Introduction

Of all psychiatric disorders, Major Depressive Disorder (MDD) is ranked as the single largest contributor to global disability (World Health Organisation, 2017). An important factor that adds to the large burden of MDD is the high risk of recurrence after remission from a depressive episode. MDD recurrence rates are typically reported to be above 50% (Eaton et al., 2008; Hardeveld et al., 2013; Steinert et al., 2014), with rates as high as 90% within 10-15 years in clinical samples with 3 or more previous episodes (Beshai et al., 2011; Bockting et al., 2015). Clinical characteristics such as the number of previous episodes and residual symptoms have been identified as among the strongest predictors of recurrence (Hardeveld et al., 2010; Kessing et al., 2004). Whether cognitive and psychological processes associated with MDD (e.g. habitual maladaptive thinking patterns, deficits or biases in cognition) predict recurrence of MDD is less well established.

One important cognitive risk factor for MDD is rumination: a type of repetitive negative thinking (RNT), that has been defined as 'repetitively and passively focusing on the symptoms of distress and the possible causes and consequences of these symptoms' (Nolen-Hoeksema et al., 2008). High levels of rumination have been consistently shown to predict the onset, severity and maintenance of depressive episodes (Nolen-Hoeksema et al., 2008; Watkins, 2008). Further, residual rumination during remission from earlier episodes is considered a risk factor for recurrence of depression (Watkins, 2009). A small number of studies have specifically examined a possible role for rumination in predicting depressive recurrence. Michalak and colleagues (2011) found that higher levels of rumination predicted shorter time to recurrence within 12 months after a mindfulness based treatment (Michalak et al., 2011). Scores on a cognitive reactivity measure (Leiden Index of Depression Sensitivity; LEIDS (Van der Does, 2002, 2005)) including the rumination subscale were also associated with time to recurrence of depression (Figueroa et al., 2015). In contrast, Timm and colleagues (2017) did not show a relationship between trait rumination and time to recurrence, but found that rumination predicted levels of residual symptoms at 6 and 30 months after treatment (Timm et al., 2017).

A key vulnerability that might underlie both depression and rumination is deficits in cognitive control or flexibility (CC): cognitive control/flexibility concerns is a set of processes including controlling and shifting attention, inhibiting irrelevant information, and updating working memory (Miyake et al., 2000). Attentional control, i.e. the ability to direct attention flexibly according to current goals, is considered to be one of the core abilities supporting and serving cognitive flexibilityCC (Mackie et

al., 2013). Experimental evidence from a range of tasks indicates that theseCC impairments not only occur in clinically depressed groups but also in vulnerable populations, including individuals with subclinical symptoms and remitted groups (Koster et al., 2017b; Snyder, 2013).

Empirical studies now indicate that rumination is also closely associated with deficits in cognitive flexibilityCC, particularly impairments in attentional inhibition and shifting (De Lissnyder et al., 2011; Mor and Daches, 2015; Vanderhasselt et al., 2011; Whitmer and Banich, 2007). Several theoretical models have proposed that CC cognitive deficits increase vulnerability to rumination, by reducing the ability to exert control over these thought processes and impairing the use of other emotional regulation strategies, such as reappraisal or distraction (Hirsch and Mathews, 2012; Koster et al., 2011; Mor and Daches, 2015; Watkins and Nolen-Hoeksema, 2014). For instance, Demeyer et al. (2012) showed that CC deficits on an attentional control task were associated with depressive symptoms one year later and this relationship was mediated by rumination. Similarly, Hsu et al. (2015) showed that rumination mediated the relationship between self-reported attentional control and symptoms of depression/anxiety. However, possible relationships between CC deficits in cognitive flexibility, rumination and depressive *recurrence* have been less well examined. Most existing studies are limited by reliance on self-report measures of cognitive flexibilityCC and use of cross-sectional designs.

In the current study we therefore consider the potential role of rumination and deficits in CC in predicting depressive recurrence, in a group of patients remitted from at least 2 previous episodes of MDD. To examine cognitive flexibility we use two different tasks: 1. The IST (Internal Shift Task), which allows theo examinexamination ofe whether recurrence is related to impairments in the capacity to shift between emotional or non-emotional information held in working memory (De Lissnyder et al., 2012b) and 2. the ECT (Exogenous Cueing Task), which presents a fine-grained measure of attentional bias, differentiating between engagement and disengagement for emotional stimuli and short and longer durations of presentation (Koster et al., 2005). Further Eexamining the role of CCcognitive flexibility deficits and rumination in depression is theoretically important in understanding vulnerability to onset and recurrence of this disorder. These models also have potential clinical utility; both CCcognitive flexibility deficits and rumination are possible targets for treatment and preventative interventions (Koster et al., 2017b; Martell et al., 2013; Mor and Daches, 2015; Siegle et al., 2014; Topper et al., 2017; Topper et al., 2010; Watkins et al., 2007).

