cingulate cortex (BA 32/24), whereas altruistic/survivor guilt activated frontopolar regions (BA10 and BA9) (Basile et al., 2010). Similar results were also obtained when using script paradigms where significant frontopolar cortex activations were observed for guilt and STS activations for embarrassment in healthy participants undergoing functional brain imaging (Moll et al., 2007b). Koenigs and colleagues (2007) showed that carers of patients with ventromedial prefrontal cortex lesions, including the frontopolar cortex (BA10), observed less guilt; providing support for the engagement of frontopolar cortex while people experience guilt. Furthermore, guilt induction by using abstract socio-moral values and showed that activation in the septal and subgenual cingulate region reflected individual differences during the experience of guilt but not indignation whilst controlling for valence, the influence of other emotions such as embarrassment and the psycholinguistic properties of the stimuli (Zahn et al., 2009b). Zahn and colleagues also found the frontopolar cortex to be selectively activated for guilt. In another study, activation in the subgenual cingulate region for guilt relative to a neutral condition correlated significantly with off-line individual empathic concern ratings; an important component of empathic moral sentiments such as guilt and compassion (Zahn et al., 2009a).

Taken together, guilt was most reliably associated with frontopolar activations (i.e. BA10). This result was obtained whilst using various control conditions (other-critical emotions such as indignation (Moll et al., 2007a, Zahn et al., 2009d); anger towards self (Kedia et al., 2008a); embarrassment (Takahashi et al., 2004); regret with no consequences for others (Morey et al., 2012b); as well as sadness (Basile et al., 2011a)). The subgenual cingulate cortex (including the posteriorly adjacent septal area in some studies) was selectively activated for guilt compared
with indignation towards others, when modelling individual variability in empathic concern (Zahn et al., 2009a), or guilt-proneness (Zahn et al., 2009d, Green et al., 2012a). Subgenual cingulate activations for guilt were also reproduced by independent groups using quite different ways of inducing guilt (Morey et al., 2012b, Basile et al., 2011a).

The findings of a study experimentally probing moral sentiments in patients with focal neurodegeneration of anterior brain regions (frontotemporal dementia; FTD) confirmed the fMRI evidence for involvement of the frontopolar and septal region in prosocial sentiments (Moll et al., 2011). Resting state hypometabolism, as a measure of neuronal dysfunction in the frontopolar cortex and the septal region, was associated with impairments of processing prosocial sentiments whilst controlling for experimentally probed disgust and anger. Whilst frontopolar cortex dysfunction was associated with loss of guilt, pity, and embarrassment; septal dysfunction was specifically associated with loss of empathic moral sentiments (guilt and pity but not embarrassment).

Other research groups investigated the impact of perceived audience on the way people processed moral and social transgressions (Finger et al., 2006). In this study, participants rated guilt to be most relevant to moral transgressions without an audience, whereas highest shame ratings were given to social transgressions with an audience. This differentiation is partially in line with Tangney's assumption that shame results from moral or social transgressions in the presence of a social audience (Tangney et al., 2007b). Comparing their functional neuroanatomy, the authors showed that activation in ventrolateral prefrontal cortex is overlapping for both moral and social transgressions in the presence of an audience (Finger et al., 2006). Another study investigated brain activation changes for social gestures regarded as aversive (i.e. fascist salute) relative to a generic greeting (Knutson et al., 2008b). The participants were presented with two-
second movies of an adult male performing gestures, as they underwent a brain scan. Separately, and out of the scanner, participants were asked to complete different scales measuring various psychological traits. Here, the authors showed that post-scanning shame ratings correlated significantly negatively with the activation in bilateral inferior parietal lobe for the fascist salute versus the greeting wave.

The first neuroimaging study of guilt in patients with MDD used a psychophysiological interaction (PPI) analysis and reported selective decoupling between subgenual anterior cingulate cortex (sgACC) and right superior anterior temporal lobe for guilt compared with indignation in people with MDD, fully remitted from symptoms (Green et al., 2012b). At the time of writing this opinion paper, there are no published studies reporting regions which showed differences for shame responses compared with any other control emotions. More importantly, despite its relevance, there are no published studies addressing the neural response to shame in MDD.

The regions which are critically involved in guilt and shame have an intriguing overlap with regions implicated in depression. Specifically, functional abnormalities in subgenual cingulate cortex (sgACC) warrant specific attention. As mentioned previously, the sgACC shows selective activation for guilt. A recent review showed that after partial volume correction for the reduction in grey matter volume, there is abnormal metabolism in sgACC in a patient group relative to controls (Drevets and Savitz, 2008). Various other clinical studies suggested that MDD is associated with structural and functional abnormalities in sgACC (Greicius et al., 2007, Skaf et al., 2002, Botteron et al., 2002, Drevets et al., 1998, Drevets et al., 1997, Lehmbeck et al., 2008). Activity in sgACC is also shown to predict treatment outcome in major depression. For example, pre-treatment hypometabolism for negative words in sgACC was associated with successful outcome of cognitive behavioural therapy (Siegle et al., 2006), whereas hypermetabolism
predicted better treatment response to selective serotonin reuptake inhibitors (SSRIs) (Mayberg et al., 1997, Keedwell et al., 2010). Subgenual cingulate stimulation was further shown to lead to a remission of major depression (Mayberg et al., 2005).

2.5 Section Summary

In this section, we reviewed the literature on moral emotions and MDD. Studies consistently showed that both guilt and shame scores are elevated in patients with MDD. Neuroimaging literature provides insights for understanding overlapping mechanisms between a specific symptom of a disorder (e.g., guilt) and overall pathophysiology. Studies investigating the functional neuroanatomy of guilt and/or shame in patients with MDD are very limited. Current findings suggest that overgeneralization of guilt in MDD is associated with functional disconnection of the anterior temporal cortex and the sgACC, frontopolar, hippocampal, and hypothalamic regions showing guilt-selective disconnection. Previous behavioural studies suggest that there is a need to investigate the functional neuroanatomy of shame in patients with MDD. We provide a summary table of the cited literature for this section (Table 1a and Table 1b).
Table 1a. The literature which investigated guilt and shame in MDD

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Sample</th>
<th>Method</th>
<th>Moral emotion</th>
<th>Scale</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demiralp et al</td>
<td>2012</td>
<td>MDD</td>
<td>Behavioural</td>
<td>Guilt/Shame</td>
<td>PANAS</td>
<td>Inability to differentiate between negative emotions in MDD</td>
</tr>
<tr>
<td>Bryan et al</td>
<td>2012</td>
<td>MDD</td>
<td>Behavioural</td>
<td>Guilt/Shame</td>
<td>Harder Personal Feelings Questionnaire</td>
<td>Shame correlates significantly with depression severity</td>
</tr>
<tr>
<td>Bi et al</td>
<td>2012</td>
<td>MDD</td>
<td>Behavioural</td>
<td>Guilt</td>
<td>SCID</td>
<td>Excessive guilt in suicide attempters</td>
</tr>
<tr>
<td>Kim et al</td>
<td>2011</td>
<td>MDD</td>
<td>Meta analysis</td>
<td>Guilt/Shame</td>
<td>----</td>
<td>Significant relationship between shame and depressive symptoms</td>
</tr>
<tr>
<td>Marx et al</td>
<td>2010</td>
<td>MDD</td>
<td>Behavioural</td>
<td>Guilt</td>
<td>Laufer-Parsons Inventory</td>
<td>Combat related guilt mediates MDD diagnosis</td>
</tr>
<tr>
<td>Luby et al</td>
<td>2009</td>
<td>MDD</td>
<td>Behavioural</td>
<td>Guilt/Shame</td>
<td>Story stem task</td>
<td>Shame correlates significantly with depression severity</td>
</tr>
<tr>
<td>O'Connor et al</td>
<td>2002</td>
<td>MDD</td>
<td>Behavioural</td>
<td>Guilt</td>
<td>IPGQ-67</td>
<td>Survivor and omnipotent responsibility guilt correlates with self-reported severity of symptoms</td>
</tr>
<tr>
<td>Berrios et al</td>
<td>1992</td>
<td>MDD</td>
<td>Behavioural</td>
<td>Guilt</td>
<td>Novel guilt scale</td>
<td>Guilt scores correlate with self-reported symptoms</td>
</tr>
</tbody>
</table>

Studies were listed chronologically (the most recent first).
### Table 1b. The list of the key neuroimaging literature which investigated guilt and shame

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Sample</th>
<th>Method</th>
<th>Moral emotion</th>
<th>Scale</th>
<th>Main conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morey et al</td>
<td>2012</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>Guilt</td>
<td>Novel guilt scale</td>
<td>Guilt activates dmPFC and vlPFC</td>
</tr>
<tr>
<td>Green et al</td>
<td>2012</td>
<td>Remitted MDD</td>
<td>FMRI</td>
<td>Guilt/Shame</td>
<td>Value related Moral Sentiments Task</td>
<td>Decoupling between sgACC and aTL for guilt in MDD</td>
</tr>
<tr>
<td>Wagner et al</td>
<td>2011</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>Guilt</td>
<td>Trait guilt Questionnaire</td>
<td>Guilt activates right OFC</td>
</tr>
<tr>
<td>Moll et al</td>
<td>2011</td>
<td>Patients with FTD</td>
<td>PET</td>
<td>Guilt</td>
<td>Moral sentiments task</td>
<td>Hypoactivations in the frontopolar cortex and the septal region are associated with impairments in processing prosocial sentiments, including guilt and pity</td>
</tr>
<tr>
<td>Basile et al</td>
<td>2011</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>Guilt</td>
<td>Deontological versus altruistic guilt</td>
<td>Deontological guilt activates dorsal and ventral anterior cingulate, whereas altruistic guilt activates frontopolar cortex (BA 9/10)</td>
</tr>
<tr>
<td>Zahn et al</td>
<td>2009</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>Guilt</td>
<td>Moral sentiments task</td>
<td>Activity in the sgACC in guilt relative to neutral condition, correlates significantly with offline empathic concern ratings</td>
</tr>
<tr>
<td>Zahn et al</td>
<td>2009</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>Guilt</td>
<td>Value related moral sentiments task</td>
<td>Guilt in negative self agency conditions activates septal/sACC and regions of vmPFC</td>
</tr>
<tr>
<td>Moll et al</td>
<td>2007</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>Guilt</td>
<td>Moral sentiments task</td>
<td>Guilt relative to neutral condition activated frontopolar cortex and STS</td>
</tr>
<tr>
<td>Berthoz et al</td>
<td>2006</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>Guilt</td>
<td>Intentional and accidental moral violations</td>
<td>Guilt activates amygdala bilaterally</td>
</tr>
<tr>
<td>Takahashi et al</td>
<td>2004</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>Guilt</td>
<td>Guilt-Embarrassment scale</td>
<td>Guilt activates mPFC and posterior STS</td>
</tr>
<tr>
<td>Shin et al</td>
<td>2000</td>
<td>Healthy participants</td>
<td>PET</td>
<td>Guilt</td>
<td>Autobiographical guilt</td>
<td>Increased regional cerebral blood flow in anterior cingulate and anterior insula, and decreased rCBF in posterior insula during guilt versus neutral condition</td>
</tr>
</tbody>
</table>

Studies were listed chronologically (the most recent first), so that advancements and limitations in this field of research can be observed.
3. Hypotheses regarding the impact of self-blaming emotions on social-economical decision making

In the previous section, we showed that it was difficult to dissociate the roles of guilt and shame in MDD on the basis of the current behavioural or functional neuroimaging evidence. In social psychology, both guilt and shame are conceptualised to be within the same category of moral emotions which help reduce socially undesirable behaviour (Tangney, 1996). However, in later work Tangney and colleagues argued that shame contributes less towards motivating moral behaviour because its adaptive functions are limited relative to those of guilt (Tangney et al., 2007b). They suggested that the main difference between guilt and shame lies in their respective motivations for subsequent action (Tangney et al., 1996). Guilt is associated with an urge for reparative action (Tangney et al., 2007b). On the other hand, the most common response to shame is to increase social distance and escape from the shame eliciting environment. Therefore, it is suggested that shame works counter to reparative altruistic tendencies by means of increasing social distance between individuals (Tangney et al., 2007b). The assumptions regarding the reparative nature of guilt find support from clinical research. Considering the significance of both survivor and omnipotent responsibility guilt in MDD, O'Connor and colleagues argue that depression may be conceptualised as a disorder in which the moral system is in "overdrive", leading patients to pathological forms of altruism and self-sacrifice (O’Connor et al., 2012, O’Connor et al., 2007). Altruistic behaviour has been defined as a form of cooperative behaviour conducted at a particular cost to the actor towards an indiscriminate receiver in the absence of short or long term expectancy of reciprocation (West et al., 2007). In conjunction with moral emotions, altruistic behaviour can be in the form of direct cooperation or implicated punishment as a result of norm violation. The unique interaction between cooperation
and costly punishment is defined as strong reciprocity, a concept which incorporates costly cooperation and costly punishment (Fehr and Fischbacher, 2003).

Understanding the relationship between MDD, guilt, shame and altruism may be more complicated than previously proposed. Both Tangney and O'Connor’s hypotheses have certain limitations. Tangney’s hypotheses are derived mainly from undergraduate student populations, which limits their validity for patients with MDD, whereas O’Connor’s hypotheses may underestimate the role of shame in interpersonal decision-making in MDD. Both of these assumptions rely on self-reported hypothetical behaviour and experience, but not actual decision-making. Although one may argue for a direct relationship between choice preferences and actual behaviour, the results of choice behaviour paradigms are usually confounded by factors such as social desirability. Therefore, computerised behavioural paradigms may have more ecological validity in terms of modelling how people interact with their social environment. Here, we propose a neuro-behavioural economical approach to investigate the extent to which guilt and shame influence social and financial decisions in patients with MDD.

4. A brief introduction to neuroeconomical paradigms

Neuroeconomical paradigms make use of quantifiable resource tangibles such as time, money or amount of water to survive, so that they activate daily life decision-making mechanisms. These experiments are referred to as "games". Neuroeconomical game is defined as; “a decision problem with structure so that one's payoffs can depend on one's own choices and some other input” (Kishida et al., 2010). These features are suggested as making neuroeconomical paradigms an ecologically valid, interdisciplinary and empirically testable framework for understanding social impairments associated with neuropsychiatric disorders (Brune, 2002).
Recently, it was suggested that average responses of individuals without any psychopathology in various neuroeconomical decision-making paradigms may be used to design realistic social partners for computerised tasks in order to define benchmarks of normative behaviour (King-Casas and Chiu, 2012). In the next step, behavioural and neurobiological deviations from the benchmark social norm may be used as quantitative biomarkers to support clinical diagnoses. A neuroeconomical approach may also facilitate translational approaches, as neuroeconomic paradigms can capture elements of social hierarchical organisation, that is readily observable in animals, but traditionally harder to evaluate in humans. Indeed authors have used neuroeconomical paradigms in order to explain optimal foraging behaviour in the wild (Dubois and Giraldeau, 2003). Although the amount of current scientific input from clinical populations is extremely limited, these recent suggestions are important in highlighting the potential of neuroeconomical paradigms as a cornerstone for the future of psychiatric research. In line with our proposal, recently other independent research groups also suggested that using quantifiable neuroeconomical paradigms may provide important insights in understanding psychosocial functioning impairments observed in patients with MDD (Billeke et al., 2013).

In the next section, we will consider studies which have investigated the impact of guilt, shame and depression on social economical decision-making, reviewing evidence from behavioural, neuroimaging and neuromodulatory studies in clinical, subclinical populations and healthy participants. Our main emphasis will be on neuroeconomical paradigms investigating various dimensions of altruistic behaviours as an important component of social and moral decision-making.

5. The impact of self-blaming moral emotions on social economical decision making
Previous studies have suggested that exogenous manipulations of emotional context influence judgements about acceptability of moral violations (Valdesolo and DeSteno, 2006). Later studies showed that emotions with similar valence, but different psychological properties, have different impacts on the way people make moral judgements (Strohminger et al., 2011). Advocating for a strong relationship between mood states and moral conduct, Kirchsteiger and colleagues (2006) showed that induction of pleasant mood states promote generosity, whereas in negative mood states people seek reciprocation in terms of effort and financial magnitude of the gifts given to another individual (Kirchsteiger et al., 2006). Here, we will discuss the diverging effects of self-blaming moral emotions on social economical decision making. In the later subsections, we will consider evidence regarding the impact of depression and neurotransmitter modulations.

5.1. The role of guilt

As discussed, previous literature suggests that guilt promotes altruistic behaviour. In this section we will consider neuroeconomical evidence regarding the impact of guilt on various dimensions of altruistic behaviour. A recent study has shown that individuals with higher levels of guilt-proneness (a trait associated with feeling negative emotions for personal moral violations) consistently made more ethical choices across different domains (Cohen et al., 2012). These individuals were less likely to engage in unethical business decisions such as violating a legal loophole, less likely to lie for financial gain or in business negotiations, and less likely to engage in counter-productive behaviours at the workplace.

The so-called “Prisoner's Dilemma” (PD) is the most frequently used neuroeconomical paradigm to investigate interpersonal cooperation in uncertain environments. Most commonly in PD, participants interact with a single partner over a one-shot or an iterated decision between
cooperation and defection, in which the payoffs for any combinations of these decisions are determined on a predefined matrix (see Figure 1).

Figure 1. Schematic diagram of Prisoner's Dilemma. In iterated games, players are forced to choose between cooperation and defection in each round blindly to the other player's choice. Adapted from Mokros et al., 2008.

The main uncertainty in the environment is derived from the lack of information regarding the intentions of the partner. It was shown that communication prior to the experiment in PD increases the frequency of cooperation (Ostrom, 2006). One study investigated the emotional reactions of responders in the PD where communication was allowed before the experiment. It was shown that individuals felt significantly more guilt upon violating a previous agreement to cooperate, especially when their partners cooperated (Miettinen and Suetens, 2008). Another study investigated the impact of moral emotions on interpersonal cooperation in PD. Using computer simulations, the authors showed that in mixed populations (with equal numbers of altruists and defectors) moral emotions are important for a social group’s survival (Bazzan et al., 2002). However, it is important to emphasise that these computational models consider general
principles (i.e. capacity to acquire moral emotions) as opposed to specific involvement of guilt.

Another laboratory-based study showed that manipulating guilt in an experimental design increased corporation in PD (Ketelaar and Au, 2003). The effect of guilt induction was especially significant for uncooperative individuals when they interacted with a cooperative strategy (*tit for tat*).

Polman and Ruttan (2012) have recently asked whether guilt had any impact on the way people make moral judgements when evaluating the behaviour of others versus themselves. They defined moral hypocrisy as people's tendency to judge others more severely than they would judge themselves (Polman and Ruttan, 2012). Intriguingly, following guilt-induction, participants rated their own moral violations as less acceptable, whereas they acted more fairly when judging the moral violations of other individuals. This study suggests that guilt may have a fine-tuning role in adjusting perceptions regarding fairness norms. In neuroeconomics, the Dictator Game (DG) is the most frequently used paradigm to evaluate how strongly people endorse the fairness norm. This paradigm is based on an individual's decision in a single shot interaction with another person in which the dictator (the active participant) proposes to split an amount of money received from the researcher (e.g., for £10; any split above £7 versus £3 is considered as a fair offer) (Hoffman et al., 1996). In the DG, the responder is absolutely passive and cannot decline the proposed amount, whereas any proposal can be declined in the Ultimatum Game (UG). This difference makes the DG a behavioural method for monetary quantification of the fairness norm for the proposing dictator by the amount of money being offered, whereas the Ultimatum bargaining models an interaction between two individuals negotiating for usually an imbalanced equilibrium point of fairness, proverbially trying to establish a point that is “fair enough”. In the UG, the proposer receives a sum of money from the bank (often the researcher) and is asked to
propose usually an uneven split. If the responder accepts the split, the money is distributed as proposed. If the responder rejects the split both sides get nothing. The rational actor model (Gintis, 2007) suggests that individuals should be inclined to accept unfair offers in the UG as any financial gain is better than zero gain (Loewenstein et al., 2008). However, empirical evidence suggests that responders only accept around 50% of the unfair offers (defined as proposals which offer less than 30% of the total sum) (Harle et al., 2010). In the altruism literature, the amount of money responders sacrifice in order to punish unfair proposers in the UG is regarded as "altruistic punishment". Anthropological research using predictive computer simulations showed that the frequency of cooperation can only be maintained in larger groups of individuals when there is costly, altruistic punishment (Boyd et al., 2003). In these simulated environments altruistic punishers, who share a similar payoff with the cooperator but also incur the costs of punishment, were the stabilizing agents in sustaining the level of cooperation (Boyd et al., 2003). Therefore, altruistic punishment is an important domain of altruism, which requires special attention.

Early studies reported that the influence of negative emotions on rejection of unfair offers is significant even after a cooling off period lasting one hour (Bosman et al., 2001). Experimentally induced guilt by recalling guilt-evoking autobiographical memories leads to increased offers in the UG in a population of healthy volunteers (Ketelaar and Au, 2003). Furthermore, the effects of guilt emerging from previous unfair offers proposed to an assigned partner in the UG extend over time and yield similar results of increased offers in subsequent encounters with the same partner (Ketelaar and Au, 2003). The latter findings suggest that participants display an extended reparative tendency to counter the effects of the initial guilt-eliciting interaction. Similar results were reported by another study which showed a significant correlation between anticipated guilt
and the amount of money the proposers offered in the UG (Nelissen et al., 2011). These authors have also shown that Ultimatum offers were significantly higher following a guilt induction procedure by recalling autobiographical events, confirming previous findings.

We consider charitable donation behaviour to be another important domain of altruism. Charitable donation behaviour explores individuals’ interactions with the social environment by measuring their responsiveness to various societal causes weighed against their selfish monetary interest. It differentiates from the previously reviewed tasks (PD, DG and UG) in two respects. Firstly, the financial impact of charitable donation behaviour is far reaching, relative to the other paradigms which are based on the interaction between two individuals. Secondly, it measures individuals’ responsiveness to concrete societal causes rather than a universally accepted abstract norm such as “fairness” on which the altruistic punishment in the UG is based. In the case of charitable donations, survivor guilt may motivate individuals to restore a sense of fairness with respect to a specific societal issue, by making donations to those who are in need (e.g., it is not fair that children in Africa are suffering from malnutrition). A recent study showed that guilt induction, irrespective of health concerns, significantly increased the amount of money people were willing to donate to cancer research (Polman and Ruttan, 2012). Secondly, the people who underwent guilt induction showed similar preferences for how much other individuals should be donating to the same cause. There may be parallels between charitable donation behaviour observed in the laboratory and real-life donation behaviour; especially in the case of organ donations. It was recently shown that anticipated guilt is one of the key factors influencing people's decisions to register as organ donors (Wang, 2011). However, another study screening kidney donors, showed that one in five individuals reported clinically significant levels of depression following their donation (Wiedebusch et al., 2009). In post-operative cases, survivor
guilt may be an important construct for further investigation, regardless of whether potential research participants are donors or receivers. It has been proposed that survivor guilt operates with similar principles to that of a mathematical construct called “the zero sum game” which defines limited availability of resources (Blacher, 2000). Under certain conditions, post-operative patients may report clinically significant depression when they perceive their current state of well being (i.e. surviving a traumatic event) as achieved at the expense of another person’s misery (i.e. only limited number of people can survive) (Blacher, 2000). In these situations, the individuals receiving donations are prone to experiencing survivor guilt, whereas for generic charitable donations behaviour survivor guilt may motivate individuals to provide financial help to those who are in need. On the other hand, it is important to highlight that the interpersonal bargaining games that we reviewed in this section (such as UG and DG), adhere to the rules of zero-sum games and therefore, these paradigms may also be effective for probing survivor guilt when proposers decide to keep the bigger proportion of the stake. Considering other studies which showed that making charitable donations is important for psychological well-being (Anik et al., 2009), it is hard to come up with a uniform model for donation behaviour which is solely driven by either negative or positive emotions and explain donation behaviour across different modalities. Whilst conceptually discussing the impact of personal motivations on altruistic behaviour, helping behaviour resulting from a need to feel "warm glow" or ward off negative emotions can was framed as impurely altruistic (Andreoni, 1990).

5.2 The role of shame

The impact of shame on social economical decision making has been widely neglected as a research question. One study investigated the threat of shame in anonymous public goods game and showed that it led to higher levels of contributions to the common pool (Jacquet et al., 2011).
A public goods game is played in a multiplayer environment in which each player contributes a proportion of their endowment to a common pool. The amount collected in the common pool is escalated by a pre-defined factor and then evenly distributed back to the players. In these experiments, Jacquet and colleagues (2011) manipulated the threat of shame by revealing the identity of two of the least generous/cooperative individuals. In a more recent study, the same research group argued that the evolutionary/moral function of a threat of shame is comparable to costly altruistic punishment and it has a fundamental role in sustaining cooperation in society (Jacquet et al., 2012). Following Tangney’s hypothesis regarding the negative influence of acute shame on altruistic behaviour, de Hooge and colleagues (2007) asked whether guilt and shame have opposing effects on interpersonal cooperation. They used an interpersonal donations paradigm in which the value of the endowment was escalated for the donatee (De Hooge et al., 2007). They showed that guilt promoted cooperation only in selfish individuals, whereas they did not provide any support for shame to be reducing altruism, contrary to Tangney's hypothesis. In a later work, these authors aimed to differentiate the prosocial influence of shame by investigating the nature of the shame-eliciting event and its relevance to the decision making task (de Hooge et al., 2008). They raised a general question about mood induction paradigms and suggested that emotions triggered by an external cause (i.e. exogenous) should have limited influence on decision-making. These exogenous manipulations include experimental conditions when participants are manipulated to feel an emotion that would not normally arise from the decision-making context. Using the same interpersonal monetary donations game, they show that only endogenous shame lead to significantly higher levels of contributions only in selfish individuals, regardless of whether it was imagined, recalled or currently experienced.
Earlier studies manipulated the social distance between interacting individuals. Increasing social distance as a result of escaping from a shame-eliciting situation has been purported as one of the behavioural manifestations of incidental shame (Tangney et al., 2007b). It has been shown that an experimentally increased social distance by increasing the level of anonymity between players in the Dictator Game resulted in lower proposals in a population of healthy volunteers (Hoffman et al., 1996). This study suggests that increasing the social distance leads to compromises in the perception of fairness and actual cooperative behaviour. This finding supports one hypothesis proposing that shame serves to reduce altruistic behaviour (Tangney et al., 1996) through mechanisms of increasing social distance (Tangney et al., 2007b). De Jong et al. (2002) investigated whether the physiological manifestations of shame communicated intentions to sustain cooperation in the PD. They suggested that prosocial individuals who were forced to defect had significantly higher levels of self-reported shame, skin conductance and face colouration response (De Jong et al., 2002). However, the intensity of these physical manifestations was not sufficient to maintain the social credibility of the defecting individuals in the eyes of the victim of the defection. Another study compared participants’ reactions to unfair proposals offered by either human or computer partners (Van’t Wout et al., 2006). Overall, individuals accepted unfair offers at a higher rate when they came from computer partners. Furthermore, rejection rates for the unfair offers correlated significantly with skin conductance activity when these offers came from human partners. Considering the physiological manifestations of shame, this study may suggest that shame could also promote altruistic punishment in healthy participants.

We have previously mentioned that healthy functioning of moral emotions can only be conceived within an appropriate context. For example, blaming oneself following unfair
treatment would be pathological. This issue was investigated in healthy participants and it was shown that participants did not display any feelings of shame relative to other outwardly directed negative emotions such as envy, anger, irritation or contempt following unfair offers in the UG, in line with our perspective (Bosman et al., 2001).

5.3 The impact of depression

The debate surrounding the relationship between altruistic behaviour and depression has been mostly theoretical and best to our knowledge, there is no neuroeconomical evidence to support it. The main limitation of the pathological altruism hypothesis is that it does not differentiate between different types of altruism as we have reviewed in the previous sections. Secondly, the majority of the studies supporting this hypothesis are based on self-reported behavioural tendencies as opposed to actual behavioural choice in neuroeconomical paradigms. For example, one retrospective survey suggested that making charitable donations is associated with vulnerability to MDD (Fujiwara, 2009). In this study, the author followed up people who participated in a national survey 10 years ago, and assessed individual tendencies for altruistic behaviours via an e-mail survey. According to the results of the survey, Fujiwara claims that providing emotional and financial support exceeding $10 per month constitutes harmful effects which may be considered as a risk factor for MDD. Although survey studies reach out to larger populations, they may bear significant confounding factors such as social desirability or inaccurate responses. We propose that neuroeconomical paradigms, together with studies investigating self-reported behavioural tendencies, would improve our understanding of social impairments in MDD. Similar opinions have been recently expressed by other authors (Ernst, 2012).
Earlier studies using the PD showed that individuals with self-reported depressive symptoms defected at a significantly higher rate when they were assigned to a high power role, exploiting the vulnerability set by the individuals in the low power role (Hokanson et al., 1980). In this experiment, the individuals in the low power role were asked to make a decision openly and before the individuals in the high power role, therefore making them vulnerable to defection. However, another study reported that people with depressive symptoms were more likely to give an aggressive response to betrayal in the PD compared with healthy controls (Haley and Strickland, 1986). This pattern may suggest that individuals with depressive symptoms process moral violations differently when they are the agent or the victim of such violations. Despite higher levels of negative emotions in the face of defection in the PD, one study showed that patients with MDD had significantly higher acceptance rates for unfair offers in the iterated UG, punishing unfair players less than healthy participants would do (Harle et al., 2010). However, a more recent study showed no significant differences between patients and healthy participants in terms of acceptance rates, although patients made more frequent fair proposals when they were playing as the proposer (Destoop et al., 2012). Two more contributions are made to the UG literature in MDD. Unlike the previous studies these subsequent research showed higher rejection rate in patients with MDD (Scheele et al., 2013, Radke et al., 2013). Importantly, it was shown that patients with MDD rejected both unfair and hyperfair offers significantly more frequently than healthy participants, which seems to suggest that they have hypersensitivity to deviations from the fairness norm (Scheele et al., 2013). It is important that perhaps one has to digests these findings considering possible effects of cultural context on game behaviour (Henrich et al., 2012) with a random effects approach, pointing out to the need for more studies until a conclusive judgement could be made about the impact of depression on UG decision-
making. Taken together, these findings support the view that following undesirable social outcomes, patients with MDD may feel negative emotions more intensely, yet under certain conditions these emotions may not translate into punishing behaviour. There are few previous studies which investigated the impact of affective states on Ultimatum bargaining. Bosman and colleagues (2001) investigated the impact of emotions on rejecting unfair offers in the one-shot UG in healthy participants. They showed that sadness was significantly higher in participants who rejected the unfair proposals compared with those who accepted them. Further, they showed that the intensity of sadness significantly increased the probability of unfair offers being rejected. In their earlier work, Harle and Sanfey (2007) questioned the impact of acute sadness on decision-making in the UG. They showed that incidental sad mood disturbed mechanisms associated with a rational actor model of decision making, and participants who underwent sad mood induction rejected unfair offers more frequently (Harlé and Sanfey, 2007). We think that findings reported by Harle and Sanfey are important as they suggest that impairments in social decision-making mechanisms in patients with MDD are different to the impairments caused by external mood induction.

As is evident from our review, social economical decision making studies in MDD are very limited, and it is certainly not possible to argue for selective deficits in neuroeconomical decision-making. The other area of psychopathology where these paradigms have been used is psychopathy. Interestingly, a lack of guilt has been hypothesised in psychopathy which is directly opposite to the proposed exaggerated manifestation of guilt in MDD. The findings which we will briefly review below may suggest that neuroeconomical paradigms are sensitive to detecting these opposing aspects of psychopathology. For example, it was shown that individuals with high psychopathic tendencies accepted unfair offers in the UG at a significantly higher rate.
than healthy participants (Osumi and Ohira, 2010). The authors proposed that the affective impairment in individuals with high psychopathic tendencies, as measured by skin conductance, is not necessarily a maladaptive one but can be linked to successful adaptations to the social environment (Harpending and Sobus, 1987, Osumi and Ohira, 2010). Another study compared primary and secondary psychopaths with healthy participants, and showed that only primary psychopaths displayed hypervigilant punishing behaviour in the UG (Koenigs et al., 2010). This finding highlights the possibility of using neuroeconomical measures to probe aberrant social decision-making in clinical populations, potentially revealing different profiles within the same clinical diagnostic group. Behaviour of inpatient psychopaths has also been associated with a higher pay-off defecting strategy in a social variant of the PD in which participants interacted over daily rations of water in a survival situation (Mokros et al., 2008). The authors suggested that the game behaviour validly reflects real life decision making and that the amount of environmental rewards obtained by the inpatients may reduce motivation for recovery.

