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Measuring blame-related action tendencies and prediction of prognosis in depression

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Measuring blame-related action tendencies and prediction of prognosis in depression

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Thesis submitted in fulfilment for the degree of Doctor in Philosophy

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Abstract

Action tendencies are implicit cognitive and motivational states before an action is taken, such as feeling like hiding when experiencing shame or guilt, independent of the actual actions people choose to take. As precursors of social actions, action tendencies provide the key link between depressive emotions and behaviour. However, no empirical study had systematically examined the role of action tendencies in depression. The purpose of this thesis was to measure blame-related action tendencies and determine their role in predicting prognosis in major depression.

In Study 1, I examined the relationship between blame-related emotions and action tendencies and used a text-based task to investigate the role of action tendencies in the vulnerability to depression. 76 participants with remitted depression and 44 control participants had previously been recruited for this study. The results showed that people with remitted depression had a maladaptive profile of action tendencies, including feeling like hiding and creating a distance from oneself.

In Study 2, I developed a novel virtual reality task to assess blame-related action tendencies in people with and without current depression. 98 participants with current and treatment-resistant depression and 40 control participants were recruited and included in the data analysis. Consistent with the finding in Study 1, using Multivariate Analysis of variance, I found that people with current depression also demonstrated a distinct profile of maladaptive action tendencies including feeling like hiding and punishing oneself. In addition, feeling like punishing oneself was specifically associated with a history of self-harm, but not of suicide attempts.

In Study 3, I used these maladaptive action tendencies to determine their role in predicting prognosis of depression after four months of treatment-as-usual in primary care along with other relevant predictors previously described in the literature. All participants with

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depression enrolled in Study 2 completed monthly online questionnaires during the 4-month follow-up period. I found that maladaptive action tendencies, such as punishing oneself for other people's wrongdoing, was associated with a poorer prognosis of depression after four months.

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Personal contribution

This thesis is the result of my own work under the supervision of my primary supervisor Professor Roland Zahn and my secondary supervisor Professor Lucia Valmaggia. Other sources of support are all acknowledged in the references. For all chapters, Professor Roland Zahn and I developed the study concept and design together. I independently undertook writing of all chapters including tables and figures, which both of my supervisors have provided critical revisions on.

In Chapter 2, the data was already collected in a previous clinical trial led by Professor Roland Zahn. I conducted all the statistical analyses with conceptual input and feedback provided by Professor Roland Zahn and additional statistical assistance from Dr Andrew Lawrence.

In Chapter 3, I wrote the ethics application, recruited all the participants, developed and conducted all the assessments of participants, conducted all the statistical analyses, with the guidance and active support from Professor Roland Zahn. The Virtual reality task was designed by me and developed by Mr Jerome Di Pietro with kind support from both of my supervisors.

In Chapter 4, I wrote the ethics application, recruited all the participants, developed and conducted all the assessments of participants, conducted all the statistical analyses, with the guidance and active support from Professor Roland Zahn. Some additional statistical assistance was obtained from Dr Andrew Lawrence.

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Abbreviations

ANOVA: analysis of variance

BDI: Beck's depression inventory

CAD: contempt, anger, disgust

dCVnet: doubly Cross-Validated elastic-net regularised generalised linear model

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

GAD-7: Generalised Anxiety Disorder-7

GP: general practitioner

HC: healthy control

HPA: hypothalamic-pituitary-adrenal

MANOVA: multivariate analysis of variance

MDD: major depressive disorder

MM-PHQ-9: Maudsley-Modified Patient Health Questionnaire

MSM: Maudsley staging method

NICE: National Institute for Health and Care Excellence

PCA: Principal Component Analysis

PDD: Persistent Depressive Disorder

PHQ-9: Patient Health Questionnaire-9

PSI-II: Personal Style Inventory-II

QIDS-SR-16: Quick Inventory of Depressive Symptomatology – self-reported -16

SSRIs: selective serotonin re-uptake inhibitors

SSS: Social Support Scale

VMST: Value-related Moral Sentiment task

VQIDS-SR-5: Very Quick Inventory of Depressive Symptomatology

Abbreviations

VR: Virtual Reality

WHO: World Health Organization

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1.1) Background

Around 2,500 years ago, Greek physician Hippocrates proposed his four-temperament theory that classified fundamental personality types as sanguine, choleric, melancholic and phlegmatic (Ekstrand, 2022). He attributed the causes of these personalities to an excess or lack of different kinds of body fluids (so-called humors). Originating from these four temperaments, a distinct disease called melancholia was defined at that time by long-lasting fear and despondencies (Ekstrand, 2022). In 1886, Carl Lange, who was famous for his theory of emotions, introduced the term “depression” to refer to patients with melancholia without any psychotic symptoms (Shorter, 2007). Since then, depression has been conceptualised and categorised in various possible ways, such as Emil Kraepelin’s model of manic-depressive illness as comprising both what we call unipolar and bipolar affective disorders (Shorter, 2007).

Nowadays, depression is usually used as an umbrella term to describe a range of depressive disorders characterised by a persistent feeling of low mood and lack of interest in pleasurable activities, as well as other symptoms including insomnia or hypersomnia, tiredness, poor appetite or overeating, feeling of worthlessness, lack of concentration, psychomotor agitation or retardation and suicidal thoughts. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), there are two major categories of depression: major depressive disorder (MDD) and persistent depressive disorder (PDD). The most common type, MDD, can be diagnosed based on having at least one symptom of low mood or lack of interest in activities and more than five other symptoms most of the day nearly every day for at least two weeks.

As a leading cause of disability, more than 322 million people worldwide suffer from depression, with nearly half of these people living in the South-East Asia and Western Pacific Region (WHO, 2017). Depression can affect people at any time point in their lives, although many patients experience their first episode during adolescence. The detrimental nature of

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depression lies in its profound negative impact on one's life quality, especially social and occupational functioning. As described by a patient, "depression is rather like dying from thirst while looking at a glass of water, just beyond one's reach" (Ratcliffe, 2010). Such painful feeling of hopelessness is one of the most prevalent features of depression. Depression greatly increases the likelihood of symptoms such as self-harm and suicide. While suicide is the fourth leading cause of death among teenagers and young adults, at least 50% of those who committed suicide suffer from depression (WHO, 2017). Depression is highly co-morbid with other psychiatric disorders, most commonly anxiety disorders. More than half of individuals with lifetime depression reported at least one type of lifetime anxiety disorder (Kaufman & Charney, 2000). Following anxiety disorders, alcohol and drug use disorders were reported second and third most prevalent in depressed patients (Hasin et al., 2005). Such co-morbidity of psychiatric disorders in patients with depression is usually associated with greater severity, higher suicidality and more severe treatment resistance, hence resulting in slower recovery (Steffen et al., 2020).

1.2) Risk factors for depression

Given its high prevalence and detrimental outcomes, it is important to identify risk factors for depression as early as possible. A few prominent biological risk factors were thought to be involved in the development and maintenance of depression, including dysfunction or dysregulation in inflammatory responses and in the hypothalamic-pituitary-adrenal (HPA) axis as well as imbalances in neurotransmitters. Specifically, there were increased inflammatory processes and cytokine levels that might cause structural and functional alternations of neurons that contribute to depression. In addition, HPA axis hyperactivity with higher cortisol levels has been reported in patients with depression (Stetler & Miller, 2011), and correlated with the severity of depressive symptoms (Zobel et al., 2001) and a poor response to treatment (Fisher

et al., 2017). While meta-analyses have confirmed such association between the HPA axis, inflammatory responses and depression (e.g. Erjavec et al., 2021), the effect sizes of individual studies vary greatly. One explanation is that these findings are highly dependent on the sensitivity of the test used to detect abnormal HPA axis and also on specific subtypes of depression (Nedic Erjavec et al., 2021). For example, Lamers et al. (2013) found that higher cortisol levels were detected in patients with melancholic depression compared with atypical depression and controls, whereas patients with atypical depression had higher levels of inflammatory responses relative to the other two groups. These findings revealed a substantial difference in the biological underpinnings that are related to different subtypes of depression (Cattaneo et al., 2015; Lamers et al., 2013).

While HPA axis hyperactivity and altered inflammatory processes may play a crucial role in understanding the pathophysiology and probably also predicting outcomes of depression (Nedic Erjavec et al., 2021), most licensed pharmacological treatments of depression were primarily developed to target monoaminergic neurotransmitters. It is beyond the scope of this thesis to discuss neurochemical models of depression, but Price and Drevets' model, one of the most advanced to my knowledge, proposed the complex interplay between monoaminergic, cholinergic, glutamatergic and GABAergic systems (Price & Drevets, 2010).

In addition to biological risk factors, cognitive vulnerability factors have been proposed for depression in the past half century. As stated by Aaron Beck, the father of cognitive therapy, individuals vulnerable to depression are prone to focus on negative information around them, especially around loss and depletion (Beck & Haigh, 2014). However, these cognitive tendencies are not necessarily maladaptive, at least in the short term. As Beck described, there are different "modes" to explain adaptive and maladaptive responses, which he defined as networks of cognitive, affective, motivational, and behavioural components that help individuals pursue specific goals and manage specific demands. Negative thinking in

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depression was thought to be an exaggeration of the self-expansive mode that deals with the saving of energy and enhancement of personal resources. Composed of various schemas of evaluative beliefs towards oneself, self-expansive mode can influence one's self-image and expectations of specific outcomes (Beck & Haigh, 2014). For example, it was hypothesised that when people experience failure, their self-expansive mode leads to the devaluation of the self. According to this model, in contrast to depression, anxiety results from an exaggeration or dysfunction of the self-protective mode that concerns early detection of danger or threat (Beck & Haigh, 2014). The model further hypothesises, that an imbalance in these cognitive modes consisting of schemas towards oneself and others could potentially lead to some dysfunctional beliefs such as negative thinking, and ultimately give rise to the symptoms of depression and anxiety.

However, the model of generally increased negative (A. T Beck & E. A Haigh, 2014) is incompatible with blame attribution models of depression which hypothesised that depression vulnerability arises from a tendency to overgeneralize blame towards oneself relative to others (Abramson et al., 1978). which was confirmed by showing reduced negative emotions towards others in remitted depression (Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015). The focus on self-criticism in the attributional models of depression are consistent with Freud's conceptualisation of depression as being driven by self-reproach/self-attack and anger directed towards oneself (Freud, 1917). Freud, however, focused on the emotional and motivational aspects of self-blame, whereas Abramson hypothesised that self-blame arose from cognitive styles which they thought were separable from emotions (Abramson et al., 1978). Rather than stating an increased negative thinking in general, Abramson et al. (1978) proposed that the specific attribution of an uncontrollable negative event plays a more important role in depression. Specifically, they postulated three dimensions of attribution: interval vs. external; stable vs. unstable; general vs. specific. It was

hypothesised that whereas an uncontrollable negative event will commonly induce learned helplessness, an internal, stable and general attribution of such event could give rise to chronicity and generality of one's learned helplessness that will consistently impact their self-esteem and ultimately lead to depression. In a later revision of the learned helplessness theory of depression, Abramson et al. (1989) mentioned that the relationship between attributional styles and depression might be more relevant for a specific subtype of depression termed "hopelessness depression" which they thought was fundamentally distinct from other subtypes of depression. This idea was supported by some empirical findings (Joiner Jr, 2001) which, in line with possible different biological underpinnings for different subtypes, further emphasized the inherent heterogeneity of depression.

1.3) The role of blame-related emotions in depression

Emotions as fundamental mental states of human beings play an evolutionarily important role in the social survival of individuals. Blame-related emotions or moral emotions as defined by researchers (Haidt, 2003; Tangney et al., 2007) are members of a family of "self-conscious emotions" that are evoked by self-reflection and self-evaluation. Such emotions are particularly relevant to depression as a mental disorder characterised by low self-esteem. When measured by the emotion labels, it is possible to distinguish different types of blame-related emotions including shame, guilt, contempt/disgust, indignation/anger (Zahn, Lythe, Gethin, Green, Deakin, Young, et al., 2015). Shame and guilt have been most widely studied both as emotional phenomena alone and in their relationship with various mental disorders, especially depression (Tangney et al., 2007). For example, Janoff-Bulman et al. (2009) distinguished shame and guilt based on their two faces of moral regulation: proscriptive versus prescriptive. They conceive of proscriptive morality as associated with shame and focused on what one should not do, as condemnatory and strict; whereas their concept of prescriptive morality is

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associated with guilt and focuses on what one should do, and is commendatory and not strict. Lewis suggested that shame is correlated with a negative evaluation of the global self, whereas guilt involves a negative evaluation of a specific behaviour (Lewis, 1971). Accordingly, Robins (2006) found that people were more likely to attribute internal, stable and uncontrollable failures to shame, but unstable and controllable failures to guilt (Robins, 2006). Tangney et al. (2007) proposed that guilt, which could benefit individuals and their relationships in various ways, is more adaptive than shame and found that only shame-proneness was associated with depressive symptoms in general population samples. However, it is worth mentioning that many researchers (e.g. Tangney et al., 2007) mainly conceptualised shame with its maladaptive form and guilt with its adaptive form, which is similar to a form of characterological versus behavioural self-blame as proposed by Janoff-Bulman (1979). These differences in researchers' definitions of shame and guilt might ultimately explain the findings they obtained. Indeed, in studies where researchers measured overgeneral forms of guilt, guilt was found to be associated with depression (O'Connor et al., 2002), and both shame and guilt can be adaptive and maladaptive under different circumstances (Taihara & Malik, 2016). For example, shame and guilt towards one's behavior are thought to be more adaptive, whereas shame and guilt towards one's character are thought to be maladaptive. The latter is called the generalized form of self-blame. This points to the shortcomings of defining blame-related emotions based on the emotion labels alone, which will be more thoroughly discussed in the next section of this thesis. Only negative emotions were investigated in this thesis as they are most relevant in depression.

In addition to shame and guilt, other blame-related emotions such as contempt, disgust and anger and their relationship with depression were investigated and are understood to a lesser extent (Rozin & Fallon, 1987; Rozin et al., 1999). One relevant and influential theory is the CAD (contempt, anger, disgust) triad hypothesis proposed by Rozin et al. (1999) which states that contempt, anger, disgust are associated with violation of three different moral codes:

community, autonomy and divinity. Like most researchers in this field, the authors primarily considered contempt, anger, disgust as blame-related emotions directed towards others. However, an interesting study by Zahn, Lythe, Gethin, Green, Deakin, Workman, et al. (2015) showed that biases towards self-contempt/disgust were more relevant to depression.

1.4) Action tendencies and theories of emotions

While blame-related emotions were found to contribute to the social survival of individuals as well as the vulnerability and maintenance of depression, there are inconsistent findings regarding how specific blame-related emotions are related to depression. One reason for such inconsistency lies in the subjective definitions of blame-related emotions, rendering the measures of emotions heterogeneous with regard to their functional implications. Indeed, not only does the exact difference between shame and guilt remain controversial in the literature, but some people also may use these two words interchangeably (Blum, 2008). As suggested by Scherer (2009) in his cognitive process model of emotions, emotions measured by verbal report such as emotion labels are only the visible tip of a huge iceberg, as only a small part of our emotional experience may be verbalized and communicated.

Emotion is a complicated cognitive and motivational process that involves multiple different components. The definition of emotions and their related components are not well-defined in the literature and remains controversial. Nevertheless, most theories of emotion define emotions based on part of the following components (Moors, 2009): 1) a cognitive component that involves stimulus evaluation or appraisal, 2) a feeling component which refers to the emotional experience and serves to monitor and regulate the emotion, 3) a motivational component that consists of action tendencies or states of action readiness such as the tendency to hide or flee when experiencing shame or fear, 4) a somatic component that consists of central and peripheral physiological responses that support specific actions and 5) a motor

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component that ultimately acts out the actions such as fight and flight. Emotion theorists disagree on the components that are included in the emotion as well as how these components interact with each other such as whether they occur sequentially or in parallel (Moors, 2009). For example, as James said “we feel sorry because we cry, angry because we strike, afraid because we tremble” (James et al., 1890). He only equated emotions with the feeling components and conceived of the somatic or motor components preceding emotions. While his theory has been influential at the time, it has faced wide criticism such as its lack of specificity and being unable to explain how emotions are elicited. Following James, other theories of emotions such as Schachter’s theory (Schachter, 1964) and the appraisal theories of emotions (Arnold, 1960; Frijda, 1986; Roseman et al., 1994) addressed these limitations. In the appraisal theories, a cognitive component called cognitive appraisal, responsible for both emotion elicitation and differentiation, is automatically and unconsciously triggered after specific emotional stimuli are perceived (Arnold, 1960). Appraisal of the emotional stimulus then causes an action tendency (the motivational component of emotions) which then triggers the somatic and motor components. Finally, these components are combined to form individuals’ conscious emotional experiences (Moors, 2009). It is worth mentioning that although most appraisal theorists emphasize the role of cognitive appraisal and action tendency in emotions, how they interact with each other (e.g. serially or in parallel) and whether there are other components involved in emotions, remains controversial. The term “action tendency” is also referred to differently by some appraisal theorists such as “action readiness” in Frijida’s theory (Frijda et al., 1989).

Action tendencies as the primary focus of this thesis will be operationally defined here as the implicit motivational states that are present before an action is taken (Haidt, 2003). Similar to the adaptiveness of emotions in general, action tendencies in themselves also play an evolutionarily crucial role in one’s social survival (Darwin & Ekman, 1872; Haidt, 2003;

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Roseman et al., 1994). It might be difficult to imagine how one is able to survive a dangerous situation (e.g. coming across a tiger in the forest) without the action tendency to flee the situation in the first place. Based on the appraisal theories of emotions, most of the components remain largely unconscious (particularly the cognitive component). However, the specific action tendency that the individual perceives remains available in one's conscious awareness and could be verbalized. Therefore, measuring action tendencies makes it possible to differentiate emotions in a relatively objective way. It is hypothesised that specific emotions are associated with specific action tendencies. To illustrate, there is a difference in the tendency to hide versus amend for shame and guilt, which has been partially confirmed in an empirical study (Roseman et al., 1994). Shame corresponds to attempts to deny, hide, or escape the shame-inducing situation, whereas guilt was associated with reparative actions including confessions, apologies, and undoing the consequences of the behaviour (Haidt, 2003; Tangney et al., 2007). While indignation, contempt and disgust are similar in a way that they are mostly triggered when blaming others, indignation/anger was hypothesised to involve a tendency to approach the triggering stimulus, whereas contempt and disgust to motivate the individual to move away or create a distance from the stimulus (Haidt, 2003). Furthermore, it was hypothesised that measuring action tendencies could determine the adaptive and maladaptive nature of blame-related emotions. For example, Tangney et al. (2007) suggested that adaptive blame-related emotions and action tendencies promote constructive and proactive pursuit, whereas maladaptive blame-related emotions and action tendencies motivate defensiveness, social withdrawal and interpersonal separation. This conceptualisation of shame included its association with hiding and social withdrawal, and thereby its maladaptive nature compared with guilt (Tangney et al., 2007), although the Test of Self-Conscious Emotions developed by Tangney J. P. et al. (2000) to measure shame and guilt-proneness, confounds their constructs with the way they have measured them by not asking for the subjective label of the emotion

and instead operationalise emotions on the basis of the hypothesised components (characterological vs. behavioural and reparative actions vs. hiding).

Cultural difference can also play a role in inducing different blame-related emotions and motivating action tendencies. For example, a study found that individuals from collectivistic cultures respond more with shame and guilt to normative violations than individuals from individualistic cultures (Bierbrauer, 2007). Another study shows that individuals from collectivistic cultures are more likely to engage in reparative actions following transgression while individuals from individualistic cultures are more likely to withdraw from threatening interpersonal relationships (Young et al. 2021).

1.5) The role of action tendencies in depression

Despite the crucial adaptive roles of action tendencies in motivating social behaviour of individuals, there is surprisingly little empirical research that examines the relationship between blame-related action tendencies and emotions. Even fewer studies have investigated the role of blame-related action tendencies in depression. In Gray's reinforcement sensitivity theory (Gray, 1970), he proposed two dissociable neural systems as dimensions of human action tendencies: behavioural "activation" and "inhibition" – the latter, also referred to as "withdrawal", is more associated with introversion. Gray (1970) hypothesised that a higher level of behavioural inhibition renders introverts more sensitive to punishment and frustration, which then makes them more likely to develop "reactive" depression. His prediction is consistent with later findings that stronger behavioural inhibition/withdrawal and impaired behavioural activation were associated with affective disorders (e.g. Kasch et al., 2002). People who classified themselves as high in behavioural inhibition had overall higher depressive and anxiety symptoms than those who self-classified as moderate or low in behavioural inhibition (Muris et al., 2001). Further, using the Sensitivity to Punishment and Sensitivity to Reward

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Questionnaire (Torrubia et al., 2001), both participants with current and remitted major depression had a hyperactive behavioural activation system and a hypoactive behavioural activation system. This suggests that a higher tendency to inhibit or withdraw could be a trait-vulnerability marker for depression even after recovery (Pinto-Meza et al., 2006). Although these studies did not focus on blame-related emotion and action tendencies specifically, their findings are in line with the hypothesis that maladaptive blame-related action tendencies motivate defensiveness, social withdrawal and interpersonal separation (Tangney et al., 2007).

In a study that specifically investigated the relationship between blame-related emotions, action tendencies and psychopathology, Mu and Berenbaum (2019) found that the use of action tendencies predicted a variety of outcomes indicative of psychopathology and psychological well-being including depression, social anxiety, relationship quality. Specifically, withdrawal-related action tendencies, but not global self-devaluation, predicted depressive symptoms. This was the first empirical study, to my knowledge, that has demonstrated a direct relationship between blame-related action tendencies and depressive symptoms. The authors also advocated the use of action tendencies to measure emotions as opposed to emotion labels, as no single emotion label will be sufficient to capture the richness of blame-related emotions. Nevertheless, the study did not involve any clinical population with depression or other mental disorders, which limits the generalisation of their findings. While the authors define social withdrawal as “the tendency to withdraw from social relationships when feeling negative about oneself” (Mu & Berenbaum, 2019), they did not specify different types of social withdrawal such as feeling like hiding or creating a distance from oneself and whether these different types predict specific outcomes of participants.

A recent study measured blame-related emotions and action tendencies using a text-based description of social scenarios and used prospective prediction models including baseline maladaptive self-blame-related action tendencies and anterior temporal fMRI connectivity

patterns to predict the recurrence risk of depression (Lawrence et al., 2021). The authors found that withdrawal-related maladaptive action tendencies, including feeling like hiding and feeling like creating a distance from oneself showed a high potential as multimodal signatures of self-blaming biases to predict recurrence risk at an individual level. This was the first study that demonstrated maladaptive action tendencies as predictive of outcomes of depression and their potential role as neuro-cognitive markers in depression. Further study was needed to examine the role of maladaptive blame-related action tendencies in participants with current depression. As with all previous measures of action tendencies, the Lawrence et al. (2021) study used abstract text-based descriptions to measure blame-related emotions and action tendencies, which may limit participants' engagement in the task. More importantly, participants' blame-related emotions might have depended in part on how well they can imagine the scenarios and indeed there was an association between visual imagery ratings and emotional intensity ratings during this task in an earlier study (Zahn et al., 2009). Another study showed that structural anatomical differences in posterior cortical areas known to be relevant for visual imagery could partly explain individual differences in this text-based moral sentiment task which was used to measure blame-related emotions (Zahn et al., 2014). It is therefore important to develop more immersive tasks to measure blame-related action tendencies in future studies, which rely less on the ability to create one's own imagery (Fulford et al., 2018) that is affected by mood disorders (Holmes et al., 2016).