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Aims and hypotheses

The aim of the current study was to examine performance on two cognitive flexibility tasks in a remitted patient group: firstly, a version of the exogenous cueing task (ECT), and secondly the Internal Shift Task (IST). Further, we aimed to consider how cognitive flexibility performance related to both rumination and time to depressive recurrence. Previous studies using the ECT have shown that clinically depressed participants show stronger attentional engagement with, and slower disengagement from, angry faces compared to healthy controls, respectively (Leyman et al., 2007). Previous work using the IST has demonstrated that patients with MDD show general shifting impairments across emotional and neutral conditions, and rumination is associated with the degree of impairment (De Lissnyder et al., 2012c). For both tasks, there is a lack of previous research in remitted depressed groups.

We hypothesised that 1. Cognitive flexibility is poorer in the remitted patient group compared to controls; 2. Within the remitted patient group, rumination is associated with difficulties in disengaging and shifting attention, particularly when processing negatively valenced emotional stimuli; 3. High rumination and cognitive flexibility deficits (difficulties in disengaging and shifting attention) are associated with shorter time to recurrence of depression, and 4. Rumination mediates the relationship between cognitive flexibility deficits and recurrence.

Method

Participants

Participants were recruited in the context of the DELTA neuroimaging study (Mocking et al, 2016) from several psychiatric institutions across the Netherlands, via general practitioners, advertisements, patient organizations, and previous research projects. The study was approved by a local research ethics committee (ref: AMC-METC-Nr.:11/050). Informed consent was obtained from all participants. Remitted depressed (rMDD) patients had experienced ≥2 depressive episodes and were in stable remission for at least 8 weeks (according to the Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition [SCID-I/P] and a Hamilton Depression Rating Scale score [HDRS] ≤7). Patients were not using any psychotropic medication for > 8 weeks. Only controls without personal (SCID-I/P) or first-degree familial psychiatric history were included. Exclusion criteria were: alcohol/drug dependency; psychotic/bipolar disorder; primary anxiety disorder; personality disorder; electroconvulsive therapy within 2 months of recruitment to the study; history of severe head trauma; neurological disease; severe general physical illness; no Dutch language proficiency.

Study design and procedure

At the baseline visit, we conducted the neuropsychological tests in two blocks with a break in between, in the context of a larger assessment. After this baseline visit, all participants received a booklet including the Ruminative Response Scale (RRS – see measures) to complete before the second visit (mean time from visit 1 to visit 2 was 39.8 days [SD=24.1]). To prospectively assess recurrence, we conducted follow up assessments of rMDD participants every 4 months by phone. These assessments included administration of the SCID and HDRS. The number of previous episodes was also assessed with the SCID-I. To maximize recurrence detection, we also instructed participants to contact the study team at the moment they subjectively experienced a recurrence and to inform a person close to them of these instructions. A published protocol containing details of the full study is available (Mocking et al., 2016).

Measures

Depression
Severity of depressive (residual) symptoms was assessed with the HDRS in both the rMDD and controls group. Primary outcome for hypotheses 3 and 4 was the time until occurrence of a major depressive episode (assessed by the SCID-I/P) in the 2.5-year follow-up period.

Internal Shift Task (IST) (De Lissnyder et al., 2012a; De Lissnyder et al., 2012c)

The IST (De Lissnyder et al., 2012a; De Lissnyder et al., 2012c) is a working memory task involving updating and shifting functions, executed on internally represented stimuli. The task includes a gender and an emotion condition. These are completed sequentially, with order of conditions counterbalanced across participants. For each condition, participants completed 3 practice blocks and 12 experimental blocks, with a random number of 10-14 trials per block. Each trial consists of presentation of a single face in the centre of the screen. Participants were asked to keep a mental count of the number of faces seen across two categories. In the gender condition, this equates to the number of male and female faces; in the emotion condition to the number of neutral and angry faces. Angry faces are specifically used due to the salience of social threat and interpersonal evaluation in depression (De Lissnyder et al., 2012c). As each face is presented, participants are asked to press the space bar as quickly as possible when they have updated their internal counts (reaction time [RT] measure). The next stimulus is presented following an inter-stimulus interval of 200ms. At the end of each block, participants are asked to enter the number of faces seen from each category (accuracy measure).