5.4 Neuromodulatory and neuroimaging studies

It is possible that social impairments associated with MDD have neuronal origins. However, whether these impairments are caused by structural differences in cytoarchitecture existing before the onset of MDD, or caused by the scaring effect of recurrent episodes remains unknown. It was recently shown that in asymptomatic patients with MDD there is hypoactivation to pictures of social interactions (irrespective of valence) in regions of the brain associated with behavioural planning (Elliott et al., 2012). This may suggest that social decision-making deficits reviewed in the previous sections may originate from disruptions in neural networks purported to mediate social perspective taking and planning. In this section we will consider evidence from
neuroimaging and neuromodulatory studies in order to identify potential neuronal correlates of moral emotions in depression.

Zak (2001) proposed a triangular model in which he considered the influence of oxytocin, serotonin and dopamine on guiding human social behaviour. He suggested that these neurochemicals act selectively on affiliative bonding, mood states and reward mechanisms respectively (Zak, 2011). In successive UG experiments, it was shown that oxytocin promoted generosity and increased the magnitude of the UG offers significantly, whereas inhibiting oxytocin binding reduced both generosity and the magnitude of the offers, while increasing the threshold for altruistic punishment (Zak, 2011). Another study showed that a genetic polymorphism associated with the oxytocin receptor may have a direct influence on the amount of money people offered in DG interactions (Israel et al., 2009), providing further support for the role of oxytocin in guiding such altruistic decisions. Later studies investigated whether oxytocin enhances different kinds of behaviours associated with altruism. It was shown that intranasal oxytocin infusion promotes hyper-altruism towards in-group members and territorial/defensive aggression towards out-group members; a behavioural strategy defined as parochial altruism (De Dreu et al., 2010). Impact of oxytocin on in-group hyper-altruism behaviour was reproduced whereby individuals having oxytocin infusion significantly increased the amount of money they donated to humanitarian charities providing help to their in-group members (Barraza et al., 2011). In healthy participants undergoing brain scans, it was recently shown that oxytocin augmented caudate response to reciprocated cooperation, possibly enhancing the neural response to social rewards (Rilling et al., 2012). Riling and colleagues (2012) also showed that oxytocin augments left amygdala activation to altruistic decisions and further enhancing functional connectivity between amygdala and anterior insula. Taken together, these studies provide
support for the argument that oxytocin promotes altruistic behaviour by enhancing affiliative feelings.

Other studies investigated the impact of acute manipulation of serotonin (which is one of the key neurotransmitters implicated in MDD, (Deakin, 1998)) on interpersonal cooperation in the PD as well as altruistic punishment in the UG. It was shown that acute tryptophan depletion significantly impaired interpersonal cooperation in healthy participants. Participants in a PD game showed reduced cooperation with playing partners who they were encountering for the first time, but not during subsequent encounters (Wood et al., 2006). In UG studies, it was shown that lowering serotonin levels by acute tryptophan depletion increased the frequency of altruistic punishment, whereas serotonin loading by acute citalopram increased the frequency of acceptance of unfair offers (Crockett et al., 2010, Crockett et al., 2008). Also considering the evidence previously reported by Harle and Sanfey (2007), the UG studies suggest that profiles for altruistic punishment between patients with MDD, individuals who underwent low mood induction and neurotransmitter manipulation are different from each other.

In their seminal study, Greene and colleagues (2001) showed that personal (taking active physical role) moral violations activated the frontopolar cortex (BA 10) significantly relative to non-moral conditions. Although this study was very influential in triggering scientific interest in the neural basis of moral reasoning, the dilemmas used in this study and many subsequent others, force individuals to choose between two outcomes involving harming somebody. A typical example is the “runaway train dilemma” where a train is rapidly approaching five people, but pushing a single individual onto the tracks would bring the train to a stop saving the five (Greene et al., 2001). Participants must choose whether or not to push the individual onto the track. Although such dilemmas may produce robust activations by triggering utilitarian evaluation of
the value of life, they have limited correspondence to our everyday lives. Therefore, we think that studies using interpersonal cooperation, bargaining and donation paradigms have more ecological validity in understanding the neural basis of social perception and moral decision-making. In the PD paradigm, reciprocal cooperation is associated with activations in nucleus accumbens, caudate, ventromedial prefrontal cortex (vmPFC) and ACC, whereas deactivations in ACC and dorsolateral prefrontal cortex (dlPFC) were associated with defection when the partner cooperated; both of these activations correlating significantly with self-reported psychopathy scores (Rilling et al., 2002, Rilling et al., 2007). Another study showed that during reciprocal exchange, altruistic individuals activated the frontopolar cortex more when they interacted with human partners compared with computer partners (McCabe et al., 2001). In the UG paradigms, receiving unfair offers activated the dorsal section of the ACC, whereas activity in the right anterior insula correlated significantly negatively with the frequency at which the unfair offers were accepted (Sanfey et al., 2003). One subsequent study, using PET imaging in an interpersonal reciprocal exchange paradigm, showed that healthy participants activated the right dorsal caudate nucleus when they could effectively punish unfair individuals (de Quervain et al., 2004).

The role of the dorsal ACC in evaluation of players in interpersonal economic exchanges has been a topic of interest as such evaluations are important in guiding decisions whether or not to punish unfair players. During their evaluation of the active participants, observers activated anterior insula and ACC when fair participants received unfair electric shocks, whereas activations related to empathic concern were significantly reduced in male participants when they observed unfair players receiving electric shocks (Singer et al., 2006). The involvement of dorsal ACC and right anterior insula in altruistic punishment was reproduced by a more recent
study using the impunity game paradigm, which is a variant of the UG in which the amount the proposer designated for him/herself is immune to the punishment of the responder (Takagishi et al., 2009).

The lesion literature suggests that ventral parts of the prefrontal cortex are involved in neuroeconomic decisions. Koenigs and colleagues showed that vmPFC is an important region guiding altruistic punishment decisions in the UG (Koenigs et al., 2010). Similarly in patients with bilateral vmPFC lesions, it was shown that patients offered significantly less in the DG and demanded significantly more than what they offered in the UG (Krajbich et al., 2009).

Considering the lesion evidence about functional neuroanatomy of guilt in the vmPFC, it is possible that a diminished sense of guilt disrupts regulatory mechanisms which influence these interpersonal financial decisions. Experimental studies showed that disrupting brain activation may have influence on altruistic punishment decisions. Using transcranial magnetic stimulation (TMS), which employs an external electromagnetic pulse to disrupt brain activity in cortical regions, Knoch and colleagues demonstrated that temporarily disrupting function of right dIPFC diminished altruistic punishment without changing perceptions about the fairness of proposals only when participants interacted with human partners (Knoch et al., 2006). Another similar methodology is transcranial direct current stimulation, by which brain activity in certain cortical regions is disrupted by delivering a low current through external electrodes. Using this methodology, results obtained by TMS were reproduced, highlighting the role of the right dIPFC in guiding such altruistic decisions (Knoch et al., 2008).

Charitable donation paradigms are also important for neuroeconomical studies. Moll and colleagues (2006) not only explored the functional neuroanatomy of mechanisms which modulate decisions to make donations, but also those associated with decisions to “punish”
charitable organisations when they work counter to participants' social and moral values. This study managed to incorporate both aspects of human altruistic behaviour (costly cooperation and altruistic punishment), also defined as “strong reciprocity” (Fehr and Fischbacher, 2003). They showed that septal and subgenual cingulate regions showed selective activation for decisions to donate relative to a pure monetary reward condition, whereas the activity in ventral striatum was shared for donation and monetary reward. Furthermore, they showed that decisions involving opposition activated lateral orbitofrontal regions and anterior insula bilaterally (Moll et al., 2006). Finally, they showed that activation in the anterior orbitofrontal and frontopolar cortices correlated significantly with the amount of real life altruistic engagement. Subsequent studies demonstrated that ventral striatum and the septal region showed activation irrespective of whether the donations were voluntary or not (Harbaugh et al., 2007). More recently, a study showed significant ventral striatum activity for social approval when people make donations in the presence of a social audience, providing further information about the role of ventral striatum in social reward processing (Izuma et al., 2010). Izuma and colleagues did not report any specific regions for selfish decisions in this donations paradigm. However, we think that this paradigm may be effective in probing guilt when people make selfish decisions when the social audience is absent; and shame, when the selfish decision is made in the presence of a social audience. Finally, in an interpersonal charitable donations paradigm it was shown that selfish monetary decisions deactivated vmPFC even when these decisions were more equitable based on the evaluation of the magnitude of the financial reward (Zaki and Mitchell, 2011). Considering the previous evidence regarding the role of vmPFC in guilt processing, it is possible to speculate that such selfish decisions required inhibition of guilt. Secondly, the reason why this study did not report any striatal activation may be because helping random individuals who do not give any
distress signal may not be sufficient to activate regions selective for socially rewarding decisions, which is required for altruistic behaviour.

5.5 Section summary

In this section, we have reviewed literature (summarised in table 2) investigating the influence of self-blaming moral emotions and depression on decision-making in neuroeconomical paradigms. The studies with guilt induction consistently show that guilt promotes altruistic behaviour, whereas the findings are somewhat ambiguous for studies with shame induction. There are very few studies conducted in patients with MDD. We suggest that MDD diagnosis and accompanying elevation in self blaming feelings exert an influence on altruistic behaviour, as shown schematically in Figure 2a. Functional neuroimaging studies suggest that decisions in neuroeconomical paradigms activate regions of the PFC, insular cortex and subcortical regions which are purported to mediate reward processing. MDD has been associated with structural and functional abnormalities in these fronto-mesolimbic pathways (see Figure 2b legend).
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<td>Healthy participants</td>
<td>Behavioural</td>
<td>----</td>
<td>UG</td>
<td>Disrupting right dIPFC diminishes altruistic punishment</td>
</tr>
<tr>
<td>Moll et al.</td>
<td>2006</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>----</td>
<td>Donations</td>
<td>sgACC activation for decisions to make donations</td>
</tr>
<tr>
<td>Sanfey et al.</td>
<td>2003</td>
<td>Healthy participants</td>
<td>FMRI</td>
<td>----</td>
<td>UG</td>
<td>Right anterior insula activation for altruistic punishment</td>
</tr>
<tr>
<td>Ketelaar and Au</td>
<td>2003</td>
<td>Healthy participants</td>
<td>Behavioural</td>
<td>Guilt</td>
<td>PD/UG</td>
<td>Guilt increased cooperation and the amount of money offered</td>
</tr>
<tr>
<td>Hoffman et al.</td>
<td>1996</td>
<td>Healthy participants</td>
<td>Behavioural</td>
<td>----</td>
<td>DG</td>
<td>Increasing social distance reduces dictator offers</td>
</tr>
<tr>
<td>Hokanson et al.</td>
<td>1980</td>
<td>Subclinical</td>
<td>Behavioural</td>
<td>----</td>
<td>PD</td>
<td>Depressed individuals defected more in the high-power role</td>
</tr>
</tbody>
</table>

Studies were listed chronologically (the most recent first), so that advancements and limitations in this field of research can be observed.
Figure 2a. Schematic diagram showing influence of MDD on altruistic behaviour. The model considers the impact of the mood state along with abnormally elevated self blaming feelings (guilt and shame). The proposed model also considers different types of altruism, such as cooperation, altruistic punishment and making donations.
Figure 2b. Mapping of MNI coordinates of the peak region of activations of the reviewed neuroimaging literature. The studies which were included were not selected based on a systematic review of the literature. The colour coding refers to the colours in Figure 2a (e.g., green marks specifying activations selective for guilt). "R" denotes right hemisphere. There may be slight distortions when converting 3D images onto 2D T1 structural anatomical template. All mapping remains accurate within structural neuroanatomical label of the regions. Reviewed evidence suggests that frontopolar, ventromedial, right dorsolateral PFC; dorsal and subgenual ACC; striatum and amygdala are important regions of interest (ROIs) for studying affective disturbances and social economical decision making in MDD.
6. Conclusions and final word

In the present opinion paper, we have argued that MDD is associated with elevated proneness to guilt and shame. We highlighted the possible overlap in the functional neuroanatomy of guilt and shame with regions known to be functionally abnormal in MDD, and emphasised a need for more neuroimaging studies to dissociate the functional neuroanatomy of guilt and shame in patients with MDD. Following the suggestions of previous authors, we considered the idea that guilt and shame can be differentiated based on their influence on social economical decision making. We showed that there is converging literature supporting a positive impact of guilt on altruistic decisions; however literature on the impact of shame is inconclusive. Studies of social economical decision making to date have focused on healthy populations. Considering coexisting emotional processing abnormalities in MDD, it is more challenging to dissociate the impact of moral emotions on social economical decision making in clinical populations. In order to address this issue, we have argued in this opinion paper that using functional imaging with neuroeconomical paradigms could be an important direction for future psychiatric research.
References


ERNST, M. 2012. The usefulness of neuroeconomics for the study of depression across adolescence into adulthood. Biological Psychiatry, 72, 84-86.


CHAPTER 3: Temporal discounting in major depressive disorder

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Abstract

Background: Major depressive disorder (MDD) is associated with abnormalities in financial reward processing. Previous research suggests that patients with MDD show reduced sensitivity to frequency of financial rewards. However, there is a lack of conclusive evidence from studies investigating evaluation of financial rewards over time; an important aspect of reward processing which influences the way people plan long-term investments. Beck’s cognitive model (2005) posits that patients with MDD hold a negative view of the future, which may influence the amount of resources patients are willing to invest into their future selves.

Methods: We administered a delay discounting task to 82 participants; 29 healthy controls, 29 unmedicated participants with fully remitted MDD (rMDD) and 24 participants with current MDD (11 on medication).

Results: Patients with current MDD, relative to remitted patients and healthy participants, discounted large sized future rewards at a significantly higher rate and were insensitive to changes in reward size from medium to large. There was a main effect of clinical group on discounting rates for large sized rewards, and discounting rates for large sized rewards correlated with severity of depressive symptoms, particularly hopelessness.

Conclusions: Higher discounting of delayed rewards in MDD appears to be state-dependent and may be a reflection of depressive symptoms, specifically hopelessness. Discounting distant rewards at a higher rate means that patients are more likely to choose immediate financial options. Such impairments related to long-term investment planning may be an important for understanding value-based decision-making in MDD, and contribute to ongoing functional impairment.
Introduction

Major depressive disorder (MDD) has been associated with reward processing impairments (Pizzagalli et al., 2005). Abnormal reward processing may also play a role in the impaired occupational function that has been identified as a critical factor in the high economic costs of the disorder (Beddington et al., 2008). Symptoms of MDD include suicidal ideation and hopelessness, which may reflect either a bleak (negative) view of the future, an absence of any positive appraisals of future prospects or a combination of the two (American Psychiatric Association, 2000). Both these symptoms may interfere with decisions requiring long-term economical investment planning. Temporal (delay) discounting may serve as an effective experimental probe of this behaviour. Tesch and Sanfey (2008) defined delay discounting as a fundamental dimension of financial decision-making by which people choose between short-term gain maximisation and long-term equity, depending on subjective valuation of money over time. They suggested that one of the key factors in determining trends in these financial decisions is the preference of individuals for having immediate rewards and delayed costs.

Previous reward processing research mostly made use of signal detection paradigms and investigated the relationship between monetary reward processing and anhedonia (inability to gain pleasure from activities which were previously enjoyed), which is one of the core symptoms of MDD (Pizzagalli et al., 2005; American Psychiatric Association, 2000). These studies showed impaired response biases to monetary rewards in dysphoric individuals (Henriques et al., 1994, Juhasz et al., 2009), as well as in individuals undergoing an experimental stress induction procedure (Bogdan and Pizzagalli, 2006), and in people fulfilling clinical criteria for MDD (Pizzagalli et al., 2008). Time is a crucial variable in reward processing models, representing one of the fundamental costs needing to be spent in order to acquire any rewarding outcomes. Signal
detection paradigms manipulate the probability and frequency of winning monetary rewards, while keeping the reward size fixed across different conditions, but cannot address the impact of MDD on subjective valuation of different magnitudes of monetary rewards over time (i.e. delay discounting behaviour). This is because in signal detection paradigms costs per unit of reward are not usually probed explicitly and these paradigms are not commonly used to investigate how people choose between two different rewards per unit of time.

Delay discounting behaviour is typically assessed using monetary choice tasks that have been most frequently used to assess impulsive tendencies in people with various addictions (Kirby et al., 1999, Lawyer, 2008, Kirby and Petry, 2004, Bornovalova et al., 2005). However, discounting behavior tends to correlate rather poorly with self-rated impulsivity on established personality scales in non-addicted populations (McLeish and Oxoby, 2007) and even seems limited to certain subtypes of impulsive behaviour in individuals with heroin addiction (Kirby et al., 1999).

From an economical perspective, delay discounting can also be used simply to define the degree to which individuals prefer short-term over long-time economical strategies (Read and Read, 2004). Previous discounting studies suggested that these individual preferences are influenced by both biological and environmental factors. In healthy participants, discounting rates change over the lifespan, which may reflect neuroanatomical changes and/or changes in environmental factors (Whelan and McHugh, 2009; Read and Read, 2004). Environmental uncertainty imposed by external conditions also influences discounting rates. Individuals tend to prefer short-term rewards when they are traumatised by environmental conditions such as the Wenchuan earthquake (Li et al., 2012) or financial deprivation (Chao et al., 2009). Under such conditions, where there is considerable uncertainty about the future, steeper discounting may be driven by a realistic evaluation of one's life circumstances rather than impulsivity.
As stated previously, MDD is characterized by anhedonia and hopelessness about the future as well as the present (Beck, 2005). It is possible that since MDD is associated with hopelessness about the future, individuals may be expected to shift towards short-term economical decision making strategies (i.e. higher discounting rates). We predict that these depressive symptoms will exert a significant effect particularly in evaluating rewards which are presented with the farthest delays.

In a forced choice paradigm, comparison of choices in the monetary choice task becomes a question about which symptoms of depression, whether present anhedonia or hopelessness about the future, exert more influence on reward devaluation over time. It is plausible that in patients with MDD anhedonia is projected exponentially into the future (i.e. higher expected anhedonia in the future relative to the experience at the present time) therefore it may have greater influence on preferences in a forced choice paradigm. Limited number of studies have explored this exploratory hypothesis in mixed populations with bipolar as well as unipolar depression (Takahashi et al., 2011), showing lower discounting rates for the distant future but higher discounting rates for the near future in patients. A study in patients with late life depression (Dombrovski et al., 2011) showed that lower discounting rates for delayed rewards are associated with high lethality suicide attempts, whereas low lethality suicide attempters had higher discounting rates relative to both non-suicidal patients and healthy participants. Healthy individuals with higher self-reported anhedonia (Lempert and Pizzagalli, 2010) or with experimentally reduced serotonin (one of the key neurotransmitters involved in MDD) (Schweighofer et al., 2008) have lower discounting rates for delayed rewards. Whether short term experimental manipulations of serotonin is a good model for depression phenomenology is always debatable; in the context of the long-term projections involved in temporal discounting,
the model may be particularly unsuitable. The two previous clinical studies (Dombrovski et al., 2011, Takahashi et al., 2011) showed a complex pattern of temporal discounting in depression dependent on both delay and patient characteristics. Therefore we consider that temporal discounting warrants further investigation in a population of young to middle aged adults with unipolar depression (current and remitted) in an exploratory manner.

From a behavioural-economical perspective we presented earlier, we predicted that patients with current MDD may have higher discounting rates for delayed rewards (i.e. choosing the immediate reward option), particularly influenced by hopelessness about the future which may make them less likely to invest into their future selves. The Dombrovski (2011) study showed that non-suicidal depressed individuals and suicidal ideators, as well as low lethality suicide attempters, tended to have higher discounting rates than non-depressed controls, therefore it seems reasonable to predict higher discounting rates in our cohort. We wanted to explore whether preferences for immediate rewards in a forced choice paradigm were related to severity of hopelessness about the future, particularly in the depression groups.

In the well-known "Marshmallow Test", children are expected to forego one marshmallow to get a larger quantity of rewards (i.e. two marshmallows) in real-time. Similarly, preferences in the monetary choice task may require people to represent a future time point varying not in minutes as it is in the Marshmallow Test, but in days. It is a matter of debate about how well people can represent future timeframes in hypothetical settings and whether this perception could be affected in major depression. There have been suggestions about the impact of time representation on intertemporal choices, such that people have logarithmic rather than linear representations of external stimuli (Takahashi, 2005), but there is no study which investigated mathematical functions of time perception in clinical populations. There is some evidence to
suggest that in individuals experiencing depressive symptoms, the internal clock slows down, which means that delays may be experienced longer than they actually are (Gil and Droit-Volet, 2009). This may also have an impact on intertemporal choice, as time to the reward is usually considered as a cost in overall evaluation of the subjective reward magnitude (Wittmann and Paulus, 2008). This complexity of delay discounting led us to investigate it in an exploratory manner in patients with depression.

We therefore sought to investigate delay discounting in patients with current unipolar MDD. Furthermore, we investigated whether delay discounting abnormalities may represent a state feature of depression. Recent evidence suggests that even patients with remitted MDD may show some abnormalities in emotional and reward processing (Eshel and Roiser, 2010, Green et al., 2013). However, if (as hypothesised) impaired discounting reflects symptoms particularly hopelessness, abnormalities in MDD should normalize as symptoms remit. We therefore recruited patients with current and remitted MDD and healthy participants, in order to test the predictions that patients with MDD will have a higher discounting rate for future rewards in long delays and that this behavioural tendency will not be seen in a group with fully remitted symptoms.

**Methods and Materials**

**Participants**

The study obtained ethical approval from the North West/Manchester South NHS Research Ethics Committee. Participants were recruited using online and print advertisements. Initial suitability was assessed with a phone pre-screening interview and a use of an online survey. Written informed consent was obtained from all participants.
Inclusion/exclusion of participants: Patients with MDD fulfilled criteria for a current major depressive episode according to DSM-IV-TR (American Psychiatric Association, 2000). The clinical interviews were conducted by trained researchers (see below). We excluded people with current or history of substance use disorders, psychotic disorders, clinically significant levels of suicide risk (in the acute phase of a previous attempt and scores greater than or equal to 5 on MADRS item 10; see below), bipolar depression, and any other Axis-I anxiety disorders as the likely cause of the current major depressive episode and any other neurological disorders in the MDD group. Participants in the remitted group fulfilled criteria for a past major DSM-IV-TR depressive episode. Exclusion criteria for the remitted depression group were similar but included currently meeting diagnostic criteria for MDD or taking psychotropic medication. The healthy control group had no current or past axis-I disorders.

In total, 29 healthy control participants, 29 individuals with remitted MDD (rMDD) and 24 patients with current MDD (11 with medication, see Tables 1 and 2 for information on clinical groups) were included in the final analysis (one patient with current MDD was excluded on the basis of current hypomanic symptoms which were not present at the stage of the phone screening interview; male, aged 43, nonmedicated).
Table 1. Clinical characteristics of current MDD group (N=24)

<table>
<thead>
<tr>
<th>MD subtype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With melancholic features</td>
<td>20/24</td>
</tr>
<tr>
<td>With atypical features</td>
<td>1/24</td>
</tr>
<tr>
<td>No specific subtype</td>
<td>3/24</td>
</tr>
</tbody>
</table>

**Antidepressant medication and other forms of treatment at time of study**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>SSRI antidepressant (Fluoxetine, citalopram, sertraline)</td>
<td>8/24</td>
</tr>
<tr>
<td>SNRI antidepressant (Venlafaxine, duloxetine)</td>
<td>2/24</td>
</tr>
<tr>
<td>Melatonin receptor agonist (Agomelatine)</td>
<td>1/24</td>
</tr>
<tr>
<td>No medication</td>
<td>13/24</td>
</tr>
</tbody>
</table>

**Co-morbidity at time of study**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Binge eating disorder</td>
<td>3/24</td>
</tr>
<tr>
<td>Generalised anxiety disorder</td>
<td>3/24</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>4/24</td>
</tr>
<tr>
<td>Social phobia</td>
<td>6/24</td>
</tr>
<tr>
<td>Agoraphobia without panic disorder</td>
<td>3/24</td>
</tr>
<tr>
<td>Specific phobia (Shark)</td>
<td>1/24</td>
</tr>
<tr>
<td>Dysthymic disorder</td>
<td>4/24</td>
</tr>
</tbody>
</table>

**Life-time axis-I co-morbidity***

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-traumatic stress disorder</td>
<td>6/24</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>2/24</td>
</tr>
</tbody>
</table>

**Co-morbid disorders in partial remission**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic disorder</td>
<td>1/24</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>1/24</td>
</tr>
</tbody>
</table>

* All co-morbid disorders were fully remitted at time of study, unless otherwise specified. None of the co-morbid disorders was a likely primary cause of the depressive episodes (i.e. all of the patients had diagnosis of MDD with a preceding onset than other comorbid psychiatric conditions). SSRI=selective serotonin reuptake inhibitor, SNRI=serotonin norepinephrine reuptake inhibitor. MDD subtype classification was based on adapting the SCID-I for DSMIV-TR to allow lifetime assessment of the subtypes. All medication-free participants had stopped medication well before the required washout phase. Co-morbid disorders in partial remission indicate presence of subclinical threshold symptoms.
Table 2. Clinical characteristics of rMDD group (N=29)

<table>
<thead>
<tr>
<th>MD subtype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With melancholic features</td>
<td>20/29</td>
</tr>
<tr>
<td>With psychotic features</td>
<td>1/29</td>
</tr>
<tr>
<td>No specific subtype</td>
<td>8/29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of previous MDEs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9/29</td>
</tr>
<tr>
<td>2</td>
<td>7/29</td>
</tr>
<tr>
<td>3</td>
<td>7/29</td>
</tr>
<tr>
<td>4 ≤</td>
<td>6/29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Last MDE details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average length of MDE (months ± SD)</td>
<td>4.2±3 (range: 0.5-12)</td>
</tr>
<tr>
<td>Average time in remission (months ± SD)</td>
<td>57.1± 59.4 (range:3-192)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Life-time axis-I co-morbidity*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>1/29</td>
</tr>
<tr>
<td>Generalised anxiety disorder</td>
<td>2/29</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>4/29</td>
</tr>
<tr>
<td>Social phobia</td>
<td>1/29</td>
</tr>
<tr>
<td>Generalised anxiety disorder (NOS)</td>
<td>1/29</td>
</tr>
<tr>
<td>Specific phobia (Insect)</td>
<td>2/29</td>
</tr>
<tr>
<td>No life-time co-morbidity</td>
<td>18/29</td>
</tr>
</tbody>
</table>

* All co-morbid disorders were fully remitted at time of study. None of the co-morbid disorders was a likely primary cause of the depressive episodes (i.e. all of the patients had diagnosis of MDD with a preceding onset relative to other comorbid psychiatric conditions). MDD subtype classification was based on adapting the SCID-I for DSMIV-TR to allow life-time assessment of the subtypes.
**Materials and Procedures**

*Clinical interview procedure*

Participants were invited for a clinical interview in which trained researchers (EP, PDT and EJT) conducted the Mood Disorders Module A and the psychotic screening of the Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2002b). MINI (Mini International Neuropsychiatric Interview) screening (Sheehan et al., 1998) was conducted with all the participants and relevant Structured Clinical Interview for DSM-IV-TR (SCID) modules were used in order to make a full assessment. The Montgomery Asberg Depression Rating Scale (MADRS), the Global Assessment of Functioning (GAF) scale (Axis V, DSM-IV) and Social and Occupational Functionality Assessment Scale (SOFAS; only for patients with MDD) (Axis V, DSM-IV) were employed.

*The monetary choice task*

The monetary choice task was based on Kirby et al. (1999) and contained 27 items asking participants to choose between two monetary offers; one available today as opposed to a larger one available at a delay (see Table 3 for examples). In the monetary choice task, the delays varied between 7 and 186 days and rewards varied between £11 and £85 (the range comprising all immediate and delayed rewards). We followed Kirby's classification of rewards into three categories; small, medium and large, but converted the original task into UK currency (GBP; £).
Table 3. Examples of monetary choices in the delay discounting task (7 out of 27 time points)

<table>
<thead>
<tr>
<th>Discount rate ranking</th>
<th>Reward today $V$</th>
<th>Future reward $A$</th>
<th>Delay in days $d$</th>
<th>Hyperbolic discount value when indifferent (equation 2)</th>
<th>Hyperbolic discount rate ($k$) when indifferent (equation 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>£11</td>
<td>£30</td>
<td>7</td>
<td>0.090476</td>
<td>0.246753</td>
</tr>
<tr>
<td>2</td>
<td>£15</td>
<td>£35</td>
<td>13</td>
<td>0.043956</td>
<td>0.102564</td>
</tr>
<tr>
<td>3</td>
<td>£27</td>
<td>£50</td>
<td>21</td>
<td>0.021905</td>
<td>0.040564</td>
</tr>
<tr>
<td>4</td>
<td>£40</td>
<td>£55</td>
<td>62</td>
<td>0.004399</td>
<td>0.006048</td>
</tr>
<tr>
<td>5</td>
<td>£49</td>
<td>£60</td>
<td>89</td>
<td>0.00206</td>
<td>0.002522</td>
</tr>
<tr>
<td>6</td>
<td>£67</td>
<td>£75</td>
<td>119</td>
<td>0.000896</td>
<td>0.001003</td>
</tr>
<tr>
<td>7</td>
<td>£78</td>
<td>£80</td>
<td>162</td>
<td>0.000154</td>
<td>0.000158</td>
</tr>
</tbody>
</table>

Summaries of monetary choices in the delay discounting task. The selection is made so that both the delay in days and the future reward is sorted from minimum to maximum value. Kirby et al. (1999) suggested using equation 1.

Following the methodology of Kirby et al. (1999) for delayed rewards (always larger than immediate rewards) small rewards were from £25 to £35; medium rewards were from £50 to £60; and large rewards were from £75 to £85. The immediate rewards varied between £11 and £80; always being smaller in magnitude than the delayed reward size in each temporal discounting proposal. We used a computerised version of this task. The monetary choices were presented in the same order as they were presented in Kirby et al.(1999). Before beginning participants were asked to read the instructions on the computer screen and any questions were clarified. Participants completed this task in a quiet room designated for testing purposes. The participants' choices on the task did not affect the amount of reimbursement they received for participation; we used a hypothetical version of the task.
Data Analysis

The $k$ coefficient, which designates the discounting rate for delayed reward at any indifference point (i.e. the point in which participants do not discriminate between immediate and delayed rewards within any reward size category), is calculated using Equation 1.

$$k = \frac{(A / V) - 1}{D}$$

In this formula, $A$ is the amount of the delayed reward, $V$ is the subjective value of the delayed reward and $D$ is the length of delay. Established indifference points for different rewards are plotted on a graph to establish a discounting curve for any individual. Previous research shows that hyperbolic equations explain the discounting data better than alternative exponential equations which make the assumption that the rate of discounting remains constant over time (Green and Myerson, 2004, Myerson et al., 2001, Mazur, 1987, Murphy et al., 2001). The formula for the hyperbolic discount function is provided below (Equation 2).

$$F(D)_{\text{hyperbolic}} = \frac{1}{1 + kD}$$

Individual discounting coefficients ($k$) for small, medium and large rewards, along with their geometric means as a separate score, were computed in Microsoft Office Excel. Descriptive and between-group analyses were conducted with SPSS version 20.0. We used a general linear model (GLM) to explore any interaction between clinical status and temporal discounting at different rewards sizes. In order to investigate the appropriateness of this model for the data we undertook investigations of the model assumptions using residual plots ((Neter et al., 1996); see pages: 778-781). Both the normal quantile-quantile plot of the model residuals and the plot of the residuals against the fitted-values of the model indicated that the errors were not satisfactorily normally distributed, and that the variance was not equal across all groups. In order to
successfully transform the data so that these assumptions were better met we used the Box-Cox procedure (Sakia, 1992) to search for a possible power transform. The Box-Cox procedure suggested a maximum likelihood estimate of $\lambda = 0$, and as such a natural log transform was performed on the outcome vector. Re-fitting the model on the transformed data and inspecting the residual plots suggested that the model assumptions were now satisfactorily met. We further used one way analysis of variance (One-Way ANOVA) to compare discounting behaviour between our groups. In line with our specific hypothesis, we undertook a simple main effects post-hoc investigation of the significant delayed reward size x group interaction term from the full-model for large sized rewards only (which were presented with the farthest mean delays; see below). We fit a One-Way ANOVA model using diagnostic group as the single between-participants factor. The simple main effects F-ratio was computed using the estimated mean-square for the main effect of group from the one-way model as the numerator, and the mean-square of the error from the original full-model (GLM) as the denominator (as the best unbiased estimator of the residual error (Langsrud, 2003)). The p-value was then computed from the upper-tail of the null F distribution with df = (2,79). We used the Tukey-Kramer pairwise comparison procedure for unequal group sizes (Hayter, 1984) on significant differences. We also investigated the relationship between continuous clinical measures and discounting rates by means of conducting correlational analyses and used Bonferroni correction when reporting significant correlations. The reward magnitude and reward delay correlated significantly ($r = 0.533, p = 0.004$) in the monetary choice task (i.e. larger rewards were associated with longer delays). In order to maintain consistency with the rest of the literature using the same paradigm, we will present the results with respect to reward magnitude (i.e. large sized rewards) instead of reward delay.
Discount Rate Estimation Procedure

Using the methodology suggested by Kirby et al. (1999), a discounting coefficient for each of the monetary choices was established by using the above formula (Equation 1). Calculation of an individual composite discounting coefficient for any given reward size utilises "indifference points" at which participants cannot choose between two monetary choices. For example, in a question which asks participants to choose between "£14 today" and "£25 in 19 days", a participant with a discounting rate higher than 0.041 would choose the immediate monetary option. If the same participant chooses the reward at a delay when they are asked to choose between "£15 today" and "£35 in 13 days", they would have a discounting rate less than 0.10. The composite discounting coefficient for this participant for small sized rewards would be somewhere between these two anchoring points and, following the recommendations of Kirby and colleagues, it is calculated by taking the geometric mean of these two indifference points, therefore it would be 0.064.