1.6) Rationale for and aims of the present thesis

In the previous sections, I have introduced a historical understanding of depression and the crucial risk factors that might contribute to its psychopathology. I have demonstrated the potentially important roles of blame-related emotions and maladaptive action tendencies in the vulnerability, maintenance and recurrence of depression as well as a lack of empirical studies

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that examine their relationships. Determining whether these action tendencies play a role in depression is an essential step not only towards a better understanding of the psychopathology, but also towards designing novel interventions and risk prediction markers.

There are three major aims of this thesis. In Chapter 2, based on Tangney's model, I aimed to investigate the relationship between blame-related emotions and action tendencies, as measured by a text-based task and whether remitted major depressive disorder is associated with higher proneness towards maladaptive action tendencies, such as creating a distance from oneself and hiding compared with control participants without a history of mood disorders. 74 participants with remitted major depressive disorder and 40 control participants without a history of axis-I disorders and no first-degree family history of mood disorders were recruited as part of a previous study (Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015). All participants completed the text-based task of blame-related emotions (value-related moral sentiment task, VMST) and action tendencies.

The results showed the limitations of previous measures of blame-related emotions based on emotion labels and suggested to use action tendencies as a more objective measure that could potentially distinguish the adaptive and maladaptive nature of blame-related emotions. In addition, previous measures blame-related action tendencies are mainly based on text which limits the ecological validity and immersiveness in the task (e.g. Zahn, 2015). To assess action tendencies in a more ecologically valid and immersive way, Virtual reality (VR)-based assessment was identified as a promising method for cognitive evaluation compared with the traditional paper-and-pencil or computerized assessment. VR scenarios were suggested to be promising tools for cognitive assessment (Henry et al., 2012) and have been demonstrated as safe for the assessment of anxiety disorders and depression (Diaz-Orueta et al., 2012; Falconer et al., 2016). Importantly, the interactive and immersive nature of virtual reality

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renders it possible to develop a cognitive task that is engaging and realistic. This was the reason for developing a novel VR-based assessment of action tendencies as part of my thesis.

Based on the findings of Chapter 2, in Chapter 3, I aimed to further understand whether participants with current depression had a higher proneness towards maladaptive blame-related action tendencies as measured by a virtual reality task and whether these action tendencies are associated with clinical characteristics of depression. An independent sample including 98 participants with current depression and 40 control participants without a depression history were recruited online. Participants completed all the assessments remotely during the COVID-19 pandemic, including both the text-based action tendency task and the novel virtual reality action tendency.

Understanding the prospective influence of maladaptive action tendencies on the outcomes and prognosis of current depression is important but so far unexplored in previous studies. In Chapter 4, I aimed to examine whether maladaptive blame-related action tendencies are associated with a poor prognosis for current depression when treated as usual in primary care and whether they can be used to predict prognosis at the individual level when combined with other clinically established predictors. All participants included in Chapter 3 were followed up 1, 2, 3 and 4 months after their baseline assessments. 93 participants completed the final follow-up assessment.

Chapter 2: The role of maladaptive blame-related action tendencies in the vulnerability to depression

2.1) Abstract

Biases towards self-blaming emotions, such as self-contempt/disgust, were previously associated with vulnerability to major depressive disorder (MDD). Self-blaming emotions are thought to prompt specific action tendencies (e.g. “feeling like hiding”), which are likely to be more important for psychosocial functioning than the emotions themselves. Systematic investigations, however, of these action tendencies in MDD are lacking. Here, we investigated the role of blame-related action tendencies for MDD vulnerability and their relationship with blame-related emotions. 76 participants with medication-free remitted MDD and 44 healthy control (HC) participants without a history of MDD completed the value-related moral sentiment task, which measured their blame-related emotions during hypothetical social interactions and a novel task to assess their blame-related action tendencies (feeling like hiding, apologising, creating a distance from oneself, attacking oneself, creating a distance from other, attacking other, no action). As predicted, the MDD group showed a maladaptive profile of action tendencies: a higher proneness to feeling like hiding and creating a distance from themselves compared with the HC group. In contrast, feeling like apologising was less common in the MDD than the HC group. Apologising for one’s wrongdoing was associated with all self-blaming emotions including shame, guilt, self-contempt/disgust and self-indignation. Hiding was associated with both shame and guilt. Our study shows that MDD vulnerability was associated with specific maladaptive action tendencies which were independent of the type of emotion, thus unveiling novel cognitive markers and neurocognitive treatment targets.

Keywords: self-blame; action tendencies; depression; moral emotion; guilt

2.2) Introduction

Previous studies have demonstrated the significance of moral emotions and self-blaming emotional biases as vulnerability factors for major depressive disorder (MDD; (Janoff-Bulman et al., 2009; O'Connor et al., 2002; Power & Dalgleish, 2015; Surguladze et al., 2010). Self-blaming emotions were hypothesised to be associated with action tendencies (Haidt, 2003; Janoff-Bulman et al., 2009; Tangney et al., 2007) which describe a motivational and cognitive state in which there is an increased tendency to engage in certain goal-related behaviours (Haidt, 2003), such as “feeling like hiding”. Determining whether these action tendencies play a role in the vulnerability to MDD is an essential step not only towards a better understanding of the psychopathology, but also towards designing novel interventions and risk prediction markers.

Imbalances in blame-related emotions have been shown to be closely related to individuals' negative mental health outcomes and risks of MDD. For example, overgeneralised guilt (O'Connor et al., 2002) and shame have been observed in people with MDD even on remission (S. Green et al., 2013). In a further study (Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015), individuals with remitted MDD exhibited a self-contempt/disgust bias and a reduction in contempt/disgust towards others. These findings demonstrated the potential role of self-blaming emotions as vulnerability traits for MDD that remain present during remission.

Despite the importance of previous findings, existing measures of self-blaming emotional biases have some critical limitations, one of which is the difficulty to distinguish different emotion labels such as shame and guilt, using these measures (Mu & Berenbaum, 2019). In addition, their mechanism in motivating adaptive or maladaptive social actions is elusive. As proposed by Tangney et al. (2007), adaptive moral emotions promote constructive and proactive pursuit, whereas maladaptive moral emotions motivate defensiveness, social withdrawal and interpersonal separation (Tangney et al., 2007). This difference is possibly

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determined by an individuals' action tendencies associated with their moral emotions (Haidt, 2003; Tangney et al., 2007). Action tendencies are fundamental characteristics of emotions that closely relate to emotion differentiation and its evolutionary function for the social survival of individuals (Roseman et al., 1994). Previous researchers have proposed associations between moral emotions and action tendencies as well as the adaptive or maladaptive nature of their relationships. For example, although shame and guilt could be either adaptive or maladaptive under different circumstances (Taihara & Malik, 2016), Tangney and colleagues conceived of guilt as being more strongly associated with adaptive action tendencies such as reparative actions including confessions and apologies, whereas they operationalised shame as associated with maladaptive action tendencies such as an attempt to deny, hide, or escape the shame-inducing situation (Haidt, 2003; Janoff-Bulman et al., 2009; Tangney et al., 2007).

Indeed, the nature of action tendencies (adaptive vs. maladaptive) might be important in guiding the behavioural consequences of moral emotions, thereby providing a direct link to vulnerability to psychopathology (O'Connor et al., 1997; Tangney et al., 2007). Of particular relevance in MDD is the action tendency related to self-blaming emotions such as self-contempt and shame. Consistent with this idea, a previous study suggests that action tendencies associated with self-blaming emotions (e.g. withdrawal) predicted higher depressive symptoms in undergraduate students, although they did not differentiate specific types of withdrawal related to depression (Mu & Berenbaum, 2019).

Here, we focus on two types of withdrawal-related maladaptive action tendencies that potentially contribute to MDD vulnerability: hiding and creating a distance from oneself. Feeling like hiding has been entailed in the operationalisations of self-blaming feelings such as shame (Tangney et al., 2007) shown to be associated with depressive symptoms, but their systematic investigation in clinical depression is lacking. Whilst the action tendency of creating a distance from others has been well described in relation to disgust and we have previously

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found self-disgust to be increased in MDD (Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015), the associated action tendency of creating a distance from oneself has not been investigated in depression. Some of our patients have described this as wanting to escape their body and feelings. This is similar to the feeling of depersonalisation found in classical descriptions of depression (Kendler, 2017), which has been classified as a disturbance of the ego perception in its identity or unity (Faehndrich & Stieglitz, 1997). However, depersonalisation is an involuntary sensory experience rather than a feeling of wanting to experience it. These dissociation-related phenomena in depression have been conceptualised as a form of cognitive avoidance (Holmes et al., 2016; Lemogne et al., 2006). Indeed, individuals with MDD had more escape/avoidance coping styles (Haskell et al., 2020), which might be associated with an action tendency to hide, or create a distance from themselves in the first place. In contrast, action tendencies such as repair and apologising, were found to predict lower depressive symptoms in a non-clinical sample (Mu & Berenbaum, 2019), which shows their possible adaptive role in the vulnerability to MDD.

Despite the potential distinctive psychopathology of feeling like creating a distance from oneself and feeling like hiding, to our knowledge, these action tendencies have so far not been directly assessed in individuals with MDD. Furthermore, there is no systematic investigation of how action tendencies and moral emotions are linked in MDD. The present study aimed to elucidate these questions by directly examining the relationship between blame-related emotions and action tendencies, and their potential role in MDD vulnerability. To identify potential vulnerability traits associated with MDD (Bhagwagar & Cowen, 2008), understanding the differences between remitted MDD and healthy control groups is a first step, as the risk of depressive episodes MDD even after a single episode (50%) is far higher than in people with no personal history (15%) (Eaton et al., 2008). We developed a novel action tendency task that specifically assessed different action tendencies (feeling like: apologising,

hiding, creating a distance from oneself, attacking oneself) when people experienced self-blame-related emotions (shame, guilt, self-contempt/disgust, self-directed anger) and comparing them against emotions and action tendencies associated with blaming others. We hypothesised that individuals with fully remitted MDD were more likely to have maladaptive action tendencies reflecting their vulnerability to further episodes despite current symptom remission, when compared with a control group without a personal and family history of MDD. More specifically, we firstly hypothesised that individuals with MDD have an increased maladaptive action tendency to create a distance from themselves and/or to hide. Secondly, based on the distinctive role of self-contempt and shame in MDD (Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015), we hypothesised that self-contempt/disgust is associated with feeling like creating a distance from oneself and thirdly, that shame is distinctively associated with feeling like hiding. In addition, overgeneralised forms of self-blame and control is one central feature of MDD (O'Connor et al., 1997) and this overgeneralization might lead to a higher sense of responsibility in their actions in people with depression. Therefore, we also explored whether there is an overgeneralised perception of control and responsibility of action tendencies in the MDD group.

2.3) Materials and Methods

2.3.1) Participants

Seventy-six medication-free participants with remitted MDD and 44 healthy control (HC) participants took part in the study and completed both value-related moral sentiment (VMST) and action tendency task. Participants were recruited via online and print advertisements as part of a bigger project and results of the VMST and psychopathological characteristics have been previously reported (Zahn, Lythe, Gethin, Green, Deakin, Young, et al., 2015).

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A total of 707 people took part in an initial phone screening interview to establish whether they would be invited to a clinical assessment using the Structured Clinical Interview-I for DSM-IV (First et al., 1997). The inclusion criteria were a diagnosis of MDD and a remission period for at least six months for the MDD group as defined by DSM-5. To make sure that the control group has low risks of mood disorder and schizophrenia, participants with history of an axis-I disorder or first-degree relatives with mood disorders or schizophrenia were excluded for the HC group. After the initial phone screening interview, 276 people passed the screening with 184 in the MDD group and 92 in the HC group (431 people were excluded at this stage, the exclusion reasons following the phone screening interview are listed in Table 2-1). Participants were then invited to see a senior psychiatrist (RZ) and take part in a face-to-face clinical assessment to further exclude the possibility of current co-morbid axis-I and relevant past axis-I disorders (full inclusion and exclusion criteria and assessment details can be found in Zahn, Lythe, Gethin, Green, Deakin, Workman, et al. (2015). Following the face-to-face assessment, 76 participants with MDD and 44 HC participants met all the criteria and took part in the current study. The details of the exclusion and inclusion process of participants can be found in Table 2-1.

Demographic information and clinical characteristics of the included participants are shown in Table 2-2 and Table 2-3, respectively. There were no significant differences regarding the age, sex, nor the years of education of the two groups. As to be expected, depressive symptoms of MDD participants were slightly but significantly higher than those of HC participants as measured by the Beck Depression Inventory (Beck et al., 1961) total score and the Montgomery-Asberg Depression Rating Scale (Montgomery & Åsberg, 1977) total score.

2.3.2) *Ethical approval*

This study was approved by the South Manchester NHS Research Ethics Committee. All participants have given written informed consent after the procedures of the study have been fully explained.

2.3.3) *Assessment of blaming emotions and action tendencies*

Participants were asked to complete two tasks for assessing their blame-related emotions and blame-related action tendencies respectively. Both was completed at home using excel macros, following their baseline assessment.

Participants' blame-related emotions were assessed using the value-related moral sentiment task (VMST), which has been described and validated in our previous studies (Green et al., 2012; Lythe et al., 2015). At the beginning of the VMST, participants were asked to enter the name of their best friend. Then they were presented with sentences containing hypothetical social interactions in which either the participant (in the self-agency condition) or their best friend (in the other-agency condition) acts contrary to social and moral values [e.g. you act bossily towards (the name of the participant's friend)]. The same social interactions were used for both self-agency and other-agency conditions, with 90 trials in each condition. 50% of the trials used negative social behaviours (e.g., does act bossily) and 50% used negated positive social behaviours (e.g., does not act bossily). For each trial, participants were asked to rate the unpleasantness of each social interaction using a 1-7 point Likert scale, where 1 indicates not unpleasant at all and 7 indicates extremely unpleasant. Valid trials were defined as those that were perceived as highly unpleasant (those rated at the individual median or above in the VMST). They were also required to choose the feeling that they would feel most strongly from four self-blaming emotions (shame, guilt, contempt/disgust towards self and indignation/anger towards self) and two other-blaming emotions (contempt/disgust towards friend or

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indignation/anger towards friend) as well as no/other emotions. One moral emotion was chosen for each trial and 180 moral emotions per participant were chosen in the VMST in total.

In the novel action tendency task, all the hypothetical social interactions (180 trials) in the VSMT were shown again. Participants were instructed to select one action that they would most strongly feel like doing from eight different action tendencies (feel like verbally or physically attacking/punishing your friend, feel like verbally attacking or physically attacking/punishing yourself, feel like apologizing/fixing what you have done, feel like hiding, feel like creating distance from your best friend, feel like creating distance from yourself, no action, other action). Participants were also asked to rate how responsible they would feel, and how much control they felt they would have for each social action using a 1-7 point Likert scale, where 1 indicated “not at all” and 7 indicated “extremely/completely”. In total, 180 action tendencies for 180 trials were chosen for the action tendency task. The proportions of choosing each action tendency across all valid trials was computed for each participant. The split-half reliability coefficients of the action tendency task were high ($>.79$) for each action tendency measure in each agency condition (see Table 2-4). Figure 2-1 shows a screenshot of self-agency condition of one social interaction in the action tendency task, in which the participant entered their best friend’s name at the beginning.

2.3.4) Data analysis

All statistical analyses in the study were carried out using R software. A complete case approach was taken for each planned analysis. To test our first hypothesis (individuals with MDD had an increased tendency to create a distance towards themselves and/or hide), a repeated measures MANOVA was conducted to examine whether the proportion of trials selected by participants differed by action tendency, agency condition (self- vs. other) and clinical group and whether there were interactions between the three variables. Post-hoc tests for between-group differences in each action tendency over both agencies were conducted.

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Multiple comparison corrections were carried out for all post-hoc tests. The assumptions of MANOVA were tested. The assumption of homogeneity of variance was not met. However, the assumptions of MANOVA are relatively robust when the Pillai-Bartlett trace test is used as I did in my study (Olson, 1974). To confirm, I also tested a non-parametric version of MANOVA (Multivariate Kruskal-Wallis test).

To test our second and third hypotheses (self-contempt/disgust was associated with feeling like creating a distance from oneself and shame was associated with feeling like hiding), the relationships between moral emotions and each action tendency were tested. Six mixed effect logistic regression models were conducted for each action tendency as outcome variable, with its related moral emotions, group (MDD vs. HC) as well as their interactions as predictors. More specifically, apologising, hiding, creating a distance from oneself and attacking oneself are likely to be motivated by self-blaming emotions (shame, guilt, self-disgust/contempt and self-indignation). Therefore, in Model 1, 2, 3 and 4, we used self-blaming emotions, group and their interactions to predict apologising, hiding, creating a distance from oneself and attacking oneself. Creating a distance from one's friend and attacking one's friend are likely to be motivated by other-blaming emotions. Therefore, in Model 5 and 6, we used other-blaming emotions, group and their interactions to predict creating a distance from one's friend and attacking one's friend. In all trials, moral emotions and action tendencies were coded as either 1 or 0 (1 for yes and 0 for no). Reference categories for moral emotions were the trials in which participants chose no/other emotion.

Participants were excluded if they chose more than one moral emotion or action tendency in more than 5% of the trials (9 trials). This ensured that all participants included in the logistic regression models understood the instruction of the tasks and could distinguish different moral emotions and action tendencies. In addition, only valid trials were included (trials that were perceived highly unpleasant and rated at the individual median or above). The

significance threshold was set to an approximate Bonferroni-corrected $p < .05$ across all 6 models, corresponding to an uncorrected $p < .008$ in each model.

Perception of control in the hypothetical social scenarios were compared between two groups using Welch's t-tests. In addition, to exclude possible role of scaring effect of previous depressive episodes, Kendall's rank correlations were used to test the correlation between proportions of choosing each maladaptive action tendency, number of previous depressive episodes, and participants' BDI scores.

2.4) Results

2.4.1) Proportion of trials for each action tendency

Means and standard deviations of proportion of trials for each action tendency are presented in Table 2-4. Over both groups clear differences in action tendency selection were seen between the self-agency and other-agency conditions, as expected. Feeling like attacking (self- or other-) was highly agency-specific with agency-incongruent options (e.g. feeling like attacking other in the self-agency condition) occurring rarely. In self-agency trials, apologising, creating a distance from self and attacking self were more common. In the other-agency condition, distancing from one's friend and feeling like attacking one's friend were more common. In contrast to feeling like creating a distance from oneself, feeling like hiding did not differ between conditions.

2.4.2) Group differences for choosing different action tendencies

Proportion of trials for each action tendency and each agency is presented in Table 2-5. We observed group differences that were action tendency- and agency-specific (see Table 2-6). Post-hoc tests for between-group differences in each action tendency over both conditions are presented in Table 2-7. Our first hypothesis was confirmed that MDD patients more frequently felt like hiding than control participants in both conditions and that there was a

significantly higher proportion of feeling like creating a distance from oneself in the self-agency condition for MDD participants. There was a lower proportion of feeling like apologizing for the MDD group compared with the control group in the self-agency condition. In contrast, participants with MDD were more likely to feel like apologising in the other-agency condition. MDD group also had a higher proportion of feeling like attacking oneself in the self-agency condition, but not in the other-agency condition (see Table 2-6 for details). In addition, participants with MDD had a significantly higher perceived control in the other-agency conditions relative to HC participants (Welch's $t=-.52$, $p=.003$) which drove the group difference in the measure of overgeneralised perception of control which we defined as the difference score between control in the self- and other-agency condition (Welch's $t=.56$, $p=.01$; also see Figure 2-2).

2.4.3) The relationship between self-blaming emotions and action tendencies

As shown in Figure 3 and Table 2-8, all self-blaming emotions were associated with a higher probability of apologising across groups. Shame and guilt were both associated with a higher probability of hiding. Interestingly, self-indignation anger rather than self-disgust/contempt was associated with a higher probability of creating a distance from oneself across groups. Reversely self-disgust/contempt correlated with a higher probability of feeling like attacking oneself rather than creating a distance from oneself. No other main effect of group or group by emotion interactions were found for any of the other self-blame-related action tendencies (apologising, hiding, attacking oneself).

2.3.4) The relationship between other-blaming emotions and action tendencies

Table 2-9 shows that the other-blaming emotions including contempt/disgust and anger/indignation towards others were both associated with a higher probability of attacking

others and distancing from others across both groups. No main effect of group nor interaction between group and other-blaming emotions were found.

2.3.5) Relationship of clinical variables with maladaptive action tendencies in MDD

There were no significant correlations between proneness to feeling like hiding, or creating a distance from oneself and the number of previous depressive episodes ($\tau=-.13$, $p=.15$, $z=-1.46$; $\tau=.07$, $p=.42$, $z=-.80$). BDI scores were weakly positively correlated with proneness to feeling like creating a distance from oneself ($\tau=.31$, $p<.001$, $z=3.47$), but not with feeling like hiding ($\tau=.14$, $p=.12$, $z=1.56$).

2.5) Discussion

We hypothesised that individuals with MDD were more likely to experience maladaptive self-blame-related action tendencies which interfere with reparative actions. We confirmed our first specific hypothesis that individuals with MDD would display an increased tendency to feel like creating a distance from themselves and hiding. Our third specific hypothesis was supported by finding that shame was associated with feeling like hiding, in line with what has been proposed in the literature (Roseman et al., 1994; Tangney et al., 2007). However, contrary to our second hypothesis, self-contempt/disgust was associated with attacking oneself rather than feeling like creating a distance from oneself. Intriguing was the finding of an overgeneralised perception of control for other people's actions and a tendency to apologise for others' wrongdoings in the MDD group.

Previous research has demonstrated the distinction between adaptive and maladaptive action tendencies. The former promotes constructive and proactive pursuit, such as apologizing, whereas the latter motivates defensiveness, social withdrawal and interpersonal separation, such as hiding and creating a distance from oneself (Tangney et al., 2007). Our study is the first to demonstrate that maladaptive action tendencies distinguish participants with MDD and

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healthy control participants, who were closely matched apart from their difference in MDD vulnerability. Despite a lack empirical studies in clinical populations, this finding is consistent with Mu and Berenbaum (2019), who also demonstrated that withdrawal-related maladaptive action tendencies are associated with vulnerability to depression in a non-clinical sample. Maladaptive action tendencies as demonstrated here could contribute to maladaptive coping styles, such as avoidance-oriented coping, which predicted anxious and fearful responding under stressful circumstances (Spira et al., 2004) and have been consistently found to be associated with MDD (Berghuis & Stanton, 2002; Burker et al., 2005). As such, creating a distance from oneself and hiding might motivate people to use social avoidance as a coping mechanism, which contribute to their MDD vulnerability in response to negative social feedback. This view is consistent with Lemogne and colleagues (Lemogne et al., 2006), who suggest that patients with MDD tend to recall memories from a third person perspective and use it as a form of cognitive avoidance. In addition, from a more theoretical perspective, feeling like creating a distance from oneself might also involve the rejection and denial of one's self-identity, as well as an increased self-discrepancy as proposed by Higgins (1987). An increase in self-discrepancy was both directly and indirectly linked to depressive symptoms (Roelofs et al., 2007) and possibly also related to one's vulnerability to MDD.

In addition, the finding that people with MDD tend to apologise more readily when their friend has done something wrong is consistent with our previous finding that individuals with MDD have increased overgeneralised self-blaming emotions and reduced blame-related emotions towards others (Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015). The overgeneralised self-blame could be explained by the attributional theory of depression (Abramson et al., 1978), which states that people with depression tend to attribute negative consequences to internal, stable and global rather than external factors. This means that when experiencing stressful events, people with depression are likely to blame themselves rather than

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blame others. In some situations, they might even blame themselves when they have not done anything wrong, as seen in our findings. As proposed by Abramson and colleagues, these kinds of negative attributional styles were hypothesised to reduce individuals' self-esteem and ultimately increase their vulnerability to depression (Abramson et al., 1978). Further, we also found that people with MDD tend to attribute control to themselves and this demonstrates that overgeneralised control over other people's wrongdoing could also be a vulnerability trait of MDD which is in keeping with increased omnipotent responsibility guilt in MDD (O'Connor et al., 2002).

