Executive control and emotion regulation in remitted depression

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Abstract

Depression is the worldwide leading burden of disease and one of the most prevalent psychological disorders. Clinical depression tends to be episodic and transient but relapse rates are high and individuals may be emotionally and cognitively affected even between episodes. The currently available interventions for prevention and treatment have mediocre effects, partly because the factors that cause and preserve depression are insufficiently understood.

The last decade has seen an increased focus on the role of cognitive control processes and emotion regulation in depression. The preexisting literature on individuals in remission indicates that inhibition and shifting are the most strongly impaired cognitive control functions. Emotional activation can interfere with cognitive control processes in healthy individuals, and depression is associated with impaired disengagement from negative information. Abnormal reactions to self-made errors may also promote depression relapse, but this has rarely been studied in remitted depression. Traditional measures of executive functions are free from emotionally relevant stimuli. Their ecological validity in relation to depression and the cognitive processing of emotionally salient information is therefore insufficient.

This thesis aimed to investigate the executive functions inhibition and shifting in the processing of emotionally salient and neutral information. In order to evaluate characteristics in previously diseased individuals during non-depressed periods, individuals with depression in remission were compared to never depressed controls. Previously, inhibition was mostly studied with Stroop tasks, but inhibition is a multi-faceted construct and is only partially tapped into by the Stroop. Paper I investigated inhibitory function using Stroop and another measure of inhibition, the Stop Signal Task. Behavioral adjustments following self-made errors were also investigated. Paper II described the development of a new computerized cognitive task to assess executive function in the context of emotional stimuli. Paper III investigated emotion regulation and executive control functions in unmedicated, previously depressed and control participants, using both neutral and emotional executive tasks. Whether executive control of neutral and emotional material was related to depressive rumination, and to the emotion regulation strategies cognitive reappraisal and expressive suppression, was also investigated.

The previously depressed participants matched the never-depressed individuals on most of the neutral and emotional executive functions tasks. However, they were slower to inhibit a response in one version of the Stop Signal task. On self-report measures of emotion regulation

and rumination, the previously depressed individuals reported that they more often responded to negative emotion with rumination and suppression and less frequently with cognitive reappraisal. Higher levels of rumination, and of the emotion regulation factor expressive suppression, predicted previous depression. The remitted participants were prone to depressive rumination and to the use of relatively unhealthy emotion regulation strategies, despite intact executive functions. Thus, good executive functioning were not sufficient to protect against these negative cognitive-emotional processes or against depressive episodes.

Although recovery from depression is statistically associated with less effective executive function, many individuals who recover from mild to moderate depression do not have executive impairments. This is a reminder that people suffering and recovering from depression is a heterogeneous group. Approaches to prevention and treatment should therefore be adapted for subgroups and even for the individual patient.

List of papers

I: Aker, M., Bø, R., Harmer, C., Stiles, T. C., & Landrø, N. I. (2016). Inhibition and response to error in remitted major depression. *Psychiatry Research, 235,* 116-122. doi: 10.1016/j.psychres.2015.11.038

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III: Aker, M., Harmer, C., & Landrø, N. I. (2014). More rumination and less effective emotion regulation in previously depressed women with preserved executive functions. *BMC Psychiatry, 14,* 334. doi: 10.1186/s12888-014-0334-4

Abbreviations

BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory II
CCT	Computerized Cognitive Training
CWI	Color-Word Interference test
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EF	Executive functions
ERQ	Emotion Regulation Questionnaire
ESST	Emotional Stop Signal Task
EPST	Emotional Picture Sorting Task
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
rMDD	remitted Major Depressive Disorder
RCT	Randomized Controlled Trial
RRS	Ruminative Responses Scale
SST	Stop Signal Task
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sorting Test

1 Introduction

Depression is globally the leading burden of disease (Ferrari et al., 2013) and it is one of the most prevalent psychological disorders. This has not gone unnoticed by academic and clinical communities; research on treatment for depression has flourished during the last three decades. Many new approaches have emerged, but the efficacy of psychological and pharmacological treatments for depression still prove unsatisfying (Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). Preventive interventions have been developed, and although they may help, the effect is small - typically requiring treatment of 22 people to prevent one case of depression (Cuijpers, van Straten, Smit, Mihalopoulos, & Beekman, 2008). Arguably, the mediocre effects of treatment and prevention are in large part due to a lack of understanding of factors that cause and mediate depression.

Cognitive processes are necessarily heavily involved in development and sustainment of depression. Diminished ability to think or concentrate is a diagnostic criterion of depressive episode (American Psychiatric Association, 2013; World Health Organization, 1993). Beck's (1967) cognitive theory of depression has been the most influential contribution to psychological understanding of depression and to psychotherapeutic treatment over the last 50 years. The theory highlights the content of cognition of people who experience depression, which is often dominated by negative self-evaluations, expectancies and memories. Beck (1967) suggested that dysfunctional negative attitudes are embedded within cognitive structures, called schemas. The activation of these schemas induces the subject to expect negative experiences, to more effectively process information that is in accordance with the schemas and reinforces the schemas through biased processing of schema-congruent information. Cognitive therapy is based on highlighting the distorting effects of the schemas and help the patient to counter negative automatic thoughts (Beck, 1967). From this description one can also reason that affecting the formation, activation and reinforcement of negative schemas through cognitive control may be an important aspect of preventing and relieving depression.

1.1 Depression

1.1.1 Diagnostic criteria

The empirical studies in this thesis used the DSM-IV (American Psychiatric Association, 2000) criteria for major depressive episode (MDE). The DSM-IV defines MDE based on five

criteria, A to E, of which all must be met for a diagnosis to be correctly assigned. Criterion A is the symptom criterion. It asserts that depressed mood and/or loss of interest or pleasure must be present. Other possible symptoms include disturbances to appetite, sleep, or psychomotor function, fatigue, feelings of worthlessness or inappropriate guilt, indecisiveness or diminished ability to think or concentrate, and recurrent thoughts of death or suicidal ideation. At least five of these sub-symptoms must be present during the same two-week period. Criterion B dissociates this disorder from the diagnosis Mixed Episode which is given when depression coexists with mania. Criterion C underscores that the symptoms must cause "clinically significant distress or impairment in social, occupational, or other important areas of functioning". The final two criteria exclude diagnosis when the depressive symptoms can be explained by biological factors such as a chemical substance or a medical condition (D), or when the symptoms may be considered natural reactions to the loss of a loved one (E).

In 2013, the American Psychiatric Association published an updated diagnostic manual, the DSM-5, with some changes to Major Depressive Episode. The symptoms (Criterion A) are identical. Some of the criteria have gone through superficial changes in wording or order of presentation (i.e. clinically significant impairment is B, medical or chemical disqualifiers are C, relation to mania is E). Two substantial differences can also be found. According to DSM-IV, symptoms of depression that succeed personal loss should be understood as depression if lasting longer than two months. In DSM-5, a modified version of this, without the two-month definition, is presented merely as a "Note". It recommends careful consideration, with the exercise of clinical judgement, of a possible major depression in addition to normal responses to loss. The other substantial difference is the explicit disqualification when the symptoms may be better explained by disorders in the schizophrenic spectrum (criterion E in DSM-5). This new disqualifier may cause different diagnostic conclusions in certain cases; a person who is diagnosed with a major depressive episode based on DSM-IV may not qualify for the same diagnosis in DSM-5 if (s)he has a disorder in the schizophrenia spectrum that better explains the depressive symptoms.

1.1.2 Prevalence, treatment and prognosis

The twelve-month prevalence of major depressive disorder is 7% in both Norway and the United States; lifetime prevalence in Norway is around 16%. There is a substantial gender difference, with females about twice as likely to become depressed (American Psychiatric Association, 2013; Kringlen, Torgersen, & Cramer, 2001; Nes & Clench-Aas, 2011). While some variation between studies will naturally occur, the gender differences and prevalence of

depression is similar in most Western countries. Recommended treatment for mild to moderate depression includes psychosocial intervention, psychological therapy and medication (National Institute of Clinical Excellence, 2009/2016). Treatments are effective for some individuals, but overall, treatment effects are modest (Cuijpers et al 2010; Turner et al 2008) and, from a public health perspective, unsatisfying. MDD is typically an episodic disorder. Individuals who recover from a depressive episode have substantial risk of recurrence. Over a ten-year period following recovery from a depressive episode, between half and two-thirds are expected to have at least one recurrence. The duration of recovery reduces the risk of recurrence, but each recurrence increases the probability of another recurrence (Solomon et al., 2000). On average, individuals with a history of depression will have five to nine depressive episodes during their lifetime (Burcusa & Iacono, 2007). Increased knowledge about what constitutes vulnerability to relapse, and how to target the vulnerability, is required. The ability to process and regulate negative emotion, and the phenomenon of depressive rumination, are two of the most prominent candidates for research in this endeavor.

1.1.3 States, traits, and scarring

Cognitive deficits can relate to depression as states, traits or scars – or a combination of these. State related deficits occur and diminish in parallel with the coming and going of the depressive state. Alternatively, cognitive deficits that are related to depression as traits must be present before, during and after depression. Traits are thus not consequences or symptoms of a depressive episode; they are vulnerability factors which may contribute to initiation of depression. A third alternative is a scenario where impairments occur with depression but remain when the depression passes, referred to as a scar (Lewinsohn, Steinmetz, Larson, & Franklin, 1981). In this context the term scar can refer to any possible change in cognition, emotion, behavior or biology that was caused by a depression and leaves a stable, lasting vulnerability (Wicher, Geschwind, van Os, & Peeters, 2010).