When participants’ choices were not consistent within a single value of the discounting coefficient, inconsistencies were resolved by taking the geometric mean of all the indifference points within the streak of inconsistent responses; as suggested by Kirby (1999).

Results

Participants and demographics

The groups did not differ significantly for age and years of education, but the current MDD group had significantly higher number of males (see Table 2 for basic demographic and clinical information). Healthy participants and people with rMDD had MADRS scores that were well below the cut-off for depression (<10) (Hawley et al., 2002), but the remitted MDD group
showed slightly higher scores than controls. Both of these groups had GAF scores indicating minimal or absent symptoms (>80). Patients with current MDD had significantly higher MADRS and lower GAF scores (see Table 4). All of the patients with current MDD reported clinically significant levels of anhedonia based on SCID-I assessment. Hopelessness scores were based on 9th item of the MADRS. It has been suggested that this methodology is a clinically valid approach in measuring the severity of individual depressive symptoms (Desseilles et al., 2011). Currently depressed patients had significantly higher hopelessness scores (see Table 4 for further results).

**Table 4. Group comparison on demographic and basic clinical variables** (mean± SD)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Remitted MDD</th>
<th>Current MDD</th>
<th>Test statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38 ± 6.6</td>
<td>38.34 ± 5.9</td>
<td>38.25± 10.5</td>
<td>0.015^F</td>
<td>0.985</td>
</tr>
<tr>
<td>Education (years)</td>
<td>17.3 ± 2.8</td>
<td>17 ± 3.1</td>
<td>16.2± 3.5</td>
<td>0.901^F</td>
<td>0.411</td>
</tr>
<tr>
<td>Gender</td>
<td>19 Female</td>
<td>23 Female</td>
<td>11 Female</td>
<td>6.61^c</td>
<td>0.037*</td>
</tr>
<tr>
<td>MADRS</td>
<td>2± 2.7</td>
<td>3.9 ± 3.4</td>
<td>33± 4.3</td>
<td>52.193^x</td>
<td>0.000*</td>
</tr>
<tr>
<td>MADRS-9</td>
<td>.27± .58</td>
<td>.39 ± .58</td>
<td>3.75± .94</td>
<td>57.715^x</td>
<td>0.000*</td>
</tr>
<tr>
<td>GAF</td>
<td>90 ± 5.6</td>
<td>87.1 ± 5.1</td>
<td>58.7± 8.7</td>
<td>54.521^x</td>
<td>0.000*</td>
</tr>
<tr>
<td>SOFAS</td>
<td>-</td>
<td>-</td>
<td>57.1± 10</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

F = One-Way ANOVA (df = 2, 79), c = Pearson's chi-square (df =2), *=significant at p<0.05 threshold, 2-tailed; x = Chi-Square value in Kruskal Wallis test (df =2, showing asymptomatic significance). Control: N= 29, Remitted MDD: N=29, MDD: N= 24. MADRS-9 refers to hopelessness scores.

*Discounting rates*

We analysed the discounting task by fitting a GLM where delayed reward size (small, medium, large) was treated as a within-participants factor and diagnostic group (control, remitted MDD, current MDD) was treated as a between-participants factor.
Results from the re-fitted log-transformed model suggested that there was a significant reward size x diagnostic group interaction (F(4, 158) = 3.968, p = 0.004) with a significant Type-III main effect of delayed reward size (F(2, 158) = 53.146, p < 0.001), but no significant Type-III main effect of diagnostic group (F(2,79) = 1.230, p = 0.298). Results of the simple main effects analysis of the large rewards condition indicated a significant main effect of group (F(2,79) = 8.955, p<0.01). Post-hoc pairwise comparisons using the Tukey-Kramer procedure with studentized range critical value (q<0.01 for df (2, 79) = 4.24), suggested that patients with MDD have significantly higher discounting rate relative to healthy participants and remitted patients (absolute difference > critical range; MDD> CON = (0.71> 0.53); MDD>rMDD = (0.57> 0.53); both significant at p<0.01; healthy participants and the remitted group were not significantly different (0.14<0.50)).

Finally, we computed one sample t-tests separately in each group using a “triangular” area under the curve (AuC) measurement to test how much discounting rates change from medium to large sized rewards (see equation 3 below, describing these supporting post-hoc analyses. Please note that this formula should not be confused with the model-free area under the curve approach proposed by Myerson and colleagues (2001) to be used for calculating discounting rates for each reward size category) and to investigate whether the amount of change is significant. The AuC analysis helps us to confirm that clinical group by reward size interaction is influenced by abnormal temporal discounting in current depression, whereby depression selectively affects evaluation of medium to large sized rewards over time.

\[
AuC = \frac{((\mu_{Mk} - \mu_{Lk}) \times Y)}{2}
\]
In this formula, $Y$ is a constant based on the difference between mean large-sized rewards (£80) and mean medium-sized rewards (£55); therefore 25. We used the mean discounting rate for large sized rewards ($\mu_{Lk}$) of each group as the test value in their respective one sample t-tests. The results showed that in healthy participants (df = 28, $t = 2.178$, $p<0.05$) and remitted patients (df = 28, $t = 3.957$, $p<0.001$) the change from medium to large sized rewards is significant, whereas in patients with current MDD it is non-significant (df = 23, $t = -1.030$, $p = 0.314$). The groups did not differ significantly for the amount of change in discounting rates from medium to large sized rewards ($F(2, 79) = 1.569$, $p = 0.215$). Taken together, these analyses suggest that remitted patients and healthy participants display comparable temporal discounting behaviour, whereas patients with current depression have significantly higher discounting rates for large sized rewards, which is mainly influenced by inability to evaluate medium to large sized rewards differently over time, resulting in a plateau of the discounting curve (Fig 1).
**Figure 1.** The graph showing mean discounting coefficients against the monetary reward size using the raw data before natural log transformation. The scale bar shows +/- 1 mean Standard Error cross all reward sizes (= 0.01); the mean Standard Error for large sized rewards is 0.008 (Control: 0.006, rMDD: 0.002, Current MDD: 0.015). The mean the reward size for small, medium and large sized rewards are £30, £55 and £80, respectively.

*Post-hoc correlation analyses*

We investigated the relationship between depressive symptoms, particularly hopelessness, and discounting rates for large sized rewards. Exploratory analyses comprising all participants revealed that there was a significant correlation between MADRS and GAF scores (Spearman’s $r_s = -0.777$, $p<0.001$), and in the pooled MDD sample (comprising of patients with current and remitted MDD; $n = 53$) we observed this relationship more strongly (Spearman’s $r_s = -0.855$, $p<0.001$). Our specific hypotheses concerned correlations between discounting behaviour and (i)
GAF scores and (ii) Hopelessness scores. Since both these scores correlated with depression severity (MADRS), we controlled for MADRS scores in these analyses. In the pooled MDD sample, GAF scores (as an indicator of general psychosocial functioning impairment) and discounting coefficient for large sized rewards showed a significant relationship (Pearson’s $r = -0.308$, $p<0.01$), controlling for MADRS scores. Furthermore, in the pooled MDD sample, discounting scores correlated significantly with hopelessness scores (Pearson’s $r = 0.394$, $p<0.01$), again controlling for MADRS; all correlations survive Bonferroni correction).

Finally, in order to control whether our findings were driven by medication effects or the gender distribution in the MDD group, we compared patients with and without medication and male patients with female patients. There were no significant differences for any of the delayed reward sizes within the MDD group between medicated and medication free patients ($t = -0.787$, df = 22, $p = 0.440$); and between male and female participants ($t = 0.051$, df = 22, $p = 0.960$).

**Discussion**

The results of our study suggest that financial decision-making in patients with MDD is associated with shorter term financial reward preferences indicated by higher discounting rates for large sized rewards relative to healthy participants and remitted patients. We showed that differences in discounting rates across reward sizes were modulated by clinical groups, such that MDD patients, relative to both control and rMDD group, do not show a decrease in discounting rates between medium and large rewards. Higher discounting rates for large sized rewards appear to be associated with lower scores on a measure of general psychosocial functioning (i.e. GAF) even when controlling for depression severity (i.e. MADRS scores). Furthermore, we showed that discounting rates for future rewards correlated significantly with the severity of hopelessness.
in the depression group. Finally, we showed that patients with fully remitted symptoms did not differ significantly from healthy participants in terms of temporal discounting behaviour.

As expected, we showed a significant clinical group by delayed reward size interaction with no significant main effect of clinical diagnoses consistent across all delayed reward sizes. One-way analysis of variance confirmed our a priori hypothesis that our groups would be different in delay discounting coefficients for large sized rewards. Post-hoc pairwise comparisons revealed that patients with current MDD had significantly higher discounting rates relative to both healthy participants and remitted patients. Significant correlations between severity of hopelessness in the joint MDD group and the discounting coefficient for large sized rewards supported our prediction based on Beck's cognitive triad (Beck, 2005).

Previous studies argued that individuals with self-reported anhedonia demonstrated farsighted decisions because present anhedonia blunts responses to immediate rewards and these individuals would imagine themselves enjoying monetary rewards more in the distant future than in the present time (Lempert and Pizzagalli, 2010). However, it is questionable that self-reported anhedonia in healthy participants is a reliable model for MDD. Beck's cognitive triad model (Beck, 2005) argues that MDD is characterized by a negative view of the future as well as the present. In a forced choice paradigm, it may be that pessimism about the future is a stronger influence on behavior than present anhedonia. Remission of future pessimism and hopelessness may explain the absence of significant differences between the remitted group and healthy participants for large sized rewards.

The present findings advance understanding of impairments in MDD associated with reward processing. Previous studies mainly considered impairments contingent upon frequency and
probability of winning financial rewards, but not how patients with MDD subjectively evaluated their magnitudes over time (Pizzagalli et al., 2008, Henriques et al., 1994, Pizzagalli et al., 2005). Here, we showed that patients with MDD were insensitive to the changes in the magnitude of medium to large sized financial rewards. We suggest that this preference may be driven by the impact of the time course rather than the changes in reward magnitude alone. For example, when monetary options in the monetary choice task are ranked from lowest to highest with respect to their corresponding k coefficients there is a 70% escalation from the lowest medium sized reward (£50) to the highest large sized reward (£85), whereas the delay escalation across these monetary choices is approximately 303% (from 30 days to 91 days). This means reward value per unit of time dramatically decreases, and it is possible that patients with MDD are more sensitive to these changes. It has been argued that individuals with impairments in time perception may have an altered perception of distant reward magnitude based on a higher cost per time unit (Wittmann and Paulus, 2008). There is some evidence to suggest that patients with MDD may have distorted time perception, experiencing a slowing effect on time relative to healthy participants and patients with bipolar disorder (Bschor et al., 2004). This could mean that patients with MDD perceive delays as longer than they actually are, thus devaluing delayed rewards by associating a higher overall cost for delays even if their cost per a unit of delay is comparable to healthy participants.

Paradoxically, impairments evaluating rewards over time could enhance overall financial performance in the monetary choice task. For example, from an evolutionary-financial point of view, steeper discounting behaviour in the monetary choice task, such as we observed in patients with MDD, can lead to individuals banking larger amounts of money at any given point in time. An alternative explanation of our findings is that patients with MDD may hold a more realistic
view of their prospects at any time point. Depressive realism may be a mechanism by which patients with MDD hold a more accurate estimation of control over environmental contingencies and more accurate evaluation of uncertainties between the present time and the future compared to healthy participants (Moore and Fresco, 2012). Such realism may influence preferences for immediate rewards and confer an advantage in some specific contexts. However, the present task does not explicitly quantify such uncertainties about the future; the hypothesis could be explicitly tested using an adaptation of the monetary choice task to test whether lowering the probability of receiving the delayed reward results in depressed patients outperforming controls.

Other studies have reported that patients with MDD may outperform healthy participants in certain socially contingent decision-making paradigms, requiring sacrifice of financial rewards and investment of time to reach an optimal solution to a problem (Harle et al., 2010, von Helversen, 2011). Therefore, abnormalities in rewarded decision-making in MDD may be advantageous in some contexts but disadvantageous in others depending on specific task contingencies. This may have implications for occupational performance which warrant further exploration.

Our study had some limitations. Firstly the monetary choice task was hypothetical in nature. However, it has previously been shown that hypothetical monetary proposals produce discounting behaviour that is similar to that obtained in studies using real currency (Murphy et al., 2001). Secondly, in the present design, the reward magnitude and the delays were correlated, therefore it is not possible to determine whether the effects we showed here are driven by reward magnitude or rewards delay; and future studies could address this issue by having a design in which both factors vary independently. Thirdly, although we showed that temporal discounting for large sized delayed rewards were particularly influenced by severity of hopelessness and
overall impairments in psychosocial functioning, we did not use an external measure of impulsivity to rule out its possible confounding impact. However, we think that impulsivity should have limited influence on delay discounting in MDD relative to addicted clinical populations, as impulsive behaviour is not one of the core clinical symptoms of MDD. Finally, about half of our MDD group were currently medicated and therefore it is possible that some of the effects were driven by medication. A post-hoc comparison between medicated and unmedicated participants showed no significant difference; however this issue should be explored in future studies with greater power to explore effects of medication (and other treatments).

Conclusions

We have shown that patients with MDD have significantly higher discounting rates for future rewards relative to both healthy participants and remitted patients, whose discounting behaviour is comparable. Correlations between clinical measures and the discounting rates suggest that the differences between our groups are driven by depressive symptomatology, especially future directed pessimism. We also showed that patients with MDD are less sensitive to changes in the reward size, as indicated by discounting rates which plateau from middle to large sized rewards. We suggest that the overall costs associated with long delays may be driving steeper devaluation of the reward magnitude.
Acknowledgements

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References


CHAPTER 4: Social-economical decision making in major depressive disorder: evidence from neuroeconomical experiments

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Number of tables: 11
Supplemental information: 1 APPENDIX
At the time of resubmission, this chapter is being revised for publication in Psychological Medicine.
Abstract

Background: Prosocial emotions related to self-blame (guilt and shame) are important in guiding human altruistic decisions. These emotions are elevated in major depressive disorder (MDD), whereby MDD is associated with guilt driven pathological hyper-altruism. However, the impact of such emotional impairments in MDD on different types of social-economical decisions is unknown.

Methods: We administered neuroeconomical tasks related to different kinds of altruistic behaviours (interpersonal cooperation, altruistic punishment and charitable donation) to 33 healthy participants, 35 patients in full remission (unmedicated) and 24 currently depressed patients (11 on medication).

Results: We showed that interactions between clinical status and altruistic decisions were mainly influenced by the clinical status but not by different subtypes of altruism. Tests for task-specific hypotheses revealed that the groups did not differ significantly for the frequency of interpersonal cooperation and altruistic punishment behaviour. However, our results suggest that patients with current MDD experience significantly more guilt upon receiving unfair offers in the Ultimatum Game, and make significantly lower charitable donations regardless of the personal costs associated with these decisions. Furthermore, we showed that altruistic forms of characterological guilt influence costly altruistic decisions only in healthy participants.

Conclusion: Taken together, our results do not provide support for the guilt driven pathological hyper-altruism hypothesis in current MDD and we suggest that it should be revised particularly to exclude forms of altruistic punishment which require blaming other individuals for moral/behavioural transgressions.
Introduction

Interpersonal cooperation is a major feature of human social life, promoting survival fitness both at individual and group levels. As human societies have developed, acts of altruism between individuals have given way to cultural organisation of social groups around a moral system defining various normative behaviours (Boyd and Richerson, 2009). Prosocial/moral emotions (e.g., guilt, shame, etc.) are important in terms of forming a motivational basis of altruistic behaviours (Zahn et al., 2012), and the capacity to experience such sentiments is shown to create further selection advantages (Bazzan et al., 2002). Experimental elevation of guilt and shame increases altruistic acts in decision-making situations (De Hooge et al., 2007, Ketelaar and Au, 2003, Jacquet et al., 2011), although there is controversy regarding the positive influence of shame (Jacquet et al., 2011, de Hooge et al., 2008), with some authors suggesting that shame influences social decisions in opposition to altruistic tendencies by increasing social distance (Tangney et al., 2007a).

Major depressive disorder (MDD) is associated with elevated self blaming moral emotions (for reviews see Kim et al., 2011, Puleu et al., 2013) as well as abnormalities in social decision making (Destoop et al., 2012, Harle et al., 2010). Abnormalities associated with moral emotions may be responsible for social decision making impairments as well as conflicts in real life, contributing to increasing social and economical costs of psychiatric disorders (Beddington et al., 2008). Independent clinical studies show increased experience of both guilt and shame in MDD (O’Connor et al., 2007, O’Connor et al., 2012, O'Connor et al., 2000a). However, evidence as to how this affects altruistic decisions is lacking.

Addressing this issue, O'Connor and colleagues proposed a "pathological hyper altruism hypothesis" based on elevated levels of altruistic forms of guilt in current MDD patients
relative to healthy participants (survivor guilt: defined as feeling guilty for being better off than other individuals; and omnipotent responsibility guilt: defined as blaming oneself for the consequences of events which take place beyond one's control), predicting that patients will make altruistic decisions more frequently (O’Connor et al., 2007, O’Connor et al., 2012, O’Connor et al., 2000a). Survivor and omnipotent responsibility guilt were also shown to differentiate patients with fully remitted symptoms from healthy participants (Green et al., 2012b, Green et al., 2013), suggesting their important role in depression vulnerability. Recent epidemiological studies provide complementary evidence showing that depression vulnerability may indeed be associated with elevated levels of altruism (Fujiwara, 2009), although without addressing whether this is influenced by elevated levels of self blaming emotions. On the other hand, Tangney and colleagues consider that shame may increase interpersonal/social distance, and consequently predict that patients are less likely to make altruistic decisions (Tangney et al., 2007a). However, direct evidence to measure the influence of guilt and shame-proneness on different aspects of altruistic behaviour is lacking, and therefore it is unclear whether either of these conflicting hypotheses is supported.

Both O’Connor and Tangney did not distinguish between different types of altruistic behaviours. Recent developments in behavioural research suggest that the notion of "altruistic behaviour" can be stratified further into different components with different interpersonal/social functions; such as cooperation, altruistic punishment or making donations. For example, previous research suggested that if there are not enough individuals who engage in altruistic punishment (defined as sacrificing resources in order to punish individuals who violate social/behavioural norms), interpersonal cooperation within a society cannot be sustained over time (Boyd et al., 2003). Therefore, in order to evaluate existing
hypotheses of altruism in MDD, it is important to dissociate the impact of affective disturbances on different kinds of social-economical decision making. Here, we used West and colleagues’ definition of altruistic behaviours; as a form of cooperative behaviour towards an indiscriminate recipient at a particular cost to the actor in the absence of short or long term expectancy of reciprocation (West et al., 2007). Using nonzero-sum (i.e. tasks in which both players may win mutually, e.g., Prisoner's Dilemma) and zero-sum (i.e. tasks in which players can only win mutually exclusively, e.g., Dictator Game, Ultimatum Game, charitable donations) neuroeconomical paradigms, we tested the guilt driven hyper-altruism hypothesis in MDD. Neuroeconomical paradigms make use of various tangible resources such as money or time within an interpersonal decision problem designed to probe real-life decision-making mechanisms. The specifications of each paradigm are given in more detail in the Methods section. We defined two sets of hypotheses; a primary hypotheses relating to zero-sum (i.e. costly forms of altruism) and secondary hypotheses relating to nonzero-sum outcome measures and to the correlations between altruistic forms of guilt, trait shame and altruistic outcome measures. Furthermore, in order to address the role of self blame on altruistic punishment behaviour, we conducted a stimulus rating task (see below) following Ultimatum Game decision-making.

**Prisoner's Dilemma**

Rand and colleagues argued that humans have a predisposition for cooperation (Rand et al., 2012). We wanted to test whether this hypothesis is applicable to patients with current MDD (cMDD). Secondly, we wanted to test whether patients with cMDD would be less cooperative overall (as previously demonstrated for other psychiatric populations (Mokros et al., 2008)) and whether they would be prone to defect when they could estimate when a mutual
relationship will be terminated. On the other hand, if altruistic forms of guilt motivate cooperation despite psychopathology, patients with cMDD would be more cooperative in line with O'Connor's hypothesis.

**Dictator Game**

We wanted to test whether patients with cMDD would offer less of the stake when making Dictator offers to anonymous partners who do not have power to reject their proposals. A recent study showed that patients with cMDD undergoing inpatient psychiatric treatment make more generous offers relative to healthy participants (Destoop et al., 2012). We wanted to test whether there are any differences in proposing behaviour between inpatients and outpatients with MDD.

** Ultimatum Game**

We investigated whether we could replicate the findings previously published by Harle and Sanfey (2010), who showed that patients with cMDD accepted unfair offers at a higher rate than healthy controls in the Ultimatum Game (UG). In the iterated UG, both the proposer and the responder earn nothing when a proposal is rejected. Therefore, rejecting unfair offers in the UG would mean sacrificing provisional monetary earnings in order to punish an unfair proposer, and is considered as an act of altruistic punishment. Secondly, we tested the prediction that patients with cMDD would experience more self-blaming (guilt and/or shame) feelings when receiving unfair offers from anonymous partners.
Charitable donations task

Charitable donation behaviour is a form of altruism which is unique to humans. Recent independent reviews argued that charitable donation paradigms have the highest ecological validity in terms of studying human altruistic behaviours (Rilling and Sanfey, 2011). Experimental studies suggest that humans display different altruistic preferences to in and out-group members (De Dreu et al., 2010). Thus, although some previous studies have used charities operating internationally in their experimental design (Milinski et al., 2002), it is potentially important to identify charities which operate in the UK to maintain high ecological validity of studying this type of altruism. Considering that there were not any previous publications studying charitable donation behaviour experimentally by using UK charities, we needed to conduct a pilot study in order to identify the most suitable charities for our purpose. This approach is also in line with that of our collaborators in United States, who also followed a similar methodology to identify the most suitable charities for their experimental design (Moll et al., 2006).

Our primary prediction was that patients with cMDD would make fewer costly altruistic decisions. Consequently, we predicted that patients with cMDD would have better financial performance than the comparison groups. Finally, recruiting remitted MDD patients (rMDD) we tested whether any abnormalities associated with cMDD are likely to normalise upon remission of symptoms.
Methods

Participants

The pilot study received approval from the University of Manchester Ethics Committee. The main behavioural study received ethical approval from the North West/Manchester South NHS Research Ethics Committee. Participants were recruited using online and print advertisements. Initial suitability was assessed with a phone screening interview based on participants' responses to an online survey. Written informed consent was obtained from all participants.

Inclusion/exclusion of participants.

Patients with cMDD fulfilled criteria for a current major depressive episode according to Diagnostic and Statistical Manual IV-TR (American Psychiatric Association, 2000). We excluded people with psychotic disorders, clinically significant levels of suicide risk (in the acute phase of a previous attempt or > 5 on Montgomery-Asberg Depression Rating Scale item-10 (MADRS; (Montgomery and Asberg, 1979)), bipolar depression, and patients with a diagnosis for anxiety disorders preceding the diagnosis for MDD. Participants in the rMDD group fulfilled criteria for a past major depressive episode according to DSM-IV. Exclusion criteria for the remitted depression group were similar but we also excluded current major depression or psychotrophic medication. The control group had no current or past Axis-I or Axis-II disorders. No participant had a history of neurological disorder or substance abuse.

In total, 33 healthy control participants, 35 individuals with rMDD and 24 patients with cMDD (11 with medication, see Tables 1 and 2 for information on clinical groups) were included in the final analysis (one patient with cMDD was excluded on the basis of current
hypomanic symptoms which were not present at the stage of the phone screening interview; male, aged 43, nonmedicated).
Table 1. Clinical characteristics of current MDD group (N=24)

<table>
<thead>
<tr>
<th>MD subtype</th>
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</tr>
</thead>
<tbody>
<tr>
<td>With melancholic features</td>
<td></td>
</tr>
<tr>
<td>With atypical features</td>
<td>1/24</td>
</tr>
<tr>
<td>No specific subtype</td>
<td>3/24</td>
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</table>

<table>
<thead>
<tr>
<th>Antidepressant medication and other forms of treatment at time of study</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>SSRI antidepressant (Fluoxetine, citalopram, sertraline)</td>
<td>8/24</td>
</tr>
<tr>
<td>SNRI antidepressant (Venlafaxine, duloxetine)</td>
<td>2/24</td>
</tr>
<tr>
<td>Melatonin receptor agonist (Agomelatine)</td>
<td>1/24</td>
</tr>
<tr>
<td>No medication</td>
<td>13/24</td>
</tr>
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<table>
<thead>
<tr>
<th>Co-morbidity at time of study</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Binge eating disorder</td>
<td>3/24</td>
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<tr>
<td>Generalised anxiety disorder</td>
<td>3/24</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>4/24</td>
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<tr>
<td>Social phobia</td>
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</tr>
<tr>
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<td>3/24</td>
</tr>
<tr>
<td>Specific phobia (Shark)</td>
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<tr>
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<tr>
<th>Life-time axis-I co-morbidity*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-traumatic stress disorder</td>
<td>6/24</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>2/24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-morbid disorders in partial remission</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic disorder</td>
<td>1/24</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>1/24</td>
</tr>
</tbody>
</table>

* All co-morbid disorders were fully remitted at time of study, unless otherwise specified. None of the co-morbid disorders was a likely primary cause of the depressive episodes. SSRI=selective serotonin reuptake inhibitor, SNRI=serotonin norepinephrine reuptake inhibitor. MDD subtype classification was based on adapting the SCID-I for DSM-IV-TR to allow lifetime assessment of the subtypes. All medication-free participants had stopped medication well before the required washout phase. Co-morbid disorders in partial remission indicate presence of subclinical threshold symptoms.
**Table 2. Clinical characteristics of the remitted MDD group (N=35)**

<table>
<thead>
<tr>
<th>MD subtype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With melancholic features</td>
<td>23/35</td>
</tr>
<tr>
<td>With psychotic features</td>
<td>1/35</td>
</tr>
<tr>
<td>No specific subtype</td>
<td>11/35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of previous Major Depressive Episodes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13/35</td>
</tr>
<tr>
<td>2</td>
<td>7/35</td>
</tr>
<tr>
<td>3</td>
<td>9/35</td>
</tr>
<tr>
<td>4 ≤</td>
<td>6/35</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Last MDE details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average length of MDE (months)</td>
<td>4.6 ±3.3 (range: 0.5-12)</td>
</tr>
<tr>
<td>Average time in remission (months)</td>
<td>57 ± 59 (range:3-192)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Life-time axis-I co-morbidity*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>1/35</td>
</tr>
<tr>
<td>Generalised anxiety disorder</td>
<td>4/35</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>5/35</td>
</tr>
<tr>
<td>Social phobia</td>
<td>4/35</td>
</tr>
<tr>
<td>Generalised anxiety disorder (NOS)</td>
<td>1/35</td>
</tr>
<tr>
<td>Specific phobia (Insect)</td>
<td>2/35</td>
</tr>
<tr>
<td>No life-time co-morbidity</td>
<td>18/35</td>
</tr>
</tbody>
</table>

* All co-morbid disorders were fully remitted at time of study. None of the co-morbid disorders was a likely primary cause of the depressive episodes. MDD subtype classification was based on adapting the SCID-I for DSMIV-TR to allow life-time assessment of the subtypes.

**Clinical interview procedure.**

Participants were invited for a clinical interview in which trained researchers (EP, EJT and PDT) conducted the MINI screening (Sheehan et al., 1998) and the psychotic screening of the Structured Clinical Interview for DSM-IV-TR ((First et al., 2002b);SCID-I). Relevant SCID-I modules were then used in order to make a full assessment. The Global Assessment of Functioning (GAF) scale (Axis V, DSM-IV) and Social and Occupational Functionality Assessment Scale (SOFAS; only for patients with cMDD) (Axis V, DSM-IV) were employed
to provide measures of functional impairment. All participants also completed a battery of affective measures, including Positive and Negative Affect Scale (PANAS; (Tellegen et al., 1988)), Rosenberg Self Esteem Scale (Rosenberg, 1965), Test of Self-Conscious Affect (TOSCA measuring characterological forms of guilt and shame based on their behavioural manifestations; (Tangney, 1990)) and Interpersonal Guilt Questionnaire (IPGQ-67 measuring characterological forms of guilt including survivor and omnipotent responsibility; (O'Connor et al., 1997)). IPGQ-67 contained 67 items with statements probing guilt, such as: I sometimes feel I don't deserve the happiness I have achieved. Similarly, TOSCA scale aims to capture behavioural manifestations of guilt and shame in hypothetical scenarios with such items as: “You break something at work and hide it”. Participants respond to each questionnaire by selecting the likelihood of how they would feel or act in those hypothetical scenarios on a Likert scale. Both scales have established alpha reliability values for healthy participants: TOSCA-guilt: .78; TOSCA-shame: .77 (Tangney, 1990); IPGQ-survivor guilt: .85; IPGQ-omnipotent responsibility guilt: .83 (O'Connor et al., 1997).

**Materials and Procedures.**

All testing was conducted in a quiet room designated for testing purposes. For each experiment, the participants read relevant instructions on paper and they were allowed time to ask any questions before the experiment. All tasks were run on a laptop computer using E-Prime v2.10.

**Prisoner's Dilemma Task.**

The participants engaged in a 31 round iterated PD task based on a hypothetical water shortage scenario, adapted from Mokros et al. (2008) (see Supplementary Materials; Appendix I). The
participants were allowed to read and ask questions about the water shortage scenario and the PD matrix were explained to them. Overall, the computer strategy was set to tit-for-two-tats (Farrell & Ware, 1989). This strategy defects only when participants defect twice in a row and keeps on defecting until the participant cooperates and then restores back to cooperation. It is regarded as a forgiving/compassionate strategy and we selected this strategy as the most suitable model for real world social interactions with friends/family. No deception was used in this paradigm (i.e. participants knew that they were interacting with a computer partner in an imagined water shortage scenario) and participants did not receive any real financial rewards based on their task performance.

Dictator Game.

Before completing the Ultimatum Game experiment, participants were asked to make three Dictator offers by choosing from a list of offers to split £10 between themselves and other players (see below for details). The offers varied between £9 versus £1 (most unfair) and £5 versus £5 (fair). The offers were based on hypothetical money and participants did not receive the amount they decided to keep for themselves (also for the Ultimatum Game).