On the other hand, our findings are inconsistent with the view that shame is specifically associated with maladaptive action tendencies that promote defensiveness, interpersonal separation and distance, and only guilt is specifically associated with adaptive action tendencies that motivate constructive and reparative actions such as apologising (Ketelaar & Tung Au, 2003; Tangney et al., 2007). Instead, our results show that all self-blaming emotions were associated with a tendency to apologise, but that guilt and shame can also both be associated with feeling like hiding. These differences indicate that shame and guilt could be either adaptive or maladaptive under different circumstances, which is consistent with the findings of some researchers (Taihara & Malik, 2016). The different forms of shame and guilt (adaptive vs. maladaptive) cannot be distinguished based on the emotion labels alone, which reveals the limitations of measuring self-blaming emotions using emotion labels and implies that action tendencies could be a more appropriate measure of self-blame (Mu & Berenbaum, 2019). Further, the finding that self-contempt/disgust was associated with feeling like attacking oneself is at odds with our second hypothesis and the hypotheses proposed by previous researchers which state that contempt/disgust is specifically associated with creating a distance (Haidt, 2003). However, these hypotheses mainly concern contempt towards others, not oneself.

Therefore, it might reveal that contempt towards others and towards oneself are not comparable and motivate very different action tendencies.

Interestingly, our unexpected finding of the association between self-contempt and self-attacking might help to explain why depressed individuals who have biases towards self-contempt also had a high rate of self-harm (Stanicke, 2021). That is, the proneness to self-contempt in depressed individuals motivates a tendency to attack themselves during stressful events, which then promotes their self-harming behaviours. Nevertheless, the hypothesised relationship between self-attacking and self-harm needs to be further examined. Evolutionarily speaking, self-contempt might be more important than self-indignation as an emotion of self-reflection, because the former involves stronger action tendencies such as self-attacking compared with the latter. Self-contempt might be adaptive in the short term as it helps the formation and development of moral standard, however, it will negatively impact one's mental health in the long term.

2.5.1) Limitations

On a more cautionary note, our study was limited firstly by its cross-sectional design, which made it difficult to infer a causal relationship between MDD vulnerability and action tendencies. While maladaptive action tendencies could be a vulnerability trait for MDD, it is also possible that these represent scarring effects of previous depressive episodes (Wichers et al., 2010). Nevertheless, this is unlikely as no correlation was found between maladaptive action tendencies and the number of previous depressive episodes. Future studies are needed to determine whether feeling like creating a distance from oneself is a pure trait marker of vulnerability or is also modulated by depressive state which its correlation with residual symptoms suggests. Secondly, the task was in a verbal format and included abstract descriptions of scenarios. Thus, participants' self-blaming emotions might have depended in part on how well they can imagine the scenarios and indeed we previously found an association

between visual imagery ratings and emotional intensity ratings (Zahn et al., 2009). It is therefore important to develop more immersive and ecologically valid tasks to measure moral emotions and blame-related action tendencies in future studies, which rely less on the ability to create one's own imagery, which recent research shows is a widely varying ability (FeldmanHall et al., 2012; Fulford et al., 2018). Another limitation of the study is the lack of control of residual depressive symptoms, which might limit the generalization of our findings to more specific populations.

2.5.2) Conclusions

Taken together, feeling like creating a distance from oneself and hiding were distinctive for remitted MDD compared with the control group, thus unveiling a novel marker of psychopathology, which was present even when symptoms had subsided. Future studies are needed to probe the prognostic value of maladaptive action tendencies. If replicated, our findings further suggest the development of novel psychological and neurocognitive treatments specifically aiming at self-distancing and hiding which are so far neither assessed nor addressed in standard psychotherapeutic approaches.

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Table 2-1| Exclusion reasons for participants following phone pre-screening interview

| Reason for exclusion | n |
|--|-----|
| Current antihypertensive medications or statins | 20 |
| Current antidepressant or other centrally active medications | 52 |
| Diabetes | 4 |
| Epilepsy | 5 |
| Multiple sclerosis | 3 |
| Past cancer | 7 |
| Past stroke | 1 |
| Thyroid function problems | 19 |
| Vitamin D deficiency | 1 |
| Other psychiatric disorders than MDD | 54 |
| Substance or alcohol abuse | 23 |
| Other general medical condition | 5 |
| Family history of MDD/bipolar/schizophrenia (control group) | 26 |
| Excluded because of age-matching (control group) | 3 |
| Left-handed | 20 |
| MRI contraindications | 77 |
| Non-native English speaker | 19 |
| Out of age range | 4 |
| No reason recorded | 5 |
| Withdrawal after phone pre-screening | 33 |
| Not meeting full screening criteria for MDD | 30 |
| Not remitted for long enough | 7 |
| Fulfilling criteria for current MDD | 13 |
| Total excluded after phone pre-screening | 431 |

Table 2-2| Demographic characteristics of participants

| | Sample | | p-value |
|--------------------|----------------|--------------|---------|
| | rMDD (n=76) | HC (n=44) | |
| Age | 35.9 (13.1) | 33.7 (12.9) | 0.379 |
| Sex*[Female] | 55 (72.4%) | 28 (63.6%) | 0.428 |
| Years of Education | 16.8 (2.16) | 17.3 (2.48) | 0.245 |
| BDI Score | 3.71 (3.73) | 0.84 (1.63) | <0.001 |
| MADRS Score | 1.08 (1.49) | 0.59 (1.19) | 0.051 |
| GAF Score | 85.3 (5.87) | 89.1 (2.60) | <0.001 |

BDI = Beck Depression Inventory; MADRS = Montgomery-Asberg Depression Rating Scale; GAF - Global Assessment of Function. Values are Mean (Standard Deviation) for approximately continuous variables and Count (Percentage%) for categorical variables. Summary p-values are obtained from Welch's t-tests and Fisher's exact test respectively.

Table 2-3 | Clinical characteristics of included MDD participants (n=76)

| | |
|--|---------------------------------|
| <i>Mean age at onset (Years)</i> | 22.74 ± 9.96 (range:11-52) |
| <i>Past MDD subtype</i> | |
| With melancholic feature | 42 |
| With atypical feature | 8 |
| No specific subtype | 26 |
| <i>Number of previous MDEs</i> | |
| 1 | 17 |
| 2 | 22 |
| 3 | 14 |
| 4 | 9 |
| 5 or more | 14 |
| Average number of previous MDEs | 3.84 ± 6.39 (range:1-53) |
| <i>Last MDE details</i> | |
| Average length of MDE (months) | 13.29 ± 17.49 (range:.5-96) |
| Average time in remission (months) | 28.85 ± 37.30 (range:5.5-282.0) |
| Total illness duration | 112.11 ± 107.71 (range:2-552) |
| <i>Life-time axis-I co-morbidity</i> ^a | |
| Eating disorder | 2 |
| Post-traumatic stress disorder | 2 |
| No life-time co-morbidity | 56 |
| Unknown | 14 |
| <i>Family history</i> | |
| First degree relative with MDD | 27 |
| No family member with history of MDD | 26 |
| First degree relative with schizophrenia or bipolar disorder | 6 |
| Unknown or diagnostically unclear | 15 |

MDE: major depressive episode; MDD: major depressive disorder; MDD subtype classification was based on adapting the SCID-I for DSM-IV-TR to allow lifetime assessment of subtypes. a. All co-morbid disorders were fully remitted at time of study and none of the co-morbid disorders was a likely primary cause of the depressive episodes. All ± refer to standard deviations.

Table 2-4 | Split-half reliability of the action tendency task

| Action tendency task response | Self-agency condition | Other-agency condition |
|--------------------------------------|-----------------------|------------------------|
| Apologising [%] | .89 | .90 |
| Hiding [%] | .86 | .93 |
| Attacking self [%] | .95 | .87 |
| Creating a distance from oneself [%] | .94 | .79 |
| Attacking friend [%] | .84 | .93 |
| Creating a distance from friend [%] | .86 | .93 |
| Perceived control [mean] | .96 | .96 |
| Perceived responsibility [mean] | .96 | .98 |

Split-half reliability was calculated for each action tendency response per condition using the Spearman-Brown formula after randomly splitting items into parallel forms based on the alphabetic order of stimuli.

Table 2-5 | Means and standard deviations of proportion of trials for which a particular action tendency was chosen

| Action | Healthy Control (n=44) | | MDD (n=76) | |
|----------------------|------------------------|---------------|---------------|---------------|
| | self-agency | other -agency | self-agency | other-agency |
| No action | 0.356 (0.233) | 0.572 (0.282) | 0.320 (0.206) | 0.467 (0.257) |
| Apologise | 0.530 (0.230) | 0.050 (0.068) | 0.451 (0.219) | 0.093 (0.120) |
| Distance from friend | | 0.296 (0.234) | 0.046 (0.055) | 0.319 (0.230) |
| Distance from self | 0.034 (0.051) | 0.006 (0.017) | 0.055 (0.081) | 0.012 (0.033) |
| Hide | 0.023 (0.061) | 0.008 (0.020) | 0.056 (0.085) | 0.049 (0.107) |
| Attack friend | 0.025 (0.050) | 0.053 (0.121) | 0.002 (0.011) | 0.051 (0.095) |
| Attack self | 0.001 (0.004) | 0.015 (0.048) | 0.070 (0.143) | 0.011 (0.045) |

Table 2-6 | Action tendencies by group and condition

| Effect | df | F-value | p-value |
|----------------------------------|------------|---------|---------|
| group | 1, 118 | 8.95 | .003* |
| action tendency | 2.7, 323.3 | 206.45 | <.0001* |
| group x action tendency | 2.7, 323.3 | 2.59 | .06 |
| agency | 1, 118 | 0.10 | .75 |
| group x agency | 1, 118 | 5.35 | .02* |
| action tendency x agency | 3.7, 435.4 | 189.45 | <.0001* |
| group x action tendency x agency | 3.7, 435.4 | 4.16 | .003* |

The proportion of trials for which a particular action tendency was selected was arcsine square root transformed for this repeated-measures multivariate analysis of variance (MANOVA). Repeated measures MANOVA revealed a significant omnibus interaction: action tendency x agency x clinical group, $F(3.69, 435.37) = 4.16, p = .003$.

Table 2-7 | Action tendencies by group and condition - post-hoc tests

| agency | action tendency | estimate | t-value | p-value |
|--------------|--------------------------------|----------|---------|---------|
| self-agency | no action | 0.05 | 1.14 | 0.25 |
| | apologise | 0.09 | 2.15 | 0.03* |
| | create a distance from other | -0.04 | -0.91 | 0.36 |
| | create a distance from oneself | -0.09 | -2.27 | 0.02* |
| | hide | -0.08 | -1.99 | 0.05* |
| | other-attack | -0.01 | -0.24 | 0.81 |
| | self-attack | -0.09 | -2.36 | 0.02* |
| other-agency | no action | 0.13 | 3.43 | <.001* |
| | apologise | -0.08 | -2.15 | 0.03* |
| | create a distance from other | -0.03 | -0.76 | 0.45 |
| | create a distance from oneself | -0.02 | -0.52 | 0.60 |
| | hide | -0.10 | -2.51 | 0.01* |
| | other-attack | -0.01 | -0.20 | 0.84 |
| | self-attack | 0.00 | 0.07 | 0.94 |

Estimated effect of MDD group: HC mean - MDD mean

Table 2-8| Self-blame-related action tendencies and emotions

| | Apologising | | | Hiding | | | Distancing from self | | | Attack self | | |
|-----------------------------|-------------|-----|---------|--------|-----|---------|----------------------|------|---------|-------------|------|-------|
| | B | SE | p | B | SE | p | B | SE | p | B | SE | p |
| Shame | 1.96 | .22 | <.001** | 3.67 | .84 | <.001** | 1.38 | .77 | .07 | 2.31 | 1.18 | .05 |
| Guilt | 1.93 | .18 | <.001** | 2.32 | .78 | .002* | 1.20 | .63 | .06 | 2.06 | 1.10 | .06 |
| Self-disgust/contempt | 1.83 | .23 | <.001** | 2.03 | .91 | .03 | .92 | .70 | .19 | 3.20 | 1.17 | .006* |
| Self-anger | 2.00 | .23 | <.001** | 1.33 | .75 | .03 | 2.67 | .68 | <.001** | 1.89 | .152 | .13 |
| Group | .24 | .27 | .38 | 1.63 | .85 | .02 | 2.21 | 1.03 | .03 | 2.29 | 1.49 | .12 |
| Group*Shame | -.71 | .28 | .01 | -1.38 | .81 | .03 | -.27 | .88 | .76 | .65 | 1.36 | .63 |
| Group*Guilt | -.40 | .23 | .09 | -.80 | .77 | .11 | -.70 | .75 | .34 | .65 | 1.27 | .61 |
| Group*Self-disgust/contempt | -.34 | .30 | .24 | .03 | .89 | .84 | -.71 | .82 | .39 | .01 | 1.35 | .99 |
| Group*Self-Anger | -.37 | .31 | .23 | .005 | .89 | .79 | -1.50 | .87 | .08 | 1.20 | 1.47 | .41 |

Four mixed effect logistic regression models were conducted, one for each self-blame-related action tendency as outcome variable. Predictors were agency-congruent moral emotions (Shame, guilt, self-disgust/contempt, self-anger), group (MDD vs. HC) as well as their interactions as predictors. Reference categories for moral emotions in all models were the trials in which participants chose no/other emotion. The significance threshold was set to an approximate Bonferroni-corrected $p < .05$ across all 6 models, corresponding to an uncorrected $p < .008$ in each model. **=.001, *=.008. B=estimate, SE=standard error.

Table 2-9 | Other-blame-related action tendencies and emotions

| | Attacking friend vs. Reference categories | | | Distancing from friend vs. Reference categories | | |
|--|--|-----|---------|--|-----|---------|
| | B | SE | p | B | SE | p |
| Disgust/Contempt towards friend | 2.39 | .58 | <.001** | 1.70 | .20 | <.001** |
| Anger/Indignation towards friend | 2.76 | .46 | <.001** | 1.46 | .14 | <.001** |
| Group | 1.03 | .86 | .23 | .61 | .36 | .09 |
| Group * Disgust/contempt towards friend | -.50 | .73 | .49 | -.46 | .26 | .08 |
| Group * Anger/indignation towards friend | .26 | .58 | .65 | .03 | .19 | .87 |

Two mixed effect logistic regression models were conducted, one for each other-blame-related action tendency as outcome variable. Predictors were agency-congruent moral emotions (disgust/contempt towards friend, anger/indignation towards friend), group (MDD vs. HC) as well as their interactions as predictors. Reference categories for moral emotions in all models were the trials in which participants chose no/other emotion. The significance threshold was set to an approximate Bonferroni-corrected $p < .05$ across all 6 models, corresponding to an uncorrected $p < .008$ in each model. **=.001, *=.008. B=estimate, SE=standard error.

Figure 2-1 | A trial in the self-agency condition of the action tendency task

Social Action Evaluation

What would you feel like doing in response to this behaviour?

you do act bossily towards Lucy

Please select the action that you would most strongly feel like doing (check only one box):

Feel like verbally or physically attacking/punishing your best

Feel like verbally or physically attacking/punishing yourself

Feel like apologizing/fixing what you have done

Feel like hiding

Feel like creating distance from your best friend

Feel like creating distance from yourself

Other Action

No Action

How responsible would you feel?

Not at all | Extremely

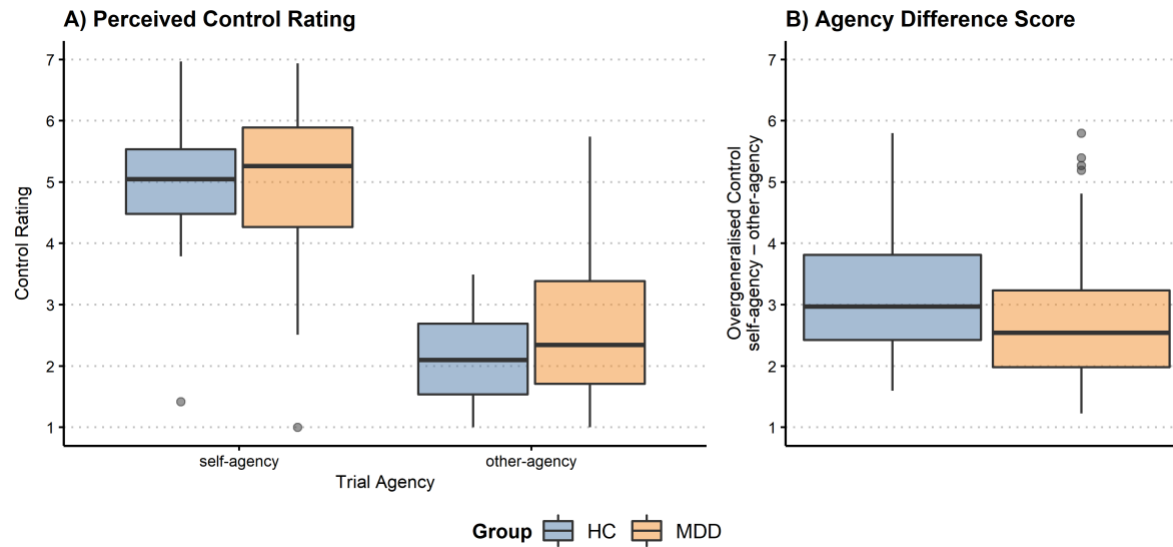
How much control would you have?

None at all | Complete

Continue

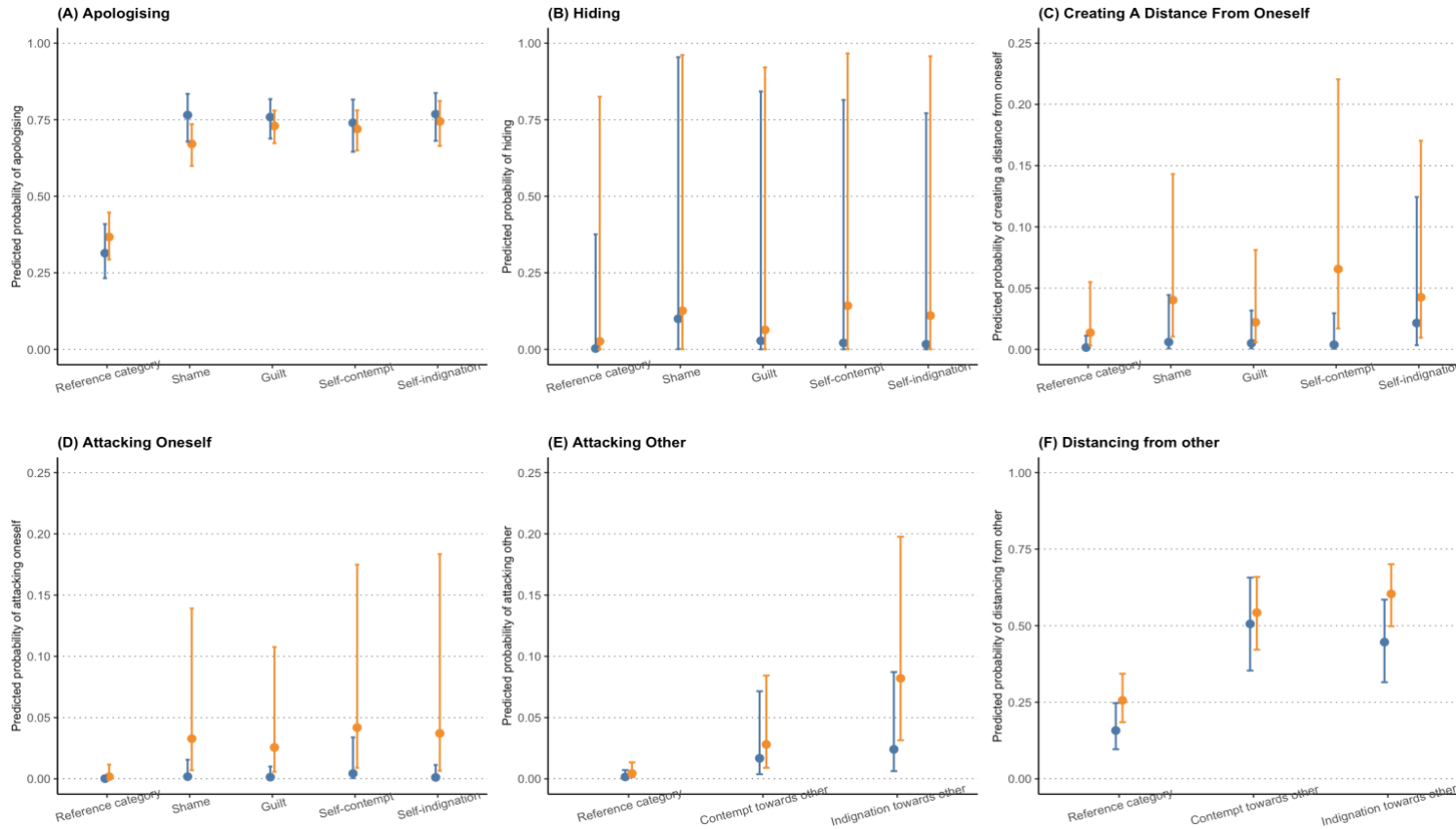
The trial shows a hypothetical social interaction between the participant and her best friend (The participant does act bossily towards her best friend, Lucy). There are 180 trials in total, with 90 of them in the self-agency and other-agency condition respectively. Participants were asked to choose between eight action tendencies as well as how responsible they felt and how much control they had for all trials. Everything will stay the same in the other-agency condition, except that the scenario will change to “Lucy does act bossily towards you”.

Figure 2-2| Perception of control (A) and the level of overgeneralised control (B) by clinical groups with 95% confidence intervals as measured by the valued-based moral sentiment task



Overgeneralised control was calculated by the other-agency control rating subtracted from the self-agency control rating for each subject. A higher value indicates less overgeneralisation of control ratings.

Figure 2-3| Means and 95% confidence intervals for the predicted probability of different action tendencies



Feeling like apologising (A), hiding (B), creating a distance from oneself (C), attacking oneself (D), attacking other (E) and distancing from other (F) and their relationships to different moral emotions in both groups (HC=Healthy Control, MDD = major depressive disorder). Reference category included trials in which participants selected other or no emotion.

Chapter 3: Measuring maladaptive blame-related action tendencies using a virtual reality task and their association with current depression

3.1) Abstract

Darwin stated that humans have an involuntary tendency to perform certain actions when a specific state of mind is induced. Such “action tendencies” are key to understanding the maladaptive impact of self-blame in depression. For example, feeling like “hiding” in a text-based task was previously associated with recurrence risk in remitted depression. Despite their functional importance, action tendencies have not been systematically investigated in current depression, which was the aim of this pre-registered study. We developed and validated the first virtual reality (VR) assessment of blame-related action tendencies and compared current depression (n=98) with control participants (n=40). The immersive VR-task, pre-programmed on devices sent to participants’ homes, used hypothetical social interactions, in which either participants (self-agency) or their friend (other-agency) were described to have acted inappropriately. Compared with controls, people with depression showed a maladaptive profile: particularly in the other-agency condition, rather than feeling like verbally attacking their friend, they were prone to feeling like hiding, and punishing themselves. Interestingly, feeling like punishing oneself was associated with a history of self-harm but not suicide attempts. Current depression and self-harm history were linked with distinctive motivational signatures, paving the way for remote VR-based stratification and treatment.