Blocks contain both switch and non-switch trials, i.e. trials in which the category to be updated is different from or the same as the preceding trial. The design of the task thus allows examination of switching costs under both emotional and non-emotional conditions. Switch costs are calculated as the difference in RT between switch and no-switch trials (i.e. switch trial RT - non-switch trial RT) and provide an index of the efficiency of shifting between representations in working memory.

The IST was programmed using E-prime 2.0 and displayed on a Windows 7 desktops with a 60Hz, 22-inch colour monitor. The face stimuli were extracted from the Karolinska Directed Emotional Faces picture set (Lundqvist et al., 1998) and included 24 angry and 24 neutral faces, selected on the basis of a previous validation study (Goeleven et al., 2008). Images were presented at a consistent size (326 x 326 pixels) and adjusted to remove external features, e.g. hair.

Exogenous Cueing Task (ECT)

This task (Fox et al., 2001; Koster et al., 2006), is based on the exogenous cueing paradigm (Posner, 1980), and designed to investigate attentional effects when processing emotional stimuli. Emotional facial expressions of four different valences – angry, sad, happy and neutral – were used as cue stimuli. All face stimuli were extracted from the Karolinska Directed Emotional Faces picture set (Lundqvist et al., 1998) and adjusted to the same size (326 x 326 pixels). Sixteen pictures were

selected for each emotional category. Participants were asked to respond to the location of a visual target, presented to either the left or right of a central fixation point. This target was preceded by a visual cue, either in the same location as the target (valid cue) or in the opposite location (invalid cue). Several key indices can be calculated based on the reaction times for different cue types. Attentional engagement for each valence is calculated by comparing RTs for validly cued emotional trials to validly cued neutral trials (i.e. RT valid emotional trial – RT valid neutral trial). Attentional disengagement for each valence is calculated by comparing RTs for invalidly cued emotional trials to invalidly cued neutral trials (i.e. RT invalid emotional trial – RT invalid neutral trial).

The ECT was programmed using E-prime 2.0 and presented as described before the IST. Participants completed 10 practice trials and 256 test trials. There were 16 test trials of each type (2 presentation durations [200, 1000msec], 2 conditions [valid, invalid cue], 4 face valences). Order of trial types and target location was pseudo-randomised across the task (all subjects received the same randomized order). Each trial began with two white frames, presented at either side of a fixation cross for 500msec. The cue stimulus was then presented in the location of one of these frames, for either 200 or 1000msec, and followed by white mask presented for 50msec. The target (black square) then appeared in one of the frames and participants were asked to respond to its location as quickly as possible by pressing the left or right arrow key on a standard keyboard. To minimise anticipatory responding, 12 'catch trials' were included. These are trials in which a cue stimulus is presented but not followed by a target. On these trials, participants were required to withhold responding.

RRS-NL
The Dutch adaptation of the original RRS is a self-report rumination measure (Raes, 2012; Raes and Hermans, 2007; Raes et al., 2003; Raes et al., 2009; Schoofs et al., 2010), which consists of 26 items that describe responses to depressed mood focused on the self, symptoms, or consequences of depressed mood (Nolen-Hoeksema and Morrow, 1991). Items are rated on a 4-point scale (*almost never* to *almost always*) based on the extent to which respondents engage in these thoughts or actions when feeling sad, down or depressed. Cronbach's α for the total RRS-NL was .92 in a validation study (Schoofs et al., 2010) and .96 in the current study. The introductory statement was reframed so that, instead of asking participants what they generally do when depressed, the focus was on their responses in the past week.