In the existing literature one can find evidence to support each of these models, at least for different cognitive functions. For example, major depression is associated with broad impairments in executive function (Hammar & Årdal, 2009; Snyder, 2013), and those impairments are less pronounced when depression is in remission (Bora, Harrison, Yücel, & Pantelis, 2013). This could indicate that the effect of depression on executive function is state dependent. However, remitted MDD (rMDD) is still associated with significant deficit in a global index of cognitive function as well as in executive function (Bora, Harrison, Yücel, &

Pantelis, 2013; Hasselbalch, Knorr, & Kessing, 2011). Individuals in remission score lower on cognitive measures, compared to never-depressed controls. Studies of brain activity have indicated that the striate part of basal ganglia is dysfunctional in current MDD, and this activity does not change with treatment (Graham et al., 2013). These and similar findings confirm that a state perspective is not sufficient to describe the relationship between cognitive function and depression.

Vulnerability studies have looked at young people who have never experienced clinical depression but who has one or more first-degree relatives with depression. These individuals, who have a statistically elevated risk of depression, tend to show relatively impaired emotional categorization and overactivity in brain regions supporting working memory (Mannie, Bristow, Harmer, & Cowen, 2007; Mannie et al., 2008). Altered neural responses to a working memory task might represent a vulnerability marker of depression (Mannie, Harmer, Cowen, & Norbury, 2010). This evidence fits the definition of a trait effect, as neither states nor scars ca be present before the individual has experienced a depressive episode (Trivedi & Greer, 2014). The existence of trait- and state-dependent deficits does not rule out the possibility of scaring in addition to trait effects. According to associative network theory, frequent activation of cognitive patterns strengthens the patterns and increases the likelihood of their future activation (Segal, Williams, Teasdale, & Gemar, 1996; Wicher et al, 2010). With this mechanism, negative though patterns are strengthened each time they are activated – which is very often during depression. When the depression goes into remission it can leave a scar in the form of strengthened negative cognitive-emotional networks that are more easily activated, and perhaps less easily inhibited, than before the depressive episode.

1.2 Emotion regulation

Emotion regulation is "the process by which individuals influence which emotions they have, when they have them, and how they experience and express these emotions" (Gross, 1998, p. 275). Negative mood is generally associated with, or consists in part of, the activation of mood-congruent representations in working memory. Executive functions perform the manipulation of information in working memory and are therefore important in the regulation of emotion.

Individual differences in the use of emotion regulation strategies appear to play an important role in depression (De Lissnyder, Koster, Derakshan, & De Raedt, 2010; Joormann & Gotlib, 2010; Nolen-Hoeksema, 1991). Two such strategies, proposed by Gross and John (2003), are "cognitive reappraisal" and "expressive suppression". The reappraisal strategy is a

form of cognitive change that involves construing a potentially emotion-eliciting situation in a way that changes its emotional impact. Hence, reappraisal is directed at what causes or elicits an emotion. Suppression is a form of response modulation that involves inhibiting ongoing emotion-expressive behavior. Suppression is directed at the expression of the emotion and not so much at the inner emotional experience. The tendency to use one, as compared to the other, of these strategies is related to a range of differences in emotional aspects (Gross and John (2003). Reappraisers tend to experience and express greater positive emotion and lesser negative emotion, whereas suppressors experience and express lesser positive emotion yet experience greater negative emotion. Using the reappraisal strategy is associated with better interpersonal functioning and well-being (Gross & John, 2003). The reappraisal strategy requires flexible interpretation and cognitive representation of the meaning of experiences. The ability to inhibit a (negative) representation, and construe a new representation, is essential to this regulatory process. Thus, efficient cognitive control through inhibition of negative information and shifting to positive and constructive appraisal of the situation may be a prerequisite to the application of a healthier and more adaptive emotion regulation. In both depressed and non-depressed individuals, reduced cognitive inhibition of negative information is associated with less use of reappraisal and more use of expressive suppression (Joormann & Gotlib, 2010).

1.3 Depressive rumination

A transient depressed or dysphoric mood state is not unusual or unhealthy. But some people seem to be at risk of preserving this mood state over a longer period of time, and of developing depression. Nolen-Hoeksema (1991) proposed that individuals differ in how they tend to respond to dysphoric mood states, and that some people's response tendencies increase the probability of developing clinical depression. Rumination is a cognitive style characterized by recurrent series of thoughts united by a common theme. When rumination is a response to depressive mood, and the ruminative theme is symptom focused, negatively self-focused, or focused on possible causes and consequences of a depressive mood, it is called depressive rumination (Spasojevic & Alloy, 2002). Individuals who respond to dysphoric mood by consistently engaging in rumination tend to have more persistent and severe depressive episodes than those who constructively distract themselves from their dysphoric mood. People who engage in depressive rumination experience more numerous, more severe, and longer lasting depressive episodes (Alloy, Abramson, Walshaw, & Neeren,

2006; Hasegawa, Kunisato, Morimoto, Nishimura, & Matsuda, 2018; Lyubomirsky & Nolen-Hoeksema, 1993, 1995; Nolen-Hoeksema, 1991; Spasojevic & Alloy, 2001, 2002).

Rumination can be construed as an effortful, controlled, and conscious form of emotion regulation. It seems to be aimed at reducing depressive feelings, although its actual effect is usually the opposite (Gross, 1999). An alternative response to the negative state is to use pleasant, distracting activities to relieve the mood before attempting to focus on the problems and possible solutions. Evidence suggests that depressive rumination is related to affective coping as well as problem solving. Dysphoric persons who ruminate endorse more negative, biased interpretations of hypothetical situations. They generate less effective solutions to interpersonal problems and are more pessimistic about positive events in the future (Lyubomirsky & Nolen-Hoeksema, 1995). A study found that subjects who engaged in a ruminative task while in a depressed mood were less able to generate possible solutions to a life problem than subjects induced to distract in response to the depressed mood (Morrow, 1990, referred in Nolen-Hoeksema, 1991). Dysphoric persons who were able to distract themselves from negative thoughts were as optimistic and effective in solving problems as non-dysphoric persons. Experimental induction of self-focused attention and rumination increases or maintains depressed mood in dysphoric or clinically depressed participants (Lyubomirsky & Nolen-Hoeksema, 1995). This supports the suggestion that self-distraction is a more productive strategy than rumination, and indicates that inhibiting a negative mind set may be an important strategy for effective coping (Nolen-Hoeksema, 1991).

1.4 Inhibition

Instincts, reflexes and impulses drive the survival and procreation of organisms. Drives are powerful and, for most organisms, sufficient. But under highly complex circumstances such as social functioning or navigating towards a long-term goal, suppressing the drives may be more beneficial. Humans have evolved the ability to modulate the effects of drives through inhibition. Inhibition is complex, and like other mental phenomena, we cannot observe it directly. We can only infer inhibition from behavioral observations. In fellow human beings we can perceive actions or personalities as more or less impulsive. Inhibition and impulsivity can be understood as two sides of the same coin, in the sense that where there is little inhibition, impulsive behavior may occur. Alternatively, we can envision inhibition and impulsivity as a car's brake and gas pedals, respectively. The driver's ability to stop the car – e.g. when a child suddenly runs into the road – will depend on how fast the driver was going, but also on how good the car's brakes are. Like gas and brake pedals, impulsivity and

inhibition are separable phenomena, but they both make essential contributions to the observed outcome. This analogy may also be seen as a parallel to a top-down (inhibitory control) and bottom-up (impulsive activation) perspective.

1.4.1 Theoretical and empirical models of inhibition

Inhibition is a core feature of executive function and hence paramount for cognitive control. The majority of theories and evidence indicates that inhibition is multi-faceted, but the precise nature and description of facets remains unclear. In the following, a few perspectives which constitute the foundational understanding of inhibition in the research conducted for this thesis will be briefly reviewed.

Harnishfeger (1995) discussed inhibitory processes under the lights of three opposing pair concepts. First, inhibition can be *unintentional* or *intentional*. Whereas the *unintentional* is automatic and requires little conscious or attentional effort, *intentional* inhibition requires effort and attention. Intentional inhibition is slower and is turned off more easily (disinhibition), compared to the unintentional kind. Second, inhibition is *behavioral* or *cognitive*. Behavioral inhibition is the restraint of overt behavior, typically the ability to stop locomotion. The *cognitive* counterpart refers to stopping a cognitive process. Third, Harnishfeger distinguished *inhibition* from *resistance to interference*. Whereas resistance to interference includes dealing with competition between stimuli or responses and shifting of attention and responses, inhibition is active suppression.

Nigg (2000) delineated four aspects of effortful inhibition as forms of suppression. In Nigg's terms, *interference control* is suppression due to resource or stimulus competition. *Cognitive inhibition* is suppression of irrelevant information from working memory. *Behavioral inhibition* is suppression of prepotent responses. Last, Nigg described oculomotor inhibition as effortful suppression of reflexive saccades. Compared to the other forms described, oculomotor inhibition has received little attention in cognitive neuroscience and will not be of further focus in this thesis.

Whereas Harnishfeger (1995) and Nigg (2000) presented inhibition somewhat differently, there was highly similar underlying function of the described processes. Variations of these concepts of inhibition is found as a basis for empirical research on inhibition, a field which involves a large number of paradigms and tests. In an attempt to tackle this challenge, Friedman and Miyake (2004) used data and statistical procedures to deduce an empirically based model of inhibition. They applied nine common test paradigms presumed to measure three facets of inhibition. Friedman and Miyake's (2004) study

supported a two-factor model of inhibition. One factor included inhibition of both prepotent responses and distracting stimuli and was named "response-distractor inhibition". The second factor was named "resistance to proactive interference" and comprises the ability to resist intrusions of information that has been relevant in a similar context but is currently irrelevant. In other words, to inhibit an overt response and to inhibit distracting external stimuli are highly overlapping in Friedman and Miyake's model, and inhibiting distracting "internal stimuli" is different.