3.2) Introduction

Proneness to overgeneralised self-blaming emotions plays a central role in cognitive models of depression (Abramson et al., 1978; Janoff-Bulman, 1979). Self-blaming emotions are associated with a tendency to perform specific actions such as hiding and apologising (Duan, Lawrence, et al., 2022). In his seminal chapter “The Expression of the Emotions in Man and Animals”, Darwin stated that humans have a strong and involuntary tendency to perform certain actions when a specific state of mind is induced and emphasised the evolutionary importance of these tendencies (Darwin, 1872). Such implicit tendencies, so called “action tendencies”, describe a cognitive and motivational state before an action is taken (Haidt, 2003), thereby providing the crucial link between emotion and action. Due to its immersive nature, virtual reality (VR) is ideally suited to uncover usually implicit experiences. Here, we employed a novel remote VR task to investigate the role of blame-related action tendencies in depression. Identifying depression-related maladaptive action tendencies is an essential step towards understanding the link between emotions and actions and developing novel interventions and cognitive markers.

Over the past 50 years, a growing body of research has focused on the importance of negative and self-blaming emotions in the development of depression (e.g. Power & Dalgleish, 2015). Beck identified thinking styles of people with depression as an overgeneralization of negative thoughts and proposed a cognitive bias towards negative thinking in depression (e.g. Beck et al., 1985). Further, the feeling of overgeneralised guilt (O'Connor et al., 2002) and a bias towards self-contempt have been found in people with depression even on remission of their symptoms (Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015). These findings suggested self-blaming emotions as vulnerability factors for depression. However, it might be misleading to understand the relationship between self-blaming emotions and depression based on the emotion labels alone. For example, there are different forms of guilt which can be either

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adaptive or maladaptive. Adaptive guilt was associated with good social adjustment and was not related to depression vulnerability (Tangney et al., 2007). In contrast, an overgeneralised form of guilt was maladaptive and increased in major depressive disorder (O'Connor et al., 2002). Consequently, to understand self-blaming emotions in depression, one needs to unveil their link with motivating either adaptive or maladaptive social actions.

These implied adaptive (e.g. “feeling like apologising”) and maladaptive social actions (e.g. “feeling like hiding”) have been referred to as “action tendencies” in the social psychology literature (Haidt, 2003). Maladaptive action tendencies have been defined as attempts to deny, hide or escape the emotion-inducing situation, whereas adaptive action tendencies were defined as implying reparative actions that help people face and deal with a difficult situation (Haidt, 2003; Tangney et al., 2007). It was shown that people with higher depressive symptoms exhibited higher levels of maladaptive action tendencies such as withdrawal compared with those with lower symptoms (Mu & Berenbaum, 2019). In support of this, our recent study also found that people with remitted depression had more maladaptive action tendencies including feeling like “hiding”, “creating a distance from oneself” and “attacking oneself” than those without a history of depression (Duan, Lawrence, et al., 2022). These maladaptive action tendencies were related to either escaping the situation, denial of one’s identity, or self-punishment which might further contribute to depressogenic cognitive styles in stressful situations and ultimately increase the likelihood of developing depression. Indeed, maladaptive action tendencies were a prospective risk factor for recurrence risk in remitted major depressive disorder (Lawrence et al., 2021).

While maladaptive blame-related action tendencies were associated with vulnerability to depression (Lawrence et al., 2021), so far, their role in current depression and associated maladaptive behaviours is elusive. Specifically, self-harming and suicidal behaviours are of the highest clinical relevance in depression. Both have been associated with self-blaming

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emotions (Sheehy et al., 2019) and punishment-related behaviours (Stanicke, 2021), but the role of action tendencies in self-harming behaviours is unknown. In addition, previous measures of self-blaming emotions and action tendencies used abstract verbal descriptions (Lawrence et al., 2021), which heavily relied on how well participants could imagine and contextualise these action tendencies. Also, these measures did not allow participants to act out their action tendencies, which further limited their immersiveness and engagement in the scenarios. VR-based assessment is a new experimental paradigm for psychometric evaluation compared with traditional paper-and-pencil or computerised tasks. VR scenarios were suggested to be safe and promising tools for cognitive assessments in people with psychiatric disorders (Falconer et al., 2016; Henry et al., 2012). The interactive and immersive nature of the VR environment makes it well suited in depicting blame-related social scenarios and allows to measure action tendencies in controlled experimental conditions.

For the present study, we developed and validated such a novel VR task to assess blame-related action tendencies with the following aims: firstly, to probe our pre-registered hypothesis that people with current depression exhibit higher levels of maladaptive blame-related action tendencies, such as feeling like hiding and creating a distance from oneself (clinicaltrials.gov: NCT04593537, research question a.); and secondly to investigate the hypothesis, that maladaptive action tendencies, specifically feeling like punishing oneself, are associated with a higher risk of self-harm and suicide attempt based on self-reported history.

3.3) Methods

3.3.1) Participants

This study was approved by the King's College London PNM Research Ethics Subcommittee (Project Reference:HR-19/20-17589) and pre-registered NCT04593537 with a cross-sectional part which we reported in the current paper and a prospective prognostic study which will be reported separately. The eligibility of participants was determined by an online pre-screening questionnaire, which participants accessed via the online adverts.

General inclusion criteria were: age of 18 years or over and being able to complete self-report scales orally or in writing. General exclusion criteria were: a personal or family history of schizophrenia, schizoaffective disorder, or bipolar disorder, a personal history of psychotic symptoms, drug or alcohol abuse over the last 6 months, a suspected central neurological condition, a planned or current pregnancy, or currently being treated by a mental health specialist in secondary care. In addition, participants were excluded if they had hypomanic symptoms [The Hypomanic Checklist-16 (Forty et al., 2010) score > 8 , symptoms lasting ≥ 2 days] and endorsed two of the first three screening questions of the Composite International Diagnostic Interview bipolar screening scale (Kessler et al., 2006). Figure 3-1 shows exclusions reasons for participants and a flow chart of the participant recruitment. Specific depression group inclusion criteria were: Patient Health Questionnaire-9 (PHQ-9, Kroenke et al., 2001) score ≥ 15 as in our related but independent Antidepressant Advisor Trial (Harrison et al., 2020) and early treatment resistance to antidepressants [here defined as having tried at least one antidepressant medication in primary care according to (Fekadu et al., 2018)]. Specific control group exclusion criteria were: a personal or family history of depression, a personal history of taking antidepressants, and a PHQ-9 score > 9 . Specific control group inclusion criteria were matching for demographic variables with the depression group. The rationale for these

inclusion/exclusion criteria was to allow comparison with our primary care Antidepressant Advisor Trial. We used a conservative PHQ-9 score cut-off (≥ 15) for including participants in the depression group, which has a specificity of .96 for MDD (Manea et al., 2012) and a rigorous way of excluding people with a bipolar history, as well as used validated scales for excluding substance and alcohol use disorders.

897 participants completed the online pre-screening questionnaires, 164 participants were eligible for the depression and 198 for the control group. One hundred-and-one participants with depression and 40 control participants agreed to participate and completed the online baseline assessment of the study; with 98 in the depression group and all control participants completing the VR task. All participants were compensated with a £25 Amazon voucher on completing the study or £15 for only completing the online baseline assessment. Participants were recruited via online advertising on social media as well as the King's College London department circular.

3.3.2) *Statistical power*

The sample size of the depression group was primarily powered for the prospective prognosis study, which will be reported separately (clinicaltrials.gov: NCT04593537). We aimed for a control group sample size of at least 35 to allow for reliable standard deviation estimates which are needed for effect size estimates in feasibility studies in the absence of known effect sizes (Teare et al., 2014). For our main question in this paper (aim 2), our overall attained sample size of $n=138$ allowed us to detect a Cohen's F^2 effect size of ≥ 0.16 (i.e. medium effect size), corresponding to $\eta^2 \geq .14$ with 90% power at a 2-sided $p \leq .05$ in the MANOVA with 10 action tendency outcome variables and one predictor variable (group, $df=[127,10]$, G-Power software version 3.1.9.7).

3.3.3) *Assessment of clinical characteristics*

In the online baseline assessment, questionnaires were developed to collect participants' demographic information as well as to measure their depressive and anxiety symptoms [the Quick Inventory of Depressive Symptomatology – self-reported -16 [QIDS-SR-16, (A. J. Rush et al., 2003)], Maudsley-Modified Patient Health Questionnaire [MM-PHQ-9, (P. Harrison et al., 2021)] and Generalised Anxiety Disorder-7 Scale [GAD-7, (R. L. Spitzer et al., 2006)]. Participants in the depression group were also asked to select the antidepressants they were currently taking or had taken in the past two months as well as the antidepressants they had taken prior to that.

History of self-harm was measured by two questions: “Have you ever deliberately injured yourself without intending to kill yourself?” and “How many times have you deliberately injured yourself over your lifetime?”. History of suicide attempts was also measured by two questions: “Have you ever made a suicide attempt?” and “How many times have you made suicide attempts over your lifetime?”.

3.3.4) *Procedure*

This study was conducted fully remotely between June 2020 to June 2021, thereby allowing us to conduct the study during the COVID-19 pandemic. After participants enrolled in the study, they received the links to complete the online baseline assessment, the text-based action tendency task by email and a VR headset by courier. Participants were asked to complete the online baseline assessment first, followed by the text-based action tendency task and finally the VR action tendency task following the instructions provided by the researcher. The VR task was completed by participants unsupervised, however, if participants had any questions during the completion of the task, the researcher was available on the phone or via video conference

if needed. Participants sent the VR headset back to the researcher after they completed all the tasks.

3.3.5) Virtual reality assessment of blame-related action tendencies

The virtual reality environment was developed by the King's College London, Institute of Psychiatry, Psychology and Neuroscience VR Research Lab in Unity, deployed to Oculus Go. The design of the VR task was based on the value-related moral sentiment task (VMST) which has been described in Zahn, Lythe, Gethin, Green, Deakin, Workman, et al. (2015). In order to make the task both brief and sensitive to detect blame-related emotions, 15 social scenarios were chosen from previous normative studies (Sophie Green et al., 2013) where participants were asked different scenarios when their self-blaming or other-blaming emotions were triggered. Each scenario was in both the self-agency and other-agency condition (30 trials in total, 15 per condition). In the self-agency condition, the participant acted counter to social and moral values in the interaction with their friend (the participant was the agent). In the other-agency condition, the participant's friend was the agent and the participant the recipient of the action.

At the beginning of the VR task, participants were presented with the welcome message and asked to enter their participant ID. As the task began, participants were taken to a scene in the street, a shopping centre, or a coffee shop, while a narrator described a hypothetical social scenario that happened between the participants and their friends. The full list of the narrative of the hypothetical social scenarios is included in the Table 3-1. One example of the narrative in the self-agency condition is "You drove your friend's car, caused an accident and damaged it". Participants then saw the VR avatar entering the scene and moving towards them. The narrator said, "You just saw your friend, what would you feel like doing?". Participants saw choice options displayed on the screen and asked to choose one of them (See Figure 3-2). Among the choices were seven different action tendencies: "Verbally attacking my friend",

“Punishing myself”, “Apologising”, “Hiding”, “Creating distance from my friend”, “Creating distance from myself”, and “Other/no action”. As soon as participants made their choices using their virtual hands, the display changed accordingly to perform the corresponding actions. At the end of each trial, participants were asked to rate their levels of self-blame (how strongly would you blame yourself?) and other-blame (how strongly would you blame your friend?) from 1 to 7, where 1 corresponded to “not at all” and 7 to “very much”, shown on the screen as visual analogue scroll bars. Response time taken for participants to choose different action tendencies was recorded by measuring the duration between action tendency options displayed on the screen and participants selecting one of the action tendencies. Screenshots and video of the VR task can be found in Figure 3-2 and <https://youtu.be/agWahwvYDXc>. Qualitative feedback from the participants showed that the VR task was overall easier to focus on and more immersive than the text-based task.

In addition, the text-based action tendency task was completed by participants to compare with the virtual reality action tendency task. This task has been validated in our previous study (Duan, Lawrence, et al., 2022).

3.3.6 Text-based assessment of blame-related action tendencies

The text-based action tendency task was completed by participants to compare with the virtual reality action tendency task, either using Excel Macro or using PsychoPy (Peirce et al., 2019). This task has been validated in our previous study (Duan, Lawrence, et al., 2022) but here, we used a modified, shortened version with 54 trials (27 trials in the self-agency condition and 27 trials in the other-agency condition). The original task consisted of 180 statements, resulting in a long session duration, and not all social concepts were deemed relevant to overgeneralised feelings of self-blame. In addition to shortening the task, the statements themselves were optimised by excluding negated positive social concepts (e.g. “does not act generously”) and replacing “does act [social concept]” with “is [social concept]”).

In the task, participants were presented with hypothetical social interactions between them and their friend, during which either the participant (self-agency condition) or the participant's friend (other-agency condition) acted counter to social and moral values. To personalise the statements, participants were asked to name their friend in the initial set-up. For each interaction/trial, participants were asked to choose one emotion from six moral emotions: shame, guilt, contempt/disgust towards oneself, contempt/disgust towards friend, indignation/anger towards friend, or no/other feeling, and one action tendency from six action tendencies: apologising, hiding, creating a distance from oneself, creating a distance from friend, verbally or physically attacking friend, or no/other action. In addition, participants were asked to indicate how strongly they would blame themselves and their friend for the imagined behaviour on a scroll bar from 1 ("not at all") to 7 ("very much").

3.3.7) Data analysis

All data were analysed using IBM SPSS statistics version 27. Means and standard deviations were calculated for the proportion of choosing each action tendency for each participant in each condition (self-agency and other-agency). The effect of depressive symptoms (QIDS-SR-16 score), anxiety symptoms (GAD-7 score) and medication status on average action tendency proportions in the depression group were examined by a multivariate analysis of variance (MANOVA).

The newly developed VR task was validated by comparing it with the text-based action tendency task. Self-blame rating bias measures were calculated for each participant and agency-condition (self- vs. other-) by subtracting the average other-blame ratings from self-blame ratings. Pearson correlation analyses were carried out to examine the relationship between pairs of corresponding action tendencies and self-blaming bias measures in the text-based and VR-based tasks. The reference correlation was computed by taking the average of the Pearson correlation coefficients across all action tendencies, except the action tendency of

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interest. The correlation for each action tendency was compared against the reference correlation using the Fisher-Z-transformation. A significant Pearson correlation and Fisher's z value indicated construct. The VR task was further validated by investigating the relationship between action tendencies and self-blame rating bias measures using a MANOVA, with different action tendencies as dependent variables and self-blame rating bias measures in both conditions as independent variables.

For aim 1, the effects of group on action tendencies were examined using a MANOVA with different action tendencies as dependent variables and group as the only independent variable. For aim 2, the role of punishing oneself in relation to past self-harm and suicide attempt were examined by another MANOVA with punishing oneself in both conditions as dependent variables and self-harm and suicide attempt as the independent variables. For all MANOVAs, post-hoc univariate tests were carried out if significant multivariate effects were found. Multiple comparison correction at a two-sided $p=.05$ using the Benjamini–Hochberg procedure was employed for all post-hoc univariate tests. Repeated measures analysis of variance (ANOVA) was used to examine the differences of response time taken to choose action tendencies in each agency condition and group.

3.4) Results

3.4.1) Clinical characterisation of the participants

The characteristics of participants with depression and control participants are shown in Table 3-2. There were no significant group differences on any demographic variables including age, years of education, sex ratio, ethnicity, native language, or employment status. The clinical characteristics of participants with depression are shown in Table 3-3. Most of them had one to two treatment failures as defined by the Maudsley Staging Method (Fekadu et al., 2018), a duration of their current depressive episode of ≤ 12 months, depressive symptoms that fell into the severe range, and were currently taking a single SSRI as their antidepressant medication.

3.4.2) Validation of the VR task

Action tendencies and self-blame rating biases were compared between the VR- and text-based tasks to probe their construct validity (see Table 3-4). Overall, most action tendencies in the VR task were significantly correlated with those in the text-based task (r ranging between 0.27-0.55), except hiding in the self-agency condition and distancing from oneself in the other-agency condition. After the Fisher-Z-transformation, there were also significant differences found between these action tendencies and the reference correlations, showing that associations were specific for corresponding action tendencies. In addition, self-blame rating biases in the VR task were highly correlated with self-blame rating biases in the text-based task in both conditions ($r=0.68$ in the self-agency and $r=0.75$ in the other-agency).

The VR task was further validated by demonstrating a significant association between multivariate action tendency profiles as outcomes and self-blaming biases as predictors across groups (self-agency condition: $F(10,126)=7.19$, $p<.001$, Wilk's $\Lambda = .36$, partial $\eta^2 = .36$; as well as other-agency condition: $F(10,126)=10.45$, $p<.001$, Wilk's $\Lambda = .45$, partial $\eta^2 = .45$).

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After applying multiple comparison correction, post-hoc univariate ANOVAs showed significant associations of feeling like punishing oneself and apologising with higher self-blaming biases in the corresponding self- and other-agency conditions. Furthermore, the association of agency-incongruent self-blaming biases (blaming oneself when one's friend has acted badly) with a lower tendency to verbally attack one's friend in the other-agency condition survived multiple comparison correction (see Table 3-5).

3.4.3) Response time for action tendency choices in the VR task

The average time taken to choose action tendencies in each agency and group is shown in Table 3-6. Interestingly, a repeated measure ANOVA revealed that all participants took a longer time to respond in the other-agency compared with self-agency condition as shown by a main effect of agency: $F(1, 136)=19.21$, $p<.001$. The discrepancy between conditions was greater in the depression group, as shown by an interaction between agency and group: $F(1,136)=5.80$, $p=.02$. There was no main effect of group: $F(1,136)=.81$, $p=.37$.

3.4.4) Descriptive statistics of action tendencies in the VR task

Means, standard deviations and standard errors for proportions of selecting different action tendencies are presented in Figure 3-3. Feeling like apologising was the most frequently chosen action tendency in the self-agency condition for both groups (0.58 and 0.65 for the depression and the control group). In contrast, feeling like creating a distance from one's friend (0.30 for both groups) and other/no action (0.31 and 0.30 for the depression and the control group) were most commonly chosen in the other-agency condition. There was no association of VR action tendencies and clinical characteristics in the depression group (See Table 3-7).

3.4.5) Group differences on action tendencies in the VR task

Verbally attacking friend and distancing from friend in the self-agency condition were removed from MANOVA because very few participants have chosen these action tendencies.

As predicted, the MANOVA showed a significant effect of group on the multivariate action tendency profile: $F(10,127)=2.72$, $p=.005$, Wilk's $\Lambda = .18$, partial $\eta^2 = .18$. Post-hoc univariate ANOVAs showed that compared with the control group, participants with depression had a higher proneness to feeling like punishing themselves and hiding irrespective of agency, a higher frequency of feeling like creating a distance from themselves in the other-agency and a lower frequency of feeling like apologising in the self-agency condition, as well as of verbally attacking one's friend irrespective of agency (see Table 3-8 and Figure 3-4). After multiple comparison correction, depressed participants continued to show a significantly higher tendency to punish themselves in both agency conditions, as well as a higher tendency to hide and a lower tendency to verbally attack their friend in the other-agency condition compared with the control participants. We also explored a corresponding MANOVA using the text-based action tendency measures which replicated the multivariate difference between groups. Univariate post-hoc comparisons, showed similarly increased feelings of hiding in the depression group, using the text-based task, but no other significant univariate group differences even before multiple comparison correction (see Table 3-9).

3.4.6) The role of feeling like punishing oneself in relation to self-harm and suicide attempts

Based on our finding that feeling like punishing oneself was the action tendency which most strongly distinguished the depression from the control group in both agency conditions, we investigated its relationship with reported history of self-harm and suicide attempts as recorded in our baseline assessment. History of self-harm exhibited a significant multivariate

association with feeling like punishing oneself irrespective of agency: $F(2,91)=3.42$, $p=.037$, Wilk's $\Lambda = .07$, partial $\eta^2 = .07$. Interestingly, this effect was not found for history of suicide attempts: $F(2,91)=.46$, $p=.64$, Wilk's $\Lambda = .01$, partial $\eta^2 = .01$. Post-hoc univariate ANOVAs showed that a previous history of self-harm was more specifically associated with an agency-incongruent (i.e. overgeneralised) feeling like punishing oneself when one's friend had acted badly towards oneself (i.e. in the other-agency condition, see Table 3-10 and Figure 3-5).

3.5) Discussion

In the present study, we developed and validated a novel VR task to assess blame-related action tendencies. Our first hypothesis is that people with current depression exhibit higher levels of maladaptive blame-related action tendencies, including feeling like hiding, creating a distance from oneself and self-punishing. Our results confirmed this hypothesis by showing that the depression group exhibited a higher proneness to all hypothesised maladaptive blame-related compared with the control group at a multivariate level and was most pronounced for feeling like punishing oneself and hiding. Although the group difference for creating a distance from oneself did not survive multiple comparison correction, the trend was still consistent with our prediction and also in line with previous findings that people with depression had a tendency to imagine things from a third-person perspective (Holmes et al., 2016). Furthermore, people with depression showed reduced adaptive feelings of verbally attacking one's friend when they were described to have acted badly towards them, which is consistent with previous findings of reduced anger towards others in remitted depression (Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015). The lack of significant findings in the text-based task confirmed the higher sensitivity of the VR task in identifying the group difference of action tendencies in people with current depression.

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Our second aim was to investigate the hypothesis that maladaptive action tendencies, specifically feeling like punishing oneself, are associated with a higher risk of self-harm and suicide attempt based on self-reported history. This hypothesis was partially supported by our findings that participants with higher likelihood of punishing oneself had higher rate of self-harm, but not of suicide attempts.

Our study is the first demonstration of maladaptive self-blame-related action tendencies in people with current depression who are also likely to exhibit a much higher level of co-morbid conditions such as anxiety disorders, thus providing crucial evidence for the generalisability to non-remitting forms of depression. Although the link between depression and maladaptive action tendencies requires further investigation, it might reflect depressogenic coping styles. As action tendencies are implicit motivational states before an action is taken (Haidt, 2003), they are highly likely to play a role in subsequent behaviour (Roseman et al., 1994). As a result, people with a tendency to hide and self-punish might adopt maladaptive actions as coping methods, such as avoidance and self-harm. These coping methods may relieve tension in the short term, but reduce the likelihood of problem-solving in the long term, which ultimately contribute to depressogenic schemata (Aaron T Beck & Emily AP Haigh, 2014).

The other-agency condition was also where people with depression showed the longest response times as a potential reflection of emotional ambivalence, and exhibited the most distinctive profile of agency-incongruent self-blame-related action tendencies, particularly feeling like punishing oneself. The finding that a higher likelihood of punishing oneself was associated with a higher likelihood of a history of self-harm, but not of suicide attempts, is consistent with previous findings that self-harm in depression was related to punishment-related behaviours (Stanicke, 2021). Given the high prevalence and the detrimental effect of self-harm in people with depression, especially adolescents (Stallard et al., 2013), our finding

revealed a novel target for treatment planning and the development of prevention strategies of self-harm in depression. As feeling like self-punishing was not associated with suicide attempts, this points to self-harm as a more specific clinical feature with a distinct motivational underpinning. Although studies found that a history of self-harm increased the likelihood of suicide attempts, it was not specifically linked with thoughts of dying (Mitchell & Dennis, 2006). Self-harm, unlike suicidality, is also less likely linked to hopelessness, shown to be of particular relevance for suicidality (Abramson et al., 1989).