Ultimatum Game.

The participants were told that they will be interacting anonymously over financial decisions with other players sitting in computer labs in two other locations within the University of Manchester. Participants were told that in situations when arranging such appointments were not possible, they would be seeing financial offers recorded previously from other participants. This measure is taken in order to ensure that participants feel they are interacting with individuals rather than a random computer strategy. In fact, all participants were engaged in an UG
experiment with predetermined offers. All participants completed a 30 round UG task using designated "Accept" and "Reject" buttons to make decisions. The positioning of these labels on the computer screen was counterbalanced across participants (also in the donations task, below). As in the DG paradigm, the offers varied between £9 versus £1 (most unfair) and £5 versus £5 (fair). There were 11 fair offers (equal split of £5 vs. £5), 16 unfair offers (below 30% of the stake; any split below £7 versus £3) and 3 offers falling between these extremes (splits of £6 vs. £4 and £6.50 vs. £3.50). The offers were presented in text for 4 seconds and did not contain any human pictures (i.e. The proposer gets £6, You get £4). The participants had 10 seconds to respond to the offers. The offers were presented in random order and full debriefing was provided at the end of the testing session.

**Ultimatum Game Emotion Ratings.**

In order to investigate whether receiving unfair offers in the UG probes self blaming feelings, we asked participants to rate how they felt upon receiving financial offers from anonymous partners. A representative sample of UG offers were re-presented in random order and following each offer the participants were asked to choose a single emotion from an open list of moral emotions (Tangney et al., 2007; containing guilt, shame, pride, gratitude, self-contempt, and indignation) which also contained a "other/none" option. Secondly, the participants were asked to make a rating for the pleasantness/unpleasantness of the offers that they received on a 1 to 7 Likert scale on which 1 corresponded to “very unpleasant" and 7 corresponded to “very pleasant". Trials on this task did not have any time restrictions.
Charitable Donations Task.

Pilot Study

Replicating the methodology used by Moll et al. (2006) for their normative data collection stage we identified 95 registered charities working for variety of societal causes (e.g., cancer research, animal rights, abortion, religion, poverty, firearms, agriculture, global warming etc.) by using the database of The Charity Commission for England and Wales (http://www.charity-commission.gov.uk). The mission statements of the charitable organisations were recorded in a verbatim manner from this database. Participants were asked to rate each charity anonymously on an online survey tool. For each charity, participants gave ratings for familiarity, the extent to which they agreed/disagreed with the charitable organisation’s mission statement and likelihood of making a donation on a bipolar Likert scale ranging from -5 (strongly disagree) to 5 (strongly agree). The order in which the participants saw the list of charities were counterbalanced; the first list containing charities in A-Z, the second list containing charities in Z-A order. The participants were entered into a prize draw for £25 worth of High Street vouchers.

Pilot Study Results

Participants. Ninety two individuals participated in the online survey. Participants who did not respond to at least 90% of the items, those who resided outside of the UK and those whose first language was not English were excluded from the final analysis. Final analysis was conducted for 45 eligible participants. The majority of the participants were females (80%). The mean age in this sample was 28.35 years (SD=10.64). In this sample, 51.1% were educated to Degree level, followed by 24.4% of the sample who were educated to the A-Levels and 22.2% to the
GCSE level. The majority of the sample (77.8%) declared that they were still studying for a degree.

**Charitable Organisations**

As expected, there was a significantly positive correlation between mission statement ratings and likelihood of making a donation across all of the 95 charities ($r=0.683$, $p<0.01$), showing that the participants were more likely to make donations to the charitable organisations whose mission statements they liked better.

After this initial correlational analysis, the dataset containing individual ratings for each charity was aggregated in order to get average ratings of the three variables under investigation, for each charitable organisation. In order to discriminate between charities based on their rating values the aggregated dataset was ranked in ascending order first by mission statement ratings, then by likelihood of donation ratings and finally by familiarity. The charitable organisations were ranked based on these sorting criteria. Table 3. summarizes the ratings for the 36 most positively rated charities whereas, Table 4. summarizes the ratings for the 11 most negatively rated charities (those which had mission statement ratings lower than -1). The positively rated cluster had a mean familiarity of -1.41 ($SD = 3.1$), a mission statement rating of 3.34 ($SD=0.48$) and a likelihood of making a donation of 0.94 ($SD=0.95$). The correlations between these variables are summarized in Table 5.
Table 3. List of most positively rated charities (n= 36).

<table>
<thead>
<tr>
<th>Name</th>
<th>Familiarity</th>
<th>Mission Statement Agreement</th>
<th>Donation Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRUK</td>
<td>4.53</td>
<td>4.36</td>
<td>2.96</td>
</tr>
<tr>
<td>Oxfam</td>
<td>4.56</td>
<td>4.33</td>
<td>3.58</td>
</tr>
<tr>
<td>British Heart Foundation</td>
<td>4.40</td>
<td>4.18</td>
<td>2.18</td>
</tr>
<tr>
<td>The Stroke</td>
<td>0.71</td>
<td>4.16</td>
<td>2.42</td>
</tr>
<tr>
<td>Raincatcher</td>
<td>-4.62</td>
<td>3.98</td>
<td>1.49</td>
</tr>
<tr>
<td>Recycle</td>
<td>-3.73</td>
<td>3.96</td>
<td>2.24</td>
</tr>
<tr>
<td>Respect</td>
<td>-0.91</td>
<td>3.91</td>
<td>0.53</td>
</tr>
<tr>
<td>The Fairtrade</td>
<td>3.59</td>
<td>3.76</td>
<td>0.91</td>
</tr>
<tr>
<td>Age UK</td>
<td>1.91</td>
<td>3.73</td>
<td>1.76</td>
</tr>
<tr>
<td>International AIDS</td>
<td>-0.60</td>
<td>3.70</td>
<td>1.53</td>
</tr>
<tr>
<td>Child Poverty</td>
<td>0.11</td>
<td>3.56</td>
<td>1.69</td>
</tr>
<tr>
<td>Action for Children</td>
<td>-1.16</td>
<td>3.56</td>
<td>1.60</td>
</tr>
<tr>
<td>Healthy Africa</td>
<td>-4.56</td>
<td>3.49</td>
<td>1.16</td>
</tr>
<tr>
<td>International Refugee</td>
<td>-2.71</td>
<td>3.42</td>
<td>1.31</td>
</tr>
<tr>
<td>Bosnian Orphans</td>
<td>-3.64</td>
<td>3.33</td>
<td>0.82</td>
</tr>
<tr>
<td>Pride London</td>
<td>-0.40</td>
<td>3.29</td>
<td>0.24</td>
</tr>
<tr>
<td>BLESMA</td>
<td>-3.49</td>
<td>3.27</td>
<td>0.58</td>
</tr>
<tr>
<td>Friends of the Earth</td>
<td>3.00</td>
<td>3.27</td>
<td>1.18</td>
</tr>
<tr>
<td>The Gaia Foundation</td>
<td>-2.62</td>
<td>3.22</td>
<td>1.00</td>
</tr>
<tr>
<td>Pink Triangle</td>
<td>-2.73</td>
<td>3.16</td>
<td>0.51</td>
</tr>
<tr>
<td>I am Who I am</td>
<td>-4.36</td>
<td>3.16</td>
<td>1.40</td>
</tr>
<tr>
<td>Greenpeace</td>
<td>3.44</td>
<td>3.13</td>
<td>-0.11</td>
</tr>
<tr>
<td>Acts of Hope</td>
<td>-4.47</td>
<td>3.11</td>
<td>0.89</td>
</tr>
<tr>
<td>War on Want</td>
<td>-1.98</td>
<td>3.11</td>
<td>1.18</td>
</tr>
<tr>
<td>Hope for Chernobyl</td>
<td>-2.27</td>
<td>3.09</td>
<td>0.27</td>
</tr>
<tr>
<td>Amber Pregnancy</td>
<td>-4.60</td>
<td>2.98</td>
<td>0.09</td>
</tr>
<tr>
<td>The Converging World</td>
<td>-4.16</td>
<td>2.98</td>
<td>0.36</td>
</tr>
<tr>
<td>BBC Wildlife</td>
<td>-0.73</td>
<td>2.98</td>
<td>0.11</td>
</tr>
<tr>
<td>Name</td>
<td>Familiarity</td>
<td>Mission Statement Agreement</td>
<td>Donation Likelihood</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------</td>
<td>-----------------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Achor Pregnancy Trust</td>
<td>-4.70</td>
<td>2.93</td>
<td>-0.40</td>
</tr>
<tr>
<td>Kid VIP</td>
<td>-4.56</td>
<td>2.82</td>
<td>-0.40</td>
</tr>
<tr>
<td>Reprieve</td>
<td>-2.27</td>
<td>2.82</td>
<td>0.11</td>
</tr>
<tr>
<td>The Royal British</td>
<td>2.78</td>
<td>2.80</td>
<td>0.96</td>
</tr>
<tr>
<td>Help Stop Climate Change</td>
<td>-2.02</td>
<td>2.80</td>
<td>0.29</td>
</tr>
<tr>
<td>Asylum Sport</td>
<td>-3.29</td>
<td>2.69</td>
<td>-0.22</td>
</tr>
<tr>
<td>Afghan Association</td>
<td>-4.84</td>
<td>2.67</td>
<td>0.04</td>
</tr>
<tr>
<td>Global Cool</td>
<td>-4.33</td>
<td>2.67</td>
<td>-0.36</td>
</tr>
</tbody>
</table>

Table 4. List of most negatively rated charities (n=11)

<table>
<thead>
<tr>
<th>Name</th>
<th>Familiarity</th>
<th>Mission Statement Agreement</th>
<th>Donation Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhonda Evangelical Church</td>
<td>-4.47</td>
<td>-3.93</td>
<td>-4.49</td>
</tr>
<tr>
<td>Catholic Charitable</td>
<td>-4.04</td>
<td>-3.47</td>
<td>-4.42</td>
</tr>
<tr>
<td>UK World Evangelical</td>
<td>-4.18</td>
<td>-3.11</td>
<td>-4.09</td>
</tr>
<tr>
<td>Bible Heritage</td>
<td>-4.18</td>
<td>-2.91</td>
<td>-3.69</td>
</tr>
<tr>
<td>UK Practical Shooting</td>
<td>-4.53</td>
<td>-2.67</td>
<td>-4.24</td>
</tr>
<tr>
<td>Museum of Hunting</td>
<td>-4.40</td>
<td>-2.33</td>
<td>-3.82</td>
</tr>
<tr>
<td>Bread of Life</td>
<td>-4.38</td>
<td>-2.29</td>
<td>-3.73</td>
</tr>
<tr>
<td>The Galton Institute</td>
<td>-4.16</td>
<td>-1.86</td>
<td>-3.64</td>
</tr>
<tr>
<td>The Ascombe</td>
<td>-4.76</td>
<td>-1.66</td>
<td>-3.71</td>
</tr>
<tr>
<td>The Q’uran Project</td>
<td>-3.91</td>
<td>-1.51</td>
<td>-3.51</td>
</tr>
<tr>
<td>Newspaper Press</td>
<td>-4.13</td>
<td>-1.42</td>
<td>-3.13</td>
</tr>
</tbody>
</table>
Table 5. Non-parametric correlations between variables for the positively rated cluster

<table>
<thead>
<tr>
<th></th>
<th>Familiarity</th>
<th>Mission Statement</th>
<th>Donation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familiarity</td>
<td>1</td>
<td>.476**</td>
<td>.471**</td>
</tr>
<tr>
<td>Mission Statement</td>
<td>.476**</td>
<td>1</td>
<td>.829**</td>
</tr>
<tr>
<td>Donation</td>
<td>.471**</td>
<td>.829**</td>
<td>1</td>
</tr>
</tbody>
</table>

n=36, **p<0.01

The negatively rated cluster had a mean familiarity of -4.28 (SD=0.24), a mission statement rating of -2.47 (SD=0.83) and a likelihood of making a donation of -3.86 (SD=0.41). The correlations between these variables for the negatively rated cluster are summarized in Table 4.

Table 4. Non-parametric correlations between variables for the negatively rated cluster

<table>
<thead>
<tr>
<th></th>
<th>Familiarity</th>
<th>Mission Statement</th>
<th>Donation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familiarity</td>
<td>1</td>
<td>.214</td>
<td>.446</td>
</tr>
<tr>
<td>Mission Statement</td>
<td>.214</td>
<td>1</td>
<td>.873**</td>
</tr>
<tr>
<td>Donation</td>
<td>.446</td>
<td>.873**</td>
<td>1</td>
</tr>
</tbody>
</table>

n=11, **p<0.01

The most positively rated 36 charitable organisations were selected for the behavioural task. Before the experiment, participants were given a document containing the full name and the mission statement of these charities and the payoff conditions were explained to them. The charitable donations task lasted for 72 rounds containing costly and non-costly donation options and participants started with £20 of funds corresponding to real currency. In each round, charity information was presented to the participants, comprising the name of the charity and a shortened version of its mission statement (for 6 seconds). On the next screen, participants saw the payoff conditions (for 3.5 seconds). £1 of donation in the costly donation condition cost participants 30p, whereas non-costly donations did not have any financial cost to the participants. Participants responded by using "Accept" and "Reject" buttons to make decisions. A 20p penalty
was enforced when participants failed to respond within 3.5 seconds. On the final screen, participants were presented with the outcome of their decisions and the amount of remaining funds (see Figure 1 for the sequence of screens). At the end of the game, the amount of remaining funds was rounded to the nearest pound and given to participants; they knew at the outset that they would receive this money.

![Experimental timeline of the charitable donations task showing the non-costly donation proposal. Adapted from Moll et al 2006.](image)

**Figure 1.** Experimental timeline of the charitable donations task showing the non-costly donation proposal. Adapted from Moll et al 2006.

**Main Study Results**

*Data Analysis for the Main Study.*

Between group analyses were conducted using SPSS version 20. We used appropriate chi-square tests for comparing group demographics. Nonparametric tests were used to compare group
scores on psychological scales consisting of ordinal categorical variables. Parametric tests were used for behavioural-economical measures, due to adequate sample size.

Following discussion with an expert biostatistician (Dr Richard Emsley, University of Manchester), we used an overarching general linear model (GLM; repeated measures ANOVA) to investigate the effect of clinical grouping on different types of altruistic decisions. The 5 dependent variables (DVs) in the model were the main outcome measures for each task; the frequency of cooperation in the PD, average Dictator offers, average acceptance rate in the UG, the frequency of costly and non-costly donations. In order to avoid any confounding effects of scaling on these DVs, we applied z-transformations and used the z-transformed variables in the model. Follow up analysis on GLM main effects and interactions were done by using appropriate One-WAY analysis of variance (ANOVA) tests with post-hoc pairwise comparisons (using Tukey-Kramer procedure where group sizes were imbalanced (Hayter, 1984)).

Using an overarching GLM allows us to investigate the impact of clinical grouping on "altruism" in a hierarchical way (as guilt driven pathological hyper altruism hypothesis does not specify which subtype of altruistic decisions are performed more frequently by patients with MDD), while controlling for any potential Type I Errors.

**Correlations between altruistic guilt, shame proneness and altruistic decisions**

In order to test the prediction that altruistic forms of guilt (survivor and omnipotent responsibility) promote altruistic behaviour, whereas shame-proneness (TOSCA-Shame subscale) works counter to altruistic tendencies, we conducted correlational analyses. We investigated the relationship between affective measures and the number of costly donations, separately for each group in order to avoid the possible confounding impact of clinical status on
these correlations. We restricted the correlational analyses to costly donations, so that our results have the highest ecological validity for real-life financial consequences. All correlational analyses were conducted on the 76 participants who completed all tasks.

Results

Participants

The groups did not differ significantly for age and years of education, but the cMDD group had a higher number of males (see Table 6 for basic demographic and clinical information). Healthy participants and people with rMDD had MADRS scores that were well below the cut-off for full remission from depression (<10) (Hawley et al., 2002), but the rMDD group showed slightly higher scores than controls. Both of these groups had GAF scores indicating minimal or absent functional impairment (>80). Patients with cMDD had significantly higher MADRS and lower GAF scores (see Table 6).

| Table 6. Group comparison on demographic and basic clinical variables |
|---------------------------------|----------------|----------------|----------------|
|                                 | Control       | remitted MDD   | current MDD    |
| Age                             | 38.03 ± 6.4   | 38.54 ± 6      | 38.25 ± 10.5   |
| Education(years)                | 17.6 ± 2.8    | 17.1 ± 2.8     | 16.2 ± 3.5     |
| Gender                          | 10 Males      | 9 Males        | 13 Males       |
| MADRS                           | 1.8 ± 2.6     | 3.2 ± 3.2      | 33 ± 4.3       |
| GAF                             | 90.3 ± 5.3    | 86.9 ± 5.7     | 58.7 ± 8.7     |
| SOFAS                           | -             | -              | 57.1 ± 10      |

Patients with cMDD had significantly lower scores on positive affect subscale of PANAS and self-esteem, whereas they had significantly elevated scores on TOSCA-Shame as well as all the subscales of the IPGQ-67 (survivor, separation, self-hate and omnipotent responsibility guilt) compared with healthy participants and remitted patients (see Table 7 for further results).

Table 7. Summaries of affective measures

<table>
<thead>
<tr>
<th></th>
<th>Control mean ±SD</th>
<th>remitted MDD mean ±SD</th>
<th>current MDD mean ±SD</th>
<th>chi-square*</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PANAS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive affect</td>
<td>30.1 ± 7</td>
<td>33.3 ± 7.7</td>
<td>21.9 ± 6.9</td>
<td>25.423</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>negative affect</td>
<td>11 ± 2.2</td>
<td>11.6 ± 2.5</td>
<td>21.1 ± 6.3</td>
<td>40.735</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Rosenberg Self-Esteem</strong></td>
<td>25.3 ± 3.7</td>
<td>23.1 ± 5.4</td>
<td>12.2 ± 6</td>
<td>40.416</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>TOSCA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>shame</td>
<td>25.8 ± 6</td>
<td>27.8 ± 7.5</td>
<td>36.2 ± 9.1</td>
<td>19.053</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>guilt</td>
<td>45 ± 6</td>
<td>44.8 ± 7.4</td>
<td>45.9 ± 8.8</td>
<td>2.019</td>
<td>.364</td>
</tr>
<tr>
<td>detachment</td>
<td>27.8 ± 6</td>
<td>28.3 ± 7.7</td>
<td>25.1 ± 6.3</td>
<td>3.741</td>
<td>.154</td>
</tr>
<tr>
<td>externalisation</td>
<td>19.3 ± 5</td>
<td>19.9 ± 4.6</td>
<td>23.8 ± 5.9</td>
<td>5.246</td>
<td>.073</td>
</tr>
<tr>
<td><strong>IPGQ-67</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>survivor guilt</td>
<td>63.2 ± 8.1</td>
<td>66.6 ± 9.1</td>
<td>76.8 ± 13.9</td>
<td>15.586</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>separation guilt</td>
<td>34.3 ± 7.3</td>
<td>34.9 ± 9.6</td>
<td>43.2 ± 10.8</td>
<td>12.006</td>
<td>.002</td>
</tr>
<tr>
<td>omnipotent responsibility</td>
<td>45.2 ± 6.6</td>
<td>45.1 ± 7.5</td>
<td>53 ± 8.3</td>
<td>14.517</td>
<td>.001</td>
</tr>
<tr>
<td>self-hate</td>
<td>24.8 ± 6.2</td>
<td>29.3 ± 10.6</td>
<td>47.1 ± 14.7</td>
<td>32.895</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Summaries of between-group differences on affective measures, differences are significant at p<.01, two-sided (control group: N=33, rMDD group: N=35, MDD group: N=24). *= Kruskal-Wallis test.

Table 8 Summaries of altruistic outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Control mean ±SD</th>
<th>remitted MDD mean ±SD</th>
<th>current MDD mean ±SD</th>
<th>p-values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD cooperation</td>
<td>29.1 ± 3.9</td>
<td>29.65 ± 3.9</td>
<td>27.45 ± 6</td>
<td>.184</td>
</tr>
<tr>
<td>DG Average offer (£)</td>
<td>4.20 ± 0.9</td>
<td>4.26 ± 0.8</td>
<td>4.26 ± 1</td>
<td>.950</td>
</tr>
<tr>
<td>UG Average acceptance (%)</td>
<td>32.5 ± 39.3</td>
<td>26.7 ± 31</td>
<td>36 ± 32.2</td>
<td>.576</td>
</tr>
<tr>
<td>Donations-Costly</td>
<td>18.2 ± 11.1</td>
<td>19.3 ± 12.8</td>
<td>12.3 ± 10.2</td>
<td>.05</td>
</tr>
<tr>
<td>Donations-Non-costly</td>
<td>29.8 ± 9.7</td>
<td>31 ± 6.4</td>
<td>28 ± 11.8</td>
<td>.01</td>
</tr>
<tr>
<td>Total funds remaining (£)</td>
<td>14.5 ± 3.3</td>
<td>14 ± 3.9</td>
<td>16.2 ± 3.2</td>
<td>.08</td>
</tr>
<tr>
<td>-20p penalty</td>
<td>0.3 ± 0.6</td>
<td>0.3 ± 0.6</td>
<td>1 ± 1.6</td>
<td>.02</td>
</tr>
</tbody>
</table>

Impact of clinical diagnosis on social-economical decision making

The summaries of means and standard deviations for all altruistic outcome measures are available in Table 8. In order to investigate whether assignment to a clinical group interacted with different kinds of social economical decision making, we fitted a 5x3 GLM (i.e. repeated measures ANOVA with 5 different kinds of altruistic outcome measures related to each paradigm (as the within-subjects factor) by 3 clinical groups (as the between-subjects factor, computed for participants who completed all of the tasks). The analysis showed that there was a significant clinical group by altruistic outcome interaction (F (8, 292) = 2.242, p = 0.025) with significant main effect of clinical grouping (F (1, 73) = 3.245, p = 0.045) but no main effect of the type of altruism (p = 0.951). Using an overarching One-Way ANOVA, we aimed to explore whether the effect of clinical grouping is consistent towards one direction (enhanced or reduced altruism). This supplementary analysis revealed that the groups were comparable in terms of the frequency of engagement in altruistic behaviours (when using a composite altruism score based on linear transformation of the same measures in the GLM, F (2, 73) = 1.117, p = 0.333). For this analysis, the group mean scores (and standard deviations) were; rMDD 106.8 (29.2); controls 117.2 (43.8); cMDD 102.6 (33.6). We provide the analyses for task specific hypotheses below.

Paradigm 1: Prisoner's Dilemma

We investigated whether there were group differences in decisions to defect on either the first round, or the 30th round (when participants expected the task to end). There were no significant differences between the groups for the frequency of cooperative decisions on the first and the 30th round of the task (Pearson's chi-square: 4.199, df =2, p = 0.122). In terms of cooperation frequency, patients with cMDD cooperated 27.45 times out of 31 rounds (SD =6), whereas the
control group cooperated 29.1 times (SD = 3.9) and rMDD group cooperated 29.65 times (SD = 3.9). However, a simple main effects analysis showed that the groups did not differ on this measure (F (2, 89) = 1.725, p = 0.184). Consequently, the groups did not differ for the amount of water the subject and the computer banked, and the competitive gain (the difference between the amount of water the subject and the computer banked; see Table 9). There were no significant differences within the cMDD group between medicated and unmedicated patients (t = 0.815, df = 22, p = 0.425).

### Table 9. Summary of Prisoner's Dilemma decision-making

<table>
<thead>
<tr>
<th></th>
<th>Control mean ±SD</th>
<th>Remitted MDD mean ±SD</th>
<th>Current MDD mean ±SD</th>
<th>F*</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject Total</td>
<td>158 ± 5.8</td>
<td>156 ± 3.9</td>
<td>157 ± 12.6</td>
<td>.515</td>
<td>.599</td>
</tr>
<tr>
<td>Computer Total</td>
<td>146.6 ± 16.1</td>
<td>149.3 ± 15.9</td>
<td>140 ± 24.9</td>
<td>1.792</td>
<td>.173</td>
</tr>
<tr>
<td>Competitive Gain</td>
<td>11.4 ± 20.8</td>
<td>6.8 ± 17</td>
<td>17.3 ± 27.6</td>
<td>1.634</td>
<td>.191</td>
</tr>
</tbody>
</table>

Control group: N=33, rMDD group: N=35, MDD group: N=24. The unit of the outcome measure is litres.*= One-way ANOVA test (df =2, 89).

### Paradigm 2: Dictator Game

We investigated whether there were any differences between the groups in the amount of money offered to an anonymous partner in the DG. Out of £10, on average participants in the control group offered £4.20 (SD = 0.9), whereas cMDD and rMDD groups both offered £4.26 (SD =1 and 0.76, respectively). These average offers did not differ significantly across groups (F (2, 89) = 0.052,p = 0.950). Within the cMDD group there was no significant difference between medicated and unmedicated individuals (£4.45 (SD = 1.11) versus £4.10 (SD = 0.85); t = -.858, df = 22, p =0.400).

### Paradigm 3: Ultimatum Game
Our main variable of interest was the acceptance rate of unfair offers, with every offer below a £7 versus £3 split was considered as an "unfair offer", as established by previous literature on neuroeconomics (Crockett et al., 2008). On average, the control group accepted unfair offers at 32.5% (SD = 39.3), whereas the cMDD group accepted at 36% (SD = 32.2) and the rMDD accepted at 26.7% (SD = 31). The groups did not differ in terms of acceptance rates (F (2, 89) = 0.554, p = 0.576; see Figure2), and there was no significant effect of medication in the cMDD group (t = -0.955, df = 23, p = 0.349). Secondly, we looked at the acceptance/rejection patterns for the two most unfair offers (which are £9 versus £1 and £8 versus £2 offers). The proportion of individuals accepting or rejecting these offers were not significantly different between our groups (for 9vs1 offers: Pearson's chi-square: 4.127, df = 4, p = 0.389; for 8vs2 offers: Pearson's chi-square: 7.259, df = 4, p = 0.123).
Figure 2. Figure showing the mean acceptance rate for each level of the Ultimatum Game offers.

**Paradigm 4: Self- versus Other-blame patterns in the UG**

Following UG decision-making, we investigated whether receiving unfair offers from anonymous partners in the UG triggered increased self-blaming feelings in patients with cMDD. Secondly, we compared our groups for the pleasantness of receiving fair offers (£5 vs. £5) and unpleasantness of receiving unfair offers (ratings were made on a 1 to 7 Likert scale). There were no participants reporting self blame for receiving fair offers. Patients with cMDD experienced significantly more guilt compared to both control and rMDD groups when they received unfair
offers (cMDD: 1.38 (SD = 3.85); Control: 0.18 (SD = 0.77); rMDD: 0.03 (SD = 0.17); F (2, 89) = 3.582, p = 0.032; see Figure 3).

**Figure 3.** Error bars represent +/- 1 Standard Errors.

Post-hoc pairwise comparisons using Tukey-Kramer procedure and using studentized critical range values (at q<0.05 for df (2, 89) = 3.37; absolute difference > critical range value) suggested
that the cMDD group was significantly different from the rMDD group (1.35 > 1.27; t-test equivalent p = 0.043), but marginally different from the healthy participants (1.20 < 1.29; t-test equivalent p = 0.088). Within the cMDD group, guilt ratings were not significantly different between medicated and unmedicated patients (t = -1.225, df = 22, p < 0.235). There were no significant differences for guilt ratings between the rMDD and the healthy participants (0.15 < 1.16). There were no significant differences between groups for the amount of shame or indignation participants experienced upon receiving unfair offers (F (2, 89) = 0.421, p = 0.658; F (2, 89) = 1.012, p = 0.368, respectively). Finally, there were no significant differences between groups for the pleasantness ratings of fair or the unpleasantness ratings of unfair offers (see Table 10).

### Table 10. Pleasantness/unpleasantness of offers in the Ultimatum Game

<table>
<thead>
<tr>
<th></th>
<th>Control mean ±SD</th>
<th>remitted MDD mean ±SD</th>
<th>current MDD mean ±SD</th>
<th>F*</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair-Pleasantness</td>
<td>4.6 ± .62</td>
<td>4.7 ± .86</td>
<td>4.8 ± .86</td>
<td>.382</td>
<td>.684</td>
</tr>
<tr>
<td>Unfair-Unpleasant</td>
<td>3.1 ± .99</td>
<td>2.7 ± .84</td>
<td>2.8 ± .95</td>
<td>1.730</td>
<td>.183</td>
</tr>
</tbody>
</table>


**Paradigm 5: Charitable Donation Task**

Only 76 participants completed this task (16 individuals randomly chosen from the control and the remitted group participated in a functional neuroimaging version of the charitable donations experiment and therefore did not complete this behavioural version to avoid repetition effects; Controls: 29, cMDD: 23, rMDD: 24). On average, patients with cMDD made significantly (F (2, 73) = 3.124, p = 0.05) fewer costly donations (12.34, SD = 10.2) than healthy participants (18.20, SD = 11.05) or remitted patients (19.31, SD = 12.77). Similarly, patients with cMDD made significantly lower levels of non-costly donations (28, SD = 11.76) compared with healthy
participants (29.75, SD = 9.73) and remitted patients (30.95, SD = 6.38. F (2, 73) = 4.806, p = 0.01; see Figure 4).

**Figure 4.** Between group differences for the frequency of charitable donation decisions. *p<0.05. Error bars represent +/- 1 Standard Error.

Post-hoc pairwise comparisons using Tukey-Kramer procedure and using studentized critical range values (at q<0.05 for df (2, 73) = 3.39; absolute difference> critical range value) suggested that behaviour in the cMDD group is significantly different than both the rMDD (8 > 6.4, t-test
equivalent $p = 0.004$) and the healthy participants ($6.8 > 6.4$, t-test equivalent $p = 0.028$) for non-costly donations, but only significantly different from the rMDD group for costly donations ($7 > 6.9$). Remitted patients did not differ from healthy participants for either non-costly ($1.2 < 6.3$) or costly ($1.1 < 7.5$) donation comparisons. In terms of donation decisions, medicated and unmedicated patients within the cMDD group did not differ for either the number of costly ($t = -0.504$, df = 21, $p = 0.62$) or non-costly donations ($t = -0.362$, df = 21, $p = 0.58$). The groups were marginally different for the amount of monetary earnings (see Table 3 for means and SDs, $F(2, 73) = 2.642$, $p = 0.08$), though this may be due to the number of penalties patients with current MDD received for failing to respond within the given timeframe in the decision screen (each penalty cost 20p, see Table 8). Patients with cMDD received significantly more penalties ($1.04$, SD = 1.61) than healthy participants ($0.34$, SD = 0.61) or rMDD patients ($0.25$, SD = 0.55; $F(2, 73) = 4.409$, $p = 0.02$).

Finally, we investigated whether past or present clinical diagnosis influenced response times to donation decisions. There were no significant differences between the groups for the response times of acceptance or rejection under any of the donation conditions (see Table 11).