The main elements of inhibition are described in Table 1. *Interference inhibition* is the same as Friedman and Miyake (2004) called resistance to distractor interference: "… the ability to resist or resolve interference from information in the external environment that is irrelevant to the task at hand." It follows from the definition that senses are the source of the information inhibited here. *Behavioral inhibition* is equal to Friedman and Miyake's prepotent response inhibition, i.e. the ability to deliberately suppress dominant, automatic, or prepotent responses.

Table 1. Aspects of effortful inhibition

Effortful inhibition	*Stage of information flow*	*Target of inhibition*
Interference inhibition	Initial stage, input	External stimulus interference
Cognitive inhibition	Intermediate stage	Internal source interference (associated knowledge)
Behavioral inhibition	Late stage, output	Muscular activation/motor output

Table 1. These categorizations were primarily based on the works of Harnishfeger (1995), Nigg (2000) and Friedman & Miyake (2004).

1.4.2 Inhibition and psychopathology

With inhibition defined as an aspect of executive control, it may briefly seem like a phenomenon of interest only to clinical neuropsychologists and to some neuroscientists. However, problems with impulse control and with the regulation of emotion and behavior is integral of many mental disorders as specified by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5). "Disruptive, impulse control, and conduct disorders include conditions involving problems in the self-control of emotions and behaviors." (p 461).

Inhibitiory deficit is widely considered a central element of developmental disorders such as ADHD and conduct disorder (American Psychiatric Association 2013; Lansbergen et al 2007; Nigg et al 2000). Substance use disorders, including alcohol abuse and dependence, are also associated with impaired inhibition; in these disorders the inhibitory impairment is a combination of preexistent vulnerability and substance-induced impairment (Stavro, Pelletier, & Potvin, 2013). In contrast, the diagnostic criteria for depression do not include impaired inhibition, but empirical studies have shown that depression is associated with impaired performance on neuropsychological tests of inhibition as well as other aspects of executive function (Bora et al., 2013; Snyder, 2013). Which role impaired executive function plays in depression is not clear, but it may influence depression through impaired regulation of negative emotion and rumination (Joormann & Gotlib, 2010; Koster, De Lissnyder, Derakshan, & De Raedt, 2011). In summary, the profound involvement of inhibition in cognitive, emotional and behavioral control underscores its importance to psychosocial functioning and mental health.

2 Aims

This thesis aimed to investigate the executive functions inhibition and shifting in the processing of emotionally salient and neutral information in remitted depression. In order to evaluate characteristics in previously diseased individuals during non-depressed periods, people with current depression were excluded. Individuals with depression in remission were compared to never depressed controls.

It was proposed that shifting and inhibition mediate emotion regulation by controlling which set of information and response strategy is actively guiding cognition and behavior. Impaired ability to inhibit a dysfunctional response set, and to engage and maintain a new and more adaptive set, may directly impair emotion regulation and subsequently cause depressive rumination and sustained negative affect. It was proposed that impaired inhibition and shifting constitute cognitive vulnerability markers for depression. On these grounds, it was investigated how inhibition and shifting relate to measures of ruminative tendencies, and to the two emotion regulation strategies cognitive reappraisal and expressive suppression.

2.1 Paper I

The existing research literature on individuals in remission indicated that inhibitory control is more strongly impaired than other cognitive functions. Inhibition is a multi-faceted construct, and previous studies have mostly used Stroop tasks. It was unclear how this population performs on other measures of inhibition. Abnormal reactions to self-made errors may also promote depression relapse, but this has rarely been studied in remitted depression. The first aim of this study was to investigate inhibitory function in remitted depressed individuals compared to controls, using the Stop Signal Task in addition to a Stroop task. The second aim was to investigate post-error behavioral adjustments. We expected to find impaired inhibition, indicated by higher stop signal reaction time, and larger post-error adjustments, in the remitted sample.

2.2 Paper II

Emotional activation can interfere with cognitive control processes in healthy individuals, and depression is associated with impaired disengagement from negative information. However, traditional measures of executive functions are free from emotionally relevant stimuli. The purpose of this study was to develop a computerized cognitive task to assess executive function in the context of emotional stimuli. The Wisconsin Card Sorting Test (WCST) (Grant & Berg, 1947; Heaton, 2005) has a prominent status in assessment of executive function for clinical and research purposes and was chosen as a template for the new,

emotional task. The design of the new task was based on the structure of the Wisconsin Card Sorting Test (WCST), using emotional faces as stimuli. The functional properties of the new emotional set-shifting task were tested in comparison with WCST on the basis of six outcome variables.

2.3 Paper III

The aim of the third study was to investigate emotion regulation and executive control functions in unmedicated previously depressed and control participants, using both neutral and emotional executive tasks. Inhibition was measured with the traditional Stroop paradigm and an emotional version of the Stop Signal Task. A second aim was to investigate whether executive control in general, and in the processing of emotional material in particular, was related to depressive rumination and to the emotion regulation strategy called cognitive reappraisal. We expected to find impaired performance in depressed participants compared to controls. Furthermore, we hypothesized that the executive functions inhibition and shifting would be related to the ability to apply cognitive reappraisal and to avoid unhealthy rumination.

3 Methods

3.1 Participants

The samples used in the three papers are non-overlapping and were recruited separately. All studies were performed in compliance with the Helsinki Declaration and the Ethical principles for Nordic psychologists as issued by the Norwegian Psychological Association. The research was conducted under approvals #2010/635 North Regional Committee for Medical Research Ethics and #2011/2593 D South-East Regional Committee for Medical Research Ethics.

Participants included in papers I and III were recruited by advertisements in local newspapers, in online social media, and in certain public places such as grocery shops. For paper III, we also contacted and invited people who were discharged from a public mental health outpatient clinic. This clinic offered short-term treatment to patients who had a job and experienced common mental health issues such as depression and anxiety which interfere with their ability to comply with work requirements and put them at risk of long-term sick leave. All the former patients of this clinic who were asked to participate in this research had previously consented to being contacted for research purposes. These people were sent a letter from the clinic, explaining that they would be contacted about participation in a research project about depression and emotion regulation. All individuals were contacted by telephone. Individuals who declined participation were not contacted again.

For information about participant age, education, general cognitive abilities, and symptoms of depression and anxiety, see participant information printed in each paper.

3.2 Clinical assessment

3.2.1 Diagnostic interviews

All participants were subject to a structured diagnostic interview. SCID I (Structured Clinical Interview for DSM-IV, Axis I) was used in Paper I. Assessments for Paper III were based on the MINI (Mini international neuropsychiatric interview). A slightly modified version of MINI 6.0 was used, where modules I (alcohol abuse), J (substance abuse), and P (antisocial personality disorder) were omitted to save time and constraints on participants. Alcohol and substance use were covered by other instruments. The diagnostic interviews were audio recorded. An expert was consulted for general quality control of the interview execution and for advice when the interviewer was uncertain about diagnostic decisions.

3.2.2 Symptom scales

Symptom levels of depression and anxiety were measured using the Beck Depression Inventory II (BDI-II) (Beck, Steer, & Brown, 1996) and the Beck Anxiety Inventory (BAI) (Beck & Steer, 1990). The BAI consists of 21 items, each a symptom of anxiety. Respondents are asked to rate the extent with which they experienced the symptoms during the last week, on a four-point scale. BAI has a maximum score of 63, and the following anxiety severity indicators are recommended: 0-7 minimal, 8-15 mild, 16-25 moderate, 26-63 severe (Beck & Steer, 1990).

BDI-II is a self-report scale of 21 items, describing depressive symptoms in accordance with the DSM-IV. Participants rate their experience of each symptom during the last 14 days. Each item has response alternatives that are scored 0-3 and the maximum total score is 63. BDI-II provides an estimate of symptoms and distress in the individual but cannot determine whether a diagnosis according to DSM-IV is present. In participants that are diagnosed with a depression the following severity descriptors are recommended, based on BDI-II total score: 0-13 minimal; 14-19 mild; 20-28 moderate; 29-63 severe (Beck, Steer, & Brown, 1996).

3.3 Behavioral tests of cognitive function

3.3.1 Wechsler intelligence subtests

General cognitive abilities were assessed with the subtests Similarities and Picture completion from WAIS III (Paper I) and with the subtests Vocabulary and Matrix reasoning from WASI (Paper III). Similarities and Vocabulary assess verbal comprehension; Picture completion and Matrix reasoning assess perceptual reasoning (Wechsler, 1999, 2003).

3.3.2 D-KEFS Color-Word Interference test (CWI)

The Color-Word Interference test (Delis, Kaplan, & Kramer, 2001) is based on the traditional Stroop (1935) paradigm and includes the four conditions color naming, reading, inhibition, and inhibition/switching. Baseline processing speed is assessed in the first two conditions. In the third condition, colors are printed in letters with a different color than the word names, which creates interference when the respondent is asked to report the printed color. The fourth condition, inhibition/switching, has similar non-congruent color words and requires the respondent to switch between reading and color naming. The primary outcome measures from this test were the times to complete inhibition (Papers I and III) and inhibition/switching (Paper III only).