3.5.1) Limitations

On a more cautionary note, our study was limited by not including a diagnostic interview and so we were unable to establish a formal diagnosis of current major depressive disorder (MDD). It is, however, highly likely that our depression group consists almost exclusively of people who fulfil MDD criteria, given that: 1) we only included participants who were deemed to require pharmacological treatment of their depression by their GP, and used a highly conservative PHQ-9 score cut-off, used a rigorous way of excluding people with a bipolar history, and used validated scales for excluding substance and alcohol use disorders. A further limitation was the cross-sectional design of the study, which did not allow us to examine the causal relationships between maladaptive action tendencies and depression. Longitudinal studies are needed to examine state and trait-related aspects of maladaptive action tendencies. The fact that we found no association of symptom severity with action tendencies suggests that these may reflect vulnerability traits rather than states. Due to recruiting a pragmatic sample of people who have not benefitted from antidepressant treatments, we were unable to rule out the effect of medication, although we did not find an influence of medication status on action tendencies.

3.5.2) Conclusions

Taken together, our self-administered VR task of blame-related biases showed good construct validity and excellent suitability for remote use in depression. As shown by the task, feeling like hiding and self-punishing were distinctive for participants with depression compared with those without depression, consistent with our previous findings based on a text-based assessment. In addition, feeling like punishing oneself was specifically associated with a history of self-harm, but not suicide attempts in people with depression. Our finding unveils novel cognitive markers, neurocognitive prevention and treatment targets, as well as provides the first step in validating the task as a measure of self-blaming biases in depression.

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Table 3-1 | Scenarios used in the VR task

| No. | Self-agency condition | Other-agency condition |
|-----|---|---|
| 1. | You drove your friend's car, caused an accident, and damaged it. | Your friend drove your car, caused an accident, and damaged it. |
| 2. | At your friend's party, you stained their carpet. | At your party, your friend stained your carpet. |
| 3. | You spoke negatively about your friend to their boss. | Your friend spoke negatively about you to your boss. |
| 4. | At your friend's house, you cheated during a game. | At your house, your friend cheated during a game. |
| 5. | When babysitting for your friend, you shouted at their child. | When babysitting for you, your friend shouted at your child. |
| 6. | Your friend lent you money, and you did not pay them back. | You lent your friend money, and they did not pay you back. |
| 7. | Your friend caught you in a lie | You caught your friend in a lie |
| 8. | Whilst your friend was on holiday, you kissed their partner. | Whilst you were away on holiday, your friend kissed your partner. |
| 9. | When with other friends, you exposed your friend's secret. | When with other friends, your friend exposed your secret. |
| 10. | You arrived very late to a lunch with your friend and ruined some of the fun. | Your friend arrived very late to a lunch with you and ruined some of the fun. |
| 11. | You have gossiped about your friend. | Your friend has gossiped about you |
| 12. | To avoid seeing your friend, you lied about your plans. | To avoid seeing you, your friend lied about their plans. |
| 13. | During a disagreement, you swore at your friend. | During a disagreement, your friend swore at you. |
| 14. | When your friend rang the doorbell, you pretended not to be at home. | When you rang the doorbell, your friend pretended not to be at home. |
| 15. | When your friend needed some help, you did not lend a hand. | When you needed some help, your friend did not lend a hand. |

Table 3-2 | Comparison of participants' demographic characteristics and clinical characteristics

| | Depression Group (n=101) | Control Group (n=40) | p-value |
|--|--------------------------------|--------------------------------|---------|
| Age | 32.05 ±12.32 (Range: 18-66) | 32.12 ±11.82 (Range: 18-63) | .97 |
| Years of Education | 16.40 ±2.97 (Range: 4-22) | 16.85 ±2.82 (Range: 10-22) | .41 |
| Sex [female (%)] | 89 (85.6%) | 32 (80%) | .60 |
| Ethnicity [n (%)] | | | .39 |
| <i>Asian or Asian British: Bangladeshi</i> | 4 (4%) | 1 (2.5%) | |
| <i>Asian or Asian British: Chinese</i> | 1 (1%) | 2 (5%) | |
| <i>Asian or Asian British: Indian</i> | 3 (3%) | 2 (5%) | |
| <i>Asian or Asian British: Pakistani</i> | 2 (2%) | 0 | |
| <i>Asian or Asian British: Other</i> | 1 (1%) | 1 (2.5%) | |
| <i>Black or Black British: African</i> | 0 | 1 (2.5%) | |
| <i>Black or Black British: Caribbean</i> | 1 (1%) | 0 | |
| <i>Black or Black British: Other</i> | 3 (3%) | 0 | |
| <i>Mixed: White & Black Caribbean</i> | 2 (2%) | 0 | |
| <i>Mixed or Multiple: Other</i> | 3 (3%) | 0 | |
| <i>White: British</i> | 64 (63.4%) | 22 (55%) | |
| <i>White: Irish</i> | 2 (2%) | 0 | |
| <i>White: Other</i> | 9 (8.9%) | 6 (15%) | |
| <i>Other</i> | 6 (5.9%) | 5 (12.5%) | |
| Native language | | | .18 |
| <i>English</i> | 87 (86.1%) | 30 (75%) | |
| <i>Other</i> | 14 (13.9%) | 10 (25%) | |
| Employment status | | | .31 |
| <i>In full-time employment</i> | 26 (25.7%) | 15 (37.5%) | |
| <i>In part-time employment</i> | 11 (10.9%) | 7 (17.5%) | |
| <i>Retired</i> | 2 (2%) | 1 (2.5%) | |
| <i>Student</i> | 37 (36.6%) | 13 (32.5%) | |
| <i>Unemployed</i> | 13 (12.9%) | 3 (7.5%) | |
| <i>Other</i> | 12 (11.9%) | 1 (2.5%) | |
| PHQ-9 total score at pre-screening | 18.86±3.07 (Range:15-27) | 1.33±1.51 (Range:0-7) | <.001 |
| MM-PHQ-9 total score at baseline | 18.08±4.75 (Range:5-27) | 1.85±1.94 (Range:0-8) | <.001 |
| QIDS-SR-16 total score at baseline | 16.90±4.07 (Range:5-26) | 3.1±2.25 (Range:0-9) | <.001 |
| GAD-7 total score at baseline | 12.14±5.44 (Range:0-21) | 1.10±1.65 (Range:0-7) | <.001 |

QIDS-SR-16: The Quick Inventory of Depressive Symptomatology-Self-Report-16; MM-PHQ9: Maudsley Modified Patient Health Questionnaire-9; GAD-7: General Anxiety Disorder-7. Values are Mean±Standard Deviation for approximately continuous variables and Count (Percentage%) for categorical variables. Summary p-values are obtained from independent sample t-tests and chi-square tests respectively.

Table 3-3 | Clinical characteristics of depression group at baseline

| | |
|--|----------------------------|
| Number of failed treatments | |
| <i>1-2</i> | 61 (60.4%) |
| <i>3-4</i> | 34 (33.7%) |
| <i>5-6</i> | 5 (5%) |
| <i>7-10</i> | 1 (1%) |
| Duration of current depressive episode | |
| <i>≤12 months</i> | 76 (75.2%) |
| <i>13-24 months</i> | 10 (9.9%) |
| <i>>24 months</i> | 15 (14.9%) |
| Age at first onset | 16.41±6.48 (Range:4-55) |
| Maudsley Staging Model total score | 6.47±1.40 (Range:4-11) |
| Maudsley Staging Model severity | |
| Mild | 60 (57.7%) |
| Moderate | 40 (38.5%) |
| Severe | 1 (1%) |
| Current medication | |
| <i>Single SSRI</i> | 58 (55.8%) |
| <i>Single SNRI</i> | 13 (12.5%) |
| <i>Other</i> | 14 (13.4%) |
| <i>None</i> | 19 (18.3%) |
| Self-reported co-morbid psychiatric conditions | |
| <i>PTSD</i> | 10 (10.0%) |
| <i>Anxiety disorders</i> | 7 (6.9%) |
| <i>Eating disorders</i> | 7 (6.9%) |
| <i>Personality disorders</i> | 5 (4.9%) |
| <i>OCD</i> | 5 (4.9%) |
| <i>ASD</i> | 3 (3.0%) |
| <i>ADHD</i> | 1 (1.0%) |
| <i>Other</i> | 4 (4.0%) |

n=101. SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin and norepinephrine reuptake inhibitors. PTSD: posttraumatic stress disorder; OCD: obsessive-compulsive disorder; ASD: autism spectrum disorder; ADHD: attention deficit hyperactivity disorder; Values are Mean ± Standard Deviation for approximately continuous variables and Count (Percentage%) for categorical variable.

Table 3-4| Pearson correlations between action tendencies and self-blaming biases in the text-based and VR action tendency task

| | Distancing from oneself | Hiding | Apologising | Self-blame rating biases | Distancing from oneself | Hiding | Apologising | Attacking friend | Distancing from friend | Self-blame rating biases |
|---|----------------------------|--------|-------------|-----------------------------|----------------------------|----------|-------------|---------------------|---------------------------|-----------------------------|
| Pearson correlation | .43 | .17 | .42 | .68 | -.03 | .55 | .19 | .34 | .27 | .75 |
| p-value for Pearson correlation | <.001*** | .07 | <.001*** | <.001*** | .77 | <.001*** | .03* | <.001*** | .003** | <.001*** |
| Fisher’s z against reference correlation | 4.84 | 1.29 | 5.57 | | -0.35 | 6.20 | 1.85 | 4.41 | 3.13 | |
| p-value for Fisher’s z | <.001*** | .10 | <.001*** | | 0.36 | <.001*** | 0.03* | <.001*** | <0.001** | |

Fisher’s z was computed against a reference correlation for each action tendency. The reference correlation was calculated by taking the average of the Pearson correlations between all action tendencies, except the action tendency of interest in the VR action tendency task and the action tendency of interest in the text-based action tendency task. For example, the reference correlation for SA distancing from oneself was calculated by averaging the correlations between all action tendencies except SA distancing from oneself (SA hiding, SA apologising, OA verbally attacking friend, OA apologising, OA hiding, OA distancing from oneself, OA distancing from friend) in the VR action tendency task and SA distancing from oneself in the text-based action tendency task. There was one reference correlation calculated for each action tendency. Self-blame rating bias was calculated by subtracting each participant’s average other-blaming ratings from their average self-blaming ratings for each agency. Moderate rather than strong correlations between VR and text-based action tendencies are expected given that VR is more immersive and operationalises the action tendencies in a vivid rather than text-based way. An advantage of this is that unlike the text-based task, the VR task does not depend on how well participants can imagine the scenarios, given that visual imagery ratings were found to be associated with emotional intensity ratings (Zahn et al., 2009). ***<.001; **<.01, *<.05 at a significance level of alpha=.05. n=121 in all analyses.

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Table 3-5| The effects of self-blame rating biases on different action tendencies

| Dependent Variable | | B | Std. Error | t-value | p-value | 95% Confidence Interval | | Partial Eta Squared |
|---------------------------|---------------------------|-------|------------|---------|------------|-------------------------|-------------|---------------------|
| | | | | | | Lower Bound | Upper Bound | |
| SA punish self | SA self-blame rating bias | 0.02 | 0.01 | 3.20 | .002***† | 0.01 | 0.04 | 0.07 |
| | OA self-blame rating bias | 0.01 | 0.01 | 2.80 | 0.01** | 0.00 | 0.02 | 0.06 |
| SA apologise | SA self-blame rating bias | 0.04 | 0.01 | 3.41 | <.001***† | 0.02 | 0.07 | 0.08 |
| | OA self-blame rating bias | -0.01 | 0.01 | -1.20 | 0.24 | -0.03 | 0.01 | 0.01 |
| SA hide | SA self-blame rating bias | -0.01 | 0.01 | -0.73 | 0.47 | -0.02 | 0.01 | 0.00 |
| | OA self-blame rating bias | 0.01 | 0.01 | 0.84 | 0.41 | -0.01 | 0.02 | 0.01 |
| SA distance from oneself | SA self-blame rating bias | 0.01 | 0.01 | -0.67 | 0.50 | -0.01 | 0.01 | 0.00 |
| | OA self-blame rating bias | 0.00 | 0.00 | 0.50 | 0.62 | -0.01 | 0.01 | 0.00 |
| OA verbally attack friend | SA self-blame rating bias | -0.01 | 0.01 | -0.80 | 0.43 | -0.03 | 0.01 | 0.01 |
| | OA self-blame rating bias | -0.05 | 0.01 | -6.95 | <.001***† | -0.06 | -0.04 | 0.26 |
| OA punish oneself | SA self-blame rating bias | 0.01 | 0.00 | 1.75 | 0.08 | 0.00 | 0.02 | 0.02 |
| | OA self-blame rating bias | 0.02 | 0.00 | 5.13 | <.001***† | 0.01 | 0.02 | 0.16 |
| OA apologise | SA self-blame rating bias | 0.00 | 0.00 | 0.46 | 0.65 | -0.01 | 0.01 | 0.00 |
| | OA self-blame rating bias | 0.01 | 0.00 | 4.56 | <0.001***† | 0.01 | 0.01 | 0.13 |
| OA hide | SA self-blame rating bias | 0.00 | 0.00 | 0.89 | 0.38 | -0.01 | 0.01 | 0.01 |
| | OA self-blame rating bias | 0.01 | 0.00 | 2.17 | 0.03* | 0.00 | 0.01 | 0.03 |
| OA distance from self | SA self-blame rating bias | 0.01 | 0.00 | 1.63 | 0.11 | 0.00 | 0.01 | 0.02 |
| | OA self-blame rating bias | 0.01 | 0.00 | 2.25 | 0.03* | 0.00 | 0.01 | 0.04 |
| OA distance from friend | SA self-blame rating bias | 0.02 | 0.01 | 1.52 | 0.13 | 0.00 | 0.04 | 0.02 |
| | OA self-blame rating bias | 0.00 | 0.01 | -0.53 | 0.60 | -0.02 | 0.01 | 0.00 |

Self-blame rating biases were calculated by subtracting each participant’s average other-blaming ratings from their average self-blaming ratings for each condition. The table included parameter estimates for post-hoc univariate analysis following significant multivariate effect, with self-blame bias for each agency condition as predictors and action tendencies as dependent variables. Positive regression coefficients (B) indicate a

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positive association between action tendencies and self-blaming biases.*** $p < .001$, ** $p < .01$, * $p < .05$ at significance level of $\alpha = .05$. † $p < .05$ after multiple comparison correction with Benjamini–Hochberg procedure. SA: self-agency; OA: other-agency

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Table 3-6| Response times (seconds) for action tendencies in each agency condition and group

| Agency | Group | Mean | Std. Deviation |
|--------------|------------|------|----------------|
| Self-agency | Control | 7.14 | 3.19 |
| | Depression | 7.04 | 4.17 |
| | Both | 7.07 | 3.90 |
| Other-agency | Control | 7.86 | 2.94 |
| | Depression | 9.50 | 6.68 |
| | Both | 9.02 | 5.88 |

n=98 for the depression group and n=40 for the control group.

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Table 3-7 | Pearson correlations between action tendencies and symptoms in the depression group

| Group | Self-agency | | | | Other-agency | | | | | | |
|------------|-------------|-----------|-------|--------------------|------------------------|-------------|-----------|-------|--------------------|----------------------|------|
| | Punish self | Apologize | Hide | Distance from self | Verbally attack friend | Punish self | Apologize | Hide | Distance from self | Distance from friend | |
| QIDS-SR-16 | r | 0.03 | 0.03 | 0.01 | -0.14 | 0.01 | 0.08 | -0.10 | -0.04 | -0.15 | 0.12 |
| | p | 0.76 | 0.77 | 1.00 | 0.17 | 0.92 | 0.44 | 0.33 | 0.70 | 0.16 | 0.25 |
| GAD-7 | r | 0.02 | -0.05 | 0.06 | -0.10 | 0.12 | -0.04 | -0.09 | -0.15 | 0.01 | 0.02 |
| | p | 0.83 | 0.60 | 0.5 | 0.33 | 0.26 | 0.71 | 0.39 | 0.14 | 0.92 | 0.89 |

n=98 for the depression group and n=40 for the control group. QIDS-SR-16: Quick Inventory of Depressive Symptomatology-Self-Reported-16; GAD-7: generalised anxiety disorders-7 scale, r= Pearson's correlation coefficient, p=uncorrected 2-sided p-values. No correlation was significant at an uncorrected p=.05 2-sided

Table 3-8 | Parameter estimates for effects of group on action tendencies in the VR task

| Dependent Variable | B | Std. Error | t-value | p-value | 95% Confidence Interval | | Partial Eta Squared |
|---------------------------|-------|------------|---------|----------|-------------------------|-------------|---------------------|
| | | | | | Lower Bound | Upper Bound | |
| SA punish oneself | 0.06 | 0.02 | 3.19 | 0.00***† | 0.02 | 0.10 | 0.07 |
| SA apologise | -0.07 | 0.04 | -2.05 | 0.04* | -0.14 | 0.00 | 0.03 |
| SA hide | 0.04 | 0.02 | 1.97 | 0.05* | 0.00 | 0.08 | 0.03 |
| SA distance from oneself | 0.01 | 0.01 | 1.03 | 0.30 | -0.01 | 0.04 | 0.01 |
| OA verbally attack friend | -0.09 | 0.03 | -2.80 | 0.006**† | -0.15 | -0.03 | 0.06 |
| OA punish oneself | 0.03 | 0.01 | 2.71 | 0.008**† | 0.01 | 0.06 | 0.05 |
| OA apologise | 0.01 | 0.01 | 1.37 | 0.17 | -0.01 | 0.03 | 0.01 |
| OA hide | 0.03 | 0.01 | 2.66 | 0.009**† | 0.01 | 0.06 | 0.05 |
| OA distance from oneself | 0.02 | 0.01 | 2.13 | 0.04* | 0.00 | 0.03 | 0.03 |
| OA distance from friend | 0.00 | 0.03 | 0.08 | 0.94 | -0.05 | 0.06 | 0.00 |

The table included parameter estimates for post-hoc univariate analysis following significant multivariate effect, with group as predictor and action tendencies as dependent variables. The reference category for predictor is the control group. Positive regression coefficients (B) indicate a higher likelihood to have certain action tendencies in the depression group compared with the control group. *** $p < .001$, ** $p < .01$, * $p < .05$ at significance level of $\alpha = .05$. † $p < .05$ after multiple comparison correction with Benjamini–Hochberg procedure. SA: self-agency; OA: other-agency.

Table 3-9 | Parameter estimates for effects of group on action tendencies in the text-based action tendency task

| Dependent Variable | B | Std. Error | t-value | p-value | 95% Confidence Interval | | Partial Eta Squared |
|---------------------------|-------|------------|---------|---------|-------------------------|-------------|---------------------|
| | | | | | Lower Bound | Upper Bound | |
| SA apologise | -0.04 | 0.05 | -0.86 | 0.39 | -0.13 | 0.05 | 0.01 |
| SA hide | 0.10 | 0.02 | 4.27 | 0.00† | 0.05 | 0.14 | 0.13 |
| SA distance from oneself | 0.01 | 0.02 | 0.71 | 0.48 | -0.02 | 0.04 | 0.00 |
| OA verbally attack friend | -0.03 | 0.02 | -1.41 | 0.16 | -0.07 | 0.01 | 0.02 |
| OA apologizing | 0.00 | 0.02 | -0.16 | 0.87 | -0.04 | 0.04 | 0.00 |
| OA hide | 0.12 | 0.03 | 4.51 | 0.00† | 0.06 | 0.17 | 0.14 |
| OA distance from oneself | -0.01 | 0.01 | -1.25 | 0.22 | -0.03 | 0.01 | 0.01 |
| OA distance from friend | 0.05 | 0.04 | 1.15 | 0.25 | -0.03 | 0.13 | 0.01 |

The table included parameter estimates for post-hoc univariate analyses following a significant multivariate effect, with group as predictor and all action tendencies as dependent variables in a multivariate general linear model: $F(8,114)=4.59$, $p<.001$, Wilk's $\Lambda = .24$, partial $\eta^2 = .24$. The reference category for predictor is the control group. Positive regression coefficients (B) indicate a higher likelihood to have certain action tendencies in the depression group compared with the control group. † $p<.05$ after multiple comparison. correction with Benjamini–Hochberg procedure. SA: self-agency; OA: other-agency.

Table 3-10 Differences in the tendency to punish oneself in relation to past self-harm and suicide attempts in the depression group

| Dependent Variable | | B | Std. Error | t-value | p-value | 95% Confidence Interval | | Partial Eta Squared |
|--------------------|-----------------|------|------------|---------|---------|-------------------------|-------------|---------------------|
| | | | | | | Lower Bound | Upper Bound | |
| SA punish self | self-harm | 0.03 | 0.03 | 1.11 | 0.27 | 0.02 | 0.08 | 0.01 |
| | suicide attempt | 0.02 | 0.03 | 0.88 | 0.38 | -0.03 | 0.08 | 0.01 |
| OA punish self | self-harm | 0.04 | 0.02 | 2.58 | 0.01*† | -0.01 | 0.07 | 0.07 |
| | suicide attempt | 0.01 | 0.02 | 0.59 | 0.55 | -0.02 | 0.04 | 0.00 |

The table included parameter estimates for post-hoc univariate analysis following significant multivariate effect, with self-harm and suicide attempt as predictors and punishing oneself for each agency as dependent variables. Reference categories for predictors are no self-harm and no suicide attempt. Positive regression coefficients (B) indicate a positive association between action tendencies and self-harm/suicide attempt. * $p < .05$ at significance level of $\alpha = .05$. † $p < .05$ after multiple comparison correction with Benjamini–Hochberg procedure. SA: self-agency; OA: other-agency.