Statistical analysis

All analyses were conducted using SPSS v22. In order to compare performance of patients and controls on each cognitive task, a mixed ANOVA was conducted. For the IST, this included condition (emotion, gender) and switch type (switch, no switch) as within subject factors, and group (remitted patients, controls) as a between subject factor. For the ECT, the mixed ANOVA included valence (angry, sad, happy, neutral), cue duration (short, long), and cue validity (valid, invalid) as within subject factors and group (patients, controls) as a between subject factor. Relationships between task performance and rumination were examined in the remitted patient group only for the purpose of the mediation analyses and to constrict the amount of tests. Two participants with outlier scores, defined by more than 1.5 times the interquartile range from the quartiles (Schwertman et al., 2004), (RRS total ≥70) were removed from these analyses. The remaining participants were classified as high or low ruminators using a median split (RRS total ≤ or > 35) in line with previous studies (Beckwé et al., 2014; Koster et al., 2013). A mixed ANOVA was conducted for each task, as described above, but with rumination group (high/low) as the between-subject factor. Main effects and interaction effects not involving group are not reported in the text, as they are not relevant to the main study hypotheses.

Survival Analysis

Cox proportional hazards regression models were used, with time to first recurrence as the endpoint. Participants lost to follow-up or without relapse during follow-up were considered censored. Based on previous literature, we selected indices of IST (overall shift costs and emotion shift cost) and ECT (engagement and disengagement for each duration and valence) task performance as possible predictors of recurrence. First, the associations of IST, ECT performance and rumination (continuous score) with recurrence were investigated with simple Cox regression models. Besides the total score, we also examined the brooding subscale as a predictor, as it has been suggested that brooding is a particularly maladaptive form of rumination {Nolen-Hoeksema, 2008 #72}. One participant with outlier score on the RRS (70) and one participant with outlier scores on the brooding subscale (15) was excluded from this analysis. To provide a measure of effect for the analyses, we report the Hazard Ratio (HR) of one change in the Standard Deviation of predictors (Azuero, 2016) in the text. We report the HR of the continuous score in the tables. Second, for variables that were associated with time to first recurrence in this simple model, we conducted a further step-wise Cox regression model in which we adjusted for established predictors of depressive recurrence (residual depressive symptoms and previous episodes of MDD).

We planned to proceed with mediation analyses if assumptions for mediation; rumination (mediator) must be related to cognitive flexibility deficits and recurrence, were met in the simple and corrected models (Baron and Kenny, 1986). We also examined if rumination modified the relation between the ECT/IST scores and recurrence by adding a rumination interaction term in the Cox regression model. We tested this model both with and without established predictors of recurrence (residual symptoms, previous episodes).

Results

Participants

The full cohort included 73 remitted MDD-patients and 45 controls. Of these, 69 MDD-patients and 43 controls completed the neuropsychological test battery. Of the 69 MDD-patients, 64 (92.8%) had at least 1 follow-up measurement and 52 (75.4%) completed 2.5 years of follow-up.

The groups did not differ significantly on age, sex, IQ, education, living situation (*Table 1*). However, remitted MDD-patients were significantly less often employed. HDRS scores and RRS scores were higher RRS-scores in MDD-patients than in controls. Differences between groups did not change when restricting the analyses to the participants included in the IST and ECT analyses.

IST

Sixty-five rMDD patients and forty controls were included in the IST analyses. Six rMDD patients and two controls patients did not complete the IST; data from a further two rMDD patients and three controls were excluded because the task stopped prematurely. A block was scored as correct if the reported number of faces was correct for both categories. Using this criterion, average accuracy was 73% (M=17.6 correct, SD=4.71).

Comparison between remitted patients and controls

Accuracy did not differ by condition (gender/emotion) [$t(104)=-.88$, $p=.281$] or by group (rMDD/controls) [$t(103)=.212$, $p=.832$]. A mixed ANOVA showed a main effect of condition [$F_{(1,103)}=4.48$, $p=.037$], with faster responses for gender trials [M=1368.94msec, SD=428.09] than for emotion trials [M=1454.56msec, SD=433.98]. There was also a main effect of switch type [$F_{(1,103)}=271.83$, $p<.001$], with faster responses on no switch trials [M=1229.11msec, SD=367.68], than

on switch trials [M=1563.73msec, SD=444.13]. There was however no main effect of group [$F_{(1,103)}$=.003, p=.954] and no significant interaction effects [all p's >.05].

Relationships between rumination scores and IST performance

A mixed ANOVA analysis conducted only in the patients group, indicated significant main effects of condition [$F_{(1,55)}$=5.55, p=.022; faster responses for gender trials] and switch type [$F_{(1,55)}$=164.68, p<.001; faster responses on no switch trials], and a significant interaction between switch type and rumination [$F_{(1,55)}$=5.62, p=.021; high ruminators were faster in non-switch trials] (*see Figure 1*). This interaction was further explored by comparing shift costs between groups using independent samples t-tests. Shift costs were larger for high ruminators [M=375.54msec, SD=222.88] than for low ruminators [M=275.98msec, SD=158.06], although this effect was just below the significance threshold [t(55)=-1.95, p=.056].