3.3.3 Wisconsin Card Sorting Test (WCST)

In the WCST the person is presented with four key cards and a pile of stimulus cards, all displayed on a computer screen. The cards depict figures varying on three features: color, shape, and number. The assignment is to match each stimulus card with one of the key cards. The participant is not told how to match; however, he or she is told whether a particular chosen match is right or wrong. At any time during the test only one of the cards' features constitutes the correct matching principle, and after a series of correct matches, the correct matching principle silently changes. The WCST is a test of general executive function (Greve, Stickle, Love, Bianchini, & Stanford, 2005; Heaton, Chelune, Talley, Kay, & Curtiss, 1993). The most important outcome variable in this setting is perseverative errors, which primarily depends on shifting (Gamboz, Borella, & Brandimonte, 2009). A computerized version of the WCST (Heaton, 2005) was used in Paper II.

3.3.4 Emotional Picture Sorting Task (EPST)

The EPST is based on the same task structure as the WCST, but with emotional stimuli replacing the geometrical figures used in the WCST. Sixteen pictures showing four adult female Caucasian individuals displaying four different expressions (neutral, sad, happy, afraid), were selected from the Karolinska Directed Emotional Faces database (Lundqvist, Flykt, & Öhman, 1998) and used as raw material for the EPST stimuli. The colors red, green, yellow and blue were added as background colors in the pictures. Each stimulus card was made up of one picture with a colored background. The stimuli consisted of 64 unique cards varying on the three dimensions color, person, and expression, and the set of 64 was used twice to allow a maximum of 128 trials. Paper II gives a detailed description of the EPST.

3.3.5 Stop Signal Task (SST)

The SST is a choice reaction time paradigm where the subject makes a motor response by pressing a button corresponding to the direction (right or left) of a visually presented arrow. On a subset of trials, an auditory signal requires inhibition of the predominant motor response (Logan, Cowan, & Davis, 1984). It is a challenging task because it requires a combination of speed and control. The difficulty of the inhibition trials is adjusted continuously by a tracking procedure, varying the stop signal delay parameter based on the individual's performance. The purpose of this tracking procedure is to stabilize the probability of successful inhibition around 0.5 for each subject. The inhibition variable measured by the SST is called Stop Signal Reaction Time (SSRT). The SSRT is the estimated timing of the inhibitory process derived from the individual's Go reaction time distribution and the variable delay between the go and

stop stimuli (for a discussion of various calculation methods, see Verbruggen, Chambers, & Logan, 2013).

Two versions of the SST were used in this research. The Stop Signal Task from CANTAB (Cambridge Cognition Ltd., Cambridge, UK) included one practice block and five test blocks (Paper I). A trial started with a fixation cross, followed by an arrow pointing right or left, to which the participant was instructed to respond as quickly as possible by pressing a corresponding button on a press pad (go trial). In the emotional SST used in Paper III a picture of a human face displaying either a neutral or an angry expression was presented immediately before the target stimulus (right/left arrow) on all trials. The test was administered in a blocked procedure with two practice blocks and four test blocks. Two test blocks included only neutral faces and two blocks included only angry faces. The sequence of the test blocks was randomized between participants. Both SST versions had stop signals on a randomly selected 25% of the trials.

3.4 Self-report assessment of rumination and regulation

3.4.1 Emotion Regulation Questionnaire (ERQ)

The Emotion Regulation Questionnaire was developed by Gross and John (2003). It has ten items, each intended to measure one of the regulatory processes cognitive reappraisal or expressive suppression. Respondents were instructed to report how they control their emotions by responding to the ten statements on a 7-point scale, ranging from "strongly disagree" to "strongly agree". The ERQ has six items for reappraisal and four items for suppression, explicitly referring to the regulation of positive as well as negative emotions.

3.4.2 Ruminative Responses Scale (RRS)

The Ruminative Responses Scale (RRS) is a 22 items self-report assessment of tendency to ruminate. It comprises a three-factor structure that differentiates emotionally neutral and coping-oriented contemplation (reflection, five items) from passive and unproductive focus on problems and unachieved goals (brooding, five items) and depressive symptoms that are similar to BDI items (depression, 12 items) (Treynor, Gonzalez, & Nolen-Hoeksema, 2003). Respondents were instructed to use a 4-point scale to rate how often they react according to the 22 statements when feeling down, sad or depressed. With permission from S Nolen-Hoeksema, i translated the RRS from English to Norwegian using a back translation method

in collaboration with Katherine Remy who at the time was a master-level student in psychology. Table 1 gives a schematic presentation of the methods used in papers I-III.

Table 2. Methodological overview.

	Paper I	*Paper II*	*Paper III*
Participants			
Total N (% female)	216 (68 %)	110 (65 %)	173 (100 %)
Mean age (*SD*)	37.3 (11.6)	26.5 (8.9)	35.5 (12.6)
Clinical assessment			
Diagnostic	SCID I	No	MINI 6.0
Symptom scales	BDI-II, BAI	No	BDI-II, BAI
Medication use	self-reported	No	self-reported
Behavioral measures			
Intelligence	WAIS Similarities, WAIS Picture completion	No	WASI Vocabulary, WASI Matrix reasoning
Inhibition	D-KEFS Color-word, Cantab SST	D-KEFS Color-word	D-KEFS Color-Word, Emotional SST
Shifting	D-KEFS Color-word,	D-KEFS Color-word; Wisconsin Card Sorting Test; Emotional Picture Sorting Task	D-KEFS Color-word, Emotional Picture Sorting Task
Questionnaires			
Rumination	No	No	Ruminative Responses Scale
Emotion regulation	No	No	Emotion Regulation Questionnaire

3.5 Statistical analyses

Statistical analyses were performed in SPSS versions 20 and 22.

3.5.1 Paper I

Given that all dependent variables were reaction time measures, age was a necessary consideration in the analyses. To factor out age when the data was examined for outliers, we performed linear regression analyses with age as a predictor of each of the dependent variables Stroop, Go-after-go RT, SSRT, post-correct adjustment, and post-error adjustment. The unstandardized residuals from these analyses were explored for outliers using SPSS boxplots. In the boxplot analyses, extremes were defined as values deviating at least three times the range of the middle 50% residuals. If an extreme residual was detected, that participant's corresponding variable score was excluded from all subsequent analyses. In this process a given reaction time could be excluded as an outlier if it belonged to a 25-year-old participant, and not be excluded if it belonged to a 60-year-old. The residuals from the linear regression analyses were only used to detect outliers.

Group comparisons of Go-after-go RT, Stroop inhibition, SSRT, post-correct adjustment, and post-error adjustment were performed as oneway analyses of variance with MDD history (two levels) as the independent variable, and age, BDI and BAI as covariates. The general effect of failed inhibition on subsequent response was analyzed in a paired samples *t*-test, comparing post-correct adjustment to post-error adjustment.

3.5.2 Paper II

Task type (WCST or EPST) constituted the independent variable. Six dependent variables were compared in Mann-Whitney *U* tests. The dependent variables were Trials administered, Total errors, Categories completed, Perseverative responses, Perseverative errors, and Failure to maintain set. On the variable Categories completed, a higher number indicates better or more efficient performance. On all the remaining outcome variables, a lower number indicates a better performance. Within-group variance of the dependent variables was investigated with Levene’s test. We excluded extreme scores in post-hoc analyses. This substantially reduced the differences in variances and Levene’s test was no longer significant for any variables. The exclusion of extreme scores did not change the outcome of the between-groups comparisons for these variables, which were still not significant.

3.5.3 Paper III

History of depression was the independent variable with two levels: ever had an episode of depression, or never had such an episode. Demographic and symptom characteristics, and all test outcome variables including executive functions and emotion regulation, were analyzed in independent samples *t*-tests between previously depressed and never depressed participants. A logistic regression analysis was performed on the ERQ variables cognitive reappraisal and

expressive suppression, and the two RRS factors brooding and reflection, as predictors of depression. A series of linear regression analyses was also performed with executive functions variables as predictors of emotion regulation and rumination.

4 Results

Paper I describes an investigation of inhibitory function and post-error reaction time adjustments in individuals with a history of depression in comparison with never-depressed controls. When statistically corrected for age and current symptoms of depression and anxiety, the participants in remission from depression were not different from never-depressed participants on simple reaction time, adjustments in reaction time after correct or failed stops, or inhibitory control as measured by the Stroop test. However, the rMDD participants were slower to inhibit a response as indicated by the Stop Signal Reaction Time. The difference corresponded to 11% slower inhibition.

In paper II, we developed a new measure of executive control with emotional stimuli, the Emotional Picture Sorting Task (EPST), and tested its properties by comparison to the Wisconsin Card Sorting Test (WCST). Results across six outcome variables indicated that the EPST was somewhat more difficult than the WCST. The overall results patterns were similar in EPST and WCST, but significantly more trials were needed to complete the EPST. Larger standard deviations were observed on EPST, suggesting that the emotional stimuli may have had an interfering effect in some, but not in all, individuals.

In Paper III we investigated inhibition and shifting using both emotionally salient and "neutral" tasks in previously depressed participants compared to controls. The previously depressed participants matched never-depressed individuals on all neutral and emotional executive functions tasks. On self-report measures of emotion regulation and rumination, the previously depressed individuals reported that they more often respond to negative emotion with rumination and suppression and more rarely with reappraisal. A logistic regression model indicated that higher levels of the rumination factors brooding and reflection, and of the emotion regulation factor suppression, predicted previous depression. One emotion regulation factor, cognitive reappraisal, did not predict previous depression.