Figure 3-1 | Flow chart of participant recruitment

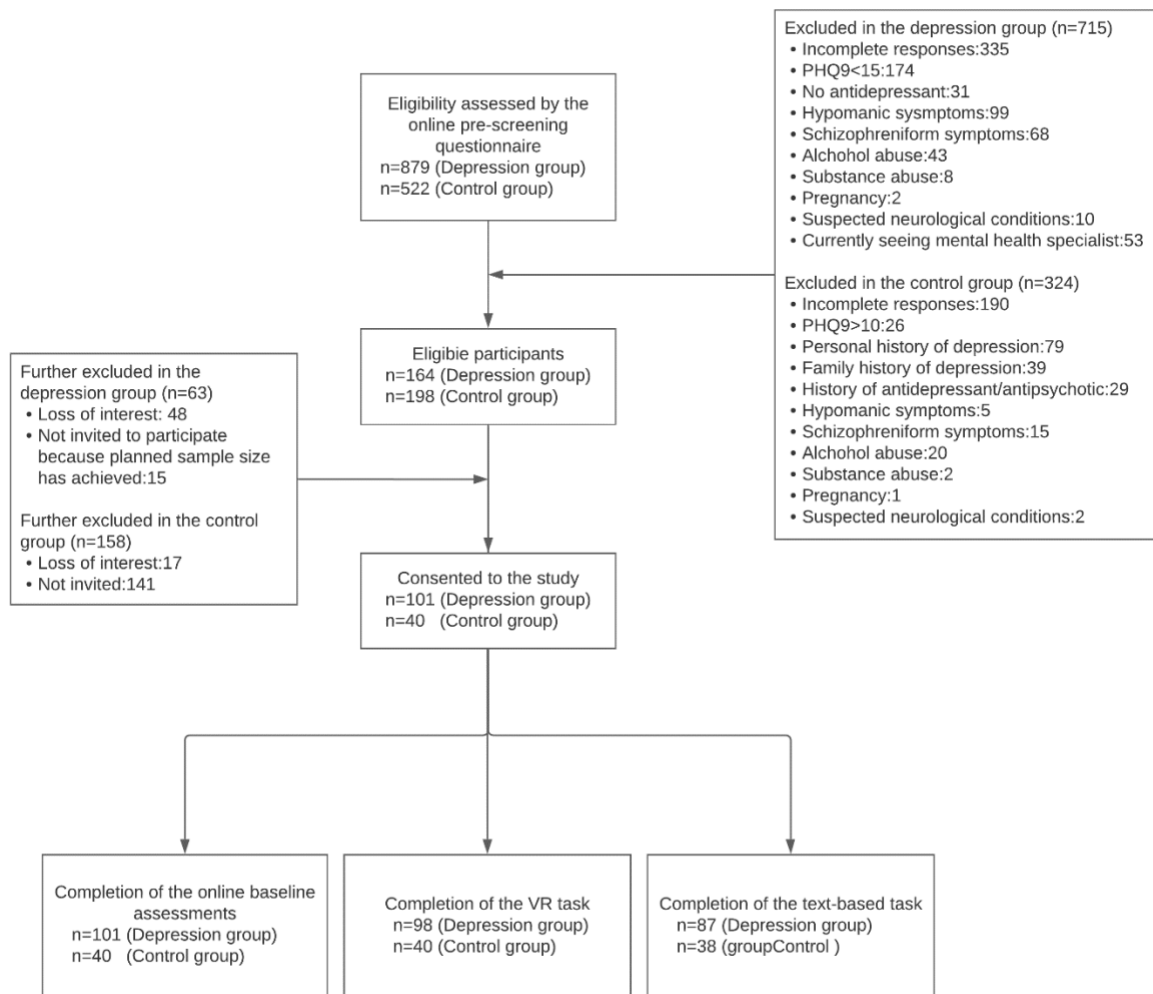
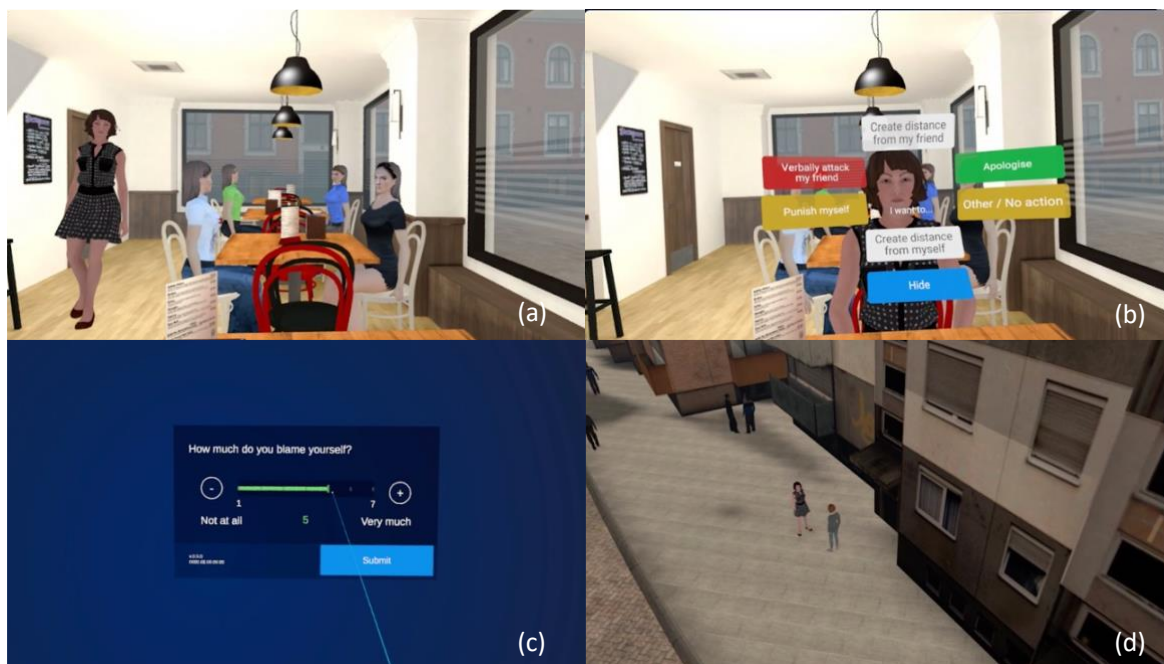
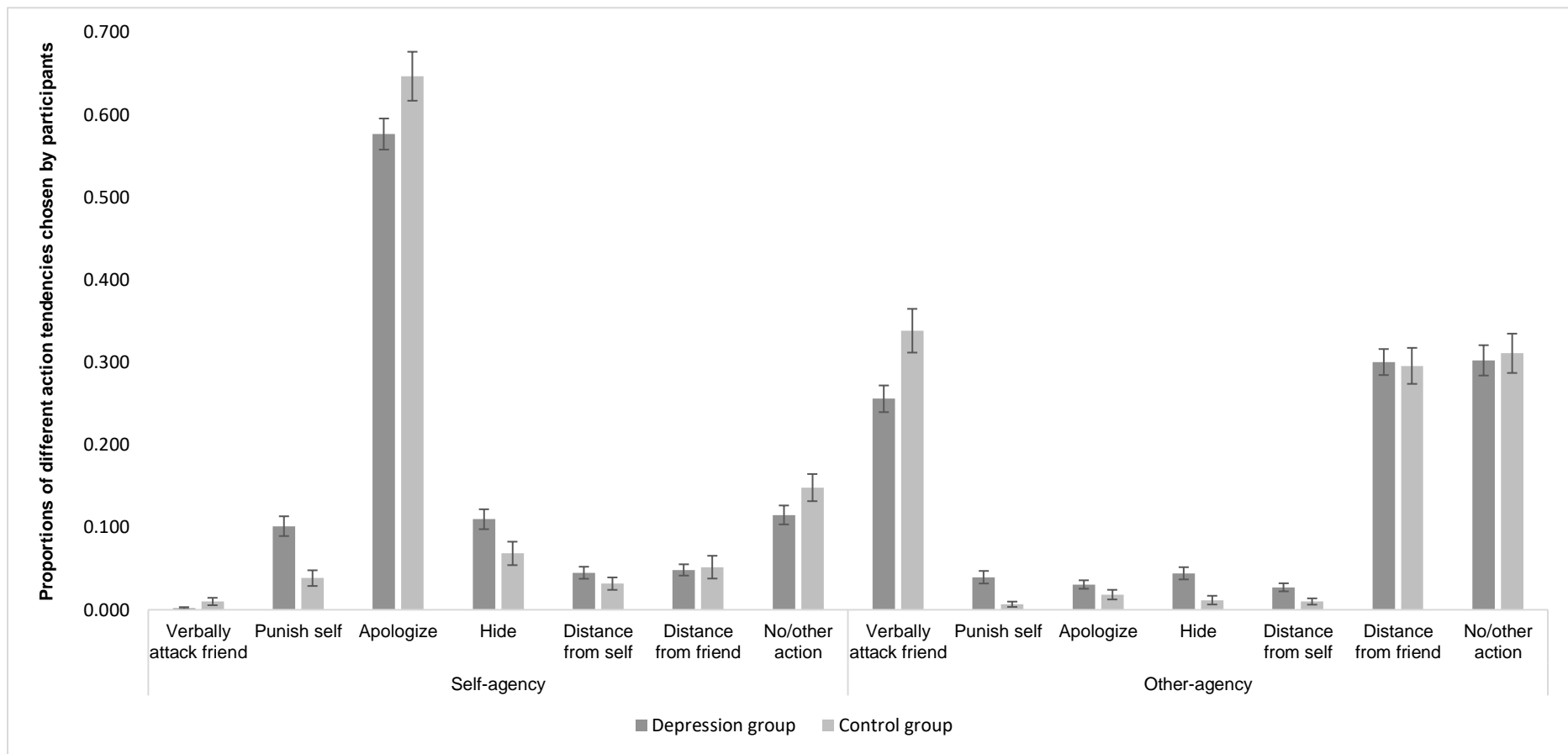


Figure 3-2| Screenshots of the VR task



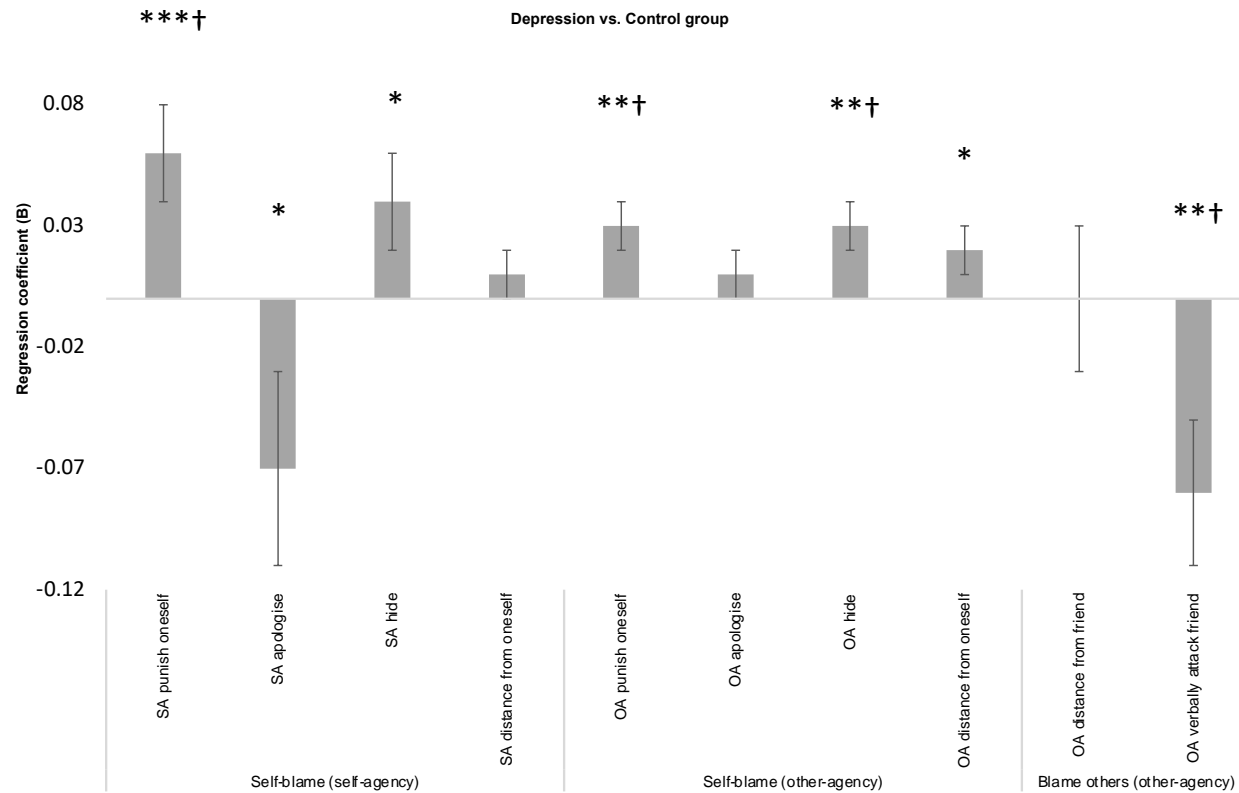
Panel (a) shows that participants meet their friends in a coffee shop, panel (b) depicts the action tendency buttons that participants were asked to choose from using their virtual hands. Panel (c) shows the screen that participants saw when for their blame ratings. Panel (d) depicts how participants viewed themselves and their friend from a bird's-eye perspective after they chose creating a distance from themselves.

Figure 3-3 | Proportions of different action tendencies chosen by participants



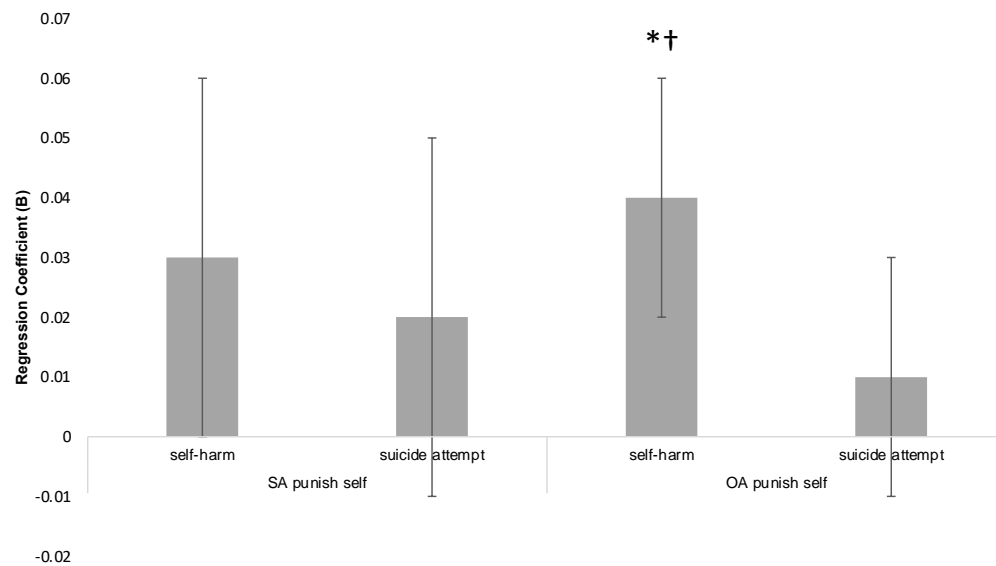
N=138 (depression group: 98; control group: 40); error bars show standard errors of the proportions.

Figure 3-4 | Regression coefficients for effects of group on action tendencies



N=138 (depression group: 98; control group: 40); positive regression coefficients (B) indicate a higher likelihood to have certain action tendencies in the depression group compared with the control group. ***p<.001, **p<.01, *p<.05 at significance level of alpha=.05. †p<.05 after multiple comparison correction with Benjamini–Hochberg procedure. SA: self-agency; OA: other-agency.

Figure 3-5 | Tendencies to punish oneself in relation to past self-harm and suicide attempts in the depression group



N=98; positive regression coefficients (B) indicate a positive association between action tendencies and self-harm/suicide attempt. *** $p < .001$, ** $p < .01$, * $p < .05$ at significance level of $\alpha = .05$. † $p < .05$ after multiple comparison correction with Benjamini–Hochberg procedure. SA: self-agency; OA: other-agency.

Chapter 4: Prediction of prognosis in current depression

4.1) Abstract

Importance: Stratification of depression for personalised treatment is urgently needed to improve poor outcomes. Excessive self-blame-related motivations such as self-punishing tendencies have been proposed to play a key role in the onset and maintenance of depression. Their prognostic role, however, remains elusive.

Objective: Use Virtual Reality (VR) to determine whether maladaptive self-blame-related action tendencies are associated with a poor prognosis for depression when treated as usual in primary care (pre-registered: [NCT04593537](#)).

Design: Remote prospective cohort study (6/2020-6/2021) with four months follow-up.

Settings: Online recruitment from primary care and self-report.

Participants: n=879 pre-screened, n=164 eligible, n=101 completed baseline (age:18-66 years, mean=32.05±12.32, n=89 female), n=98 the VR-task, and n=93 the follow-up. Main inclusion criteria: at least one antidepressant medication trial and Patient Health Questionnaire-9 \geq 15 at screening; main exclusion criteria: screening above threshold on validated self-report instruments for bipolar or alcohol/substance use disorders.

Exposure(s): All participants completed a VR assessment via headsets sent to their homes, as well as online questionnaires to measure their clinical characteristics.

Main outcomes and Measures: Primary: Quick Inventory of Depressive Symptomatology self-reported-16 score after four months. Hypotheses in the study were formulated before the data collection and pre-registered.

Results: Contrary to our specific prediction, neither feeling like hiding nor creating a distance from oneself was associated with prognosis of depression during the follow-up period in the pre-registered regression model. Using a data-driven principal components analysis of all pre-registered continuous measures, a factor most strongly loading on punishing oneself for other people's wrongdoings ($\beta=.23$, $p=.01$), a baseline symptom factor ($\beta=.30$, $p=.006$) and

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Maudsley Staging Method treatment-resistance scores ($\beta=.28$, $p=.009$) at baseline predicted higher depressive symptoms after four months. This relationship was confirmed by a significant interaction between feeling like punishing oneself for others' wrongdoings and time of monthly follow-up which was driven by higher depressive symptoms at last follow-up [$F(1,84)=6.45$, $p=.01$, partial Eta Squared=0.07] in the subgroup who had reported feeling like punishing themselves at baseline. Our pre-registered statistical learning model prospectively predicted a cross-validated 19% of variance in depressive symptoms.

Conclusions and Relevance: Feeling like punishing oneself is a relevant prognostic factor and should therefore be assessed and tackled in personalised care pathways for difficult-to-treat depression.

4.2) Introduction

Only a third of patients reach remission after their initial treatment (e.g. Rush et al., 2008) and multiple treatment-gaps at each stage of the care pathway for depression have been identified (Strawbridge et al., 2022). The ability to stratify depression by likely prognostic trajectory early on, could accelerate access to more personalised treatments in a cost-effective way. Yet, scalable measures with prognostic relevance are scarce and insufficient for stratification. Freud described self-blaming feelings and an implicit need for self-punishment as distinctive features of depression (Freud, 1917). The latter was criticised by Beck as limiting the psychoanalytical approach to depression by implying people with depression were not motivated to get better (Beck, 1985). This may be one of the reasons why the focus of empirical research over the past decades has been on self-blaming emotions in depression (O'Connor et al., 2002; Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015) rather than systematically characterising the associated implicit action tendencies (e.g. Janoff-Bulman, 1979; Tangney et al., 2007), such as feeling like punishing oneself or hiding. Action tendencies which precede social actions, are likely to play an evolutionary important role in the social survival of human beings (e.g. Darwin, 1872; Haidt, 2003). Their role in the prognosis of current depression, however, is elusive.

Action tendencies are essential components in appraisal theories of emotions (Frijda et al., 1989; Moors, 2009; Roseman et al., 1994). Self-blame-related action tendencies (e.g. feeling like hiding) are the motivational component of self-blaming emotions (e.g. shame), which could play either adaptive or maladaptive roles (Tangney et al., 2007). Gray's reinforcement sensitivity theory (Gray, 1970), proposes two dissociable neural systems as dimensions of human action tendencies: behavioural "activation" and "inhibition" – the latter is also referred to as "withdrawal". Stronger behavioural inhibition/withdrawal and impaired behavioural activation were associated with affective disorders (e.g. Kasch et al., 2002). In line

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with this, Tangney et al. (2007) postulated that adaptive self-blame-related action tendencies are more associated with behavioural activation and involve proactive pursuit such as reparative actions, whereas maladaptive self-blame-related action tendencies motivate social withdrawal and interpersonal separation (Duan, Lawrence, et al., 2022; Tangney et al., 2007). In keeping with this hypothesis, using a text-based task, we recently showed that withdrawal-related maladaptive action tendencies including hiding and creating a distance from oneself were more pronounced in patients with remitted depression compared with control participants (Duan, Lawrence, et al., 2022) and were associated with subsequent recurrence risk (Duan, Lawrence, et al., 2022; Duan, Valmaggia, et al., 2022).

For the present prospective study, we used a novel VR task developed and validated in our separately reported cross-sectional study comparing people with and without depression at baseline to examine our pre-registered hypothesis 1 (NCT04593537). The cross-sectional study revealed that people with depression showed a distinctive tendency to attack/punish themselves, which was specifically associated with a history of self-harm but not suicide attempts (Duan, Valmaggia, et al., 2022). Here, we prospectively probed the prognostic role of maladaptive self-blame-related action tendencies for depressive symptoms over four-months of follow-up whilst being treated as usual in primary care. Previous measures of action tendencies used abstract descriptions of social scenarios which limited engagement in the scenarios and ecological validity (Duan, Valmaggia, et al., 2022; Mu & Berenbaum, 2019). Our immersive VR task made it possible to act out the action tendencies as well as to increase the engagement of participants. We hypothesised that maladaptive self-blame-related action tendencies at baseline are associated with a poor prognosis for current major depression when measured four months after baseline (pre-registered hypothesis 2). Specifically, based on our previous findings (Duan, Lawrence, et al., 2022), in our pre-registered analysis plan, we highlighted two withdrawal-related maladaptive action tendencies (hiding and creating a distance from oneself),

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which we predicted to be associated with poor prognosis of depression. In addition, based on our previous study (e.g. Harrison et al., 2020; Lawrence et al., 2021) and the wider clinical literature (e.g. Chekroud et al., 2016), we pre-registered a number of clinically established risk factors, chiefly measures of depressive and anxiety symptoms, as well as treatment-resistance as further detailed in the methods section. Our pre-registered research question 3 was whether maladaptive self-blame-related action tendencies can be used to predict prognosis in MDD at the individual level when combined with other predictors using a nested elastic-net regularised doubly-cross-validated regression model [dCVnet, <https://github.com/AndrewLawrence/dCVnet>, (Lawrence et al., 2021)].

4.3) Methods

4.3.1) Participants

This study was approved by the King's College London PNM Research Ethics Subcommittee (Project Reference:HR-19/20-17589) and pre-registered (NCT04593537) prior to data collection. All participants were recruited via online advertising. Participants were compensated with a £25 Amazon voucher on completing the study or £15 for only completing the online baseline assessment. Participants' eligibility was assessed by an online pre-screening questionnaire. The inclusion criteria were: age ≥ 18 years; at least moderately severe major depressive syndrome [The Patient Health Questionnaire-9 (Kroenke et al., 2001) score ≥ 15]; early treatment resistance to antidepressants as defined as one antidepressant medication treatment trial in primary care (Fekadu et al., 2018) and being able to complete self-report scales orally or in writing. Exclusion criteria were: a previously diagnosed or likely bipolar disorder [Hypomanic Checklist-16 (Forty et al., 2010) score > 8 , with symptoms lasting ≥ 2 days, and endorsing two of the first three screening questions of the Composite International Diagnostic Interview bipolar screening scale (Kessler et al., 2006)], a personal history of schizophreniform symptoms [three clinical screening questions to exclude schizophreniform disorders (Lythe et al., 2015)], drug or alcohol abuse over the last 6 months [Primary Care Evaluation of Mental Disorders (Spitzer et al., 1994), modified to screen for drug abuse], a suspected central neurological condition, a planned or current pregnancy, or currently being treated by a mental health specialist in secondary care. More information about the inclusion/exclusion reasons can be found in the Supplementary Materials of Duan, Valmaggia, et al. (2022).

In total, 879 participants completed the pre-screening questionnaire, of which 164 were eligible. Of those, 101 consented to and took part in the study. All 101 participants completed the baseline assessment and 98 of them completed the VR task. Participants completed follow-

up assessments at one (n=94), two (n=91), three (n=80) and four (n=93) months (see Table 4-1 and Table 4-2 for demographic and clinical characteristics).

4.3.2) Assessments of clinical characteristics

All demographic information and clinical characteristics of participants were collected using online self-report. . Participants' depressive symptoms were measured by the Quick Inventory of Depressive Symptomatology (self-reported, 16 items) (QIDS-SR-16, A John Rush et al., 2003) as our primary outcome at baseline and four months' follow-up only and by the Very Quick Inventory of Depressive Symptomatology (VQIDS-SR-5, De La Garza et al., 2017)] at one, two and three months' follow-ups. Other clinical characteristics collected include anxiety symptoms as measured by the Generalised Anxiety Disorder -7 Scale (GAD-7) (Robert L Spitzer et al., 2006), information about participants' depressive episodes as well as their current and past antidepressant medications. We also used the Maudsley Modified Patient Health Questionnaire-9 (Phillippa Harrison et al., 2021) as a secondary outcome. More details on assessments of clinical characteristics can be found in Duan, Valmaggia, et al. (2022).