### Table 11 response time comparisons for acceptance and rejection of donation proposals (ms)

<table>
<thead>
<tr>
<th></th>
<th>Control mean ±SD</th>
<th>remitted MDD mean ±SD</th>
<th>current MDD mean ±SD</th>
<th>F*</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Costly Donation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptance RT</td>
<td>1053 ± 422</td>
<td>1041 ± 355</td>
<td>1148 ± 439</td>
<td>.475</td>
<td>.624</td>
</tr>
<tr>
<td>Rejection RT</td>
<td>1124 ± 417</td>
<td>1124 ± 372</td>
<td>1083 ± 356</td>
<td>.088</td>
<td>.916</td>
</tr>
<tr>
<td><strong>Non-Costly Donation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptance RT</td>
<td>940 ± 409</td>
<td>917 ± 222</td>
<td>1060 ± 360</td>
<td>1.150</td>
<td>.322</td>
</tr>
<tr>
<td>Rejection RT</td>
<td>876 ± 514</td>
<td>924 ± 404</td>
<td>1209 ± 534</td>
<td>2.356</td>
<td>.106</td>
</tr>
</tbody>
</table>

Correlational analyses

In order to test the prediction that altruistic forms of guilt (survivor and omnipotent responsibility guilt, O'Connor et al, 2012) promote altruistic behaviour in healthy participants and more strongly in patients with MDD, whereas shame-proneness (TOSCA-Shame subscale, Tangney et al, 2007) works counter to altruistic tendencies (see detailed review of this literature in Pulcu et al., 2013) we conducted correlational analyses. We investigated the relationship between affective measures and costly forms of altruistic outcome measures (the average amount of Dictator offers, mean acceptance rate of unfair offers in the UG, number of costly donations) separately for each group in order to avoid the possible confounding impact of clinical status on these correlations. We restricted the correlational analyses to costly forms of altruism, so that our results are compatible with the operational definitions we provided for altruism in the introduction section (West et al., 2007), and have ecological validity for real-life altruistic decisions. All correlational analyses were conducted on the 76 participants who completed all tasks.

a) Healthy participants

In healthy participants, there was a positive correlation between shame and survivor guilt scores (Spearman's $r_S = 0.705$, $p<0.01$), but there were no significant relationships between shame and omnipotent responsibility guilt scores. In healthy participants, survivor guilt and omnipotent responsibility guilt correlated positively with the number of costly donations (Spearman's $r_S = 0.376$, $p<0.05$ and Spearman's $r_S = 0.418$, $p<0.05$, respectively).

b) People with cMDD

In cMDD patients, omnipotent responsibility and survivor guilt scores correlated positively (Spearman's $r_S = 0.534$, $p<0.01$), and shame scores correlated positively with omnipotent
responsibility (Spearman's $r_S = 0.516, p<0.05$) and survivor guilt (Spearman's $r_S = 0.848, p<0.01$). In patients with cMDD, none of the affective measures correlated significantly with altruistic outcome measures (lowest p value for survivor guilt and costly donations; Spearman's $r_S = -0.168, p = 0.442$).

c) People with rMDD

In people with rMDD, there was a positive correlation between omnipotent responsibility and survivor guilt scores (Spearman's $r_S = 0.484, p<0.05$) and shame scores correlated positively with survivor guilt scores (Spearman's $r_S = 0.499, p<0.05$) and omnipotent responsibility guilt scores (Spearman's $r_S = 0.564, p<0.01$). As with the symptomatic patients, there were no significant correlations between the affective and the altruistic outcome measures in people with rMDD (lowest p value for omnipotent responsibility and average acceptance rate in the UG; Spearman's $r_S = 0.299, p<0.156$).

Discussion

Our findings suggest that frequency of engagement with different kinds of altruistic decisions change differently between our groups. In this cohort, symptomatic patients behaved less altruistically overall, particularly in the charitable donations domain where the behaviour was significantly different. Best to our knowledge, this finding entails the first experimental behavioural-economical evidence to show that patients act differently between symptomatic periods and remission in terms of frequency of engagement in altruistic decisions. It is important to point out that patients with MDD (whether symptomatic or asymptomatic) do not significantly differ from healthy participants in terms of their performance on neuroeconomical tasks assessing cooperation and altruistic punishment, but the differences were limited to the charitable donations domain. We also investigated the affective response to interpersonal interactions in the
UG and the extent to which trait forms of guilt and shame influenced social economical decisions. We showed that patients with cMDD experience more guilt when they receive unfair monetary offers from anonymous partners and also that patients with cMDD and rMDD did not show the relationship between altruistic forms of guilt and decisions to make charitable donations that is observed in healthy participants. This may be due to ceiling levels of self blaming emotions in cMDD which leaves less space for between subject variability in guilt scores or potentially the scarring effects of previous major depressive episodes in our remitted group which selectively impairs emotional processing related to altruistic forms of guilt. Previous studies have shown that people reporting depressive symptoms defected at a significantly higher level in the PD when their partners were experimentally made vulnerable to defection (Hokanson et al., 1980), but they were more likely to behave aggressively when their playing partner defected (Haley and Strickland, 1986). To the best of our knowledge, there are no previous studies with a PD paradigm investigating interpersonal cooperation in MDD. One study, which used a similar paradigm to ours, showed that inpatient psychopaths defected significantly more than healthy participants and consequently banked significantly more resources (Mokros et al., 2008). Considering the global evidence of affective impairments associated with psychopathy in processing guilt (i.e. lack of guilt) and elevated altruistic forms of guilt in MDD, our findings do not provide support for the hypothesis suggesting an association between trait guilt and interpersonal cooperation. However, it is possible to argue that a neuroeconomical paradigm based on a survival situation triggers more selfish decisions in psychopaths than it does in patients with MDD, consistent with the distinguishing characterological features of these two psychiatric populations.
Two previous studies of the UG conducted by Harle and colleagues suggested that acute incidental sadness and clinical depression have opposing effects on altruistic punishment, whereby individuals reject unfair offers in order to punish proposers who make them (Harle et al., 2010, Harlé and Sanfey, 2007). They showed that patients with current MDD accepted, whereas individuals with acute sadness rejected, unfair offers at significantly higher rates relative to healthy participants. Another study which manipulated serotonin levels by an acute tryptophan depletion procedure (ATD; also used in order to induce depressed mood in people with a history of depression) showed similar results with that of induced sadness, in which the experimental group rejected unfair offers at a significantly higher rate than the placebo group (Crockett et al., 2008). By contrast, here we showed that patients with MDD (whether symptomatic or asymptomatic) did not differ from healthy participants in terms of their engagement in altruistic punishment in the UG. Our findings are in line with a recent study which also reported non-significant results in terms of acceptance rates in the UG (Destoop et al., 2012). However, Destoop and colleagues also showed that patients with cMDD acted more generously when they participated as the proposer, whereas in our study neither of the patient groups differed from healthy participants in terms of the amount they offered when they were in the proposer's position (i.e. Dictator offers). There are two main differences between the study of Destoop et al. (2012) and ours. First, all of their patients were hospitalised, whereas our patients were recruited from an outpatient population. There may be differences between UK and Netherlands in terms of the psychiatric profile of patients are hospitalised for the treatment of MDD. Destoop and colleagues used the 17-item Hamilton Depression Rating Scale (HDRS) to measure the severity of depressive symptomatology. Using one methodology to convert HDRS scores to MADRS (Carmody et al., 2006) suggests that the depression severity scores across these two patient
groups were comparable. This could mean that hospitalisation may have an influence on these social economic decisions. Another important difference between our study and the one conducted by Harle and Sanfey (2010) is that they used pictures of individuals, who played the UG previously, in the proposal screen. Considering previous findings on facial emotion recognition impairments in MDD (Anderson et al., 2011, Arnone et al., 2012b, Gotlib et al., 2004), using such pictures may have an impact on interpersonal decision-making, regardless of their emotional valence. This possibility has been partially investigated by a recent study which showed that patients with MDD rejected unfair and hyperfair offers significantly more relative to healthy participants, suggesting that there may be hypersensitivity in the patient group for any deviations from the fairness norm (Radke et al., 2013). In this study, participants received offers from individuals whose facial expressions were categorised into basic emotion groups (i.e., happy, angry, sad). The authors show that the rejection rates were lowest in the patient group for offers coming from happy proposers whereas in healthy participants group the lowest rejection rates were to offers coming from sad proposers. However, these authors did not investigate the variability in emotional valence in terms of how participants in both groups perceived the facial emotion of the proposers.

It is important to highlight that we used anonymous scripts in this study which may also have an impact on interpersonal decision-making through mechanisms of social distance. For example, one previous study showed that increasing social distance between the players in the DG, by manipulating the level of anonymity, decreased the amount of monetary offers (Hoffman et al., 1996). It is possible that anonymous designs may have a negative impact on altruistic punishment as unfair proposers, who would otherwise be the target of altruistic punishment, are not confronted with the players. Taken together, these studies suggest that the extent to which
patients with MDD engage in altruistic punishment requires further research; potentially by using script based paradigms along with manipulation of facial emotions of the proposers in picture based paradigms.

In the post-UG emotion ratings, we showed that patients with cMDD had elevated levels of self blaming feelings which loaded onto guilt, but not shame. To the best of our knowledge, this is the first account of elevated self blame in patients with cMDD triggered by unfair interpersonal exchanges in laboratory conditions. Recently, Green and colleagues showed that selective self blame, relative to an overall increase in negative emotions, is a vulnerability feature in MDD which extends beyond the symptomatic phase (Green et al., 2013). Similarly, here we showed a selective increase in self blaming emotions relative to general negative emotions (e.g., guilt versus indignation) in symptomatic patients when probed with unfair financial offers. The findings of our post-UG emotion ratings may explain why there were no significant differences between our currently depressed patient group and healthy participants in terms of their level of engagement in altruistic punishment. Blaming oneself for receiving unfair offers in these interpersonal exchanges would reduce motivations to punish proposers who made them.

Considering growing evidence on affective impairments associated with processing guilt in MDD (Green et al., 2012b), our results may account for one of the mechanisms which may diminish altruistic punishment in patients with cMDD, as also shown by two previous studies (Harle et al., 2010, Destoop et al., 2012). Assuming that acute manipulations of mood would not trigger mechanisms associated with inappropriate self blame in healthy participants, these results may further validate why clinical depression and acute sadness may have different impact on altruistic punishment.
In the final experiment, we investigated charitable donation behaviour in MDD, which is a unique form of altruistic behaviour. Its uniqueness comes from the fact that the altruistic influence of donation behaviour extends to a network of benefiting individuals (those individuals who are the target population of a charitable organisation delivering donations) who do not necessarily have any genetic relatedness to the donating individual. Therefore, charitable donation behaviour challenges kin selection theories of altruism which suggest a significant relationship between genetic relatedness and the level of altruism (Hamilton, 1963). Secondly, charitable donation behaviour works on the principles of zero-sum games which define the limited availability of resources and their mutually exclusive distribution between individuals, whereby one can only increase the other's payoff by reducing one's own; closely reflecting real life decision-making mechanisms. In that respect, donation behaviour is more closely related to interpersonal bargaining games such as the UG designed to measure altruistic punishment which also work on zero-sum principles. By contrast, interpersonal cooperation games such as the PD, work on the principles of non-zero-sum games which means that both participants can win mutually on any given trial. Here, we showed that patients with current MDD make significantly lower levels of donations, even in trials where donations were free of charge. Decisions about making donations require healthy functioning of affiliative prosocial sentiments such as survivor guilt, compassion and empathy/empathic concern (Zahn et al., 2012). Our findings do not provide support for the guilt and empathy driven pathological altruism hypothesis in current depression (O’Connor et al., 2012). On the contrary, we showed that there is a significant relationship between altruistic forms of guilt and donation behaviour only in healthy participants. Considering that altruistic forms of guilt were significantly elevated in our cMDD patients, and that these measures were comparable between remitted patients and healthy participants, we
suggest that a past or current diagnosis of MDD disrupts the influence of these emotions on donation behaviour. As with the other studies from our research group (Green et al., 2013, Green et al., 2012b), here we showed that self-hate subscale of IPGQ-67 distinguished our patient groups from healthy participants, providing further evidence for selective impairments in guilt processing as a potential trait marker of vulnerability. Green and colleagues showed that such differences have neuronal origins in brain regions (subgenual anterior cingulate cortex; sgACC) commonly specified for the pathophysiology of MDD (Green et al., 2012b, Mayberg et al., 1997, Mayberg et al., 2005, Fitzgerald et al., 2008) and show selective activation when people make donations (Moll et al., 2006). Furthermore, all of the previous neuroimaging studies consistently showed ventral striatum (vSTR) activation regardless of whether people make voluntary (Moll et al., 2006) or tax like donations (Harbaugh et al., 2007), or when they could acquire additional social rewards such as social reputation by making donations publicly (Izuma et al., 2010). Well-established clinical literature associates MDD with functional impairments in reward processing in the vSTR both in its symptomatic (Pizzagalli et al., 2009) and asymptomatic phases (Eshel and Roiser, 2010). Taken together, neuroimaging literature suggests that abnormal charitable donation behaviour in patients with cMDD may have neuronal origins relating to regions with impairments in processing altruistic forms of guilt and social/financial reward value and therefore it should be investigated further.

Here, we used multiple neuroeconomical paradigms in order to test whether there is an inverse relationship between shame proneness and altruistic decisions, driven by mechanisms of increasing interpersonal distance. We showed that trait shame scores were not related different measures of altruism. Therefore, it is possible to suggest that shame proneness as a personality trait does not have interpersonal distance increasing properties similar to acute forms of shame
which were purported to influence altruistic behaviours negatively. Previously, it was suggested that shame promotes altruistic decisions only when its manipulation is based on a component of the decision-making task (i.e. endogenous), whereas unrelated (i.e. exogenous) manipulations of shame did not show any relationship with altruism (de Hooge et al., 2008). For example, two subsequent studies showed that "threat of shame" promoted altruistic decisions in the public goods game in which shaming defecting individuals by exposing them publicly worked similar to anticipated altruistic punishment and increased the amount of donations (Jacquet et al., 2011, Jacquet et al., 2012). Here, we suggest that shame proneness as a personality trait works similar to exogenous forms of manipulated shame and therefore did not influence altruistic decisions. Thus, our results may provide further support for the distinction between endogenous and exogenous subtypes of shame with respect to their influence on altruistic decisions.

Our study had limitations. Although we aimed to use multiple neuroeconomical paradigms in order to investigate altruism in depression comprehensively, not all of these paradigms made use of real currency. We tried to balance the reimbursement magnitude with suggested NHS ethical standards which aims to ensure that participants who belong to clinical or vulnerable populations are not solely motivated by the magnitude of compensation, whereby large magnitudes may blind participants to any potential risk the studies may entail (NHS guidance on information sheets, p. 127). However, there is evidence that hypothetical financial decision making paradigms produce similar results to those studies which used real currency (Murphy et al., 2001). We showed that the groups were significantly different for 2 out of 5 decision-making DVs which belonged to the task with real currency, which may suggest that real financial rewards may be needed in order to detect between group differences in clinical populations. Another important limitation of our study relates to the sample size. Although we presented
results from a larger clinical population relative to some of the earlier studies (Destoop et al., 2012, Harle et al., 2010), it is possible that some of our post-hoc comparisons remained only marginally significant due to lack of optimal power which is mostly a common limitation in psychiatry research.

Conclusions

In the present study we used multiple neuroeconomical paradigms in order to test the hyper-altruism hypothesis in MDD. The overarching models being used to investigate altruism seems to suggest that clinical status has an effect on altruistic decisions, but this is not consistently in the same direction (whether enhanced or reduced altruistic preferences) across different subtypes of altruism. Particularly, our results show that patients with MDD are not significantly different from healthy participants in terms of their level of engagement in interpersonal cooperation and altruistic punishment, whether they are symptomatic or asymptomatic. We also showed that patients with cMDD make fewer charitable donations, regardless of the cost of such decisions. Finally, we showed that altruistic forms of guilt only promote altruistic decisions in healthy participants, whereas shame proneness as a personality trait does not have any influence on altruistic decisions. Taken together, our results do not provide any support for the hyper-altruism hypothesis in current MDD and we suggest that it should be revised particularly in the light of well established pathological self-blame literature. As shown in our study, such emotional impairments may diminish certain types of altruism which require punishing other individuals. Therefore, we suggest that if MDD is associated with elevated altruistic behaviours, it can only be limited to certain types of altruism, and cannot be generalised. Furthermore, we showed that patients displayed a somewhat consistent pattern of performing altruistic decisions less frequently during the symptomatic phase. Future studies with higher degree of control in
terms of use of hypothetical rewards and computerised partners may be needed in order to fully understand how depression influence social/altruistic decisions differently during the symptomatic phase and in remission.

Acknowledgements

This study was funded by Medical Research Council, UK (Grant G0900593). We would like to thank Dr Diana Chase for her assistance in participant recruitment and study management. The authors declare no financial conflict of interest.
References:


O'CONNOR, BERRY, LEWIS & STIVER 2012. Empathy-based pathogenic guilt, pathological altruism, and psychopathy. *Pathological Altruism, 10*.


**Water Shortage Scenario:**

Imagine that you are living in a small village in the countryside and the rivers in the UK are intoxicated by an unknown type of bacteria. As a result, the British Government has decided to put a temporary water shortage policy in place for **30 DAYS or until the bacterial pollution is resolved**. This decision has been made on the scientific evidence of pollution, and researchers across the UK are confident that they will find a permanent solution to the bacterial pollution within a month. Due to organisational reasons, water distribution will be done by the governmental authorities on each day until the problem is resolved. For this reason, you are paired with another villager for the duration of this shortage to collect your daily ration of water from the governmental authorities. The maximum amount of water which will be given to each pair is **10 LITRES** per day. On each day you will have to make a decision whether or not to go with your partner to collect the available daily ration of water. If you go together you will receive 5 litres each for that day and you will need to survive with this amount until the next day. If you decide to go alone and before your partner, the authorities will think that you are there to collect the daily ration also for your partner and give you 8 litres for that day. This 2 litres reduction has been made as a precaution to avoid exploitation of the organisation. However, if both of you decide to go alone, the authorities will suspect that you are trying to exploit the organisation and will give you only 1 litre each for that day. The details of possible decisions and their payoffs are given in the matrix below. Please ask any questions you may have to the administrator. Remember you will need water for your daily activities such as drinking, cooking, washing and personal hygiene.

<table>
<thead>
<tr>
<th>Choose A or B</th>
<th>Your Partner</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td><strong>You</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>You get 5 LT. Partner gets 5 LT.</td>
<td>You get 0 LT. Partner gets 8 LT.</td>
</tr>
<tr>
<td>B</td>
<td>You get 8 LT. Partner gets 0 LT.</td>
<td>You get 1 LT. Partner gets 1 LT.</td>
</tr>
</tbody>
</table>
CHAPTER 5: Enhanced subgenual cingulate response to altruistic decisions in major depressive disorder

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Abstract

**Background:** Major depressive disorder (MDD) is associated with functional abnormalities in fronto-meso-limbic networks contributing to affective, decision making and reward processing impairments. Such functional disturbances may be contributing to an increased tendency for enhanced altruism driven by empathy-based guilt observed in some patients. However, despite the relevance of altruistic decisions to understanding vulnerability as well as everyday psychosocial functioning in MDD, their functional neuroanatomy is unknown.

**Methods:** Using a charitable donations experiment with fMRI, we compared 14 fully remitted participants with MDD (medication free) and 15 demographically-matched control participants without MDD.

**Results:** Compared with the control group, the MDD group exhibited higher activation in aseptal/subgenual cingulate cortex region (sgACC) for donation relative to reward and higher striatum (STR) activation for donation and reward relative to a low level baseline. The groups did not differ on frequency of donations or response times demonstrating a difference in neural architecture.

**Conclusions:** We showed that altruistic decisions probe residual sgACC hypersensitivity in MDD even after symptoms are fully remitted. The sgACC was previously shown to be associated with guilt which promotes altruistic decisions. In contrast, as in the current study, the STR showed shared activation to selfish and altruistic rewards and could be involved in the so-called “warm glow” of donation. Enhanced neural response in the depression group, in areas previously linked to altruistic decisions, supports the hypothesis of a possible association between hyper-altruism and depression vulnerability as shown by recent epidemiological studies.
Introduction

Charitable donation behaviour is a unique form of human altruism which challenges kin selection theories of interpersonal helping behaviours (Hamilton, 1963, Foster et al., 2006). The "warm glow utility model" posits that people engage in these helping behaviours because they are socially rewarding and pleasurable (Andreoni, 1990). The avoidance of anticipated guilt has been claimed as another important motivator of altruistic behaviour (Eisenberg, 2000, Tangney et al., 2007a). Major depressive disorder (MDD) is associated with elevated levels of self-blaming moral emotions such as shame and guilt (see reviews by (Pulcu et al., 2013, Kim et al., 2011)); particularly survivor guilt (O’Connor et al., 2000b)) persisting into remission (Green et al., 2013). It has been suggested that empathy-based guilt is associated with hyper-altruism in MDD (O’Connor et al., 2012). Epidemiological studies support this view, suggesting that hyper-altruistic tendencies (e.g., making donations exceeding $10 per month) constitute a vulnerability factor for the first onset of MDD (Fujiwara, 2009). Despite the potential role of altruistic decisions in the aetiology of MDD and their relevance to understanding everyday psychosocial functioning impairments (Beddington et al., 2008), their functional neuroanatomy in MDD remains unknown.

Previous neuroimaging studies of charitable donation behaviour showed that septal and subgenual cingulate (sgACC) regions showed selective activation for decisions to make donations relative to decisions to accept pure monetary rewards (Moll et al., 2006). The subgenual cingulate region was also found to be more active in people with higher empathic concern whilst they made decisions to sacrifice some of their money to help others to avoid an electroshock (Feldman Hall et al., 2012). The subgenual cingulate cortex (including the posteriorly adjacent septal area in some studies) was reproducibly found to be selectively
activated for guilt which may account for its involvement in donation decisions (Zahn et al., 2009a), (Zahn et al., 2009d, Green et al., 2012a) (Morey et al., 2012b, Basile et al., 2011a). The septal part of the nucleus accumbens, which is its medial aspect and often overlooked in imaging studies by describing this as ventral striatum activation, was also detected for donation decisions in two subsequent fMRI studies (Hsu et al., 2008, Harbaugh et al., 2007). Other studies investigating donation behaviour showed that activation in a more anterior and ventral area of the ventromedial frontal cortex correlated with the subjective value of the amount being donated (Hare et al., 2010) and deactivations were observed in this region when people made selfish decisions on an interpersonal donations paradigm (Zaki and Mitchell, 2011). In contrast to the selective involvement of the septal and subgenual cingulate regions in altruistic donation decisions relative to selfish rewards, activation in the lateral striatum (STR) was shared for altruistic and selfish monetary reward decisions (Moll et al., 2006), as well as when people made donations in the presence of a social audience who were, therefore, in receipt of additional social rewards such as recognition and appraisal (Izuma et al., 2010). These activations were shown against baseline fixation conditions but not against other rewarding outcomes. The decision making literature to date suggests that activity in the sgACC distinguishes altruistic decisions from those which increase individuals' financial resources. A well-established clinical literature suggests that MDD is associated with both structural (Botteron et al., 2002, Drevets et al., 1998, Drevets et al., 1997, Drevets and Savitz, 2008) and functional impairments of the sgACC during the symptomatic phase (Lehmbeck et al., 2008, Mayberg et al., 2000, Mayberg et al., 1997, Mayberg et al., 2005, Siegle et al., 2006) and abnormalities in functional connectivity (Greicius et al., 2007) extending well into remission (Green et al., 2012b). Studies also suggest functional impairments of the midbrain reward processing systems even when the symptoms fully remit
(Eshel and Roiser, 2010, Tremblay et al., 2005, Schlaepfer et al., 2007, Knutson et al., 2008a). However, brain imaging correlates of social reward processing impairments in MDD are lacking. Taken together, the literature suggests that decisions to make charitable donations may be an experimental probe for understanding clinical disorders associated with functional impairments in fronto-meso-limbic networks.

Here, we used functional magnetic resonance imaging (fMRI) with a culturally valid experimental charitable donations paradigm to investigate neural bases of altruistic decisions in MDD. In doing so, we investigated the following hypotheses: 1) People with MDD exhibit an enhanced sgACC response to donation decisions relative to selfish rewards; 2) striatal responses to selfish rewards in MDD are reduced compared with the control group. In order to address these questions in depression vulnerability we recruited patients with MDD fully remitted from symptoms (unmedicated) and a well-matched group of participants with no personal history of MDD.

**Material and methods**

*Participants*

The study obtained ethical approval from the North West/Manchester South NHS Research Ethics Committee. Participants were recruited using online and print advertisements. Initial suitability was assessed with a phone pre-screening interview and a use of an online survey. Written informed consent was obtained from all participants.

*Inclusion/exclusion of participants:* Patients with remitted MDD fulfilled criteria for a past major depressive episode in full remission according to DSM-IV-TR (American Psychiatric Association, 2000). The clinical interviews were conducted by trained researchers (see
below). We excluded people with current MDD, current or history of substance use disorders, psychotic disorders, bipolar depression, and any other Axis-I anxiety disorders as the likely cause of the initial major depressive episode and any history of neurological disorders. We also excluded patients using psychotropic medication. The healthy control group additionally had no current or past Axis-I disorders or had no first-degree relatives with a history of Axis-I disorders. All participants had normal or corrected-to-normal vision.

In total, 15 healthy control participants and 14 individuals with remitted MDD (rMDD; see Table 3 in the Results section for clinical information on rMDD group) were included in the final analysis (one patient with remitted MDD and one healthy subject were excluded because of an insufficient number of acceptance in pure reward condition (see below for the details of the fMRI paradigm)).

**Clinical interview procedure**

Participants were invited for a clinical interview in which trained researchers (EJT and PDT) conducted the Mood Disorders Module A and the psychotic screening of the Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2002b). MINI screening (Mini International Neuropsychiatric Interview; (Sheehan et al., 1998)) was conducted with all the participants and relevant Structured Clinical Interview for DSM-IV-TR (SCID) modules were used in order to make a full assessment. The Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Global Assessment of Functioning (GAF) scale (Axis V, DSM-IV) were used to assess current symptoms and social functioning.

**fMRI paradigm**
The charitable donations task was adapted from Moll et al. (2006) and the choice of charities was based on the findings of a previous pilot study, which investigated people's perceptions and preferences about charitable organisations in England and Wales. Mission statements of 95 charities were obtained from The Charity Commission for England and Wales (http://www.charity-commission.gov.uk/) for the pilot study. The 36 charitable organisations with the most positive mission statement ratings in the pilot were selected for the functional neuroimaging task. Unlike the Moll et al (2006) study, our imaging paradigms did not contain any charities probing costly/non-costly opposition behaviour. This decision was made based on the findings of the pilot study in which we only identified 11 charities (predominantly focusing on controversial religious themes) with mildly negative mission statement ratings (a detailed analysis of the pilot study is available from the authors upon request). Our pilot findings may reflect a significant cultural difference in charities between the US and the UK. US charities include political organisations and lobbying groups, for example charities promoting gun control or abortion, which elicit strong opposition in some people and strong support in others (Wright, 2002). Registered UK charities are generally less politicised and, while people are more or less likely to support these charities, there are very few organisations which people would actively oppose (and still fewer which people would pay to oppose).

Before the fMRI experiment, participants were given a document containing the full name and the mission statement of 36 charities and the payoff conditions were explained to them (see Table 1 for payoffs and their comparison with Moll et al (2006)).

The charitable donations task performed during fMRI lasted for 144 rounds (3 Runs; 48 rounds in each run) with the following conditions presented in pseudorandom order:

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Costly donation: Charity gains, participant loses
Non-costly donation: Charity gains, participant neither gains nor loses
Reinforcing donation: Charity gains, participant gains
Simple financial reward: Participant gains, charity neither gains nor loses
Neutral: No gain or loss for either charity or participant

See Table 1 for cost, donation and reward magnitudes in each condition. In total, there were three donation conditions where the charity gains: reinforcing donation (participant also gains), non-costly donation (no change for participant) and costly donation (cost/loss for participant). The costly condition best models real-life charitable giving. Donations in the costly proposals reduced participants endowment by 30p (p=pence, 1/100th of £1, 1 UK pound), which is then escalated in the experimental design of the study (as in Moll et al (2006)) and corresponded to £1 of donation to the charity.
**Table 1.** The payoffs for the participant and the charity across different conditions and comparisons between Moll et al (2006).

<table>
<thead>
<tr>
<th></th>
<th>Participant</th>
<th>Charity</th>
<th>Total number of conditions</th>
<th>Participant*</th>
<th>Charity*</th>
<th>Total number of conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Funds</strong></td>
<td>£20</td>
<td>-</td>
<td>-</td>
<td>$128</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Costly</strong></td>
<td>-30p</td>
<td>+£1</td>
<td>36</td>
<td>-$2</td>
<td>+$5</td>
<td>32</td>
</tr>
<tr>
<td><strong>Non-costly</strong></td>
<td>-0p</td>
<td>+£1</td>
<td>36</td>
<td>-$0</td>
<td>+$5</td>
<td>32</td>
</tr>
<tr>
<td><strong>Reinforcing</strong></td>
<td>+10p</td>
<td>+£1</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Reward</strong></td>
<td>+10p</td>
<td>+£0</td>
<td>24</td>
<td>+$2</td>
<td>+$0</td>
<td>32</td>
</tr>
<tr>
<td><strong>Neutral</strong></td>
<td>-0p</td>
<td>+£0</td>
<td>24</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Null-Fixation</strong></td>
<td>+</td>
<td>+</td>
<td>144</td>
<td>+</td>
<td>+</td>
<td>48</td>
</tr>
<tr>
<td><strong>Penalty</strong></td>
<td>-20p</td>
<td>-</td>
<td>-</td>
<td>-$1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Moll et al (2006) study, which also contained costly and non-costly opposition proposals which were not included in the present study due to differences in charitable giving between US and UK. At the time of writing this manuscript, $2 converted to £1.32. The main difference between the studies is the relative magnitudes of financial components of the conditions; for Moll et al (2006): penalty < reward = costly donation < charity amount; whereas in the present study: reward < penalty < costly donation < charity amount. Greater financial magnitude for penalty over reward is preferred in the present design in order to reduce the number of trials with no responses. The (+) denotes the pattern of fixation, (-) denotes not applicable information.

During the experiment, participants started with £20 of funds corresponding to real currency. In each round, charity information was presented to the participants, comprising the name of the charity and a shortened version of its mission statement (for 6 seconds). On the next screen, the participants saw the payoff conditions (for 3.5 seconds). Participants responded by using the designated "Accept" and "Reject" buttons to indicate their decisions; the designation of these two buttons was counterbalanced across participants. A 20p penalty was imposed when participants failed to respond within 3.5 seconds. The payoff screen remained visible until 3.5 seconds expired, irrespective of how quickly participants responded to the proposal. On the final screen, participants were presented with the outcome of their decisions and the amount of remaining...
funds (for 2.5 seconds; see Figure 1 for the sequence of screens on experiment timeline). At the end of the game, the amount of remaining funds was rounded to the nearest pound to be received as reimbursement for participation. The participants were told that all of the donated money would be distributed evenly to the five most frequently selected charities once the study was completed, and in a debriefing session, no participant questioned whether these donations would be made.

Figure 1: Diagram showing the experimental timeline of the charitable donations paradigm. Adapted from Moll et al (2006).
Image acquisition

Echo-planar T2*-weighted images (351 volumes in each of the 3 runs with 5 dummy scans for each run of 11 min 42 sec) were acquired on a Philips 3 Tesla Achieva MRI scanner with an 8 channel coil, 3 mm slice thickness and ascending continuous acquisition parallel to the anterior to posterior commissural line (between 35 and 40 slices depending on size of the participant’s head, Repetition Time (TR)=2000 ms, Echo Time (TE)=20.5 ms, Field of View (FOV)=220x220x120 mm, acquisition matrix=80x80, reconstructed voxel size=2.29x2.29x3 mm, SENSE factor=2) optimized for signal detection in ventral frontal areas (Green et al., 2012b). In addition 3-dimensional T1-weighted Magnetization-Prepared Rapid Acquisition Gradient Echo structural images were obtained (reconstructed voxel size=1 mm³, 128 slices, TE=3.9 ms, FOV=256x256x128, acquisition matrix=256x164, slice thickness=1 mm, TR=9.4 ms). Axial T2-weighted structural images were acquired for each participant to rule out vascular and inflammatory abnormalities.

fMRI modelling

We modelled the haemodynamic response function with time and dispersion derivatives. The six regressors in the general linear model were: the baseline fixation condition, neutral (neither the participant nor the charity gain or lose money), costly (charity gains, participant loses), non-costly (charity gains, no change for participant) and reinforcing (charity and participant both gain) donation conditions and simple financial reward (participant gains). The regressors in the model referred to onset time vectors for all proposals that were accepted (and fixation onset for the baseline). Our event-related fMRI paradigm is modelled in the same way as Moll et al (2006). In summary, we modelled the 3.5 seconds corresponding to the presentation of the
proposal (Payoff/Decision screen in Figure 1), during which participants made their decisions. This is the “Decision phase” analysis. We also modelled the 6 second window containing both the Payoff/Decision and Outcome screens (see Figure 1) to detect outcome related activations in an exploratory fashion. This is the “Outcome phase” analysis. Since the outcome is fully predictable if the payoff is accepted, the outcome is known from the point at which the proposal is presented and accepted and therefore it makes sense to model this phase including the decision screen, following the approach of Moll et al (2006).