5 General discussion

Depression is one of the most common mental illnesses. It is characterized by emotional and cognitive impairments, including depressed mood and diminished ability to think or concentrate. Although depression tends to be episodic and transient, relapse rates are high, and individuals may be emotionally and cognitively affected even between episodes. In the research presented in this thesis, non-depressed individuals with a history of depression were preferred as research subjects over currently depressed individuals. This was necessary to enable testing of the predictions regarding cognitive functions (inhibition, shifting, rumination and emotion regulation) in individuals who are at risk of developing depression. Paper I investigated inhibition and response to errors using traditional non-emotional cognitive tasks. Paper II described the development of a new shifting task with emotional stimuli. Building on and extending the research in Papers I and II, Paper III included both neutral and emotional executive function tasks in addition to self-report measures of emotion regulation and rumination.

Previous research has indicated that inhibition is impaired in both acute state depression (Hammar & Årdal, 2009; Snyder, 2013) and in remission (Bora et al., 2013), but the mechanisms through which inhibition and depression are related are less clear. Inhibitory control of the processing of negative stimuli, emotions and thoughts are potential mechanisms. The cognitive regulatory function shifting is also related to depression. The functional connection between shifting and depression is uncertain, but shifting is involved in the control of attention to negative stimuli, and in flexible use of emotion regulation strategies in different situations (Joormann & Stanton, 2016; Stange, Alloy, & Fresco, 2017). Furthermore, the relation between emotion and cognitive control is bidirectional. The cognitive control mechanisms inhibition and shifting are involved in emotion regulation, but emotion and mood also affect cognitive control (Mitchell & Phillips, 2007; Okon-Singer, Hendler, Pessoa, & Shackman, 2015).

Systematic empirical reviews have shown mild to moderate impairment of cognitive function in previously depressed individuals (Bora et al., 2013; Hasselbalch et al., 2011). Inhibitory control, indicated by the Stroop test, tends to be the most impaired cognitive function. This was not the case in our studies, where previously depressed participants performed equal to the never depressed controls on the Stroop measure of inhibition in papers I and III. The application of different versions of the Stroop task is one possible reason for the contradicting Stroop results. Despite high test–retest reliability, different versions of Stroop may have low correlation (Penner et al., 2012). Given that Stroop task correlations are low,

other versions of the Stroop task may be more sensitive to depression-related cognitive impairments.

A second measure of inhibition, stop-signal reaction time, was included in two papers. While Paper I showed significantly slower stop-signal reaction time in the previously depressed participants compared to controls, Paper III showed no difference between the two groups. There are two probable explanations for this. First, two different Stop Signal Tasks were applied. Compared to Paper I, the Stop Signal Task in Paper III had fewer trials and included inter-trial pictorial stimuli. Additionally, a more robust method for the estimation of stop-signal reaction time was applied in Paper III, which may provide more reliable results (Verbruggen et al., 2013).

Impaired ability to enforce cognitive control when exposed to negative emotional stimuli can contribute to creating and maintaining a depressed mood and likely constitutes a vulnerability factor that is present in the individual before the onset of clinical depression (De Raedt & Koster, 2010; Koster et al., 2011; Stange et al., 2017). In Paper II, the Emotional Picture Sorting Task (EPST) was developed and validated in comparison with the traditional, non-emotional Wisconsin Card Sorting Test. The results indicated that the emotional stimuli included in EPST evoked individual differences producing larger performance differences between individuals. Nevertheless, none of the measurements of cognitive shifting (Stroop inhibition/switching in Papers I and III; Emotional Picture Sorting Task in Paper III) revealed impaired shifting performance in previously depressed individuals in these studies.

Paper III investigated performance on emotionally charged cognitive tasks as well as neutral tasks, based on the hypothesis that the cognitive performance of individuals with previous depression may be relatively more impaired when the task includes processing of emotional information. This hypothesis was not empirically supported. A possible explanation for this finding is that the intensity of emotional stimuli in our tasks may have been too low to induce a significant effect. The fact that the stop-signal reaction times for “neutral” and “angry” conditions were nearly identical supports this explanation.

Paper III also investigated self-reported rumination and emotion regulation. It revealed more rumination and less beneficial emotion regulation in previously depressed individuals, but rumination and emotion regulation was not related to executive function in this sample. Although the lack of correlation between executive function and emotion regulation was contradictory to our hypothesis, it is less surprising when we know that the remitted participants had strong executive functioning.

Studies of clinical populations may include participants that have been severely depressed and hospitalized, and the severity of previous depressive episodes is variously reported in the literature. This is demonstrated by the three largest studies included in the meta-analysis by Bora and colleagues (2013). Xu and colleagues' (2012) remitted MDD participants had on average 1.6 hospitalizations, and 27% had experienced depressive episodes with psychotic features. In the study by Preiss et al. (2009), more than half had been hospitalized. Herrera-Guzman et al. (2010) did not report severity of previous episodes. Our remitted participants were relatively high functioning and this may have contributed to the contradiction between our results and the meta-analytical results. Precise data on severity of previous depressive episodes is not available for all our participants. However, we know that very few had been hospitalized or had experienced a severe state of depression. Differences in severity between studies, and the fact that the participants in the current studies had on average been less severely affected, do not make the samples less relevant from a clinical perspective. MDD is heterogeneous in nature and subjective suffering and impairment to occupational and social functioning is found in mild and moderate MDD as well as in severe states (American Psychiatric Association, 2013).

A recent review criticized the existing literature for uncritical use of the tripartite model of executive function and for reliance on descriptive explanations (Grahek, Everaert, Krebs, & Koster, 2018). The authors called for a more mechanistic explanation on the role of executive control in depression and pointed to the role of motivation and the switching between automatic and controlled processing. Increased depression levels are associated with reduced willingness to modify behavior and to obtain rewards. Anhedonia and lack of motivation can explain a disrupted ability to detect the need for cognitive control and a disrupted ability or willingness to exert effortful control, including stopping rumination and reappraising the situation. This perspective construes the executive dysfunctions related to depression as a systemic failure more than a failure of the control mechanism itself. It provides a useful frame of interpretation for the data in this thesis. The executive functions are not impaired *per se*, but they are being used less than they should be, which leads to increased rumination.

5.1 Clinical implications

Depression tends to have a relapsing progression, and its heterogeneous nature calls for personalized treatment. Identifying vulnerability factors and the underlying mechanisms of

depression is important in order to improve preventive measures, and may also enhance personalized treatment. Especially, studies of treatment effects could benefit the accuracy of subgroup definitions and allocation of different patients to the most appropriate interventions (Holmes et al., 2018). It has been established that depression is associated with impaired inhibitory control (Bora et al., 2013; Snyder, 2013). Depression is also characterized by difficulties disengaging from negative material and deficits in cognitive control when processing negative material (Gotlib & Joormann, 2010). However, it is not guaranteed that improving cognitive control through training or therapy will reduce rumination or depression. The results in Paper III provided important input in this regard. Despite intact executive functions, the remitted participants were prone to depressive rumination and to the use of relatively unhealthy emotion regulation. In lack of controlled intervention data, this at least shows that good executive functions were not sufficient to protect against these negative cognitive-emotional processes or against depressive episodes. Similar to the emotion regulation results in Paper III, a recent meta-analysis concluded that individuals with remitted MDD use more *mal*adaptive emotion regulation strategies, and there is no difference in the use of adaptive strategies (Visted, Vøllestad, Nielsen, & Schanche, 2018).

With regards to treatment, individuals prone to depression related to impaired executive control should receive training for this dysfunction. It was recently shown that negative beliefs about the uncontrollability and danger of worry, and beliefs about the need to control thoughts, is related to a decreased ability to shift between mental sets (Kraft, Jonassen, Stiles, & Landrø, 2017). On the other hand, for individuals who struggle with rumination and unhealthy emotion regulation, but whose executive function is unimpaired, metacognitive therapy may be a more appropriate intervention (Norman, van Emmerick, & Morina, 2014). The majority of the clinical participants in paper III belonged to the latter group. According to the metacognitive model of emotional disorder (Wells & Mathews, 1996) prolonged emotional disturbance is linked to the activation of a particular style of thinking. This style is a product of metacognitive beliefs, including positive beliefs about the efficacy of rumination as a means to solve a problem, and negative beliefs about the uncontrollability and significance of ones thoughts and feelings. The style consists of repetitive thinking in the form of worry and rumination which is used as a means of coping with "threat". However, this "coping" style is often unproductive and can lead to a circle of repeated negative affect. The risk of getting caught in this circle of depressing worry and rumination is linked to individual differences in metacognitive beliefs and the degree of flexible executive control over

cognitive processing (Wells & Mathews, 1996; Wells, Fisher, Myers, Wheatley, Patel, & Brewin, 2009).

Although the participants in Papers I and III matched the controls on most measured aspects of executive functioning, some impairment of executive function is the more common finding in remitted MDD populations (Bora et al., 2013; Hasselbalch, Knorr, Hasselbalch, Gade, & Kessing, 2013; Rock, Roiser, Riedel, & Blackwell, 2014). We should therefore conclude that depression is commonly associated with impaired executive functioning – in acute stage as well as in remission. This raises some important questions. Can anything be done to improve executive functioning in this population? And if so, will improvement of executive function reduce the risk of depression relapse?

The two most pressing challenges in clinical psychology are improving the effectiveness of interventions, and making these interventions more easily available to those who need them. If proven effective, computerized and internet-delivered interventions have the potential to answer both of these challenges. Computerized cognitive training is a term for exercises or games which target specific neural networks in order to improve cognitive functioning (Motter et al., 2016). A recent meta-analysis indicated that computerized cognitive training did not improve executive functions, but had a strong positive effect on a composite measure of cognitive functioning, and moderate effects on working memory, attention, daily functioning and mood symptoms (Motter et al., 2016). An important limitation in the computerized cognitive training literature is that many different training programs have been applied. Specifying the mechanisms underlying effective computerized training, and separating effective from ineffective training programs, remains to be done.