4.3.3) Virtual reality assessment of blame-related action tendencies

The virtual reality assessment of blame-related action tendencies, deployed on Oculus Go devices, was developed based on the value-related moral sentiment task (Zahn, Lythe, Gethin, Green, Deakin, Workman, et al., 2015) and has been described and validated in our previous cross-sectional study (Duan, Valmaggia, et al., 2022). There were 30 scenarios in the task, in which either the participant (self-agency condition, 15 scenarios) or the participants' friend (other-agency condition, 15 scenarios) acted counter to social and moral values in hypothetical social interactions between the participants and their friends. In each scenario, participants were taken to a scene (e.g. in the street or a shopping centre) and saw a VR avatar (their friend) moving towards them, while a narrator described the hypothetical social scenarios.

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Participants were then asked to choose an action they felt like doing from choice options displayed on the screens: “feeling like verbally attacking my friend”, “punishing myself”, “apologising”, “hiding”, “creating distance from my friend”, “creating distance from myself” and “other/no action”. After participants made their choices, the display changed accordingly to act out the corresponding actions. At the end of the scenarios, participants were asked to rate their levels of self-blame and other-blame from 1 (not at all) to 7 (very much), shown on the screen as visual analogue scroll bars. For details, videos and screenshots of the VR task, see Duan, Valmaggia, et al. (2022).

4.3.4) Procedure

This study was conducted fully remotely. After participants consented to the study, they received the link to the baseline assessment and email instructions to complete the VR task unsupervised. The headset was delivered to them by courier. Participants received the links to the online follow-up assessments one, two, three and four months after they completed the baseline assessments.

4.3.5) Data analysis

All data were analysed using IBM SPSS statistics version 27 and R studio version 4.1.3. Means and standard deviations were calculated for proportion of choosing each action tendency per condition (self-agency and other-agency) in the VR action tendency task and described in our previous study (Duan, Valmaggia, et al., 2022). A multiple regression analysis was conducted with all the pre-registered predictors in the primary analysis as independent variables and depressive symptoms as assessed by QIDS-SR-16 at four months’ follow-up as the outcome variable. Sociotropy and autonomy are two personality dimensions that represents extensive concerns about either interpersonal relationship or autonomous achievement. These two personality dimensions are thought to confer increased vulnerability to depression and

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other psychopathologies (Robbins et al., 1994). They might also be related to blame-related emotions. Thus, these two dimensions, measured by the Personal Style Inventory (Robbins et al., 1994) were included in our prediction models. The pre-registered predictors in the primary analysis include: 1) proportion of trials during which hiding was chosen as measured by the VR task; 2) proportion of trials during which distancing from oneself was chosen as measured by the VR task; 3) autonomy subscale score as measured by the Personal Style Inventory-II (PSI-II, Robins et al., 1994) 4) sociotropy subscale score as measured by the PSI-II; 5) Maudsley staging method (MSM) total score (Fekadu et al., 2018); 6) medication adherence during the four-month follow-up period as measured by a question (how regularly have you taken your antidepressants over the last month at the prescribed dose) where participants were asked to choose from: never, some of the time, more than half of the time, most of the time, almost every day, every day; 7) social support received as measured by the Social Support Scale (SSS, Krause & Borawski-Clark, 1995); 8) baseline depressive symptoms as measured by QIDS-SR-16; 9) baseline anxiety symptoms as measured by the GAD-7; 10) antidepressant changes during the four-month follow-up period where participants were classified into three categories from minor change to major change: no new antidepressant/stop current antidepressant/lower the dosage of current antidepressant, increase from effective dose to higher dose, increase from ineffective to effective dose/change to another antidepressant at effective dose.

Because there are large number of variables that were not included in our first regression model, we also used exploratory analyses to further understand the predictors of our outcome variable. Using a data-driven approach, to reduce the number of variables and avoid overfitting of our data-driven regression model, the proportions of all the maladaptive action tendencies and self-blaming rating biases as measured by the VR action tendencies task and the continuous clinical measures including subscales in the primary analysis were entered into

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a Principal Component Analysis (PCA) with varimax rotation. Factors extracted by the PCA were labelled and then used to predict depressive symptoms at four months' follow-up along with all our ordinal clinical variables in the primary analysis: MSM total score, medication adherence and antidepressant changes. The number of factors to retain was first determined by inspection of the scree-plot using an elbow method [(Thorndike, 1953), see Figure 4-1]. In addition, as suggested by Stevens (2009) to improve reproducibility, factors were only interpreted if the average of the four largest loadings was $>.60$ and only items with factor loadings above 0.51 were considered to load significantly on a factor.

In a further supporting analysis, to further understand the specific role of maladaptive action tendencies on prognosis, we selected “feeling like punishing oneself” as the action tendency which had loaded most strongly on one of the extracted PCA factors, and used a linear mixed model to examine its effect on the trajectory of depressive symptoms over the four monthly follow-up VQIDS-SR-5 scores. People with depression were sub-grouped based on whether they had or had not selected “feeling like punishing myself” at least once in the VR task at baseline, as binarizing the action tendency measure is what one would do in a clinical applied setting where people would not have factor scores. Action tendency group was then entered in the linear mixed model as a categorical independent variable, along with time and their interactions. Post-hoc analyses were conducted for significant interactions. Multiple comparison correction at a two-sided Bonferroni-corrected $p=.05$ was employed for all post-hoc univariate tests.

In addition, a doubly Cross-Validated Elastic-net regularised generalised linear model of the gaussian family (dCVnet, Lawrence et al., 2021) was performed to examine the cross-validated model performance when predicting the prognosis of depression as measured by depressive symptoms at final follow-up assessment. This method is designed (uses double cross-validation and regularisation, see Lawrence et al., 2021 for more information) to guard

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against overfitting, allowing a more accurate estimate of model performance which is more likely to generalise to independent future samples. The R package “dCVnet”

[https://www.github.com/ andrewlawrence/dCVnet](https://www.github.com/andrewlawrence/dCVnet) was used as planned in our pre-registered analysis plan (Lawrence et al., 2021). dCVnet uses a nested cross-validation scheme to simultaneously select hyperparameters which cross-validate well (the inner loop) and obtain uninflated cross-validated performance estimates (the outer loop). For these models stable hyper-parameter selection was obtained with 30 repetitions of 10-fold cross-validation in the inner loop. Stable cross-validated performance estimates were obtained with 100 repetitions of 10-fold cross-validation in the outer loop. Both alpha (type of penalty) and lambda (amount of penalty) were tuned. Six logarithmically spaced values of alpha were considered between 0.01 (mostly Ridge) and 1.0 (a LASSO model). For each alpha, 100 lambda values were determined automatically, logarithmically spaced between the lambda giving a fully penalised model and 0.0001. The hyper-parameters (Alpha and Lambda) were selected based on the minimum mean square error. More information regarding the methods can be found in Lawrence et al. (2021). Because of the built-in elastic-net regularisation of the dCVnet method, all VR-task predictors included in the PCA were included in the first dCVnet model without prior conversion to factors. In addition, all our ordinal clinical variables in the primary analysis that could not be included in the PCA (MSM total score, medication adherence and antidepressant changes) were also included in the first dCVnet model. A second dCVnet model was conducted including all the variables in the first dCVnet model and variables in the secondary analyses to compare model performance after including additional pre-registered clinical variables and so probe our pre-registered hypothesis 3.

4.4) Results

4.4.1) Pre-registered primary prospective prediction model

A multiple linear regression was conducted to predict depressive symptoms at four months' follow-up based on all the pre-registered predictors in the primary analysis. A significant regression equation was found: $F(11,77)=3.75$, $p<.001$, with an R^2 of .33. Higher MSM total scores and higher depressive symptoms at baseline predicted higher depressive symptoms at four months' follow-up. No other predictors were found to be significant (see Table 4-3).

4.4.2) Data-driven prospective prediction model based on all pre-registered predictors of interest

A principal component analysis with varimax rotation was conducted on all the continuous measures (including subscales) pre-registered for the primary analysis. The rotated component matrix is shown in Table 4-4. The elbow method of inspecting the scree-plot suggested a five-factor structure (See Figure 4-1), which cumulatively explained 47.23% of the total variance. The factors were labelled according to their constitutive items as follows: Sociotropy/Perfectionism (factor 1, 4 items), Depressive and anxiety symptoms (factor 2, 3 items), Contact with friends (factor 3, 2 items), Response time (factor 4, 2 items) and Punishing oneself/self-blaming bias (factor 5, 4 items).

A multiple linear regression was conducted to predict depressive symptoms at four months' follow-up based on these five factors along with the pre-registered ordinal predictors: MSM total score, medication adherence and antidepressant changes during the past four months. A significant regression equation was found: $F(5,83)=5.89$, $p<.001$, $R^2=.35$. A higher MSM total score, a higher depressive and anxiety symptom factor score and a higher

maladaptive action tendencies/self-blaming biases factor score predicted higher depressive symptoms at four months' follow-up (see Table 4-5).

4.4.3) Influence of the tendency to punish oneself on depressive symptoms over four months

Following the significant association between factor 5 (maladaptive action tendencies/self-blaming biases) and depressive symptoms at four months' follow-up, a linear mixed model further examined the relationship between maladaptive action tendencies, which were the two strongest items loading on factor 5 (punishing oneself in the self-agency and other-agency conditions) and depressive symptoms as assessed by monthly VQIDS-5 over the follow-up period. After controlling for baseline VQIDS-5 score, there was a significant interaction between time and punishing oneself in the other-agency condition: $B=.43$, $t(241.21)=2.08$, $p=.038$. No main effect of time, punishing oneself in both agencies, nor interaction between time and punishing oneself in the self-agency condition were found (see Figure 4-2). As shown by Figure 4-2, post-hoc analysis revealed that participants had significantly higher depressive symptoms in the group with the tendency to punish oneself in the other-agency condition compared to the group without such tendency at four months' follow-up only: $F(1,84)=6.45$, $p=.01$, partial Eta Squared=0.07. Although a similar trend was observed at other time points, there were no significant differences on depressive symptoms between the groups at these time points: $F(1,79)=1.26$, $p=.27$ (Follow-up 1); $F(1,76)=1.30$, $p=.13$ (Follow-up 2); $F(1,71)=2.54$, $p=.12$ (Follow-up 3).

4.4.4) Prediction of prognosis based on dCVnet models

Supporting our results of the simple linear regression model, four predictors were retained in the first dCVnet model (model with clinically established variables in our primary analysis): QIDS-SR-16, MM-PHQ9, MSM score and punishing oneself in the other-agency

condition. Model performance of the two dCVnet models can be found in Table 4-6 and Table 4-7 and shows that a cross-validated 19% of the variance in depressive symptoms after four months can be predicted when using all pre-registered primary and secondary variables.

4.5) Discussion

The present study used a validated novel VR task to examine the role of maladaptive self-blame-related action tendencies in prognosis of current depression when treated as usual in primary care. Our pre-registered general hypothesis on the prognostic relevance of maladaptive action tendencies was confirmed: punishing oneself for other people's wrongdoing was associated with a poor prognosis of depression after four months. However, our findings did not support the more specific predictions that feeling like hiding and creating a distance from oneself would be prognostically relevant. We also examined the influence of clinically established risk factors. As expected, higher treatment resistance and more severe symptoms at baseline were associated with poor prognosis. Notably, none of the other clinical variables had significant prognostic value in this sample. Our statistical/machine learning model also identified the same three risk factors found using standard statistics and further confirmed that despite their significant contribution, useful individual level prediction of prognosis was not achieved using these measures alone.

Our previous cross-sectional study, in this sample of participants with current depression, found that punishing oneself for other people's wrongdoing was the most clinically relevant action tendency in that it not only distinguished people with and without depression, but was also related to higher rates of self-harm (Duan, Valmaggia, et al., 2022). The present prospective study, despite not being informed by the above cross-sectional results at the pre-registration and analysis stage, further highlights the pathophysiological importance of an agency-incongruent feeling like punishing oneself by showing its selective predictive value for prognosis. This result was contrary to our more specific pre-registered hypotheses on feeling

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like hiding and creating a distance from oneself, which had been shown to be relevant to depression vulnerability in our previous studies in remitted depression (Duan, Valmaggia, et al., 2022; Lawrence et al., 2021). This may be due to the fact, that our previous studies were based on less immersive text-based measures, but may also indicate differential importance of specific action tendencies depending on symptomatic state and clinical subtype. This is because our previous studies selected fully remitting forms of depression rather than the more chronic difficult-to-treat population included in the current study.

In “Mourning and Melancholia”, Freud emphasized the role of internalised aggressive impulses such as self-attack/punishment in depression and differentiated depression from mourning on this basis (Freud, 1917). This tendency was thought to be a core feature of depression in Freudian models (Freud, 1917), but our results are more compatible with a model of depression in which a tendency to self-punish characterises a subgroup of depression. Furthermore, we share Beck’s criticism of the Freudian model in that the observation of self-punishing tendencies does not necessarily reflect a need to punish oneself (Beck, 1985). On a more cautionary note, we used an explicit measure of self-punishing tendencies, whereas an implicit measure would be more suitable to probe the Freudian model. Compared with self-punishment, hiding and creating a distance from oneself as precursors of social actions could give rise to maladaptive coping behaviours such as social avoidance (Mu & Berenbaum, 2019), which would explain their more prominent role in remitted depression at risk of recurrence. Interestingly, only punishing oneself in the other-agency, but not self-agency condition predicted prognosis of depression. This confirms theories and empirical findings that only overgeneralised forms of self-blame (e.g. punishing oneself for other people’s wrongdoing) contributes to the onset and maintenance of depression (Abramson et al., 1978; Janoff-Bulman, 1979) and confirms our finding of agency-incongruent self-blaming emotions in difficult-to-treat depression (Jaekle et al., 2021).

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Self-harm was not included in our first and second model because it was not one of the pre-registered predictors. It was included in our third model (the model with double cross-validation), however, the model did not have much predictive power given the low R square. Self-harm might partially explain the predictive value of punishing oneself action tendency, however, it is unlikely to explain all the predictive value given that their correlation is not too high (See Chapter 3).

We also found that depression severity and treatment resistance at baseline predicted the prognosis of depression after four months, confirming the importance of treatment history (Taylor et al., 2021; Webb et al., 2020). On the other hand, despite the effort of clinicians to increase medication adherence and social support among patients with depression, a higher score in these domains did not contribute to a better outcome. In addition, participants' antidepressant changes during the follow-up period did not add value to the prediction, although this could be partially explained by the fact that very few participants changed their antidepressant medication overall, a reflection of the large treatment gaps in primary care for depression (Strawbridge et al., 2022).

Our study was limited by not including a diagnostic interview, so we were unable to establish a formal diagnosis for our participants. However, this makes our findings more generalisable to primary care patients where a formal diagnostic interview is not conducted. In addition, a highly conservative PHQ-9 score cut-off (≥ 15) was used in the study, with a specificity of .96 for MDD (Manea et al., 2012). We also used validated tools to exclude participants on the bipolar spectrum and those with alcohol or drug abuse.

Taken together, our study confirmed our general hypothesis that maladaptive self-blame-related action tendencies play a significant role in prognosis of current depression and were the only factor of prognostic relevance apart from well-known baseline levels of depressive symptoms and treatment-resistance. Our more specific pre-registered predictions

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about specific action tendencies were not confirmed, instead we found an overgeneralised feeling like punishing oneself and blaming oneself for other people's wrongdoing as of distinctive prognostic importance for depression. We further showed that a simple binary categorisation of feeling like punishing oneself on our VR-task can be used to identify a subgroup of patients with poorer prognosis which could be used for personalising treatments and as a target for novel interventions.

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Table 4-1| Demographic characteristics of participants at baseline

| | |
|--|----------------------|
| Age | 32.05 ±12.32 (18-66) |
| Years of Education | 16.40 ±2.97 (4-22) |
| Sex [female] | 89 (85.6%) |
| Native language | |
| <i>English</i> | 87 (86.1%) |
| <i>Other</i> | 14 (13.9%) |
| Employment status | |
| <i>In full-time employment</i> | 26 (25.7%) |
| <i>In part-time employment</i> | 11 (10.9%) |
| <i>Retired</i> | 2 (2%) |
| <i>Student</i> | 37 (36.6%) |
| <i>Unemployed</i> | 13 (12.9%) |
| <i>Other</i> | 12 (11.9%) |
| Ethnicity | |
| <i>Asian or Asian British: Bangladeshi</i> | 4 (4%) |
| <i>Asian or Asian British: Chinese</i> | 1 (1%) |
| <i>Asian or Asian British: Indian</i> | 3 (3%) |
| <i>Asian or Asian British: Pakistani</i> | 2 (2%) |
| <i>Asian or Asian British: Other</i> | 1 (1%) |
| <i>Black or Black British: African</i> | 0 |
| <i>Black or Black British: Caribbean</i> | 1 (1%) |
| <i>Black or Black British: Other</i> | 3 (3%) |
| <i>Mixed: White & Black Caribbean</i> | 2 (2%) |
| <i>Mixed or Multiple: Other</i> | 3 (3%) |
| <i>White: British</i> | 64 (63.4%) |
| <i>White: Irish</i> | 2 (2%) |
| <i>White: Other</i> | 9 (8.9%) |
| <i>Other</i> | 6 (5.9%) |

Values are Mean ± Standard Deviation (range) for continuous variables and Count (Percentage%) for categorical variable. Sample size was n=101.

Table 4-2| Clinical characteristics of participants at baseline

| | |
|--|-------------------|
| PHQ-9 total score at pre-screening | 18.86±3.07(15-27) |
| MM-PHQ-9 total score at baseline | 18.08±4.75(5-27) |
| QIDS-SR-16 total score at baseline | 16.90±4.07(5-26) |
| GAD-7 total score at baseline | 12.14±5.44 (0-21) |
| Number of failed treatments | |
| 1-2 | 61 (60.4%) |
| 3-4 | 34 (33.7%) |
| 5-6 | 5 (5%) |
| 7-10 | 1 (1%) |
| Duration of current depressive episode | |
| ≤12 months | 76 (75.2%) |
| 13-24 months | 10 (9.9%) |
| >24 months | 15 (14.9%) |
| Age at first onset | 16.41±6.48 (4-55) |
| Maudsley staging method total score | 6.47±1.40 (4-11) |
| Maudsley staging method severity | |
| Mild | 60 (57.7%) |
| Moderate | 40 (38.5%) |
| Severe | 1 (1%) |
| Self-reported co-morbid psychiatric conditions | |
| PTSD | 10 (10.0%) |
| Anxiety disorders | 7 (6.9%) |
| Eating disorders | 7 (6.9%) |
| Personality disorders | 5 (4.9%) |
| OCD | 5 (4.9%) |
| ASD | 3 (3.0%) |
| ADHD | 1 (1.0%) |
| Other | 4 (4.0%) |
| Current medication | |
| Single SSRI | 58 (55.8%) |
| Single SNRI | 13 (12.5%) |
| Other | 14 (13.4%) |
| None | 19 (18.3%) |

QIDS-SR-16: The Quick Inventory of Depressive Symptomatology-Self-Report-16; MM-PHQ9: Maudsley Modified Patient Health Questionnaire-9; GAD-7: General Anxiety Disorder-7. SSRI: Selective serotonin reuptake inhibitors; SNRI: Serotonin and norepinephrine reuptake inhibitors. PTSD: posttraumatic stress disorder; OCD: obsessive-compulsive disorder; ASD: autism spectrum disorder; ADHD: attention deficit hyperactivity disorder; Values are Mean ± Standard Deviation (range) for continuous variables and Count (Percentage%) for categorical variable. Sample size was n=10

Table 4-3 | Regression model predicting depressive symptoms at four months' follow-up based on all pre-registered predictors

| | Unstandardized Coefficients | | Standardized Coefficients | t-value | p-value |
|--------------------------------|-----------------------------|------------|---------------------------|---------|---------|
| | B | Std. Error | Beta | | |
| Hide (VR task) | -2.91 | 6.68 | -0.05 | -0.44 | 0.664 |
| Distance from self (VR task) | 5.02 | 10.81 | 0.05 | 0.46 | 0.644 |
| Sociotropy subscale of the PSI | 0.01 | 0.04 | 0.04 | 0.32 | 0.746 |
| Autonomy subscale of the PSI | 0.06 | 0.04 | 0.16 | 1.47 | 0.147 |
| MSM total score | 1.00 | 0.46 | 0.27 | 2.20 | 0.031* |
| Medication adherence | -0.12 | 0.25 | -0.05 | -0.50 | 0.620 |
| Support received | 0.06 | 0.08 | 0.07 | 0.68 | 0.500 |
| QIDS-16 total score | 0.38 | 0.18 | 0.28 | 2.09 | 0.040* |
| GAD-7 total score | 0.02 | 0.12 | 0.02 | 0.15 | 0.882 |
| Antidepressant changes | -1.28 | 0.85 | -0.15 | -1.52 | 0.133 |

Overall model: $F(11,77)=3.75$, $p<.001$, $R^2=.33$; MSM=Maudsley staging method; QIDS-16=Quick Inventory of Depressive Symptomatology-16; GAD-7=Generalised Anxiety Disorder-7; PSI: Personal Style Inventory-II;* $p<.05$.

Table 4-4 | Principal Component Analysis: Varimax rotated factor loading of variables

| | | | | | |
|---------------------------|-------|-------|--------|-------|-------|
| PSI concern about others | 0.87* | 0.07 | 0.09 | 0.07 | 0.09 |
| PSI perfectionism | 0.62* | 0.09 | -0.12 | 0.20 | 0.26 |
| PSI pleasing others | 0.55* | 0.28 | -0.12 | 0.05 | -0.04 |
| PSI dependency | 0.54* | 0.06 | 0.33 | -0.23 | 0.02 |
| MM-PHQ-9 total baseline | 0.09 | 0.89* | 0.02 | 0.08 | 0.02 |
| QIDS-16 total baseline | -0.02 | 0.79* | -0.10 | 0.11 | 0.05 |
| GAD-7 total baseline | 0.18 | 0.71* | -0.33 | -0.04 | -0.04 |
| PSI defensive separation | -0.04 | 0.13 | -0.79* | 0.04 | 0.05 |
| SSS contact friend | 0.04 | -0.08 | 0.73* | 0.06 | 0.10 |
| rt SA actions | 0.04 | 0.06 | 0.05 | 0.91* | 0.01 |
| rt OA actions | 0.09 | 0.11 | -0.01 | 0.90* | 0.09 |
| OA punish self | 0.07 | 0.02 | 0.02 | 0.15 | 0.76* |
| SA punish self | 0.13 | 0.06 | 0.30 | -0.23 | 0.61* |
| OA self-blaming bias | 0.16 | -0.07 | -0.08 | 0.12 | 0.58* |
| SA self-blaming bias | 0.35 | 0.24 | 0.05 | -0.39 | 0.44 |
| SSS support provided | 0.09 | 0.09 | 0.00 | -0.07 | 0.12 |
| SSS support received | 0.05 | -0.22 | 0.35 | 0.05 | 0.02 |
| SSS negative interaction | 0.17 | 0.36 | -0.45 | -0.06 | 0.04 |
| PSI need for control | 0.22 | 0.09 | -0.36 | 0.20 | -0.05 |
| OA verbally attack friend | -0.14 | 0.01 | -0.06 | -0.27 | -0.30 |
| OA hide | 0.37 | -0.02 | 0.13 | -0.10 | -0.02 |
| SA apologise | 0.07 | -0.01 | 0.01 | -0.01 | -0.04 |
| SA hide | 0.34 | -0.01 | -0.20 | 0.14 | -0.23 |
| OA apologise | 0.04 | -0.12 | 0.21 | -0.01 | 0.12 |
| SSS satisfaction | -0.06 | -0.24 | 0.36 | 0.10 | 0.08 |
| OA distance from self | -0.14 | -0.02 | -0.03 | 0.08 | 0.32 |
| SSS contact family | 0.19 | -0.24 | 0.09 | 0.06 | -0.27 |
| SA distance from self | -0.39 | -0.01 | 0.30 | -0.05 | 0.01 |
| OA distance from friend | 0.00 | 0.04 | -0.10 | 0.03 | -0.07 |

Factor 1: Sociotropy/Perfectionism; Factor 2: Depressive/Anxiety symptoms; Factor 3: Contact with friends; Factor 4: Response time; Factor 5: Punishing oneself/self-blaming bias. PSI=Personal Style Inventory-II; MM-PHQ-9=Maudsley Modified-Patient Health Questionnaire-9; QIDS-16=Quick Inventory of Depressive Symptomatology-16; GAD-7=Generalised Anxiety Disorder-7; SSS=Social Support Scale; SA=self-agency; OA=other-agency; rt=response time. *=above critical value (0.51) for significance. Factors were only interpreted if the average of the four largest loadings is >0.6 Stevens, 2009.