Analysis

Behavioural and supporting data analyses were performed using a significance threshold of \( p=0.05 \), 2-sided; using chi-square, independent samples t-tests and general linear models (SPSS 20.0, www.spss.com). Functional images were realigned, unwarped and coregistered to the subject’s T1 images. These images were normalized by first normalizing the participant’s T1 image to the standard T1-template in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and applying the same transformations to the functional images. A Gaussian kernel of 5 mm at full width at half maximum (FWHM) was used for smoothing to be sensitive to small subcortical areas of activation (Sacchet and Knutson, 2012). At the first (individual) level we contrasted donation (containing all accepted costly, non-costly and reinforcing donation proposals) vs. reward (simple financial reward) in a balanced contrast. Subsequently, we contrasted these proposal options in pairwise comparisons (e.g. costly vs. non-costly, costly vs reward, non-costly vs reward) and contrasted each proposal condition against the baseline conditions of neutral and fixation. At the second level, we used the contrast images from pairwise comparisons in two different random effects models. Using one-sample t-tests in our first model, we assessed neural
differences between conditions separately in healthy subjects (n = 15) and in remitted patients (n =14). Using a two-sample t-test in our second model we compared the groups. In secondary data analyses based on the peak-voxels of the whole brain between-group comparison models (using a 1.5 mm radius around the peak voxel in MarsBar version 0.43, http://marsbar.sourceforge.net/(Brett et al., 2002)), we aimed to confirm that the detected regions survived when comparing donation/reward proposals vs. the low-level fixation condition, allowing us to infer either increased activation for the acceptance of the proposal or deactivation in the subtracted control condition.

Whole brain results were first explored at a voxel-level threshold of p=0.005 uncorrected, cluster threshold 4 voxels. However, areas are only reported that survived additional voxel- or cluster-level Family-Wise-Error (FWE)-corrected thresholds of p=0.05 across a priori ROIs (as detailed below, small volume correction) or the whole brain.

Region of Interest (ROI) definition

We defined independent structural regions of interest which were previously shown to be involved in decisions to make charitable donations and are also critically associated with depression (septal/subgenual cingulate region and bilateral striatum). In an exploratory fashion, we also investigated the activations in two additional regions which are associated with social economical decision making; dorsal anterior cingulate and ventromedial prefrontal cortex (Pulcu et al, 2013). The ROIs were defined by using Wake Forest University (WFU) PickAtlas tool (Maldjian et al., 2003) for SPM8; using a combination of anatomical and Brodmann Area masks from the automated anatomical labels. A bilateral anatomical ROI was defined for striatum using the automated anatomical labels available in Wake Forest University (WFU) PickAtlas. The
ventromedial prefrontal cortex (vmPFC) ROI contained all brain structures under z =8 (all coordinates refer to MNI space), within x =−/+/26 coordinates, and ranging from y =2 to the frontal pole. Two distinct box ROIs were defined for the anterior cingulate: dorsal and subgenual, designed by using the ROI generation tool. We defined the dorsal and the subgenual sections of the anterior cingulate cortex relative to the genu of the corpus callosum (MNI: 0; 36;8). The dorsal anterior cingulate ROI ranged from x =−/+/20; y = 18 to 46; z = 8 to 26: containing the dorsal anterior sections of the Brodmann areas (BA) 32 and 24. The subgenual anterior cingulate ROI ranged from x =−/+/10; y =8 to 34; z = -10 to 8: containing the ventromedial sections of BA 32 and 24 and the whole of BA 25.

3. Results

Participants

The groups did not differ significantly for age, years of education, distribution of gender, annual income or MADRS scores (see Table 2). The clinical information about the remitted group is available in Table 3.

<table>
<thead>
<tr>
<th>Table 2. Group comparison on demographic and basic clinical variables (mean± SD)</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Education (years)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Income (GBP)</td>
</tr>
<tr>
<td>MADRS</td>
</tr>
<tr>
<td>GAF</td>
</tr>
</tbody>
</table>

<sup>c</sup> = Pearson's chi-square (df =1). <sup>T</sup> = t-test. Control: N= 15, Remitted MDD: N= 14.
Table 3. Clinical characteristics of rMDD group (N=14)

<table>
<thead>
<tr>
<th>MD subtype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With melancholic features</td>
<td>10/14</td>
</tr>
<tr>
<td>With psychotic features</td>
<td>1/14</td>
</tr>
<tr>
<td>No specific subtype</td>
<td>3/14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of previous MDEs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8/14</td>
</tr>
<tr>
<td>2</td>
<td>3/14</td>
</tr>
<tr>
<td>3</td>
<td>3/14</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Last MDE details</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average length of MDE (months)</td>
<td>4.7 ±3 (range: 0.5-12)</td>
</tr>
<tr>
<td>Average time in remission (months)</td>
<td>56.4 ± 57.1 (range:3-184)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Life-time axis-I co-morbidity*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>1/14</td>
</tr>
<tr>
<td>Generalised anxiety disorder</td>
<td>3/14</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>4/14</td>
</tr>
<tr>
<td>No life-time co-morbidity</td>
<td>6/14</td>
</tr>
</tbody>
</table>

* All co-morbid disorders were fully remitted at time of study. None of the co-morbid disorders was a likely primary cause of the depressive episodes (preceding MDD diagnosis). MDD subtype classification was based on adapting the SCID-I for DSMIV-TR to allow life-time assessment of the subtypes.

Behavioural results

There were no differences between groups in the number of acceptance responses to any of the donation or the reward conditions or response times for acceptance or rejection in any of the conditions (see Table 4). Furthermore, the groups did not differ on how they rated the mission statements of the charitable organisations and how much they were familiar with the charitable organisations prior to their participation.
Table 4. Behavioural measures and response time (RT) comparisons (ms)

<table>
<thead>
<tr>
<th></th>
<th>Control mean ±SD</th>
<th>Remitted MDD mean ±SD</th>
<th>T*</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Donation count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costly</td>
<td>18.9 ± 9.4</td>
<td>22.5 ± 10.7</td>
<td>-0.943</td>
<td>0.354</td>
</tr>
<tr>
<td>Non-Costly</td>
<td>30.9 ± 6.7</td>
<td>33.6 ± 4.5</td>
<td>-1.270</td>
<td>0.215</td>
</tr>
<tr>
<td>Rewarding</td>
<td>22.3 ± 3.1</td>
<td>23.3 ± 1.8</td>
<td>-1.104</td>
<td>0.280</td>
</tr>
<tr>
<td>Pure Reward</td>
<td>21.1 ± 3.6</td>
<td>22 ± 2.1</td>
<td>-0.794</td>
<td>0.434</td>
</tr>
<tr>
<td>Neutral</td>
<td>13.6 ± 9.5</td>
<td>16.3 ± 9.4</td>
<td>-0.769</td>
<td>0.449</td>
</tr>
<tr>
<td>Total funds (£)</td>
<td>18 ± 2.4</td>
<td>17.6 ± 3.1</td>
<td>0.351</td>
<td>0.729</td>
</tr>
<tr>
<td><strong>Charity ratings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familiarity</td>
<td>3.05 ± 0.9</td>
<td>2.8 ± 0.6</td>
<td>0.741</td>
<td>0.465</td>
</tr>
<tr>
<td>Mission statement</td>
<td>5.3 ± 0.7</td>
<td>5.2 ± 0.5</td>
<td>0.401</td>
<td>0.692</td>
</tr>
<tr>
<td><strong>Costly Donation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptance RT</td>
<td>1604 ± 311</td>
<td>1562 ± 420</td>
<td>0.307</td>
<td>0.761</td>
</tr>
<tr>
<td>Rejection RT</td>
<td>1567 ± 396</td>
<td>1608 ± 418</td>
<td>-0.269</td>
<td>0.790</td>
</tr>
<tr>
<td><strong>Non-Costly Donation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptance RT</td>
<td>1338 ± 329</td>
<td>1454 ± 557</td>
<td>-0.677</td>
<td>0.504</td>
</tr>
<tr>
<td>Rejection RT</td>
<td>1406 ± 523</td>
<td>1639 ± 579</td>
<td>-1.129</td>
<td>0.269</td>
</tr>
<tr>
<td><strong>Rewarding Donation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptance RT</td>
<td>1394 ± 522</td>
<td>1318 ± 392</td>
<td>0.445</td>
<td>0.660</td>
</tr>
<tr>
<td>Rejection RT</td>
<td>1710 ± 708</td>
<td>1475 ± 446</td>
<td>1.074</td>
<td>0.292</td>
</tr>
<tr>
<td><strong>Pure reward</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acceptance RT</td>
<td>1366 ± 530</td>
<td>1608 ± 545</td>
<td>-1.209</td>
<td>0.237</td>
</tr>
<tr>
<td>Rejection RT</td>
<td>1452 ± 584</td>
<td>1476 ± 406</td>
<td>-0.128</td>
<td>0.899</td>
</tr>
</tbody>
</table>


**fMRI results**

Summary of all fMRI activations are reported in Table 5. Comparisons against the neutral condition did not reveal any significant activations in our regions of interest.
Table 5. Summary of BOLD fMRI results

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hemisphere</th>
<th>Region</th>
<th>X</th>
<th>MNI Y</th>
<th>Z</th>
<th>t-value</th>
<th>FWE-corr. p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>donation + reward&gt; fix</td>
<td>L</td>
<td>ventromedial PFC</td>
<td>-9</td>
<td>47</td>
<td>-14</td>
<td>6.74</td>
<td>&lt;.01c, ROI</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>septal</td>
<td>-3</td>
<td>23</td>
<td>-2</td>
<td>4.08</td>
<td>&lt;.02c, ROI</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>subgenual cingulate</td>
<td>-12</td>
<td>29</td>
<td>-8</td>
<td>5.36</td>
<td>&lt;.02c, ROI</td>
</tr>
<tr>
<td>donation&gt; fix</td>
<td>R</td>
<td>frontopolar cortex</td>
<td>6</td>
<td>65</td>
<td>-5</td>
<td>5.97</td>
<td>&lt;.001c, ROI</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>lateral OFC</td>
<td>21</td>
<td>35</td>
<td>4</td>
<td>4.99</td>
<td>&lt;.02c, ROI</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>septal</td>
<td>-3</td>
<td>23</td>
<td>-2</td>
<td>3.90</td>
<td>&lt;.04c, ROI</td>
</tr>
<tr>
<td>reward&gt; fix</td>
<td>L</td>
<td>ventromedial PFC</td>
<td>-9</td>
<td>47</td>
<td>-14</td>
<td>8.04</td>
<td>&lt;.001 wb</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>temporal gyrus</td>
<td>-63</td>
<td>-7</td>
<td>-14</td>
<td>8.07</td>
<td>&lt;.001 wb</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>temporal gyrus</td>
<td>63</td>
<td>-4</td>
<td>7</td>
<td>5.78</td>
<td>&lt;.001 wb</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>inferior frontal gyrus</td>
<td>42</td>
<td>29</td>
<td>-14</td>
<td>4.73</td>
<td>&lt;.04 wb</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>subgenual cingulate</td>
<td>15</td>
<td>29</td>
<td>-8</td>
<td>4.49</td>
<td>&lt;.05 wb</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>septal/nucleus accumbens</td>
<td>3</td>
<td>20</td>
<td>4</td>
<td>4.74</td>
<td>&lt;.02c, ROI</td>
</tr>
<tr>
<td>reward&gt; costly</td>
<td>L</td>
<td>dorsal ACC</td>
<td>-6</td>
<td>32</td>
<td>7</td>
<td>5.6</td>
<td>&lt;.03c, ROI</td>
</tr>
<tr>
<td>remitted MDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>donation + reward&gt; fix</td>
<td>R</td>
<td>subgenual cingulate</td>
<td>12</td>
<td>35</td>
<td>-14</td>
<td>6.82</td>
<td>&lt;.001c, ROI</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>septal</td>
<td>-3</td>
<td>17</td>
<td>-5</td>
<td>4.41</td>
<td>&lt;.02c, ROI</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>striatum</td>
<td>30</td>
<td>-4</td>
<td>-11</td>
<td>5.54</td>
<td>&lt;.03c, ROI</td>
</tr>
<tr>
<td>donation&gt; fix</td>
<td>R</td>
<td>subgenual cingulate</td>
<td>12</td>
<td>35</td>
<td>-14</td>
<td>8.29</td>
<td>&lt;.005 wb</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>striatum</td>
<td>30</td>
<td>-4</td>
<td>-11</td>
<td>5.57</td>
<td>&lt;.04 wb</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>head of caudate</td>
<td>15</td>
<td>23</td>
<td>13</td>
<td>5.56</td>
<td>&lt;.05c, ROI</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>septal/nucleus accumbens</td>
<td>-6</td>
<td>17</td>
<td>-8</td>
<td>5.58</td>
<td>&lt;.01c, ROI</td>
</tr>
<tr>
<td>control vs rMDD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>costly&gt; reward</td>
<td>R</td>
<td>dorsal ACC</td>
<td>15</td>
<td>26</td>
<td>16</td>
<td>4.4</td>
<td>&lt;.05 v, ROI</td>
</tr>
<tr>
<td>rMDD vs control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>donation + reward&gt; fix</td>
<td>R</td>
<td>striatum</td>
<td>18</td>
<td>20</td>
<td>1</td>
<td>3.94</td>
<td>&lt;.05 v, ROI</td>
</tr>
<tr>
<td>donation&gt; fix</td>
<td>R</td>
<td>nucleus accumbens</td>
<td>21</td>
<td>14</td>
<td>-14</td>
<td>4.73</td>
<td>&lt;.04 v, ROI</td>
</tr>
<tr>
<td>donation&gt; reward</td>
<td>L</td>
<td>subgenual cingulate</td>
<td>-3</td>
<td>29</td>
<td>1</td>
<td>4.1</td>
<td>&lt;.04 v, ROI</td>
</tr>
</tbody>
</table>

Only regions that survived voxel- or cluster-based FWE-corrected p=.05 over the whole brain or our a priori ROIs are reported. wb= whole brain, c=cluster-based, v=voxel based FWE-correction. Control group: N= 15, remitted MDD group: N= 14. fix: Fixation cross.
Healthy subjects

**Decision phase:** Against baseline fixation, decisions to donate were associated with increased BOLD response in the frontopolar and lateral orbitofrontal cortices and the septal region. When comparing decisions to accept simple rewards vs. making costly donations, healthy subjects showed enhanced response in dorsal anterior cingulate cortex (see Table 4). The comparisons between other main conditions in pairwise contrasts (i.e. all donation vs. reward, non-costly vs. reward, costly vs. non-costly) showed no significantly different responses.

**Outcome phase:** Outcomes in all donation and reward conditions against the low-level fixation baseline (i.e. all three donation conditions + reward > fixation) in healthy subjects were associated with increased responses in sgACC, septal region and ventromedial prefrontal cortex, whereas outcomes for accepting simple rewards was associated with medial temporal gyri bilaterally, inferior frontal gyrus, ventromedial PFC and septal /nucleus accumbens region and subgenual cingulate cortex.

Patients with remitted MDD (rMDD)

**Decision phase:** Decisions to make costly donations relative to accepting monetary rewards were associated with BOLD response in dorsal anterior cingulate cortex at a trend level of significance (MNI: 9, 26, 22; p = 0.08). Increased BOLD response related to direct comparison of decisions to make charitable decisions (irrespective of personal costs) to accepting simple monetary rewards (i.e. all donation > reward contrast) did not reach FWE-corrected significance level.

**Outcome phase:** Significantly increased BOLD response related to outcomes increasing the charity's and one's own financial resources against the baseline condition (i.e. all three donation conditions + reward > fixation, see Table 4) were detected in the sgACC. The inferior aspect of
the globus pallidus within right striatum, as well as the septal region, also showed increased response. Outcomes related to making donations relative to the baseline fixation cross were associated with BOLD response in the sgACC, striatum, head of caudate and septal/nucleus accumbens regions. Outcomes related to accepting simple financial rewards relative to the baseline fixation did not produce any significant change in BOLD response.

Between group comparisons

Decision phase: When comparing all three donation decisions to simple rewards, there was increased sgACC response in the rMDD group relative to control subjects (BA 24; MNI: -3, 29, 1; t = 4.1, FWE corrected over ROI: p = 0.04; see Figure 2). When comparing decisions to make costly donation vs. reward, there was increased dorsal anterior cingulate cortex response in control subjects relative to the rMDD group (BA 31; MNI: 15, 26, 16; t = 4.4, FWE corrected over ROI: p = 0.05; See Figure 2).
Figure 2:
T-maps displayed at p<0.005 uncorrected showing activation in (a) subgenual cingulate in MDD relative to healthy participants for donation> reward with regression coefficients from the peak voxel for the contrast elements against the neutral condition and the fixation shown in bar charts (as with for other activations in this figure; error bars show +/- 1 Standard Error); (b) dorsal anterior cingulate in healthy participants relative to MDD for costly donation> reward.

Outcome phase: Finally, there was increased striatum response in the rMDD group relative to control subjects when comparing all reward-related outcomes to fixation (i.e. all donation + reward> fixation; MNI: 18, 20, 1; t = 3.94, FWE corrected over ROI: p = 0.05; See Figure 3). Enhanced donation specific response (i.e. all donation conditions > fixation) in the remitted group, relative to healthy subjects, was further confirmed by post-hoc SPM analysis showing a
significant activation in nucleus accumbens extending medially to the septal region adjacent to sgACC (MNI: 21, 14, -14, t = 4.73, p = 0.04).

**Figure 2**: (c) right striatum in MDD relative to healthy participants for donation + reward fixation.

Between group comparisons for other main contrasts (i.e. non-costly vs. reward; costly vs. non-costly) did not reveal any significant response differences in our ROIs in either the decision or outcome phases.

**Supporting General Linear Models**

The between group differences represent group by condition interactions. In order to confirm group by condition interactions we used extracted regression coefficients from the peak voxels.
for the conditions of interest compared to the fixation baseline in 2x2 GLMs in SPSS (two types of decisions (e.g. to donate or to accept simple rewards) by two levels of clinical grouping). In order to understand the simple effects driving these interactions, we did between group pairwise comparisons using extracted regression coefficients from the peak voxels for the conditions of interest compared to baseline (see Figure 2).

For the sgACC response in the decision phase, there was a significant decision type by group interaction (F(1, 24)= 9.694, p = 0.005) with main effect of decisions (F(1, 24)= 4.944, p = 0.036), but no main effect of clinical group (p = 0.408). Pairwise comparisons were used to explore the interaction. Relative to healthy subjects, there was a significantly reduced response for receiving simple rewards (t = 2.295, p = 0.05), and marginally elevated response to making donations (t = -1.796, p = 0.09) in remitted patients. The magnitude of donation related activation relative to simple rewards was significantly higher in remitted patients (t = 3.887 p =0.001), whereas it was comparable in healthy subjects (t = -0.123, p = 0.903; see Figure 2b).

For the dACC response in the decision phase, there was a significant decision type by clinical group interaction (F(1, 24)= 10.336, p = 0.004) with main effect of decision type (F(1, 24)= 5.686, p = 0.025), but no main effect of clinical group (p = 0.390). Between group pairwise comparisons for simple main effects suggested that the groups were marginally different for reward related responses (t = -1.757, p = 0.09). Relative to the magnitude of responses for simple rewards, remitted patients had significantly lower response for costly donations (t = -2.182, p = 0.04), whereas in healthy subjects the magnitude of the deactivations for both conditions were comparable (t = 0.372, p = 0.713; see Figure 2a).
For the right striatal response in the outcome phase, there was a significant type of outcome by clinical group interaction (F(1, 24)= 13.159, p = 0.002) with main effect of outcome type (F(1, 24)= 6.410, p = 0.02) and main effect of clinical group (F(1, 24)= 16.763, p = 0.0006). Between group pairwise comparisons suggested that the interaction is driven by significantly elevated responses for donation conditions (t= -4.161, p = 0.001) and marginally higher response for simple rewards (t = -1.875, p = 0.08) in remitted patients. The right striatal activations for both conditions relative to the baseline were comparable in remitted patients (t = 1.029, p = 0.315), but in healthy subjects the deactivations were significantly greater for donation conditions (t = -3.476, p = 0.002; see Figure 3).

Supporting Correlation Analysis

In order to address whether between-group differences in neural response in the dACC were consistent with a role in cognitive conflict resolution (Botvinick et al., 2004), we investigated the correlations between the regression coefficients and behavioural measures related to frequency and response times for accepting donation or reward proposals. There was a positive correlation between dACC regression coefficients for reward> fixation and response times for decisions to accept simple financial rewards in rMDD group (df= 13, r = 0.573, p = 0.041); whereas an inverse correlation emerged between this measure and number of simple financial rewards accepted in healthy subjects (df = 14, r = -0.634, p = 0.011; p-values uncorrected; see Figure 2a).

Discussion

Here, we conducted a functional neuroimaging study using an experimental charitable donations paradigm in order to investigate the neural basis of altruistic decisions in patients with remitted MDD. Our behavioural results for costly donation and accepting simple financial rewards (see
Table 3) suggested that the experimental task effectively probed donation related financial decision-making; with all participants prepared to make costly donations even though these decisions reduced their overall gains from the task. We showed that during periods of remission, patients with MDD did not engage in altruistic decisions significantly more frequently than healthy subjects. However, our imaging results indicate that altruistic decisions are associated with enhanced septal/sgACC response in remitted MDD compared to controls. We also showed that outcome related striatal responses are relatively enhanced in rMDD compared to controls for both charitable and self-serving decisions. Finally, we showed that in remitted patients there is enhanced response in dACC for decisions to accept simple financial rewards, and a decreased response (i.e. negative BOLD effect) in this region for decisions to make costly donations.

We were only partially able to reproduce the findings of a previous donation study in healthy volunteers (Moll et al. 2006). We showed that in healthy subjects charitable decisions, as well as accepting simple financial rewards, activated overlapping neural circuitry with the Moll et al (2006) study, but condition specific activations were only detected against the baseline condition. These differences may be due to the differences in charitable organisations used across the two experimental paradigms, and in particular to the differences in the nature of charitable giving between the United States and United Kingdom (Wright, 2002). One key difference in the nature of charitable giving between these two countries is that in the US, donations contribute to tax relief (Harbaugh et al., 2007) and therefore there may be non-altruistic incentives to donate. In the UK, only higher earners, who pay income tax at a higher rate, receive tax relief on donations and none of our participants reported annual incomes that would include them in this tax bracket. Also, Wright (2002) argued that charitable giving is often a form of political expression in the US, where controversial mission objectives of many charitable organisations are likely to divide
public opinion (as reflected in the subset of charities which probed opposition behaviour in Moll et al (2006)). There are far fewer controversial charitable organisations in the UK and we were therefore unable to examine opposition. This difference in the nature of the charities may also explain why we did not replicate all of the previously reported results.

Our core hypotheses concerned differential responses between individuals with rMDD and healthy controls. As predicted, we showed increased response in the sgACC region for decisions to donate relative to simple monetary rewards which distinguished the rMDD from the control group. Abnormal functioning of the sgACC in MDD is well established in clinical research. Following volumetric correction for the reduction in grey matter, an abnormal hypermetabolism in sgACC has been shown in current depression (Drevets and Savitz, 2008), which normalises upon remission from symptoms (Mayberg et al., 2000). Here we observed enhanced sgACC response during remission, in response to a specific cognitive challenge, suggesting some residual hypersensitivity which can be elicited with a suitable task probe. It is important to point out that the peak activation in the sgACC that we report in our between groups comparison is almost precisely overlapping with the peak of functional abnormality reported by Drevets et al (1997).

Previous imaging studies have implicated the sgACC in prosocial decision-making, affiliative feelings and moral emotions, such as interpersonal (Zahn et al., 2009b) and altruistic guilt (Basile et al., 2010), empathic concern for others (Zahn et al., 2009a) and compassion for other's psychological pain (Immordino-Yang et al., 2009). Lesions to ventromedial parts of the prefrontal cortex (Koenigs and Tranel, 2007) have shown to influence prosocial decisions negatively in interpersonal financial exchange. More specifically, septal neurodegeneration has been associated with a lack of affiliative feelings such as guilt and pity (Moll et al., 2011),
suggesting that these prosocial emotions are important for balancing selfish motives in social economical decision making situations. Our charitable donations paradigm elicited enhanced sgACC response in remitted MDD, suggesting that donation may be a more sensitive probe of sgACC function in this group than paradigms exploring interpersonal guilt (Green et al., 2012b), which did not lead to between group BOLD signal differences in the sgACC. Given the literature relating sgACC to prosocial, affiliative and moral emotions, it is reasonable to suggest that such feelings are more strongly elicited in people with remitted MDD than controls during charitable donations. More specifically it has been argued that forms of guilt, particularly survivor guilt, may be important motivations for making charitable donations. It is therefore possible that the enhanced septal/sgACC response during donations in patients with rMDD reflect the higher levels of survivor guilt that have been suggested to underpin hyper-altruism in this group (O Connor, 2012). However while this is a reasonable hypothesis arising from our present findings, it requires direct testing in future studies, as guilt is only one component of social decision-making which a donations task potentially probes.

Counter to our hypothesis, we observed enhanced signal in the striatum in remitted MDD, particularly for donation outcomes. Meta-analytical reviews show that the striatum responds during the prediction and consumption of salient rewards (Diekhof et al., 2012), whether primary or secondary (Sescousse et al., 2013). The striatal responses observed in the striatum in healthy controls were lower than we expected. This may reflect the relatively passive nature of the task, as previous studies indicated that competing for, or winning, financial rewards under conditions of uncertainty are associated with greater striatal responses relative to passive receipt of simple rewards (Elliott et al., 2000). Another explanation for the relatively small magnitude of striatal activations in our control group may be that the magnitude of our simple rewards was much
small than those used by Moll et al., 2006 (see Table 1 and legends for detailed comparison). Cultural and task specific differences between the present study and Moll et al. (2006) may also be important factors. However, these arguments do not explain the relatively increased striatal responses observed in the remitted group. Previous studies have suggested reduced striatal responses to financial rewards in people with MDD, which may persist into remission (Eshel and Roiser, 2010, Tremblay et al., 2005, Schlaepfer et al., 2007, Knutson et al., 2008). Our findings suggest that decisions to make charitable donations enhance striatal responses in rMDD, perhaps reflecting enhanced sensitivity to social rewards. However, once again, this is a hypothesis that requires testing in future studies.

Finally, we showed between-group differences for costly donations relative to accepting simple financial rewards in the dACC. Neuroimaging evidence suggested that the dorsal section of the ACC is engaged in conflict resolution and action monitoring (Amodio and Frith, 2006, Botvinick et al., 2004). Response in the dACC has been consistently demonstrated in paradigms using economical decision making. Studies found significant activations when participants chose between conflicting outcomes in social contexts, such as accepting or rejecting unfair financial proposals (Rilling et al., 2008, Sanfey et al., 2003), evaluating the magnitude of funds to be allocated to real players in the trust game (McCabe et al., 2001) and deciding to match their partners' expectations of financial return (Chang et al., 2011). Deactivations in this region were related to evaluating outcomes on a predefined matrix prior to making uncooperative decisions (Rilling et al., 2007). In our study, decreased response was observed in this region in the patient group when they agreed to make costly forms of donation, but increased response when increasing their own payoff. This could be considered consistent with a hypothesis that patients experience more conflict when making self-serving decisions. Post-hoc analyses revealed that
differences in neural activity did not reflect patients' behavioural decisions of making costly donations or accepting simple financial rewards and did not behaviourally differentiate them significantly from healthy subjects. However, we showed that reward related deactivation has an inverse relationship with the number of simple financial rewards accepted in healthy subjects, whereas reward related activation has a positive relationship with response times for accepting the simple financial rewards in the patient group (see Figure 2a), supporting a potential conflict monitoring role of the dACC in our context.

Our study had a number of limitations. Like other key publications on neurobiology of donation behaviour (Harbaugh et al., 2007, Izuma et al., 2010, Moll et al., 2006), we did not correct our p-values for the number of exploratory ROIs that we used. Despite showing donation-related hyperactivation in the group with MDD vulnerability, our study cannot discriminate between primary (e.g. familial history) and secondary (e.g. due to a previous episode) vulnerability. This issue should be addressed by longitudinal studies which also recruit individuals before the first onset of MDD. Finally, it is important to note that the patients in this cohort were fully remitted at the time of testing, and that remission was particularly stable in this cohort (mean of nearly 5 years). It is possible that such a stably remitted group of patients are not representative and it would be important to extend these findings to more recently remitted, and indeed currently depressed participants.

**Conclusions:**

Here, we showed that there is a hyperactivation of sgACC and striatum during charitable donation decisions in patients with MDD. Our findings suggest that a charitable donations paradigm may be a particularly sensitive probe of fronto-meso-limbic circuitry in depression,
associated with neuronal abnormalities even in very stable remission. We suggest that the between-group differences that we demonstrate here related to social reward hypersensitivity may be related to biological trait markers for vulnerability to MDD for patients in stable remission.
References:


Psychiatric Institute, November 2002.


CHAPTER 6: Increased amygdala response to shame in remitted major depressive disorder

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Abstract

Proneness to self-blaming moral emotions such as shame and guilt is increased in major depressive disorder (MDD), and may play an important role in vulnerability even after symptoms have subsided. Social psychologists have argued that shame-proneness is relevant for depression vulnerability and is distinct from guilt. Shame depends on the imagined critical perception of others, whereas guilt results from one’s own judgement. The neuroanatomy of shame in MDD is unknown. Using fMRI, we compared 21 participants with MDD remitted from symptoms with no current co-morbid axis-I disorders, and 18 control participants with no personal or family history of MDD. The MDD group exhibited higher activation of the right amygdala and posterior insula for shame relative to guilt (SPM8). This neural difference was observed despite equal levels of rated negative emotional valence and frequencies of induced shame and guilt experience across groups. These same results were found in the medication-free MDD subgroup (N=15). Increased amygdala and posterior insula activations, known to be related to sensory perception of emotional stimuli, distinguish shame from guilt responses in remitted MDD. People with MDD thus exhibit changes in the neural response to shame after symptoms have subsided. This supports the hypothesis that shame and guilt play at least partly distinct roles in vulnerability to MDD. Shame-induction may be a more sensitive probe of residual amygdala hypersensitivity in MDD compared with facial emotion-evoked responses previously found to normalize on remission.
**Introduction**

The importance of excessive self-blame for the distinction between depressive emotions and healthy sadness has been recognized since Freud’s seminal observations (Freud, 1917). Excessive proneness to self-blaming emotions, such as guilt (Ghatavi et al., 2002, Green et al., 2013) and shame (Thompson and Berenbaum, 2006), occurs in episodes of major depressive disorder (MDD) and in remission. This suggests that proneness to self-blame may be a trait mechanism of continuing vulnerability to depression. Whilst standard clinical assessments do not examine shame and do not distinguish guilt from shame (First et al., 2002a), social psychologists identify distinct cognitive components (Tangney et al., 2007b). Shame entails the imagination of how others perceive oneself (Gilbert et al., 2009b, Higgins, 1987b), whereas guilt depends on internal moral evaluation (Higgins, 1987b). It is a matter of debate, however, whether people with MDD can distinguish between guilt and shame and which components are captured by currently employed self-report measures (Tangney et al., 2007b) (Green et al., 2013, O'Connor et al., 2000b, O'Connor et al., 2002). Differential neural responses to different basic emotion categories such as sadness and fear have been observed in MDD, consistent with different pathophysiological roles for these emotions (Elliott et al., 2010). Using the same approach to moral emotions, showing distinct neural activation patterns associated with shame and guilt in MDD would provide key evidence for their different pathophysiological roles. This would have important clinical implications by highlighting the need to refine future clinical assessments of self-blaming emotions in order to improve the accuracy of diagnostic criteria.
A deeper understanding of the role of different self-blaming feelings in the psychopathology of MDD requires the consideration of their distinctive qualities and social functions as outlined in a previous paper (Green et al., 2013). Shame has been shown to involve feeling that one has been lowered in the esteem of others (Higgins, 1987a), is related to external comparison and competition (Gilbert et al., 2009a) and its characterological nature is thought to make it particularly maladaptive. In contrast, guilt has been linked with failing to live up to internalized moral duties (Higgins, 1987a). Proneness to self-blaming emotions has mostly been assessed using questionnaire measures aimed at the underlying emotions as hidden constructs by asking for the hypothesized behavioural consequence of the emotion (e.g. hiding/withdrawal for shame and reparative action for guilt) rather than probing participants’ subjective intuitions about these emotions which clinical descriptions rely on. This was based on the assumption that people are not able to distinguish emotions such as shame or guilt well (Tangney et al., 2007b). Recent work on the neural basis of moral emotions (Moll et al., 2005b), however, has shown that participants exhibit distinctive neural signatures to be associated with stimuli subjectively reported as evocative of a particular moral emotion (Zahn et al., 2009c, Green et al., 2010a). This is in keeping with anthropological evidence of transcultural ubiquity of distinct moral emotions (Fessler, 1999) that must rely on transculturally stable conceptual underpinnings (Moll et al., 2008a).