Computerized training programs targeting certain cognitive biases, i.e. attention bias or interpretive bias, have in recent years received much attention in attempts to alleviate and prevent depression. The principle of cognitive bias modification is training the individual to avoid negative stimuli (or interpretations) by directing attention to neutral or positive stimuli. For example, Daches and Mor (2014) trained "ruminators" to inhibit attention to negative stimuli. Brooding, the most negative subtype of rumination, was reduced in these individuals. Despite some very promising single studies, systematic reviews are less positive (Cristea, Kok, & Cuijpers, 2015; Hallion & Ruscio, 2011). Mixed effects of cognitive bias modification on clinical outcome variables isn't necessarily due to lacking effect of bias modification on depression symptoms. It may alternatively arise from the fact that not all bias modification programs succeed in modifying the cognitive bias. Some training programs fail to modify the cognitive bias, in which case significant change on clinical variables cannot be expected.

Furthermore, trait rumination has been found to moderate the effect of cognitive bias modification, with high ruminators showing a stronger effect on early orientation to stimuli from positive bias training (Arditte & Joormann, 2014). The effect of training tasks on attention and emotional responding appears to depend on the individual's typical reaction to emotions (Arditte & Joormann, 2014).

Several types of medication have been tested for cognitively enhancing effects. The drug Modafinil appears to enhance cognitive performance in healthy individuals and in some psychiatric patient groups. One study also indicated a positive effect of Modafinil on Stroop performance in depressed patients (Minzenberg & Carter, 2008). The evidence is currently too scarce for conclusions on the use of Modafinil in depressed individuals with impaired executive functions.

5.2 Methodological considerations

The sample sizes of these studies were fairly large compared to other studies in this field of research. A meta-analysis of cognitive function in remitted depression (Bora et al., 2013) covered 30 samples with an average of 30 euthymic patients and 33 healthy controls. The studies included in this thesis had significantly larger groups. The larger samples reduce the risk of rejecting objective findings as random variations (Type 2 errors).

All participants in papers I and III, including controls, went through careful and systematic clinical assessment to establish any current or previous mental illness. When administering a structured diagnostic interview to hundreds of participants there will inevitably be some instances of doubt. In the assessment of depression in these samples we experienced that diagnostic doubt most frequently occurred with criterion C, "clinically significant distress or impairment in social, occupational, or other important areas of functioning". In such cases the participant typically described a previous episode of depressed mood and sufficient sub-symptoms. She was able to get to work; if or how the quality and quantity of her work was impaired, was uncertain. She described somewhat reduced engagement in social activity, often due to lack of energy. Drawing the line of clinically significant distress was sometimes difficult, partly due to the retrospective nature of the situation and lack of third-party information. The interviews were audiotaped in order to secure reliable diagnostic decisions and strong interviewer compliance with the structured interview. Cases of diagnostic uncertainty were discussed and decided by a group of clinical psychologists. Additionally, some randomly selected interviews were reviewed for control of the interviewer's compliance with the interview structure and with diagnostic criteria. The

time and thoroughness invested in diagnostic evaluations constitute an important strength of these studies.

In papers I and III the diagnostic status of participants were based on DSM-IV criteria. We included participants who were currently not depressed according to those criteria, i.e. who did not meet all necessary criteria for a diagnosis at the time of inclusion. Individuals with sub-threshold symptoms were included. Taking BDI-II scores as an indicator, we can see that sub-threshold, or residual, depression symptoms varied greatly in the remitted MDD groups. Some individuals scored above 20 on the BDI-II, which may indicate clinical depression. These individuals were not classified as currently depressed because they did not meet diagnostic criteria. The fact that individuals with residual symptoms were included as not currently depressed may by some be perceived as a problematic confound. However, excluding these individuals from this research would be a mistake. Excluding participants with negative emotions from studies of emotion regulation would undermine the relevance of the results, and interpretations could not validly be made about those who are emotionally vulnerable and struggle with residual symptoms and relapse. Emotion regulation tendencies are relatively stable (John & Gross, 2004), but mood and symptoms of depression vary with time within individuals. By definition the purpose of emotion regulation is to influence emotion, and the rationale for studying emotion regulation was that it may, over time, influence psychological well-being.

Two of the most important tests of executive functions included in this research, which provided several outcome measures, were new versions that combined established cognitive test paradigms with emotional stimuli. The results from these tests are not directly comparable to other studies using the traditional versions of the tests.

As in most studies of remitted samples, some participants were using psychotropic medication. The medication users were a small minority, and the published articles explicitly state that these participants were carefully controlled by double sets of analyses (paper I) or partial exclusion (paper III). Furthermore, “patient” and control groups were highly similar in education and general cognitive abilities which reduces the risk of spurious correlations.

5.3 Ethical considerations

The diagnostic interviews showed that some participants had symptoms corresponding to one or more ongoing mental disorders at the time of participation. The interviewers were prepared for these situations. They were instructed to inform the patient that she appeared to experience clinically significant psychological distress and to recommend she talk to a psychologist or

primary physician about it. It was beyond the means of the project to provide follow-up or formal referrals, unless in the event of acute suicidal risk. There were no instances of acute suicidal risk in the data collection and no indication during or after the data collection suggesting that any participant was improperly informed and advised regarding ongoing mental health problems.

All participation in this research was voluntary, and the majority of participants made contact after seeing an advertisement. Some volunteers were not allowed to participate because they did not meet all criteria for inclusion. Reasons for decline of inclusion were most often comorbid psychological or neurological disorders or previous head injuries. Understandably, some of these felt rejected and even discriminated when they were turned down on the grounds of physical or mental conditions.

6 Conclusion

Although recovery from depression is statistically associated with less effective executive function, many individuals who recover from mild to moderate depression do not have executive impairments. This is a reminder that people suffering and recovering from depression is a heterogeneous group. Different mechanisms and etiologies of depression are at play in different personalities, histories and contexts. Approaches to prevention and treatment must therefore be adapted for subgroups and even for individuals. Many clinicians know this and try to accommodate individual patient needs. Nevertheless, success rates are unsatisfying. Much research remains before our health care system can cope efficiently with depression; the search for endophenotypes and genotypes of vulnerability will go on for many years.

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Inhibition and response to error in remitted major depression

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ABSTRACT

Depression is a common illness which tends to have a relapsing progression. Revealing vulnerability factors is an important step towards improved treatment and prevention. Previous studies of individuals in remission indicate that inhibitory control is more strongly impaired than other cognitive functions. Studies have mostly used Stroop tasks; it is unclear how this population performs on other measures of inhibition. Abnormal reactions to errors may also promote depression relapse, but this has rarely been studied in remitted depression. We used a Stop Signal task and Stroop inhibition task to investigate inhibitory function and post-error reaction time adjustments in 54 individuals with a history of depression and 185 never-depressed controls. Inhibitory processing was slower among the remitted depressed individuals on the Stop Signal task, but no difference was found in Stroop inhibition. The groups were not different on post-error adjustments. This finding extends the understanding of inhibitory deficiency in this population and offers insight into trait markers of depression.

1. Introduction

Unipolar depression is the leading cause of burden of disease in middle- and high-income countries, and the third leading cause of burden of disease worldwide (World Health Organization, 2008, Part 4). Several psychological and pharmacological treatments for depression have been developed, but their effects are inadequate (Cuijpers et al., 2010; Turner et al., 2008). Many recover from acute depression either spontaneously or with help from the established treatments. However, following recovery from a first episode of major depression, 65–75% experience relapse (Boland and Keller, 2009; Solomon et al., 2000). By revealing psychological vulnerability factors that increase the probability of relapse, we may lay the ground for targeted preventive interventions and fight the major challenge in modern mental health care constituted by recurring depression.

Depression is an emotional disorder, but it is associated with disturbances in cognitive functioning. Cognitive disturbances include reduced concentration and attention, and biases in memory and in the prediction of future outcomes (American Psychiatric Association, 2000; Disner et al., 2011). For a long time it was customary in philosophy and psychology to view cognition and emotion as separate phenomena, but modern cognitive neuroscience has shown that cognition and emotion are indeed connected, both neurologically and phenomenologically (Disner et al., 2011; Okon-Singer et al., 2015). Progress in the neuroscience of emotion may have important clinical implications. Issues of particular importance to psychiatry include the impact of cognitive control functions on psychosocial functioning, in the regulation of emotion, and whether cognitive control functions can be effectively targeted in treatment and prevention of depression. Herein lays the purpose of studying cognitive function in previously depressed individuals.

Cognitive performance in individuals that have recovered from Major Depressive Disorder (MDD) varies considerably between studies. The general tendency is that individuals with a history of depression are moderately impaired on a broad range of cognitive functions, including the domains processing speed, memory, attention, and executive function (Bora et al., 2013; Hasselbalch et al., 2011). A recent meta-analysis suggested that inhibitory control is most strongly affected (Bora et al., 2013). Cognitive deficits in depression are particularly related to difficulties in return to function, including psychosocial difficulties (Bortolato et al., 2014). Inhibitory control is functionally linked to depression through its impact on emotional processing. The inability to inhibit attention to negative stimuli may lead to enhanced processing of such stimuli, which induces negative emotion and prevents recovery from a negative mood (Joormann and D'Avanzato, 2010).