Table 4-5 | Regression model predicting depressive symptoms at four months' follow-up based on the factor analysis and ordinal clinical variables

| | Unstandardized Coefficients | | Standardized Coefficients | t-value | p-value |
|--|-----------------------------|------------|---------------------------|---------|---------|
| | B | Std. Error | Beta | | |
| MSM total score | 1.04 | 0.39 | 0.28 | 2.68 | 0.009** |
| Medication adherence | -0.16 | 0.25 | -0.06 | -0.66 | 0.509 |
| Antidepressant changes | -1.26 | 0.83 | -0.14 | -1.52 | 0.132 |
| Sociotropy/Perfectionism factor | 0.19 | 0.49 | 0.04 | 0.39 | 0.701 |
| Depressive/anxiety symptom factor | 1.59 | 0.56 | 0.30 | 2.83 | 0.006** |
| Contact with friends factor | -0.16 | 0.48 | -0.03 | -0.32 | 0.748 |
| Response time factor | 0.41 | 0.48 | 0.08 | 0.87 | 0.388 |
| Punishing oneself/self-blaming bias factor | 1.22 | 0.48 | 0.23 | 2.51 | 0.014* |

Overall model: $F(5,83)=5.89$, $p<.001$, $R^2=.35$; MSM=Maudsley staging method; ** $p<.01$, * $p<.05$

Table 4-6 | Outer-loop performance of dCVnet model including all the variables in the primary analysis

| Measure | mean | SD | min | max |
|----------------|--------|-------|--------|--------|
| RMSE | 4.830 | 0.069 | 4.673 | 5.023 |
| MAE | 3.945 | 0.061 | 3.810 | 4.102 |
| r | 0.377 | 0.045 | 0.265 | 0.471 |
| r ² | 0.143 | 0.030 | 0.070 | 0.222 |
| cal Intercept | -2.512 | 2.232 | -8.389 | 2.937 |
| cal Slope | 1.169 | 0.152 | 0.792 | 1.570 |
| Brier | 23.329 | 0.666 | 21.835 | 25.230 |
| SDScaledRMSE | 0.923 | 0.013 | 0.893 | 0.960 |
| SDScaledMAE | 0.754 | 0.012 | 0.728 | 0.784 |

RMSE=root mean square deviation; MAE=mean absolute error; cal=calibration; SD=standard deviation; SDScaledRMSE = RMSE divided by the outcome standard deviation; SDScaledMAE = MAE divided by the outcome standard deviation.

Table 4-7| Outer-loop performance of dCVnet model including all the variables in the primary and secondary analysis

| Measure | mean | SD | min | max |
|----------------|--------|--------|--------|--------|
| RMSE | 4.706 | 0.078 | 4.545 | 4.882 |
| MAE | 3.783 | 0.0753 | 3.603 | 3.958 |
| r | 0.43 | 0.0342 | 0.363 | 0.487 |
| r ² | 0.186 | 0.0248 | 0.132 | 0.237 |
| cal Intercept | 1.21 | 1.2657 | -1.887 | 4.074 |
| cal Slope | 0.914 | 0.0866 | 0.722 | 1.12 |
| Brier | 22.156 | 0.7343 | 20.659 | 23.836 |
| SDScaledRMSE | 0.899 | 0.0149 | 0.869 | 0.933 |
| SDScaledMAE | 0.723 | 0.0144 | 0.689 | 0.756 |

RMSE=root mean square deviation; MAE=mean absolute error; cal=calibration; SD=standard deviation; SDScaledRMSE = RMSE divided by the outcome standard deviation; SDScaledMAE = MAE divided by the outcome standard deviation.

Figure 4-1| Scree Plot of components in the principal component analysis including all the variable in the primary analysis except the ordinal variables

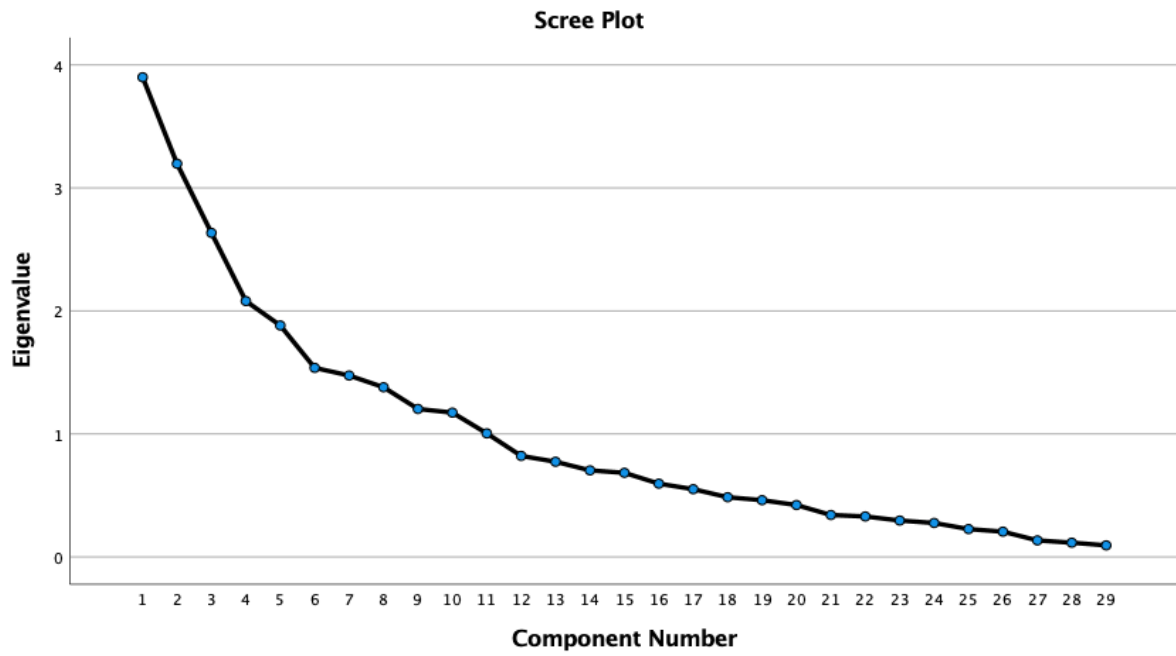
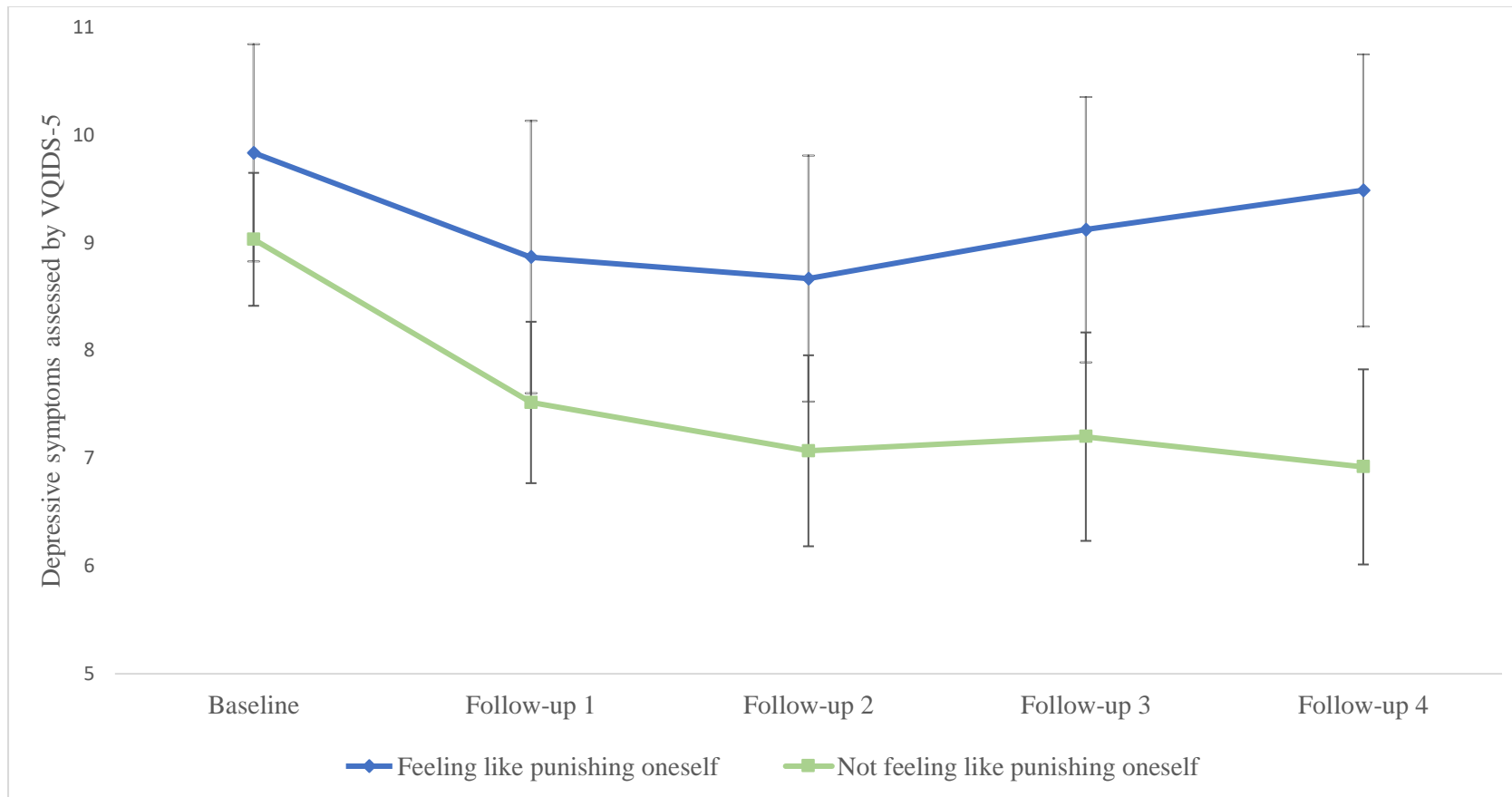


Figure 4-2| Trajectory of depressive symptoms in participants with and without agency-incongruent feeling like punishing themselves



Note. This figure shows a significant interaction between time and punishing oneself in the other agency condition: $B=.43$, $t(241.21)=2.08$, $p=.038$. No main effect of time, punishing oneself in both agencies, nor interaction between time and punishing oneself in the self-agency condition were found. Post-hoc analysis revealed that participants had significantly higher depressive symptoms in the group with the tendency to punish oneself in the other-agency condition compared to the group without such tendency at 4 months' follow-up only: $F(1,84)=6.45$, $p=.01$, (Partial) Eta Squared=0.07.

Chapter 5: General discussion

5.1) Summary of main findings

There were three major aims of this thesis. The aim of Chapter 2 was to investigate the relationship between blame-related emotions and action tendencies, as measured by a text-based task and whether remitted depression was associated with a higher proneness towards maladaptive action tendencies, such as creating a distance from oneself and hiding compared with control participants without a history depression. As expected, people with remitted depression demonstrated higher proneness towards all maladaptive action tendencies, including feeling like hiding, creating a distance from themselves, and attacking themselves compared with people with no personal or family history of mood disorders. In contrast, adaptive action tendencies such as feeling like apologising was less common in people with remitted depression compared with the control group. In addition, contrary to the previous studies that suggested associations between specific action tendencies and specific blame-related emotions (e.g. Tangney et al., 2007), we found that apologising for one's wrongdoing was associated with all self-blaming emotions including shame, guilt, self-contempt /disgust and self-indignation. Furthermore, hiding was associated with both shame and guilt.

Chapter 3 used a more immersive VR tool to measure blame-related action tendencies to further understand whether participants with current depression had a higher proneness towards maladaptive blame-related action tendencies and whether these action tendencies were associated with clinical characteristics of depression. The novel VR action tendency task, developed in this thesis, demonstrated good concurrent validity with the text-based action tendency task. As predicted, compared with people without a history depression, people with current depression showed a maladaptive profile of action tendencies, as expected they were prone to feel like hiding, but also like punishing themselves, and were less likely to feel like verbally attacking their friend. In addition, interestingly, feeling like punishing oneself was associated with a history of self-harm but not suicide attempt.

Chapter 5: General discussion

Chapter 4 examined whether maladaptive blame-related action tendencies were associated with a poor prognosis for current depression when treated as usual in primary care and whether our VR measure can be used to predict prognosis at the individual level when combined with other clinically established predictors. Our general hypothesis on the prognostic relevance of maladaptive action tendencies was confirmed: punishing oneself for other people's wrongdoing (more specifically punishing oneself in the other-agency condition) was associated with a poor prognosis of depression after four months. However, our findings did not support the pre-registered predictions of specific withdrawal-related maladaptive action tendencies (e.g. hiding and creating a distance from oneself) on prognosis of depression. We also examined the influence of clinically established risk factors. As expected, higher treatment resistance and more severe symptoms at baseline were associated with poor prognosis. Notably, none of the other clinical variables had significant prognostic value in this sample. Our statistical/machine learning model also identified the same three risk factors found using standard statistics and further confirmed that despite their significant contribution, useful individual level prediction of prognosis was not achieved using these measures alone.

To summarise findings from all three chapters, people with either remitted or current depression had a maladaptive profile of action tendencies including higher proneness to withdrawal (e.g. feeling like hiding), higher proneness to self-attacking/punishment and lower proneness to attacking others. These findings were obtained in two independent samples recruited at different time points (participants with remitted and current depression) using two different measures (text-based action tendency task and VR action tendency task), thereby pointing to their generalisability. Among these maladaptive action tendencies, punishing oneself in the other-agency condition was shown to be the most clinically relevant action tendency, as it was associated with a history of self-harm at baseline and also predicted a poorer prognosis of depressive symptoms after four months.

5.2) Maladaptive action tendencies and depression

At the outset of this thesis, I hypothesised that depression was associated with maladaptive blame-related action tendencies, including action tendencies that motivate social withdrawal, interpersonal separation, and avoidance, such as feeling like hiding (e.g. Tangney et al., 2007) and creating a distance from oneself. As suggested by Gray's reinforcement sensitivity theory (Gray, 1970), these withdrawal-related action tendencies may render people more sensitive to punishment and frustration and ultimately increase their chances to develop depression. In empirical studies, stronger behavioural inhibition/withdrawal and impaired behavioural activation were associated with affective disorders (e.g. Kasch et al., 2002; Mu & Berenbaum, 2019). In addition, Freud emphasized the role of internalised aggressive impulses such as self-attack/punishment in depression and differentiated depression from mourning on this basis (Freud, 1917). This tendency was thought to be a core feature of depression in Freudian models, which is the reason that increased tendency of self-punishment and decreased tendency of attacking others were also considered as maladaptive action tendencies in my studies.

The findings of this thesis partially supported the initial predictions. Maladaptive blame-related action tendencies did indeed distinguish people with and without a history of depression, as shown by the former having overall higher proneness towards withdrawal-related and self-punishing action tendencies as well as a lower proneness towards attacking others than the latter. To my knowledge, these findings are the first to directly demonstrate maladaptive blame-related action tendencies in people with remitted and current depression. Withdrawal-related action tendencies, which were thought to reflect behavioural inhibition that was found to be increased in depression in previous studies (Kasch et al., 2002), did not predict prognosis of depression. In contrast, the tendency to punish oneself especially for other people's wrongdoing not only distinguished people with and without depression, but also

contributed to the prediction of prognosis of depression. This might reveal the more maladaptive nature of the tendency to punish oneself compared with withdrawal-related action tendencies. One explanation is that although withdrawal-related action tendencies predispose people to developing depression, it does not necessarily contribute to prognosis of current depression. Another possibility is that withdrawal-related action tendencies might not be strictly maladaptive, but more likely to be defence mechanism specific to people vulnerable to depression, although this hypothesis needs to be examined by empirical studies.

The following ambiguity in conclusions that can be drawn from this thesis need to be discussed. Firstly, it is unclear whether maladaptive action tendencies are a result of previous depressive episodes [i.e. scarring, Wichers et al. (2010)] or are a primary vulnerability factor for depression. It is possible that maladaptive action tendencies motivate specific behaviour and coping styles that then gives rise to a vulnerability to depression. On the other hand, it is also possible that people who are vulnerable to depression develop these maladaptive action tendencies gradually in their lives as a result of depressive symptoms. More likely, maladaptive action tendencies and vulnerability to depression mutually influence each other. Secondly, it is elusive whether maladaptive action tendencies constitute traits or states. Although, I investigated maladaptive action tendencies as vulnerability traits of depression, specific action tendencies might also be temporary states that fluctuate over time. It is important to further understand why and how action tendencies change under different circumstances and whether such changes are associated with an individual's susceptibility to depression.

5.3) Limitations

There are several limitations of the studies presented in this thesis and care needs to be taken when interpreting the findings. The study in Chapter 2 was limited by a text-based task to measure blame-related emotions and action tendencies, which relied on participants'

imagination of the social scenarios and action tendencies, but visual imagery styles differ between participants (Fulford et al., 2018) and is impacted by mood disorders (Holmes et al., 2016). In addition, measuring blame-related emotions based on the emotion labels is subjective and depends on participants' semantic knowledge and specific understanding of the emotions. This could partially explain why some action tendencies (e.g. feeling like apologising) were associated with all self-blaming emotions. Such limitation in Chapter 2 was at least partially overcome by studies in Chapter 3 and 4, where the VR action tendency task was used to depict the social scenarios and action tendencies.

In Chapter 3 and 4, the studies did not include a diagnostic interview, therefore, a formal diagnosis for participants could not be established. This might make these findings more generalisable to primary care patients, however, where a formal diagnostic interview is not conducted when examining patients. Further, a highly conservative PHQ-9 score cut-off (≥ 15) was used in the study, with a specificity of .96 for MDD (Manea et al., 2012), which has also been suggested by the updated National Institute for Health and Care Excellence (NICE) guidance as the threshold for recommending pharmacological treatment for people with depression in primary care (NICE, 2022). Furthermore, our study went above usual standards in primary care, by using validated self-report screening measures to exclude participants on the bipolar spectrum and those with alcohol or drug abuse and schizophrenia. In addition, the patients in Chapter 3 and 4 are primarily primary care patients with treatment-resistant depression. This means that the results might be less generalisable to patients in secondary or tertiary care or patients with less severe depression.

A limitation of the VR task is that it was difficult to unequivocally depict the action tendency “creating a distance from oneself”. The current version of the task depicted it as a bird’s-eye perspective of seeing the participant themselves interacting with their friend. However, in their debriefing it has been mentioned by some participants that they did not

perceive the action tendency this way and seeing “themselves” as the VR avatars in the task made them feel unreal. This could partially explain why “feeling like creating a distance from oneself” was least chosen by participants in the study and there was a lack of group difference for creating a distance from oneself only when measured by the VR task. In addition, some participants mentioned that the male-like avatar movements in the VR task interfered with the immersiveness of the task. While most participants in the studies were female, the body movement of the avatar was based on a male model, reducing the ecological validity of the task. This was due to limited availability of software engineering time and resources.

While conducting VR studies remotely reduced the resources needed for the studies and allowed the studies to be carried out during the COVID-19 pandemic when lockdown was implemented in the UK, this also gave rise to some additional limitations. For example, although the detailed procedure was sent to the participants by email, it was not possible to examine whether such procedure was strictly followed, which could potentially influence the consistency of the data collection, for example if participants did the task whilst being in a noisy environment or observed by others. The advantages and disadvantages of conducting an unsupervised VR study should therefore be carefully weighted before embarking on future such studies.

5.4) Further studies

Further studies are needed to replicate the studies presented in this thesis with tasks completed under the supervision of researchers. This could make sure that the strict procedure is followed for each participant. Importantly, this would also make it easier to establish a formal diagnosis of major depressive disorder and other psychiatric disorders by conducting a diagnostic interview such as the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

The present studies have shown that maladaptive blame-related action tendencies are vulnerability factors and potential predictive markers of depression. Future clinical trials should examine these findings in more rigorous settings, such as by controlling the type of antidepressant medications that is taken during the follow-up periods. Also, the present prospective study entailed very few participants who had changed their antidepressant medication during the follow-up period, which may also partially have been caused by the lockdown procedure during the COVID-19 pandemic. Future studies could examine whether maladaptive action tendencies are associated with treatment response to specific antidepressants in depression. If such association does exist, measuring maladaptive action tendencies could potentially help to optimize the treatment of patients with depression. Furthermore, the present studies were unable to examine whether any changes in action tendencies over the course of time were associated with any changes in depressive symptoms. Future studies could assess maladaptive action tendencies at both baseline and follow-up visits, allowing to examine such correlations. Our findings suggest that novel treatments could target maladaptive action tendencies to improve the outcome of depression. Similar to some cognitive training such as attentional bias modification training that was shown to be effective for depression and anxiety (e.g. Mennen et al., 2019; Yang et al., 2015), patients with depression could be trained to reduce their maladaptive action tendencies and increase their adaptive action tendencies. For example, they could be trained to attack other more rather than attack themselves when other people have treated them badly. Given its immersive nature, virtual reality interventions could be particularly suitable for such training, although traditional computer-based or face-to-face training would also be feasible.

The findings of present studies are not necessarily incompatible with a more general cognitive biases model of depression which states that depression is characterized by a bias towards greater processing of negative compared with positive information. Although this

general model has been challenged by some studies that found diminished negative emotions towards others in remitted depression (Zahn et al., 2015), further studies are needed to examine whether similar findings can be obtained in people with current depression.

5.5) Overall conclusions

In conclusion, this thesis confirmed that maladaptive blame-related action tendencies play a relevant role in the vulnerability, maintenance, and prognosis of depression. Specifically, in Chapter 2, using a text-based action tendency task, people with remitted depression had shown a maladaptive profile of blame-related action tendencies including higher proneness towards hiding, creating a distance from oneself and attacking oneself and lower proneness towards attacking others. In chapter 3, an immersive virtual reality task was developed to measure blame-related action tendency which demonstrated good concurrent validity with the text-based action tendency task. Similarly to the findings in Chapter 2, people with current depression also showed a maladaptive profile of blame-related action tendencies including higher proneness towards hiding, punishing oneself and lower proneness towards attacking others. Interestingly, punishing oneself was associated with a history of self-harm, but not of suicide attempts. Chapter 4 found that punishing oneself for other people's wrongdoing was the only factor of prognostic relevance apart from well-known baseline levels of depressive symptoms and treatment-resistance, although prediction of prognosis at the individual level was not possible. Nevertheless, a simple binary categorisation of feeling like punishing oneself on the VR task was shown to be useful in identifying a group of people with poorer prognosis. Therefore, this thesis revealed a novel treatment target for depression that should therefore be assessed and tackled in personalised care pathways for difficult-to-treat depression.

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Chapter 5: General discussion

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