ECT

Sixty-eight remitted MDD-patients and forty-three controls were included in the ECT analysis. Four remitted MDD-patients and two controls did not complete the ECT; data from one remitted MDD-patient was excluded because the task stopped prematurely. Trials with incorrect responses were excluded from analysis (0.4% of trials). Trials were screened for very fast (<200msec) or slow (>750msec) responses, but no such trials were identified. Seven participants made 1 catch-trial error; the remaining participants made no such errors.

Comparison between remitted patients and controls

The mixed ANOVA analysis with reaction times as dependent outcome indicated no main effects of group and no significant interactions of stimulus-presentation*group, nor valence*group, nor stimulus-presentation*valence*group [all p's >.05] (Table S1).

Relationships between rumination scores and ECT performance

When examining ECT performance of high and low ruminators, there was no main effect of group and no interactions with rumination involving group [all p's>.05]. These analyses therefore suggest no evidence of differences in ECT performance between participants with high and low rumination scores.

IST/ECT performance and rumination as predictors for recurrence

Baseline characteristics of rMDD participants who experienced a recurrence during the study period, versus those who experienced no recurrence during the study period are shown in *Table 2*. Rumination scores, ECT and IST indices for these groups are shown in *Table 3*.

In the Cox regression models for the ECT performance measures, slower disengagement (i.e. RT invalid emotional trial – RT invalid neutral trial) from angry faces, happy faces and sad faces presented at a short duration was associated with a protective effect on recurrence of depression, (HR_{SD} = 0.563 [CI, 0.381-0.832]; Wald = 8.33; p=0.004, HR_{SD} = 0.561 [CI, 0.389-0.808]; Wald = 9.61; p=0.002; and HR_{SD} = 0.657 [CI, 0.436-0.990]; Wald = 4.03; p=0.045, respectively). This means that, for one SD increase in disengagement scores (36.2ms, 33.6ms, 32.8ms, respectively, the risk of recurrence within 800 days was 0.56 times lower for angry and happy faces and 0.65 times lower for sad faces. For angry and happy faces, these HRSD's correspond to medium effect sizes and for sad faces to a small to medium effect size (Azuero, 2016). For angry and happy faces, these associations remained significant when correcting for residual symptoms and previous depressive episodes (HR_{SD}=0.539 [CI, 0.360-0.805]; Wald = 9.11; p=0.003; HR_{SD} =0.556 [CI, 0.382-0.809]; Wald = 9.38; p=0.002). For sad faces however, this association was no longer significant after correcting for residual symptoms and previous depressive episodes (HR_{SD} =0.687 [CI, 0.879-1.175]; Wald = 2.97; p=0.085). Raw reaction times for responding to invalidly cued angry, sad, happy and neutral face trials were not associated with recurrence (all p's >.05).

For illustrative purposes we additionally compared patients with rapid disengagement for angry and happy faces to those with slow disengagement (dichotomized by median scores; see *Figures 2 and 3*). These analyses showed that participants with relatively fast disengagement from angry faces had a more than 2 fold, and from happy faces almost 3 fold, increase in the risk of recurrence within 800 days, compared to participants with relatively slow disengagement from angry faces (HR_{SD}=2.11 [CI,1.003-4.44], Wald=3.88; p=0.049, HR_{SD}= 2.96 [CI= 1.41-6.22]; Wald=8.23; p=0.004, respectively).

Engagement with happy faces at short duration also predicted time to recurrence (HR_{SD} = 0.74 [CI, 0.558-0.982]; Wald = 4.631; p=0.037), but this was no longer significant after correcting for residual symptoms, and previous depressive episodes (HR_{SD} =0.81 [CI, 0.595-1.103]; Wald = 1.795; p=0.18).