Abbreviations: MDD, Major Depressive Disorder; SST, Stop Signal task; SSRT, Stop Signal Reaction Time; SSD, Stop Signal Delay; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory

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A similar mechanism has been proposed for depressive rumination, in which impaired inhibition of self-referent negative material prevents the person from disrupting the repetitive depressive thoughts (Disner et al., 2011; Koster et al., 2011).

Previous studies of inhibition in remitted depressed populations have largely relied on one specific task of inhibitory capacity, the Stroop task (see Bora et al., 2013). This is a disregard of the multi-factorial nature of the construct; inhibition comprises the suppression of prepotent responses as well as internal and external distractors (Friedman and Miyake, 2004; Nigg, 2000). In the Stroop task, colors are printed in letters with a different color than the word names, and the participant is required to name the printed color and to inhibit the prepotent reading response. The consistency of inhibition on every trial in this task may result in partial automaticity, rather than top–down driven executive control. An alternative to Stroop is the Go/NoGo task, which requires a response to "go" stimuli, and no response to "no-go" stimuli. Three studies have used this task to study inhibition in remitted MDD participants. One study found impaired inhibition, but two studies did not (Georgiadi et al., 2011; Nixon et al., 2013; Westheide et al., 2007). However, learning and automaticity may confound the assessment of inhibition in the Go/NoGo task. The ability to avoid commission errors may be based on automatic bottom-up inhibitory processes due to a simple association between the stimuli and correct response (Verbruggen and Logan, 2008). These confounds are less likely to occur in a third inhibitory paradigm, the Stop Signal task. This paradigm presents the go signal in every trial, and in the event of a stop trial, a Stop Signal is presented after the go signal. The go response has already been initiated when the Stop Signal occurs. Consequently, inhibition is less predictable and requires more dynamic top–down control. Evidence suggests that the Go/NoGo and Stop Signal paradigms rely on different kinds of response inhibition (Verbruggen and Logan, 2008), and they activate overlapping, but distinct, neural circuits (Swick et al., 2011).

In studies of current MDD, as in the remitted population, Stroop type tasks are most frequently employed (Snyder, 2013). Patients with current MDD are significantly impaired on Stroop performance compared to healthy controls, but it has been difficult to delineate whether this is due to inhibitory deficiency *per se* or to overall slowing (Snyder, 2013). In the Stop Signal task, general psychomotor slowing is easily accounted for by the calculation of inhibitory processing efficiency (i.e. Stop Signal Reaction Time, SSRT), and the task is therefore apt in the pursuit of clear-cut inhibitory deficiency in this population. Previous investigations of Stop Signal inhibition in depressed populations suggest there may be no impairment, but the results are uncertain. Two studies found no significant difference in SSRT between depressed individuals and controls (Halari et al., 2009; Lyche et al., 2010), but a third study indicated possible improvement in SSRT following recovery from depression (Gruber et al., 2007). These studies used the mean method for estimating SSRT, a method which is sensitive to skewed reaction times and test-wide slowing (Verbruggen et al., 2013). The studies are therefore limited by potential inaccuracies in the estimated SSRT. In a fourth study, Lau et al. (2007) used an emotional Stop Signal task of positive, negative and neutral words, and similar non-words. The observed SSRTs were substantially higher in depressed individuals for both neutral as well as emotional words and non-words, indicating slower inhibition. However, the differences were marginally statistically significant due to relatively small samples and unusually large standard deviations.

In individuals recovered from depression, we recently found no difference in SSRT compared to never-depressed controls (Aker et al., 2014). This was based on an adapted Stop Signal task which included pictures of human faces as emotional distracters. This task included fewer trials than other established versions such as the Cantab Stop Signal task (Cambridge Cognition Ltd., Cambridge, UK). It therefore remains to be fully assessed whether Stop Signal inhibition is impaired as a trait marker in remitted depression.

Another set of variables which can be derived from the SST relates to response monitoring. Response monitoring is the ability to detect conflict or performance error, and adjust behavior accordingly (Thakkar et al., 2014). These variables might give clue to how participants react to their own mistakes, which is valuable in terms of understanding how this population handles correctives and adversities. If a mistake is committed, it may be adaptive to slow down responses in order to increase probability of success on the next trial; however, it is not adaptive to be overly conservative and withdrawn in response to feedback. Depressed patients exhibit a rapid deterioration of performance once a mistake is committed (Beats et al., 1996; Pizzagalli et al., 2006; Steffens et al., 2001). Elliott et al. (1997, 1996) showed that abnormal response to negative feedback was correlated with depression severity and specific to depression. Similarly, students with high self-reported level of depressive symptoms show slower and less accurate response in post-error trials, in various types of tasks (Compton et al., 2008; Farrin et al., 2003; Steele et al., 2007). Studies of response to feedback as reflected in behavioral adjustments following errors, are scarce in recovered individuals (but see Elliott et al., 1997). This is an intriguing issue because such behavioral patterns in remitted MDD patients may indicate specific vulnerability and promote relapse.

In summary, inhibition as indicated by the Stroop test is impaired in remitted MDD, but research based on other measures of inhibition, specifically the SST, is needed. The first aim of this study was to investigate inhibitory function in remitted depressed individuals compared to controls, using the Stop Signal task from the Cantab neuropsychological test battery. We predicted less effective Stop Signal inhibition in remitted depressed participants. A Stroop inhibition task was included for comparison. Our second aim was to investigate post-error behavioral adjustments. Based on the reviewed literature on post-error behavior in MDD, we hypothesized larger post-error adjustments in remitted MDD.

2. Methods

2.1. Participant inclusion and procedure

Participants were recruited from the general public using advertisements in a local newspaper in Oslo, Norway. After giving written informed consent, the participants provided information about their medical status and underwent psychiatric evaluation including the Structured Clinical Interview for DSM-IV, Axis I disorders (SCID I). Depression and anxiety symptoms were assessed using the Beck Depression Inventory (Beck et al., 1996) and the Beck Anxiety Inventory (Beck and Steer, 1990), respectively. The SCID interviews were administered by trained clinicians; they were also audio-recorded and subjected to consensus diagnoses. Diagnostic exclusion criteria were current depressive disorder, current drug or alcohol abuse or dependency, current or previous bipolar or psychotic disorder. Other exclusion criteria were lifetime head trauma with loss of consciousness for 30 min or more, or other neurological disorder. The full procedure of clinical and behavioral assessment was completed in one day. Participant characteristics are presented in Table 1.

2.2. General cognitive functioning

General cognitive functioning was assessed with Picture Completion and Similarities from the Wechsler Adult Intelligence Scale III (Wechsler, 2003). Results are reported as scaled scores.

Table 1
Demographic information.

	Never depressed	Remitted MDD	*t*	*p*
N	185	54		
Females	124 (67%)	39 (72%)		
Age	36.2 (SD 12.7)	38.9 (SD 13.7)	−1.349	.179
Current anxiety diagnosis	15 (8%)	6 (11%)		
BDI mean	3.6 (SD 5.5)	8.2 (SD 8.6)	−3.764	<.001
BAI mean	2.5 (SD 3.3)	5.3 (SD 5.2)	−3.727	<.001
WAIS PC scaled	13.0 (SD 3.3)	12.4 (SD 2.5)	1.350	.180
WAIS SI scaled	11.1 (SD 3.0)	11.2 (SD 2.6)	−.196	.845

MDD=Major Depressive Disorder; BDI=Beck Depression Inventory; BAI=Beck Anxiety Inventory; WAIS=Wechsler Adult Intelligence Scale; PC=Picture Completion; SI=Similarities.

2.3. Stroop inhibition

The Stroop is a test that creates a conflict between two modes of visual stimuli, requiring the inhibition of the most salient stimulus for the correct response (Stroop, 1935). Traditionally, the test was presented manually, but computerized versions have been developed. A comparison study found the strongest interference effect in a manually presented task, compared to two computerized versions. Based on this, we chose manually presented Stroop task, the Color-Word Interference Test (CWI) (Delis et al., 2001). The participant was first asked to name 50 colored squares on a chart. In a second round, the same colors were written in black ink on a chart, and the participant was asked to read the words. The third round was the traditional Stroop paradigm where colors are printed in ink of a different color than the word names, creating interference when the respondent is asked to report the ink color (Delis et al., 2001). We report the difference in completion time between the first and the third rounds as a measure of inhibitory control.

2.4. Stop Signal task

The Stop Signal task from Cantab (Cambridge Cognition Ltd., Cambridge, UK) was administered on a laptop computer. The task included one practice block (16 trials), in which there were no stop trials, and five test blocks with 64 trials per block. A trial started with a fixation cross, followed by an arrow pointing right or left, to which the participant was instructed to respond as quickly as possible by pressing a corresponding button on a press pad (go trial). In approximately 25% of the trials, an auditory beep occurred to indicate that the response should be withheld on that particular trial (stop trial). The difficulty of the inhibition trials was adjusted continuously by a tracking procedure, varying the Stop Signal Delay (SSD; the latency between go stimulus onset and stop stimulus onset) based on the individual's performance. Correct stops were followed by an increased SSD; failed stops were followed by a decreased SSD. The magnitude of these changes varied according to a complex system based on sub blocks (see Cantab manual for details).