The subjective experience of guilt in healthy control groups has most consistently been associated with fMRI activation of medial frontopolar (Zahn et al., 2009b, Moll et al., 2007b, Morey et al., 2012a, Basile et al., 2011b, Takahashi et al., 2004, Kedia et al., 2008b) and septal-subgenual cingulate areas (Morey et al., 2012a, Basile et al., 2011b, Zahn et al., 2009a, Zahn et al., 2009b). The evidence on neural signatures of shame in healthy populations is scarce. The
only fMRI study using stringent statistical methods, was unable to identify shame-selective brain activations when comparing with guilt (Wagner et al., 2011). Other fMRI studies have investigated embarrassment (Moll et al., 2007b, Takahashi et al., 2004), an emotion primarily directed at preserving one’s own social reputation rather than blaming oneself for failure as entailed in shame (Zahn et al., 2011). Evidence from social psychological research suggests that both embarrassment and shame involve imagining an observer, whereas guilt does not (Zahn et al., 2011). Mental imagery is known to activate brain areas involved in sensory perception (Kosslyn et al., 1993, Kosslyn, 2005). Embarrassment was indeed associated with heightened activation in areas linked to sensory perception, such as the visual cortex, when compared with guilt in one study (Takahashi et al., 2004). Interestingly, imagined intentional violations of social norms elicited amygdala responses in one study, but it was not measured whether people felt guilt or shame (Berthoz et al., 2006).

To our knowledge, the only neuroimaging study of self-blaming emotions in MDD found normal Blood-Oxygenation-Level-Dependent (BOLD) effects in fronto-limbic regions in people remitted from symptoms (Green et al., 2012b). This study modeled trials that were most strongly associated with guilt. Shame-associated trials, however, were not modeled and it is thus unknown whether the fMRI responses to shame were distinctly altered in MDD.

Here, we used fMRI in order to investigate whether there are distinctive neural signatures of shame relative to guilt in people with MDD remitted from symptoms. By choosing a carefully matched control group with no personal or family history of MDD, group differences, if there are any, can be interpreted as associated with trait vulnerability factors for MDD (Bhagwagar and Cowen, 2008). A few other studies also suggest that group differences found during the remission stage would be related to biological trait markers for depression vulnerability (Schiller...
et al., 2013, Dichter et al., 2012, Nixon et al., 2013, Elliott et al., 2012) considering that remitted individuals have increased susceptibility to experience another major depressive episode compared with the rest of the general population (Eaton et al., 2008). Furthermore, by studying people with remitted MDD, we were able to equate the levels of distress and emotional intensity linked to shame and guilt-related stimuli presented during fMRI between groups.

We hypothesized (i) that the neural response to shame could be distinguished from that to guilt within the fronto-temporo-limbic networks previously associated with moral emotions (Moll et al., 2008b, Moll et al., 2005a), and (ii) that people with MDD would show heightened neural responses to shame compared with the control group. More specifically, we expected shame to activate regions linked to sensory perception of emotions more strongly than guilt. This is based on the prediction that shame entails mental imagery of critical observers, whereas guilt is experienced in the absence of imagined external observers and thus less dependent on external perceptual systems (Zahn et al., 2011). Further, there is solid evidence in the non-social visual imagery literature, that mental imagery activates areas representing sensory experiences (Kosslyn, 2005, Kosslyn et al., 1993). It is thus reasonable to assume that social mental imagery involves brain regions linked to perception of external stimuli of social relevance. The amygdala is one of the key regions involved in the perception of emotionally and socially relevant stimuli, such as facial expressions (Tamietto and de Gelder, 2010, Nummenmaa and Calder, 2009, Pessoa and Adolphs, 2010, Costafreda et al., 2008). The amygdala has not been found to be activated for guilt (Zahn et al., 2009b, Zahn et al., 2009a, Basile et al., 2011b, Wagner et al., 2011). Whilst there are several interpretations for this absence of guilt-related activation, one possible explanation is that guilt does not involve a great degree of external sensory perceptual simulation because it does not require simulating external observers (Zahn et al., 2011).
compared with shame. We therefore hypothesized that shame would be associated with stronger amygdala responses relative to guilt.

Based on the importance of a visuo-spatial mental model when simulating an observer as entailed in shame (Zahn et al., 2011), but not guilt, we expected the right temporo-parietal junction to show distinctive activation for shame relative to guilt. This was based on its activation in social cognition tasks that require visuo-spatial perspective taking (Decety and Grèzes, 2006). We further expected the posterior superior temporal sulcus to be more activated for shame relative to guilt, given the solid evidence of its involvement in the perception of socially relevant cues such as biological motion (Nummenmaa and Calder, 2009, Allison et al., 2000) which could play an important part in mental models of critical observers.

Material and Methods

Participants

Ethics statement: This study was approved by the South Manchester NHS Research Ethics Committee. Participants were part of a larger clinical research project and recruited using online and print advertisements. Initial suitability was assessed with a phone pre-screening interview (described in (Green et al., 2012b)). Informed consent was obtained from all participants (oral for pre-screening and written for subsequent stages).

Inclusion/exclusion of participants: Participants were invited for a clinical interview in which psychiatric, medical and family history were assessed along with a neurological exam which was carried out by a board-certified psychiatrist (RZ). Furthermore, a Structured Clinical Interview for DSM-IV-TR (SCID-I) Mood Disorders Module A and the International Neuropsychiatric
Interview which was adapted to allow assessment of lifetime axis-I disorders including substance and alcohol abuse, a shortened version of the Weissman Family History Screen, the Montgomery Asberg Depression Rating Scale (MADRS) and the Global Assessment of Functioning (GAF) scale (Axis V, DSM-IV) were employed.

Participants in the MDD group fulfilled criteria for a past major depressive episode according to Diagnostic and Statistical Manual IV-TR (American-Psychiatric-Association, 2000), and for a moderate to severe depressive episode according to the International Classification of Diseases-10 with at least 2 months duration requiring treatment and remission of symptoms for at least 12 months. Exclusion criteria were current axis-I disorders and a history of alcohol or substance abuse or past co-morbid axis-I disorders being the likely primary cause of the depressive syndrome. The healthy control group had no current or past axis-I disorders and no first degree family history of MDD, bipolar disorder, or schizophrenia.

Twenty eight participants were confirmed as remitted MDD underwent MRI. MRI data from 21/28 scanned participants from the MDD group could be included in the analysis (N=2 were excluded because of head movement greater than 4 mm, 1 because of selecting more than one moral emotion in more than 5% of trials, 4 were excluded because they had less than 6% guilt or shame responses in one of the fMRI runs, our cut-off point for participant inclusion). All 30 participants seen on the first study day who had fulfilled phone pre-screening criteria for the healthy control group were confirmed as fulfilling inclusion and exclusion criteria on clinical assessments and were invited for MRI scanning, however, 1 was not scanned because not being reachable following the first study session, leaving 29 that were scanned. Data from 18/29 scanned control participants could be included in the final analysis (data from N=1 was excluded because of selection of more than one feeling on more than 5% of trials, N=1 due to
abnormalities of small vessels on the MRI scan, N=1 due to head movement greater than 4 mm, N=2 because of signal dropouts in important ROIs: frontopolar, ventral frontal cortex and ATL, N=6 because of less than 6% guilt or shame trials in one of the fMRI runs).

In total, 18 healthy control participants and 21 individuals with remitted MDD (15 with no current antidepressant medication) were included in the final analysis. All participants had normal or corrected-to-normal vision.

Functional connectivity analyses related to guilt (Green et al., 2012b) and behavioral data (Green et al., 2013) have been previously reported. fMRI data related to shame were modeled and reported in this paper for the first time.

*fMRI paradigm*

Any trial in the task started with a jitter, on average lasting for 4000 ms (ranging from 2000 ms to 6000 ms in 500 ms steps). After the jitter, participants were presented with written statements describing actions counter to social and moral values described by social concepts (e.g., ‘stingy’, ‘boastful’) in which the agent was either the participant (“self-agency” condition, N=90) or their best friend (“other-agency” condition, N=90, norms for the stimuli are further described in (Zahn et al., 2007, Zahn et al., 2009b) and a full list of stimuli is available on request). Self- and other-agency conditions used the same social concepts (self-agency: e.g., “[participant's name] does act stingily towards [best friend's name]”, other-agency: e.g., “[best friend's name] does act stingily towards [participant's name]”). 50% of trials used negative social concepts (e.g., ‘does act stingily’) and 50% used negated positive social concepts (e.g., ‘does not act generously’). In addition we used a low-level resting-state baseline condition: fixation of visual pattern with no button press (N=90). Stimuli were presented in an event-related design for a maximum of 5000
ms within which participants had to make a decision whether they would feel “extremely unpleasant” or “mildly unpleasant” from their own perspective.

After the scanning session, the same list of hypothetical scenarios were presented to the participants on a laptop computer and this time they were asked to rate the unpleasantness of each action (7-step scale visual analogue Likert scale) in order to control for the degree of negative valence and emotional intensity. Furthermore, participants were required to “choose the feeling that (they) would feel most strongly” from a list of: guilt, contempt/disgust towards self, shame, indignation/anger towards self, indignation/anger towards other, contempt/disgust towards other, none, other feeling. After the off-line emotion ratings, this dataset is paired with the in-scanner ratings on item by item bases for fMRI modelling. As in our previous studies (Zahn et al., 2009b, Green et al., 2010b), guilt and shame trials for the fMRI analysis were defined by individual ratings and they were restricted to agency-role-congruent responses (i.e. guilt and shame in the self-agency condition). This was because agency-role-incongruent responses occurred relatively rarely and may not be directly comparable with agency-role-congruent feelings. For example, feeling guilty for something one’s best friend has done would be mostly maladaptive and we wanted to restrict our analyses to adaptive “healthy” experiences of guilt in order to allow for a direct comparison of control and MDD group without confounding differences in the subjective experience. Likewise, only shame responses in the self-agency condition were modeled.

*Image acquisition*

Echo-planar T2*-weighted images (405 volumes in each of the 3 runs with 5 dummy scans for each run of 13 min 40sec) were acquired on a Philips 3 Tesla Achieva MRI scanner with an 8
channel coil, 3 mm slice thickness and ascending continuous acquisition parallel to the anterior to posterior commissural line (between 35 and 40 slices depending on size of the participant’s head, Repetition Time (TR)=2000 ms, Echo Time (TE)=20.5 ms, Field of View (FOV)=220x220x120 mm, acquisition matrix=80x80, reconstructed voxel size=2.29x2.29x3 mm, SENSE factor=2). In addition 3-dimensional T1-weighted Magnetization-Prepared Rapid Acquisition Gradient Echo structural images were obtained (reconstructed voxel size=1 mm3, 128 slices, TE=3.9 ms, FOV=256x256x128, acquisition matrix=256x164, slice thickness=1 mm, TR=9.4 ms). Axial T2-weighted structural images were acquired for each participant to rule out vascular and inflammatory abnormalities.

fMRI modelling and analysis

Behavioural and supporting data analyses were performed using a significance threshold of p=.05, 2-sided (SPSS16, www.spss.com). Functional images were realigned, unwarped and coregistered to the subject’s T1 images. These images were normalized by first normalizing the participant’s T1 image to the standard T1-template in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) and applying the same transformations to the functional images. A smoothing kernel of FWHM=6 mm was used.

There were three regressors in the model: trials for negative self agency (SA), negative other agency (OA) and the fixation pattern. The event related fMRI modelling considered the emotion rating onset times of these conditions. The trials in which participants selected guilt or shame were used as parametric modulators for the SA condition, where as indignation trials were used as parametric modulators for the OA condition.
At the first (individual) level we contrasted shame vs. guilt and each of the moral emotions vs. fixation. At the second level, we used shame vs. guilt contrast images in two different models. Using a two-sample t-test in our first model we compared the groups. Using a one-sample t-test in our second model, we aimed at detecting differences between conditions that were consistent across groups, by modeling group as a covariate of no interest. In secondary data analyses based on the peak-voxels of the whole brain models (using a 1.5 mm radius around the peak voxel in MarsBar version 0.43, http://marsbar.sourceforge.net/(Brett et al., 2002)), we confirmed that the detected regions did survive when comparing moral emotions vs. the low-level fixation baseline allowing us to infer increased activation for the moral emotion of interest rather than deactivation in the subtracted control emotion. We also ensured that observed effects were not driven by the subgroup taking medication. We further separated the groups and carried out supporting one-sample t-tests in order to examine whether group differences arose from activations for shame vs. guilt in one group or guilt vs. shame in the other.

Whole brain results were first explored at a voxel-level threshold of $p=.005$ uncorrected, 4 voxels. Only areas are reported that survived additional voxel- or cluster-level Family-Wise-Error (FWE)-corrected thresholds of $p=.05$ across a priori ROIs (as detailed below, small volume correction) or the whole brain. Supporting data analyses in each group used an FWE-corrected threshold of $p=.10$. A grey matter mask based on brains of all participants was used as an inclusive mask in all analyses (Green et al., 2012b).

*Region of Interest (ROI) definition*

Bilateral a priori ROIs used are further described in (Green et al., 2010b, Green et al., 2012b). We restricted the analysis to regions which were previously shown to be specifically related to
guilt (ventromedial PFC including the septal/subgenual cingulate region and frontopolar cortex (BA 10, see eMethods section at http://archpsyc.jamanetwork.com/article.aspx?articleid=1171078, for further details on ROI construction) or which we hypothesized to be specific for shame (posterior superior temporal sulcus/temporo-parietal junction ROI and amygdala ROI). In order to show the specificity of our findings we also included control regions involved in moral emotions more generally (Moll et al., 2005a, Moll et al., 2008b): dorsolateral PFC, insula, basal ganglia, hypothalamus, ventral tegmental area, anterior temporal lobes and the medial temporal lobes highlighted in cortico-limbic network models of MDD (Seminowicz et al., 2004).

**Results**

**Participants**

The summary of clinical characteristics of the remitted MDD group is available in Table 1. The groups were matched on age, gender and years of education (see Table 2 for basic demographic information). Both groups had MADRS scores that were well below the cut-off for depression (<10), but the remitted MDD group showed slightly higher scores. Both groups had GAF scores indicating minimal or absent symptoms (>80), although the control participants had significantly higher scores.
Table 1 Clinical characteristics of remitted MDD group (N=21)

<table>
<thead>
<tr>
<th>Past MDD subtype</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>With melancholic features</td>
<td>11/21</td>
</tr>
<tr>
<td>With melancholic &amp; psychotic features</td>
<td>1/21</td>
</tr>
<tr>
<td>No specific subtype</td>
<td>9/21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of previous MDEs</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13/21</td>
</tr>
<tr>
<td>2</td>
<td>5/21</td>
</tr>
<tr>
<td>3</td>
<td>3/21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Last MDE details</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Average length of MDE (months)</td>
<td>17.4 ± 20.2 (range: 3-96)</td>
</tr>
<tr>
<td>Average time in remission (months)</td>
<td>20.4 ± 17 (range: 12-84)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antidepressant medication at time of study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI/SNRI antidepressant</td>
<td>6/21</td>
</tr>
<tr>
<td>None</td>
<td>15/21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous medication in subgroup with no medication</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI/SNRI antidepressant</td>
<td>10/15</td>
</tr>
<tr>
<td>SNRI and tricyclic combination</td>
<td>1/15</td>
</tr>
<tr>
<td>No antidepressant medication</td>
<td>4/15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Life-time axis-I co-morbidity*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa</td>
<td>2/21</td>
</tr>
<tr>
<td>Anorexia nervosa, binge-eating subtype</td>
<td>1/21</td>
</tr>
<tr>
<td>Anorexia nervosa and bulimia nervosa</td>
<td>1/21</td>
</tr>
<tr>
<td>No life-time co-morbidity</td>
<td>17/21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree relative with MDD (diagnosed)</td>
<td>15/21</td>
</tr>
<tr>
<td>First degree relative with MDD (questionable)</td>
<td>2/21</td>
</tr>
<tr>
<td>Distant relative MDD</td>
<td>1/21</td>
</tr>
<tr>
<td>No family member with history of MDD</td>
<td>3/21</td>
</tr>
</tbody>
</table>

* All co-morbid disorders were fully remitted at time of study. None of the co-morbid disorders was a likely primary cause of the depressive episodes. SSRI=selective serotonin reuptake inhibitor, SNRI=serotonin norepinephrine reuptake inhibitor. MDD subtype classification was based on adapting the SCID-I for DSMIV-TR to allow lifetime assessment of the subtypes. All medication-free participants had stopped medication well before the required washout phase.
Table 2  Group comparison on demographic and basic clinical variables

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Remitted MDD</th>
<th>Test statistic</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>22.8± 3.0</td>
<td>25.7±7.8</td>
<td>t=-1.60</td>
<td>.12</td>
</tr>
<tr>
<td>Education</td>
<td>15.6±1.7</td>
<td>16.1± 1.9</td>
<td>t=-.85</td>
<td>.40</td>
</tr>
<tr>
<td>Gender</td>
<td>15</td>
<td>Female</td>
<td>CC=.04</td>
<td>.85</td>
</tr>
<tr>
<td>MADRS</td>
<td>2±7</td>
<td>1.1±1.8</td>
<td>U= 144</td>
<td>.09</td>
</tr>
<tr>
<td>GAF</td>
<td>89.4±4.3</td>
<td>83.7± 7.2</td>
<td>U = 97.5</td>
<td>.005*</td>
</tr>
</tbody>
</table>

CC=contingency coefficient, *=significant at p=.05 threshold, 2-tailed, control: N= 18, remitted MDD: N=21, U=Mann-Whitney-U. A similar table has been reported in (Green et al., 2012b).

**Behavioural results**

There were no differences between groups in the percentages of trials rated as guilt- or shame-evoking and no between-group differences on unpleasantness ratings or response times for guilt or shame trials (see Table 3).

Table 3  Summaries of moral emotion ratings and response times

<table>
<thead>
<tr>
<th></th>
<th>Control mean ±SD</th>
<th>Remitted MDD mean ±SD</th>
<th>t-values</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>guilt (self-agency)</td>
<td>29.1±10.5</td>
<td>27.5±8.9</td>
<td>.50</td>
<td>.61</td>
</tr>
<tr>
<td>shame (self-agency)</td>
<td>21±10.8</td>
<td>15.7±10.2</td>
<td>1.5</td>
<td>.13</td>
</tr>
<tr>
<td><strong>Rated unpleasantness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>guilt trials</td>
<td>4.5±.8</td>
<td>4.3±.6</td>
<td>1.15</td>
<td>.25</td>
</tr>
<tr>
<td>shame trials</td>
<td>4.4±1.1</td>
<td>4.5±.7</td>
<td>-35</td>
<td>.72</td>
</tr>
<tr>
<td><strong>Response times (ms)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>guilt trials</td>
<td>2317±572</td>
<td>2223±426</td>
<td>.57</td>
<td>.57</td>
</tr>
<tr>
<td>shame trials</td>
<td>2294±558</td>
<td>2111±414</td>
<td>1.15</td>
<td>.26</td>
</tr>
</tbody>
</table>

Summaries of between-group differences at p=.05, two-sided (MDD group: N=21, control group: N= 18). Unpleasantness ratings were obtained on a 7-step visual analogue Likert scales (range 1 to 7). Ratings for guilt trials were reported previously (Green et al., 2012b).
There were also no differences between groups on the percentage of “very unpleasant” response button choices during the fMRI scan (Control: 51.2±17.5%; MDD: 50.7±24.5%; t[37]=.07, p=.95).

Social behaviours in the negative self-agency condition that were described by negative concepts (e.g. “stingy”) were rated as more unpleasant and were more frequently associated with shame compared with those described by negated positive concepts (e.g. “not generous”) across both groups with no effect of group. This was tested using a repeated measures general linear model revealing a main effect of negation of concept on unpleasantness (F[1,37]=188.7, p<.0001) and shame (F[1,37]=11.5, p=.002) with no group by negation of concept interaction for unpleasantness (F[1,37]=.5, p=.50) or shame (F[1,37]=.2, p=.70). In contrast there were no differences in associated guilt for negated positive and negative concepts (main effect of negation of concept: F[1,37]=2.0, p=.16; group by negation of concept interaction: F[1,37]<.0, p=.97).

fMRI results

The summary of all fMRI activations are listed in Table 4.
### Table 4 BOLD fMRI results

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hemisphere</th>
<th>Region</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>t-value</th>
<th>FWE-corr. p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>in controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>shame &gt; guilt</td>
<td>R/L</td>
<td>subgenual/medial orbitofrontal cortex</td>
<td>0</td>
<td>26</td>
<td>-12</td>
<td>5.3</td>
<td>.02 c,1</td>
</tr>
<tr>
<td>guilt &gt; shame</td>
<td>-</td>
<td>no significant regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>in MDD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>shame &gt; guilt</td>
<td>R</td>
<td>amygdala</td>
<td>22</td>
<td>-4</td>
<td>-16</td>
<td>3.8</td>
<td>.06 c,1</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>posterior insula</td>
<td>46</td>
<td>2</td>
<td>4</td>
<td>4.9</td>
<td>.07 c,2</td>
</tr>
<tr>
<td>guilt &gt; shame</td>
<td>-</td>
<td>no significant regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MDD vs. Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>shame &gt; guilt</td>
<td>R</td>
<td>amygdala</td>
<td>24</td>
<td>-4</td>
<td>-18</td>
<td>3.7</td>
<td>.05 c,1</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>posterior insula</td>
<td>40</td>
<td>-16</td>
<td>0</td>
<td>4.0</td>
<td>.02 c,2</td>
</tr>
<tr>
<td>guilt &gt; shame</td>
<td>-</td>
<td>no significant regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control vs. MDD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA&gt; OA</td>
<td>L</td>
<td>temporoparietal junction</td>
<td>-42</td>
<td>-58</td>
<td>20</td>
<td>3.8</td>
<td>.03 c,1</td>
</tr>
<tr>
<td>OA&gt; SA</td>
<td>-</td>
<td>no significant regions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Only regions are reported that survived voxel- or cluster-based FWE-corrected p=.05 over the whole brain or our a priori ROIs. c=cluster-based FWE-correction. 1=ROI with strong a priori predictions. 2=Control ROI with weak a priori predictions. Control group: N= 18, remitted MDD group: N= 21.

**In healthy participants**

There was a significant activation detected in subgenual cingulate/medial orbitofrontal cortex whilst participants processed shame relative to guilt evoking scripts (see Table 4).

**In remitted MDD**

Shame relative to guilt activated the right amygdala and the right posterior insula in the remitted depression group at a more liberal statistical threshold (FWE-corrected p<0.1).

**Between-group comparisons**
When comparing shame vs. guilt, the MDD group showed greater activation within the right amygdala and right posterior insula than the control group (Table 4). This was confirmed by a supporting data analysis using the regression coefficients from the peak voxels in the amygdala (24, -4, -18) and posterior insula (40, -16, 0; see Figure 1). For both regions, there was a moral emotion by group interaction (amygdala: $F[1, 37] = 10.95, p = .002$; posterior insula: $F[1,37] = 13.54, p = .001$) and no main effect of moral emotion (amygdala: $F[1,37] = .601, p = .441$; posterior insula: $F[1,37] = .457, p = .50$) or group (amygdala: $F[1,37] = 48, p = .83$; posterior insula: $F[1,37] = 1.52, p = .23$). The increased shame-response relative to guilt compared with the control group was also found in the remitted MDD subgroup not currently taking medication (amygdala: $p = .03, t[31] = 2.3$; posterior insula: $p = .001, t[31] = 3.7$).
Figure 1
The MDD group showed higher activation in the right amygdala (panel a) and right posterior insula (panel b) for shame versus guilt compared with the control group (displayed are whole brain maps at voxel-level p=.005 uncorrected and cluster size of 4 voxels).
We also explored the contrasts self-agency vs. other-agency and other-agency vs. self-agency in all participants, as well as between groups. There was only one comparison resulting in a significantly elevated activation in healthy participants which were driven by increases in the condition of interest rather than decreases from the fixation baseline as determined by extracted regression coefficients: The left temporo-parietal junction (x=-42, y=-58, z=20) showed higher activation for self-agency vs. other-agency in the control group compared with MDD (cluster-based FWE-corrected p=.03 over temporo-parietal junction ROI, Figure 2).

Figure 2. Temporoparietal junction activation for Self Agency> Other Agency contrast.

There were no other regions with higher activation in the healthy participants group relative to the remitted depression group.

**Discussion**

We confirmed our general hypothesis that people with MDD exhibited enhanced shame-selective activation in brain regions linked to the sensory perception of emotions. This was based on
evidence that shame, unlike guilt, requires an imagined critical observer (Higgins, 1987b, Gilbert et al., 2009b) and on previously shown activations of sensory areas when engaging in mental imagery (Kosslyn et al., 1993, Kosslyn, 2005). Our more specific predictions were only partly confirmed in that indeed the amygdala showed shame-selective activation in the MDD group, but that there was no difference within the posterior superior temporal or temporo-parietal region between shame and guilt. Instead, we found an unexpected shame-selective activation increase in the right posterior insula in the MDD compared with the control group. Whilst this was unexpected, these findings are in general agreement with our hypothesis that shame is associated with higher activations in regions linked to sensory perception of emotionally relevant stimuli.

Our finding of a shame-selective increase in amygdala-response concurs with the hypothesis of a distinctive role of shame in MDD relative to guilt. The amygdala plays a prominent role in neural models of MDD (Ressler and Mayberg, 2007, Seminowicz et al., 2004, Price and Drevets, 2010, Siegle et al., 2007). Metaanalytic reviews confirm that the amygdala is more responsive to sensory stimuli than to internally generated emotional responses (Costafreda et al., 2008). Amygdala activations were reliably associated with sensory perception of emotionally and socially relevant materials (Tamietto and de Gelder, 2010, Nummenmaa and Calder, 2009, Pessoa and Adolphs, 2010). The amygdala was also shown to be activated when simulating the pain experiences of another person based on images of facial expressions of pain (Lamm et al., 2007). Shame-selective amygdala responses are therefore in keeping with the notion that mental imagery requires simulated sensory perception (Kosslyn, 2005) and that shame depends more strongly on simulated perception by others than guilt (Zahn et al., 2011).

Increased amygdala activations were reproducibly found in people with current MDD when presented with negative emotional material (Groenewold et al., 2013, Hamilton et al., 2012).
Some studies found increased amygdala responses to sad faces to be present in remitted MDD as well (Neumeister et al., 2006, Victor et al., 2010). A growing body of evidence, however, suggests normalization in amygdala response to facial expressions of emotions on remission (Norbury et al., 2010, Arnone et al., 2012a, Fu et al., 2004, Sheline et al., 2001), which in one study may have been related to the effects of antidepressant medication rather than remission itself (Victor et al., 2010). However, overall normal levels of amygdala activation could result from between-subject differences. One study showed, for example, that although amygdala activation was not elevated consistently in a group of remitted MDD, its activation predicted subsequent recall of negative self-referential memories (Ramel et al., 2007). By using random-effects models in our analyses, we demonstrated that shame-selective increases in amygdala activation were consistent across individuals with MDD compared with the control group. Our finding of increased amygdala-response to self-related negative emotions is also in keeping with the view that MDD is associated with neural changes related to increased negative self-focus (Grimm et al., 2009) involving the amygdala (Northoff, 2007).

Our finding that guilt did not activate the amygdala to significant degrees in either group is in keeping with the evidence derived from healthy control samples and MDD reviewed in the introduction. However, a recent fMRI study in healthy volunteers reported the amygdala to be activated for guilt compared with shame (Michl et al., 2012). A closer inspection of this finding reveals, however, that the peak of the large cluster of activation entailing the amygdala was located within the thalamus.

The posterior insula was not reported in metaanalyses of fMRI activation studies in MDD (Groenewold et al., 2013, Hamilton et al., 2012) (Delvecchio et al., 2012, Diener et al., 2012). However, there is evidence that posterior insular hypermetabolism predicts treatment response
(Nagai et al., 2007). Several lines of evidence suggest the posterior insula carries primary representations of emotionally relevant somato-sensory signals (Craig, 2002). It is specifically connected to sensory-motor cortices (Cauda et al., 2011) and is implicated in primary pain (Lamm et al., 2011), temperature and touch perception – particularly the perception of affiliative touch (Björnsdotter et al., 2009, Löken et al., 2009). Affiliative touch is one of the ontogenetically earliest ways of bonding with others (Sroufe and Waters, 1977) and shame entails the anticipated rejection of others (Tracy and Robins, 2006). Shame scenarios also engage posterior insula in MDD is thus compatible with the hypothesis that shame-proneness is related to sensory experiences when simulating an external observer (Zahn et al., 2011).

Except for a non-predicted activation increase in the temporo-parietal junction for self-agency vs. other-agency in the control group compared with MDD, there were no significant group differences for this contrast. This is in concordance with our previously reported BOLD results for guilt vs. indignation/anger towards others (Green et al., 2012b).

On a more cautionary note, shame-selective increases in amygdala and posterior insula response could be linked to different types of vulnerability traits for MDD. One possibility is that they are due to scarring effects of previous episodes (Wichers et al., 2010). Another possibility is that they are associated with primary vulnerability before the onset of MDD. Studies in high-risk groups, such as people with a family history but without a previous personal history of MDD may help in distinguishing primary from secondary vulnerability. Furthermore, our finding regarding the posterior insula needs confirmation because it was based on a control ROI with weak a priori rather than one of our ROIs with strong a priori predictions. Because of the variability in shame-proneness, there were some participants with a low number of trials available for analysis potentially limiting the statistical power to detect effects. The
reported group differences, however, cannot be explained on this basis, as the groups did not differ on the number of shame trials. One could argue that differences in how the groups remembered their emotional response during the scan could have affected their post-scan ratings. It is unlikely, however, that a bias in remembering emotional responses would affect guilt and shame in systematically different ways.

Further, some clinical characteristics of our MDD group need further consideration. Although, the majority of patients in our MDD group had only experienced one previous episode, they nevertheless had a largely increased life-time risk of developing another episode compared with the control group (50% (Eaton et al., 2008b) vs. 15%). This study was deliberately designed to exclude patients with MDD and relevant other axis-I disorders. Therefore our results may not be generalizable to patients with MDD and co-morbid other axis-I disorders.

We opened this paper with a quote by Jean-Jacques Rousseau. From a philosophical perspective, the quote illustrates the extent to which guilt and shame are intertwined emotions. From a medical perspective, Rousseau argues that under certain circumstances guilt may share some of the physiological reactions (i.e. blushing) which are purported to accompany feelings of shame. Despite the large overlap between guilt and shame as suggested by Rousseau, our study found that limbic brain regions distinguish between them.

Conclusion

We demonstrated that people with MDD exhibited an increased response to shame within the right amygdala and posterior insula, when compared with the control group. This increased shame response was selective relative to guilt. The results were not due to differences in perceived emotional intensity between the groups. Further, group differences were not due to effects of antidepressant medication. This supports the hypothesis that shame and guilt play
distinct roles in vulnerability to MDD. Future studies are needed to directly compare shame-induction with facial emotion recognition paradigms. Our results indicate that shame-induction may be a more powerful probe of residual amygdala hypersensitivity in MDD after symptoms have subsided. This has important implications for designing imaging biomarkers of recurrence risk in MDD.

Acknowledgements

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References

Fu CHY, Williams SCR, Cleare AJ, Brammer MJ, Walsh ND et al. (2004) Attenuation of the Neural Response to Sad Faces in Major Depression by Antidepressant Treatment: A


General discussion of the Ph.D. results:

In these Ph.D. experiments, I conducted a series of neuroimaging and neuroeconomical studies in order to provide a comprehensive understanding of altruism-related social-economical decision making in MDD and the extent to which self blaming moral emotions influence them. Relying primarily on neuroeconomical paradigms to probe real life decision making mechanisms, I investigated different dimensions of social and financial reward processing in MDD. Doing so, I believe that the present results provided novel lines of evidence for: (i) abnormal financial reward processing over time in a community sample of young adult patients with unipolar MDD; (ii) fundamental interpersonal decision making parameters related to altruism; (iii) neural correlates of these decisions in key regions associated with depression pathophysiology and the contribution of social rewards to abnormal reward processing; (iv) selective activity in neural networks associated with shame responses in MDD even during remission.