Rumination was associated with recurrence in a simple Cox regression model (HR_{SD}=1.526 [CI, 1.152-2.202]; Wald = 85.6801; p=0.00235). ~~However,T t~~his relationship ~~was no~~remained ~~longer~~ significant when correcting for residual symptoms and previous depressive episodes (HR_{SD}= 1.571349 [CI,

1.110.984-21.22849]; Wald=63.454; p=0.01163). The brooding rumination subscale was additionally associated with recurrence (HR$_{SD}$= 1.50 [CI, 1.103-2.064]; Wald=6.63; p=0.010), and after correcting for residual symptoms and previous depressive episodes (HR$_{SD}$= 1.55 [CI, 1.075-2.245]; Wald=5.51; p=0.019). Further, rumination (total and brooding) was not associated with the ECT predictors examined (all p's >0.05). Because the assumptions were not met, mediation analyses were not conducted. Continuous HR's from the Cox regression analyses for the ECT and IST variables are shown in *Table 3*.

Rumination*disengagement interaction terms were added to the two significant regression models (disengagement from angry and happy faces when presented at short durations). In neither of these models the interaction term was significant p=0.329025 and p=0.898913 respectively.

Discussion

This study investigated associations between cognitive flexibility and rumination in patients whose depression had remitted, and tested whether these factors predicted time to depressive recurrence. We found no evidence of differences in cognitive flexibility between remitted patients and controls, nor differences in task performance between high and low ruminators, except that general switch costs on the IST were larger for high ruminators. More rapid disengagement from emotional (angry and happy) faces (200ms presentation), relative to neutral faces, was associated with shorter time to recurrence over a 2.5-year follow up. In contrast to our hypotheses, this relationship was not mediated by rumination. Rumination, and its brooding subscale, was a predictor of recurrence.

It has previously been demonstrated that both depressed patients and vulnerable groups show impaired attentional disengagement, particularly for negative information (Gotlib and Joormann, 2010). Therefore, we hypothesised that remitted depressed patients would have difficulties disengaging, which in turn would be mediated by rumination and predict depressive recurrence. In this study, we find no differences in cognitive flexibility, measured by the IST and ECT task, when comparing remitted-MDD and controls, nor do we find strong relationships with rumination, which is in contrast to previous theoretical models (Demeyer et al., 2012; Koster et al., 2017b; Snyder, 2013). Importantly, we conducted a supplementary power analysis and showed that with 90% power, we were able detect small to medium effects (Supplementary Results) making it likely that our study does not miss large (clinically important) effects due to low power.

With respect to prediction of recurrence, our finding was in the opposite direction to that hypothesised – that is, participants who most rapidly disengaged from emotional faces had a higher risk of depressive recurrence, with a medium effect size. Patients with a relatively fast disengagement from angry faces had a more than 2 fold, and from happy faces almost 3 fold, increase in the risk of recurrence within 800 days. The predictive effect was not due to differences in raw reaction times, but specifically to differences in reaction time between emotional and neutral faces. Furthermore, rumination, the total score and brooding subscale, predicted recurrence. However, it was not related to more rapid disengagement and therefore did not mediate the relationship between disengagement and recurrence, which we had hypothesized. Supplementary analyses indicated that we had substantial power, of 90%, to detect a medium effect size for our survival analyses. However, we had very low power (25%) to detect a small effect (Supplementary Results).

Although we had hypothesised that difficulty disengaging with emotional faces would predict recurrence, it is notable that other studies have shown links between speeded disengagement and affective disorders. For instance, Yiend et al (2015) found evidence in two studies that patients with generalised anxiety disorder show speeded disengagement from negative faces. Here, caution is warranted in extrapolating findings across populations. Rapid disengagement from emotional faces might be related to decreased affective flexibility: the ability to flexibly attend to and disengage from emotional and non emotional situations or stimuli (Malooly et al., 2013). Affective flexibility is considered a crucial aspect of emotional resilience and might be related to better emotion regulation (ER), in particular reappraisal to down-regulate sad affect (Malooly et al., 2013).

Early life stress might result in divergent cognitive styles, associated with avoidance or increased attention towards negative/threatening stimuli (Del Giudice et al., 2011; England-Mason et al., 2018). In contrast to the vigilant style, an avoidant cognitive style might be more likely in the presence of poor ER (England-Mason et al., 2018). In line with this model, rapid disengagement from emotional facial cues is consistent with an avoidant response style. A review and meta-analysis found that MDD patients self-report more frequent use of higher maladaptive emotion regulation strategies, including avoidance and rumination, which persists in remitted MDD and might lead to a higher risk for recurrence (Visted et al., 2018). Consistent with this, we find that remitted patients who show a general emotional avoidance have shorter time to recurrence. Taken together, our findings of increased avoidance indicate that these patients have difficulty in regulating emotional stimuli, resulting in an avoidant response style and an increased risk for recurrence. Further

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research is needed to explore this issue using systematic studies of the relationship between attentional measures, ER and recurrence vulnerability.

Interestingly, only attentional disengagement from stimuli presented for short intervals (200ms) as opposed to longer intervals (1000ms) was associated with time to recurrence. Previous studies in acute depression have typically demonstrated that attentional biases exist at longer presentations, suggesting that these biases occur more at the elaborative (instead of automatic) stages of information processing (Gotlib and Joormann, 2010). We note that at longer stimulus presentations on the ECT, our pattern of results is indicative of an Inhibition of Return effect (Klein, 2000) (i.e. valid cues inhibit rather than facilitate responding to the target). Therefore, responding to these longer presentations is likely to reflect the operation of different attentional processes. Our findings suggest that it may be that attentional responses differ during remission compared to the acute phase of depression.

Clinical implications

If replicated, attentional disengagement from emotional stimuli may be an important marker for clinical and research purposes of increased risk of recurrence within remitted populations. Furthermore, increased avoidance of emotional stimuli may also be amenable to change via cognitive interventions. Specifically, approaches that focus on enhancing cognitive control by activating frontal brain areas implicated in attentional control might be particularly beneficial in decreasing avoidance, emotional vulnerability and rumination, and increasing resilience in subjects at risk for depression (Koster et al., 2017a; Swainston and Derakshan, 2018). Such approaches are likely to be clinically important, given the high recurrence rates in MDD and the need to develop more effective treatments that address this

Strengths and limitations

Strengths of the current study include the use of a drug-free clinical sample phenotyped with objective measures of cognitive flexibility and 2.5 years follow up of participants, with repeated assessments to determine timing of recurrence. Relatively few studies have used longitudinal designs to assess the role of cognitive and psychological risk factors for recurrence in this way. The use of a matched comparison group of ~~healthy~~ controls facilitates interpretation of the results.

Our findings require replication, especially given concerns about the reliability of attentional tasks that rely on RT measurement, and evidence that outcomes on these tasks are highly sensitive to

minor changes in task methodology (e.g. stimulus timing and intensity) (Cisler et al., 2009; Parsons et al., 2018). Further, while excluding participants currently taking psychotropic medication and/or with comorbid psychiatric disorder leads to a well-defined sample and precludes confounding by medication effects, this might have reduced generalizability of the current findings to a broader clinical population with recurrent depression. Additionally, relationships between rumination and attentional control were explored using a measure of self-report trait rumination. Future research should additionally look at actual changes in rumination during attentional tasks, for example after a rumination induction procedure. For both the group differences in the attentional tasks and the survival analyses we were able to detect medium effect sizes with 90% power. However, we might have missed differences with small effect sizes due to insufficient power (*Supplementary Results*).

Conclusions

Using the IST and ECT tasks of cognitive control, we found no evidence of impaired CCcognitive flexibility in patients in stable remission from MDD compared to healthy controls. Rapid disengagement from angry and happy emotional faces was a significant predictor of a shorter time to recurrence, even after correcting for other known predictors. These findings are We present novel finding.s, as very few studies have previously examined whether performance on CCcognitive flexibility tasks is associated with depressive recurrence. When replicated, Aattentional disengagement from emotional stimuli may be an interesting target for screening to establish who is at increased risk of recurrence, and may within remitted populations. It may also be amenable to change via cognitive interventions intervention, .for example through cognitive training approaches. This would be relevant, given the high recurrence rates in MDD and the need to develop more effective treatments that address this issue.

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Legends

Figure 2. Association between disengagement from angry faces presented for 200ms and time to recurrence

Survival curves for time to recurrence of participants with disengagement score from angry faces ≤ 3.56 ms (n = 30; upper red line) vs > 3.56 ms (n=33; blue line), for faces presented at short time intervals (<200msec). We controlled for age, sex, residual symptoms and number of previous depressive episodes.

Figure 3. Association between disengagement from happy faces presented for 200ms and time to recurrence

Survival curves for time to recurrence of participants with disengagement score from happy faces ≤ 2.07 ms (n = 30; upper red line) vs > 2.07 ms (n=33; blue line), for faces presented at short time intervals (<200msec). We controlled for age, sex, residual symptoms and number of previous depressive episodes.