Temporal discounting is a reward valuation process common to both humans and members of the animal kingdom (Rosati et al., 2007), guiding the way individuals shape their behaviour strategy to acquire primary or secondary rewards. In repeated interpersonal interactions, cooperative strategies may be associated with lower discounting rates as they require forgoing immediate gains of larger magnitude for sustained cooperation, whereas defecting strategies may be conceptualised as being opportunistitic and therefore associated with higher discounting rates (Stevens and Hauser, 2004). Stevens and Hauser (2004) suggested that temporal discounting is sensitive to environmental changes (also in (Li et al., 2012)) and they listed abnormal temporal discounting among the key psychological constraints on evolution of cooperation. Here, I demonstrated that temporal discounting rates are higher in patients with current depression.
particularly for rewards presented at longer delays in a hypothetical version of a commonly used monetary choice task (Kirby et al., 1999). More specifically, I showed that depression impairs reward valuation for reward sizes presented at increasing delays, such that patients with current MDD discount medium to large sized rewards almost identically, resulting in a plateau of the discounting curve relative to both healthy participants and remitted patients. Although one may assume that tasks using real currency would produce more robust results, these findings would gain validity if replicated by studies using tasks with real currency. I showed that symptoms of depression, specifically hopelessness and impairments in general psychosocial functioning, correlated with temporal discounting rates, confirming the prediction that was based on Beck’s cognitive triad (i.e. negative view of the future). I argued that higher temporal discounting rates in current MDD may be associated with elevated cost per time unit perception, driven by experiencing delays longer than they actually are (Wittmann and Paulus, 2008, Bschor et al., 2004). As suggested in the chapter dedicated to temporal discounting behaviour, this issue may be further explored using monetary choice tasks in which the reward magnitude and delays vary independently.

Abnormal reward processing in MDD can be investigated further. One possible direction may be investigating reward processing in relation to quantifiable physical costs, such as glucose metabolism over whole brain in PET imaging, changes in blood glucose levels from pre-to-post task completion, and investigating the reflection of such bodily costs in daily living by using calorie consumption measurements like doubly-labeled water (Schoeller et al., 1990). These interdisciplinary approaches may help scientists understand abnormal reward processing in major depression more comprehensively and establish distinct reward and cost per time unit parameters.
Secondly, temporal discounting rates may be important in identifying suitable treatment methods (e.g., two extremes: immediate psychotropic treatments versus psychotherapeutic interventions with long waiting lists) for different profile of patients. When one conceptualizes successful recovery from depression as a delayed reward, one would predict that more severely symptomatic patients will discount the possibility of obtaining means to a successful treatment significantly higher when these are presented at longer delays. Long waiting lists for seeing specialists for treatment, is one of the key issues in the NHS system which is often criticised. However, in order to test this prediction effectively, modified temporal discounting tasks need to be designed carefully which involve removing unpleasant stimuli presented in variable degrees (which is also rewarding; as representing negative experiences associated with depression) and at variable delays (as representing how soon patients can be seen by specialists, or expect to achieve full recovery). Finally, Stevens and Hauser's (2004) made a theoretical suggestion that preferences for immediate rewards in temporal discounting tasks may interact with preferences for selfish decisions in interpersonal decision making paradigms. I did not have any a priori hypothesis about this possible interaction, nor were our selections of interpersonal decision making tasks optimised to explore this interaction. Consequently, I did not observe this relationship in my exploratory analyses, but future studies may explore these directions by using specifically tailored temporal discounting and interpersonal decision making tasks.

In the chapter investigating altruism we used four different neuroeconomical paradigms designed to probe different subtypes of altruistic behaviours. An overarching pattern emerged: patients with current depression were generally less cooperative, but also displayed less altruistic punishment towards unfair proposals. The results suggesting a lack of altruistic punishment in current MDD is also shown by two previous independent studies (Harle et al., 2010, Destoop et
al., 2012). I argued that subtle differences across these studies may be the result of paradigm specifications; such as using pictures of proposers versus scripts and/or clinical settings in which the research was conducted. The emotion rating results showed that lack of altruistic punishment behaviour may be related to a decrease in other-blaming emotions and an increase in self-blaming emotions. I argued that the ability to blame other individuals for their behavioural/moral transgressions is one of the key ingredients of altruistic punishment, which may be diminished in current depression. Anonymous, script based, paradigms such as the one which has been used here, may have a negative influence on altruistic punishment behaviour as it would be harder for the responders to associate unfair offers with unfair individuals whom they think should be punished. As with having higher temporal discounting rates, not engaging in altruistic punishment may also increase one's payoff at any time point in iterated interactions as punishing unfair individuals in the Ultimatum Game (UG) require sacrificing provisional resources. When evaluating the financial success of individuals within a population of responders from a behavioural-economical perspective, both of these different decision making parameters suggest that during the symptomatic phase, major depression may be associated with a higher payoff decision making strategy. The rational actor model (Gintis et al., 2008), posits that decisions aimed to maximise utility require balancing the costs of emotional decisions. For example in the UG, if one's decision to punish is driven by anger/indignation, it would mean that the acute emotion drives an individual to a costly outcome (i.e. sacrificing provisional gains). This perspective suggests that in interpersonal bargaining paradigms, if one can control the influence of other-blaming emotions, one is more likely to maximise utility. However, here we showed that elevated self-blame in MDD may also produce a similar utility maximising outcome through a different network of emotions. Mainstream economical theory considers the impact of
emotions on interpersonal bargaining. However, it is possible that the impact of clinically significant levels of self-blaming emotions are not well conceptualised within the present economical framework. This may be because clinically significant levels of self-blame are less prevalent in the population and maladaptive (e.g., blaming oneself for being treated unfairly); defining one of the core symptoms of major depression. On the other hand, if one is to design computerised behaviour strategies based on real-life parameters using evolutionary game theory, the environment in which each computerised strategy lives would determine its evolutionary fitness. In a hostile environment consisting of more defectors, the strategy associated with major depression would suffer as it would not punish them effectively, whereas in an environment with high frequency of altruistic punishers, depression would suffer from altruistic punishment as it is defined by a higher defection rate relative to the behaviour displayed by healthy participants. These issues may be further investigated by using computerised simulations to understand the evolutionary dynamics of the behavioural strategy associated with major depressive disorder relative to phenotypes defining vulnerability and healthy individuals.

The comparison that I made above suggests that there is a difference between behavioural-economical perspectives and evolutionary game theory for predicting fitness based on altruistic punishment behaviour. This discrepancy raises questions about whether UG is an ecologically valid experimental probe of altruistic punishment, despite its widespread use in social-economical research. This is because altruistic punishment in the UG is based on sacrificing provisional but not real resources. Future studies should explore whether paradigms using other forms of costly punishment behaviour (e.g., costly punishment condition in the charitable donations paradigm designed by Moll and colleagues (2006)) produce different results in clinical populations. However, I have to acknowledge that elevated self-blame limits the possibility of
showing elevated altruistic punishment, as patients would be less likely to make costly decisions when they think the other party is not responsible for the inequality of the distribution of stakes. Although groups may not be different at individual behavioural level, even the smallest difference in behaviour may lead to elevated differences between groups when there are enough number of iterations. This would mimic continuous interactions between individuals across generations with fitness consequences snowballing on the evolutionary timeframe.

I have shown significantly lower levels of altruism in the charitable donation experiment in patients with current depression regardless of the level of costs associated with different kinds of donation proposals. On the other hand, although not significantly higher, our remitted (i.e. vulnerability) group made more donations relative to healthy participants. A previous epidemiological study identified elevated donation behaviour as a risk factor for MDD onset (Fujiwara, 2009), and our findings seemed to provide some experimental support for this view. Showing significant reductions in donation behaviour in current depression suggests that patients may be avoiding this behaviour, which requires helping more proximal beneficiaries. However, it was not possible to provide a consistent framework of proximity to explain this behaviour, as the currently depressed group also defected more when interacting with individuals in the Prisoner's Dilemma, who were designed to act more compassionately like caregivers. I also investigated the impact of altruistic forms of guilt and shame on different kinds of altruistic behaviours separately in each group. The correlations suggested that there was a significant relationship between altruistic forms of guilt and costly forms of altruistic behaviours in healthy participants, but not in the depression groups. I argued that, although these emotions were elevated in the depression groups, there may be abnormalities in processing these emotions which diminished their altruism promoting impact. Taken together, these experimental results
challenge the guilt driven pathological hyper altruism hypothesis in MDD. Furthermore, I showed that characterological forms of shame (i.e. shame proneness) did not have any effect on altruistic behaviours in healthy participants as well as in the depression groups. As a limitation of the main neuropsychological testing, I have to point out that as with most of the psychiatric research studies, the present study was underpowered, such that it would need 159 participants to detect medium effects for One Way ANOVA (assuming equal group sizes; $f = 0.25$) with 80% sensitivity. This may be one of the reasons why some of the between-group comparisons in post-hoc tests remained only marginally significant.

In the first neuroimaging experiment, I investigated neural correlates of altruistic decisions by using a modified version of the experimental charitable donations paradigm. I aimed to address whether individuals with vulnerability to depression engaged in these behaviours more frequently because they experience higher reward related activations relative to healthy participants during altruistic decisions. Secondly, I aimed to understand whether significant reductions in donation behaviour in current depression may have neuronal correlates, as these altruistic decisions recruited key regions of depression pathophysiology such as subgenual cingulate and striatum (Harbaugh et al., 2007, Moll et al., 2006). Indeed, I showed hyperactivity in these regions in the remitted population when they made altruistic decisions relative to healthy participants. To the best of my knowledge, this is the first study to show elevated activity in the striatum for social reward processing in depression. These findings are important in understanding the neural basis of donation responses in MDD which have been shown to create risk for its first onset (Fujiwara, 2009). It is possible that remitted patients may be experiencing helping behaviours as more socially rewarding. Although this may appear to be conflicting with the mainstream idea suggesting that helping behaviours may be promoting well-being (Anik et
al., 2009), and the present behavioural results did not provide support for an increase in altruistic tendencies in people with vulnerability to depression (i.e. the patients in remission). Future clinical studies should investigate whether hyper altruistic decisions observed in some of the patients are driven by activations related to reward processing.

When retrospectively evaluating the design specifications of the experimental charitable donations task, I have to acknowledge its limitations. Two different types of control conditions were used in order to tease apart the impact of different kinds of proposal conditions on neural activity. The analyses using the regression coefficients extracted from the peak voxels showed that the activations due to different proposals were quite consistent against the low-level fixation as well as the high level neutral condition, which also contained a similar decision-making problem but with no financial consequences. However, I suggested that the higher level neutral condition may be intrinsically rewarding, as by responding to the offer within the stipulated time, participants avoided the penalty for slow responses, which was larger in financial magnitude than the pure reward in the reward condition. Although this specification allowed us to have more registered responses by forcing people to make a decision within the timeframe, I retrospectively considered that this may have masked striatal activations. Future studies may benefit from using purely visual stimuli for high-level baselines such as neutral pictures which may predominantly activate posterior/occipital regions, so that comparisons in social decision making contrasts may have less "noisy" activations in frontal and limbic regions.

In the second imaging study, neural responses to shame in patients with remitted MDD were investigated, to address whether a distinct profile of activations may be associated with vulnerability to depression. Previous studies in healthy participants did not produce conclusive results by showing somewhat overlapping functional neuroanatomy; in line with the social
psychology literature which suggests that people have limited ability to differentiate between guilt and shame (Tangney, 1996). The neuroimaging experiment tested the prediction that these emotions may have distinct functional neuroanatomy in populations that show significant elevations in these emotions (i.e. propensity to experience self-blame) such as patients with MDD; and such neural disturbances, if they exist, may be present even during periods of remission due to the scarring effect of previous major depressive episodes. My a priori hypotheses were based on the social psychology literature which suggested that experiencing shame requires imagining critical observers within a closed social environment. Therefore, I predicted that it should activate regions associated with spatial orientation and perspective taking such as temporoparietal junction (TPJ); somatosensory perceptions of social emotions and fight or flight responses such as the amygdala. Using hypothetical scenarios which involved imagining interactions with a close friend, I assumed that this design specification would probe affiliative feelings required for experiencing social/moral emotions effectively. In the scanner, participants rated the emotional valence of each scenario from negative to positive, whereas following the scanning session they independently selected a single emotion from an open list of emotions defining their experience of that scenario. Indeed, I showed that shame activated right amygdala selectively in our patient population. However, here I did not show significant activations in the TPJ selective for shame, against the a priori prediction. On the other hand, there was a significant activation in the right posterior insula for shame in the remitted MDD group. Although I did not have strong a priori hypotheses about the posterior insula, these findings complement its role in carrying primary representations of emotionally relevant somatosensory signals. Experiencing shame requires anticipated rejection of others; defining one extreme of the affective bonding continuum. Evidence from previous studies shows the involvement of posterior insula in
affective bonding. The present results raise the possibility that posterior insula carries somatosensory signals of emotionally relevant stimuli irrespective of their valence.

Despite, Jean Jacques Rousseau's philosophical claim that guilt and shame may share certain psychophysiological properties I showed here that they have distinct functional neuroanatomy in remitted depression. Future studies may use the present dual/separate rating paradigm with designs measuring skin conductance and skin colouration in order to address whether these intertwined self blaming moral emotions have overlapping psychophysiological properties as proposed by JJ Rousseau's hypothesis. This would potentially help researchers and clinicians understand the properties of these emotions in healthy participants and abnormalities associated with processing them in clinical disorders.

In this Ph.D., I aimed to study interpersonal decision making in patients with major depression comprehensively by using multiple methodologies, looking at subtypes of behaviours and by considering the influence of different emotions. Taken together, these findings suggested that understanding self-blame in depression is highly important and self-blame may limit certain types of altruism, such as altruistic punishment behaviours which are more frequently observed in healthy participants. If altruistic behaviours require long-term social strategy planning or imagining how an interpersonal relationship may be sustained over time, I argue that abnormal decision making observed in patients with MDD may be originating from changes in long-term social-economical strategies (i.e. elevated discounting rates). In my opinion, studying cost per time unit is widely neglected in depression research and this will be one of the key elements in understanding reward processing abnormalities observed in patients. The imaging studies suggested that shame has a distinct functional neuroanatomy even during remission, particularly in regions associated with somatosensory perceptions of social emotions; and regions involved in
triggering fight or flight responses from social threats, such as the amygdala. This result suggests that using descriptions of hypothetical social behaviour probe residual amygdala hypersensitivity in remitted MDD just as effectively as facial recognition tasks such as Ekman's, if not more. Similarly, I showed that altruistic decisions probed subgenual cingulate hypersensitivity more effectively than paradigms probing guilt responses in remitted depression (i.e. no BOLD differences were shown in subgenual cingulate for guilt responses (Green et al., 2012b)). I believe that replicating these findings particularly in patients with current depression will validate our findings as well as showing the full map of regions associated with abnormal neural responses which may be present in the symptomatic stage, but normalise upon remission of symptoms.

These studies suggest that understanding self-blame it is fundamental to understanding patients' social behaviour in different ways. Although there were no significant correlations between behavioural shame ratings (i.e. TOSCA) and any of the outcome measures in interpersonal decision making paradigms, the finding that remitted MDD patients showed a distinct neural response to shame suggests that these patients may have a tendency to experience social environments as more threatening with more critical elements than healthy participants. This would surely influence individual preferences and presumably diminish altruistic behaviour. We did not investigate manipulations of acute forms of shame, therefore it was not possible to address this issue within the scope of the present PhD experiments, but future studies should investigate how alterations in moral emotion processing lead to differences in interpersonal decision making. On the other hand, here I showed that guilt particularly influences interpersonal bargaining decisions, whereby patients with current depression accept less of the stake. This may have important implications in real life for those who suffer from MDD. However, it was not
possible to establish conclusively whether currently depressed patients accept unfair offers due to worthlessness or feel more guilt when they reject them (i.e. altruistic punishment); in line with the harm aversion hypothesis. This issue could only be addressed if future Ultimatum Game studies in MDD carry on investigating the role of self-blame in guiding interpersonal bargaining decisions. I think that neuroimaging studies will be particularly important in addressing these issues conclusively. Ideally, the neuroimaging studies that I presented here (as well as the temporal discounting experiment with neuroimaging) should be replicated in patients with current depression, so that we have a full understanding of what goes on in all of the cells of a 2x2 factorial design (i.e. Depression status: current versus remitted; moral emotions and decision-making). Only in that way one can fully understand which regions respond to treatment and which regions remain hypersensitive in everyday emotion processing and decision-making challenges. One possibility to tackle such research questions may be to conduct longitudinal studies, possibly investigating the impact of different treatment methods (i.e. psychopharmacological versus psychotherapeutical treatments). I think the paradigms that I used here (both emotion priming and social economical decision making) have the potential to be used in studies assessing the efficacy of different treatment methods, as they were sensitive enough to pick up some of the neuroimaging correlates of outstanding depression vulnerability. Finally, I would like to update the decision-making schema that I provided in the introduction section of this thesis as well as the brain mapping of the key regions in the light of these new evidence (Fig 1 A and B). I suggest that future studies should focus on components of the schema which do not have many connections with the other components or where the connections are interrupted.
Figure 1 (A) Social-economical decision making schema in MDD is updated based on the evidence from Ph.D. experiments. The solid lines indicate relationships which are stronger, whereas dashed lines indicate relationships which are either weak or purely theoretical. These findings reject pathological hyper altruism hypotheses in MDD. Schema suggests that characterological forms of self-blame did not have any influence on altruism in MDD. On the other hand, acute experiences of guilt negatively influenced altruistic punishment behaviour, therefore they led to selfish decisions from the perspective of the society (i.e. not punishing unfair individuals). In the light of showing distinct neural signatures for acute forms of shame even during periods of remission, I suggest that its influence on social decision making should be investigated further by using mood induction experiments. Finally, Ph.D. experiments suggested that patients with current MDD made significantly less amount of donations irrespective of their costs.
Throughout this thesis, I have argued that neuroeconomical paradigms have strong ecological validity and therefore they are important research tools to understand real life decision making mechanisms. However, using the designs presently available allow us to investigate only a single component of decision making at a time. It would be particularly important to use crossover designs which capture multiple elements of social-economical decision making in the same design, therefore increasing the ecological validity of these already well-established paradigms. I think only this way it will be possible to understand the interaction between abnormalities present in different components of the social-economical decision making system. I think the present Ph.D. results provide a fundamental background about why studying social economical decision making in depression (an area of research which I think is widely neglected) is important, advancing understanding about abnormalities which are prominent in current depression and those still remain as vulnerability features during periods of remission. I think the behavioural paradigms maybe important for clinical stratification of patient profiles with respect to psychosocial functioning, whereas their neuroimaging correlates would help determining the
most suitable treatment option for patients, which is tailored by taking the burdens associated with specific symptoms into account.
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Neurobiology of resilience to depression: a neuropsychological and neuroimaging investigation

INFORMATION SHEET FOR VOLUNTEERS (main study)
Version 04, 23 March 2011

We would like to invite you to take part in a study investigating the styles of thinking and brain changes that are related to resilience and vulnerability to clinical depression. The study has received a favourable opinion from the North West 9 Research Ethics Committee (Ref. 10/H1014/8). Please read the following information and take time to decide if you wish to take part.

How can this study help to understand depression?

We know that life stresses are an important factor in causing some people to become depressed. However we also know that some people experience considerable stress without becoming depressed; a trait called resilience. We want to study some of the factors involved in resilience and vulnerability to depression. We know that people who experience extremely high life-threatening stress (for example combat in war) but do not experience any post-traumatic stress disorder have some distinctive characteristics. These people have particular ways of tackling problems and a particularly positive or optimistic approach to emotional material. They also have distinct patterns of brain function and levels of stress hormones. We want to see whether people who are resilient to more everyday stresses have similar distinctive profiles, as well as exploring whether vulnerability to depression has particular features. This may help us develop types of therapy that can be offered to people who are at risk of becoming depressed due to stress in their lives.

Do I have to take part?
It is up to you to decide whether or not to take part. We will describe the study and go through this information sheet with you. We will then ask you to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving a reason. This will not influence any current or future clinical care.

What is involved in the study?

About 200 people will take part in this study. Some people will take computer tests (like computer games) and also have a brain scan, others will be doing the computer tests only.

The study involves coming into the University of Manchester for an interview to talk about your experiences of stress and depression. This may take 1 to 2 hours and you will be compensated for your time with a £10 high street voucher. If you are a suitable candidate for the main study, we will ask you (i) for a sample of saliva which will be used for DNA testing to look at certain genes that might be involved with resilience and vulnerability to depression; (ii) to do some computer tests that will give us information about how people react and think in particular ways (these are like puzzles or games on a computer, and will take about 2-3 hours); (iii) to fill-in some on-line questionnaires to assess your personality, these can be done either on the same visit as the interview, or in your own time afterwards; (iv) to provide some more saliva samples – one when you go to bed at night, and five the following morning (we will provide the tubes and detailed instructions). These samples will be used to measure cortisol, which is a natural stress hormone; the levels in the body are known to change when people become depressed so we want to see if there are any significant differences in cortisol levels with individuals who show resilience to depression. If you are participating only in this part of the study, that is the end of the procedure and we will compensate you for your time with an additional £15 high street voucher.

For people taking part in the scanning study as well, you will then be asked to have a brain scan. This involves lying still in a strong magnetic field and using computers to picture the brain and how it is working during certain tasks. The machine is noisy and you have to lie in quite a small tube so you can feel ‘closed in’. No radiation or x-rays are involved. The only known danger is with certain types of metallic objects, either in your body (like a pacemaker, surgical clips, metal implants) or carried with you. In order to check for this we will go through a confidential questionnaire before each examination that asks you about possible metal in your body. You will be asked to take leave anything metal (like jewellery or watches) outside the scanning room, and anything with a magnetic tape (credit card or audio tape) which can be wiped clean by the magnetic field. There are no known health dangers from being scanned.
During the scan we will ask you do some short computer tests. These will last about an hour in total. After the scan, we will talk to you about your experiences and answer any questions you may have. After the scan, you will be compensated for your time with a £25 high street voucher (in addition to the £10 and £15 for earlier involvement).

**Genetic testing and your DNA sample**

Many genes have been identified that might be involved in depression. We also ask your permission to use your DNA sample to look at common genes that might be involved in resilience and vulnerability. We will not be testing for rare genes that cause illnesses so we will not have information that is directly relevant to your health. If you wish, you can take part in the rest of the study but not in the genetic study; however, it would help us more if you joined in both parts of the research. For legal purposes, your DNA sample would be regarded as ‘gifted’ to us, which means that it becomes the property of the researchers and the University.

**Confidentiality**

All information collected during the course of the research will be kept strictly confidential. The same coded number will be used to identify all your results (including your DNA and any genotype data) and your personal details (name and address etc.) which will be kept securely and completely separately from all the rest of your results. If we need to link the results (including the genetic results) back to individuals this will only be done by members of the research team and no-one will be able to recognise you from any of your results or other information that you have provided which will be completely anonymised.

**Are there any risks and benefits in taking part?**

There have been no adverse effects reported from MRI scanning, although the scanner is noisy and some people find it claustrophobic. If you have suffered from claustrophobia, let the investigators know beforehand. You can stop the procedure at any time.

We ask you to agree that we notify your GP of your participation in the study, so we will need his or her name, and the address of the surgery. If any brain abnormality is detected we will inform you and your GP. Also if there is any other information we find out during the study that has important consequences, such as for your health, we will inform you and ask your permission to pass this on to your GP. If you don’t wish us to do so, we will do our utmost to respect your wishes and we will abide by the rules on confidentiality set out by the General Medical Council.
Are there any reasons why I can’t take part in the study?

You will not be able to take part in the study if:

You are under 30 or over 50 years of age

You have, or have had, some medical or psychiatric conditions other than depression. We will discuss your medical history with you to determine whether you can take part.

You are currently being treated for depression

You have a history of drug or alcohol abuse

You are on regular medication that might affect the results

You are in, or have recently taken part in, another research study that could interfere with this one

You have metal implants inside your body or any metal in your body from an accident or injury

You are, or might be, pregnant

For your own well-being please be honest about the information you tell the investigator.

What happens if I don’t want to carry on with the study once I have started?

You can withdraw from the study at any time without having to give any reason. Information collected during your participation in the study will be destroyed if you wish.

What if there is a problem?

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Coordinator on 0161 275 7583 or 0161 275 8093 or by email to researchgovernance@manchester.ac.uk.

Harm
In the event that something does go wrong and you are harmed during the research you may have grounds for a legal action for compensation against The University of Manchester and Hope Hospital but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

The University of Manchester has cover for no fault compensation for bodily injury, mental injury or death where the injury resulted from a trial or procedure you received as part of the trial. This would be subject to policy terms and conditions.

Any payment would be without legal commitment.

The University would not be bound to pay this compensation where the injury resulted from a drug or procedure outside the trial protocol or the protocol was not followed.

**How do I get help if I am concerned about anything?**

During working hours you can contact a member of the study team (the details are at the head of this information sheet).

**Further information**

If you would like more information, or to discuss the study with a member of the research team, please feel free to contact us at the address on the top of this leaflet.

If you would like to have a picture of your brain scan and/or the findings of the study we will be happy to provide you with either an electronic or printed copy. Please let us know during the study and we can arrange to send it to the address of your choice when it is available.

For independent advice please contact Dr Richard Drake (who is not directly involved in the research) at the same address as at the top of this leaflet or via Tel. 0161 275 7427.

**Thank you for reading this.**

Dr Rebecca Elliott Dr Paula Trotter Professor Ian Anderson
(Senior Research Fellow) (Research Assistant) (Consultant Psychiatrist)
Social Economical Decision Making in Patients with Major Depression

Participant Information Sheet v.2 Date: 02/11/2011

You are being invited to take part in a research study as a part of a PhD project. This study aims to investigate social and financial decision making in patients with major depression. The study will consist of paper and pencil personality measures and computerised tasks. These tasks are computer games involving decisions about social and financial scenarios. Before you decide whether to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

Who will conduct the research?

Mr. Erdem Pulcu, PhD student
University of Manchester Medical School Stopford Building Neuroscience and Psychiatry Unit (NPU).

Title of the Research

Social economical decision making in patients with major depression.

What is the purpose of the research?

The current project aims to investigate different aspects of social and financial decision making in patients with depression. We will explore how depression and personality affect people’s decisions in various computerised social economical decision making tasks. You will be asked to complete some scales about moral emotions (for example: guilt, shame) and computer tasks of social and/or financial decision making. Looking at how people carry out these tasks will help us understand how low mood influences real-life decision making. The findings of this study may have potential to explain the individual differences in the experience of depression as well as the response to different types of treatment.

Why have I been invited?
You have been invited to take part because you are between the ages of 30 and 65 and are experiencing symptoms of low mood. We will recruit up to 25 participants with depression for this study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, please keep this information sheet for future reference. You will be free to withdraw at any time without giving a reason and without any detriment to yourself.

What will happen to me if I take part?

You will be asked to provide background information (age, sex, years of education and whether English is your first language). After this, the researcher may conduct a clinical interview with you, depending on the time when you were diagnosed with major depression and he/she will rate the intensity of your symptoms in the past two weeks. After this, you will be asked to complete ratings about moral emotions, personality measures and various computerised social economical decision making tasks.

Expenses and Payments

Travel expenses

We will be reimbursing all reasonable travel expenses up to £20 per visit. The travel expenses will be paid by cheque.

Reimbursement for participation

One of the tasks you will complete is a charitable donations game. In this task you will be asked to make a decision about whether or not to make a donation to various charities working in England and/or Wales. You will be playing this charitable donations game with real money. You will be given £20 to play with at the beginning of the game, and if you decide not to make any donations, you will still have £20 at the end. Even if you decide to make donations, the minimum amount you will have at the end will be £10. We will give you High Street vouchers corresponding to the amount you end the game with (i.e. between £10 and £20 depending on how much you choose to donate).

What are the possible disadvantages and risks of taking part?

This study does not involve any invasive procedures; therefore it does not pose any physical risks or disadvantages. Depending on your pace of responding to the items, the study may take up to 2 hours which you may find tiring. However, our previous experience with similar research in participants with depression suggests that this testing time is well tolerated by the majority of people. Should you feel tired, please inform the researcher that you would like to take a break. Alternatively, it will be possible to complete the testing session on two consecutive days if you prefer.
What are the possible benefits of taking part?

There will be no direct benefit to you from taking part in the research but it may help people with major depression in the future.

What should I do if I find taking part in the study distressing?

The tasks and questionnaires involve thinking about social situations and could potentially cause you to reflect on your social and interpersonal experiences. This may make you feel uncomfortable. If you feel any discomfort or distress during the testing session please tell the researcher. If you feel that you require immediate attention you will be able to talk to a psychiatrist at the Neuroscience and Psychiatry Unit or we will take you to the Manchester Royal Infirmary. Whether or not you find the study distressing, if your interview indicates that you have depression, we will advise you to contact your GP to discuss your mood symptoms. Regardless of whether you completed the full testing session, you will be given a verbal debriefing about the study and the researcher will provide you a leaflet which contains the contact details of various mental health support options, including local and national counselling services.

What happens to the data collected?

The data will contribute to the thesis of the chief investigator who is a PhD student. After data collection has ended, we are aiming to publish the results in medical and/or psychological journals. There will not be any personally identifiable information on any of the publications coming out of this study.

How is confidentiality maintained?

All information collected during the course of the research will be kept strictly confidential. The same coded number will be used to identify all your results and your personal details (name and address etc.) which will be kept securely and completely separately from all the rest of your results. If we need to link the results back to individuals this will only be done by members of the research team and no-one will be able to recognise you from any of your results or other information that you have provided which will be completely anonymised.

What if there is a problem?

If you want to contact the researcher for more information or for help either prior or subsequent to your participation please do so by sending an email to Erdem Pulcu: Erdem.pulcu@postgrad.manchester.ac.uk

Complaints

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. If they are unable to resolve your
concern or you wish to make a complaint regarding the study, please contact a University Research Practice and Governance Co-ordinator on 0161 275 7583 or 0161 275 8093 or by email to research-governance@manchester.ac.uk.

Harm
In the event that something does go wrong and you are harmed during the research you may have grounds for a legal action for compensation against The University of Manchester but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

The University of Manchester has cover for no fault compensation for bodily injury, mental injury or death where the injury resulted from a trial or procedure you received as part of the trial. This would be subject to policy terms and conditions.

Any payment would be without legal commitment.

The University would not be bound to pay this compensation where the injury resulted from a drug or procedure outside the trial protocol or the protocol was not followed.

Where will the research be conducted?
This research will be conducted at the Neuroscience and Psychiatry Unit, Stopford Building G.803, University of Manchester, Oxford Road, M13 9PT.

Further information
If you would like more information, or to discuss the study with a member of the research team, please feel free to contact us at the address on the top of this leaflet.

For independent advice please contact Dr Richard Drake (who is not directly involved in the research)
At the same address as at the top of this leaflet or via Tel. 0161 275 7427.

Thank you for reading this.

Dr Rebecca Elliott Erdem Pulcu Professor Ian Anderson
Senior Research Fellow PhD Student Consultant Psychiatrist
Social Economical Decision Making in Patients with Major Depression: a neuropsychological investigation

CONSENT FORM

Version 02, 01/11/11

PLEASE COMPLETE THIS IF YOU AGREE TO TAKE PART IN THE STUDY

Please initial the box if you agree with the statement

1. I confirm that I have read and I understand the information sheet v.1, Dated 08/08/2011.

2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

3. I understand that my participation is voluntary and that I can withdraw at any time, without giving any reason, and that my medical care and legal rights will not be affected.

4. I understand that data collected during the study may be looked at by individuals from the University of Manchester, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

5. I agree to take part in this study.

_________________________ / / ____________________________
Name of participant (please print your name)   Date   Signature

_________________________ / / ____________________________
Name of the researcher   Date   Signature

THANK YOU