In the SST, most trials are go trials that require the participant to respond to a simple visual stimulus. The behavior during these trials can be quantified by accuracy (which is typically high and will not be described any further in this paper), and by reaction time (RT). The remaining trials are stop trials, in which pressing a button constitutes an error. From the participant's perspective, stop trials occur randomly, and when the on-screen stimulus appears, it is impossible to know whether it is a go or a stop trial. In principle, the faster you respond, the more likely you are to fail whenever a stop trial occurs. If you fail to withhold your response on a stop trial, slowing down subsequent responses should increase the likelihood of success on the next stop trial. Due to the competition between speed and accuracy, an occasional failure may induce a subsequent adjustment, specifically a slowing of response. The potential change in reaction time that is induced by the stop trials is what we refer to as adjustment. Adjustment can be investigated by comparing the RT on go trials that occur after a stop trial to the RT on go trials that occur after a go trial.

We derived four measures from the SST. The Stop Signal Reaction Time (SSRT) is a timed estimate of the effectiveness with which the participant is able to inhibit an initiated motor response (Logan et al., 1984). The SSRT was calculated according to the block-based integration method described by Verbruggen et al. (2013). In the integration method, the SSRT is estimated by subtracting the mean SSD from the percentile of the Go RT distribution that corresponds to the person's proportion of failed stops. If a person fails to stop on 55% of the stop trials, the mean SSD is subtracted from the reaction time at the 55th percentile of that person's Go RT distribution. This is based on the assumption that the finishing time of the stop process corresponds to the reaction time at this point (Logan et al., 1984; Verbruggen et al., 2013). An integration SSRT was calculated for each of the five test blocks, and the mean of these five SSRTs was used as the participant's SSRT. Simulations have shown that block-based integration is more robust against test-wide changes in RT, e.g. due to practice effects or strategic slowing (Verbruggen et al., 2013).

Median Go-after-go reaction time (Go-after-go RT) comprises reaction time on go trials that succeed go trials. We used this as a baseline measure of reaction time because, as opposed to the overall Go RT, the Go-after-go RT is not influenced by adjustments that may occur immediately after a stop trial. This variable was also used in the calculation of adjustments in go reaction time following stop trials. Adjustments in RT on go trials following stop trials were calculated separately for correct and failed stops. Post-correct adjustment is the difference between median Go-after-correct-stop RT and median Go-after-go RT. Post-error adjustment is the difference between median Go-after-failed-stop RT and median Go-after-go RT.

2.5. Statistical analyses

Statistical analyses were performed in SPSS 22.0 for Windows. The dataset consisted of 239 individuals who met the clinical criteria. Given that all dependent variables were reaction time measures, age was a necessary consideration in the analyses. In order to factor out age when the data was examined for outliers, we performed linear regression analyses with age as a predictor of each of the dependent variables Stroop, Go-after-go RT, SSRT, post-correct adjustment, and post-error adjustment. The unstandardized residuals from these analyses were explored for outliers using SPSS boxplots. In the boxplot analyses, extremes were defined as values deviating at least three times the range of the middle 50% residuals. If an extreme residual was detected, that participant's corresponding variable score was excluded from all subsequent analyses. The residuals from the linear regression analyses were only used to detect outliers. A consequence of this process is that a given reaction time could be excluded as an outlier if it belonged to a 25 year old participant, and not be excluded if it belonged to a 60 year old.

No extremes were detected in the Stroop inhibition variable, but Stroop data for one person was missing. On Go-after-go RT, three high extremes were detected, of which two were in the never-depressed group, and one in the remitted MDD group. No outliers were detected in the variables SSRT and post-correct slowing. On post-error slowing, two high extremes and two low extremes were detected; all were in the never-depressed group. Group comparisons of Go-after-go RT, Stroop, SSRT, post-correct

adjustment, and post-error adjustment were performed as one-way analyses of variance with MDD history (two levels) as the independent variable, and age, BDI and BAI as covariates. The general effect of failed inhibition on subsequent response was analyzed in a paired samples t test, comparing post-correct adjustment to post-error adjustment.

3. Results

Descriptive information on participant groups is presented in Table 1. Both groups included a few individuals who met the criteria for one or more anxiety diagnoses at the time of testing. The anxiety diagnoses included specific phobia (9), social phobia (6), panic disorder (6), generalized anxiety disorder (4), agoraphobia (3), and obsessive compulsive disorder (3). Twelve individuals in the remitted MDD group reported using psychotropic medication, herein five SSRI, three SNRI, one tricyclic, two sedative/hypnotic (zopiclone, alimemazine), and two anxiolytic (clonazepam, oxazepam). Six persons in the never-depressed group reported using psychotropic medication, of which two SSRI, one SNRI, and three sedative/hypnotic (zopiclone, zolpidem, and alimemazine).

Reaction time data are presented in Table 2, univariate analyses of covariance are presented in Table 3. When controlling for age, BDI and BAI, the groups were not different on Go-after-go RT, Stroop, post-correct adjustment, or post-error adjustment. There was a significant difference in SSRT, see Table 3. The remitted MDD group had 17 ms higher SSRT (estimated means). This corresponds to 11% slower inhibition in the remitted MDD group, compared to controls. The difference remained significant when participants on psychotropic medication were excluded from both groups, $F(1,218)=4.701$, $p=0.031$.

Due to no significant differences between groups in post-correct and post-error adjustments, the effect of error was analyzed independent of groups. Participants responded significantly slower after failed stop, than after correct stop ($t(235)=5.087$, $p<.001$).

4. Discussion

We investigated inhibitory control and adjustments in reaction time following correct and failed inhibition, in individuals with a history of depression compared to a never-depressed group. The remitted depressed individuals were significantly slower on Stop Signal inhibition, but no difference was found in Stroop performance. The groups did not differ in go reaction time adjustments after correct and failed stop trials.

The inhibition findings part from the previous literature in two ways. First, if remitted depression is associated with slower SSRT compared to controls, it should be qualitatively similar, and perhaps stronger, in currently depressed samples. This is not supported by previous research; two studies found no significant differences in SSRT between depressed individuals and healthy controls. Lyche et al. (2010) studied 37 patients, of which 13 were on antidepressant medication. They observed a slightly slower SSRT (9 ms) in the depressed group; this was not statistically significant. Halari et al. (2009) studied a small sample of unmedicated depressed adolescents and a matched control group. The difference between groups was very small and non-significant. However, studies of inhibition in adolescents have limited generalizability to adults because prefrontal brain regions mature late, and prefrontal brain activation associated with response inhibition is different in teenagers and adults (Vidal et al., 2012). A third study followed hospitalized and medicated MDD patients through discharge and a follow-up (Gruber et al., 2007). They observed an improvement in SSRT corresponding to an effect size of .56, but this was marginally significant in the sample of 30 patients. A further limitation in all of these studies is that SSRT was estimated with the mean method, which is sensitive to skewing of the reaction time distributions and experiment-wide reaction time slowing (Verbruggen et al., 2013). In the current study, we used the more robust block-based integration method for estimating SSRT, and we had larger samples. Our analyses also confirmed that SSRT remained significantly slower in remitted MDD when participants on psychotropic medication were excluded. In a previous study we observed a non-significant 10 ms slower SSRT in remitted MDD (Aker et al., 2014). The samples in our previous and the current study are highly similar on demographic factors such as age, education, general cognitive abilities, and presence of anxiety disorders. The divergent findings on SSRT are most likely caused by different versions of the SST. The SST in our previous study had fewer trials and included pictures of human faces as distractor stimuli (Aker et al., 2014). In the current study, four times as many trials are included in the estimation of

Table 2
Group comparisons.

	Group	Observed mean (SD)	Estimated mean[a]
Go-after-go RT	Never depressed	405 (112)	408
	Remitted MDD	416 (117)	407
Stroop	Never depressed	20.2 (8.5)	20.4
	Remitted MDD	21.7 (9.1)	20.7
SSRT[b]	Never depressed	156 (39)	157
	Remitted MDD	176 (45)	174
Post-correct adjustment	Never depressed	5.7 (42.3)	6.2
	Remitted MDD	19.5 (53.9)	18.0
Post-error adjustment	Never depressed	24.3 (39.0)	25.6
	Remitted MDD	35.6 (55.1)	31.1

Stroop (contrast) reported in seconds, all other values in milliseconds.

[a] Adjusted for age, BDI and BAI.

[b] SSRT=Stop Signal Reaction Time.

Table 3
Univariate analyses of covariance, with depression history (never depressed, or remitted) as the independent variable.

Dependent	Covariate	df	F	p	
Go-after-go RT		1,232	0.011	.916	
	Age		63.485	$<.001$	*
	BDI		1.261	.263	
	BAI		1.526	.218	
Stroop		1,235	0.059	.808	
	Age		28.004	$<.001$	*
	BDI		1.572	.211	
	BAI		0.005	.943	
SSRT		1,235	7.613	.006	*
	Age		17.997	$<.001$	*
	BDI		0.025	.874	
	BAI		0.233	.630	
Post-correct adjustment		1,235	2.545	.112	
	Age		0.465	.496	
	BDI		2.675	.103	
	BAI		1.105	.249	
Post-error adjustment		1,231	0.619	.432	
	Age		7.307	.007	*
	BDI		0.075	.784	
	BAI		1.441	.231	

Asterisks mark statistical significance at alpha .05.

SSTRs. The higher number of trials increases the reliability, and the sensitivity, of the task.

Second, contrary to a recent meta-analysis (Bora et al., 2013), we found no difference in Stroop performance. This finding corresponds to our previous study, which used the same Stroop task in highly similar remitted and never-depressed samples. We have no certain explanation for this, but a relatively high level of functioning in our remitted participants is a plausible cause. In general, studies of clinical populations may include participants that have been severely depressed and hospitalized. Precise data on severity of previous depressive episodes is not available for all our participants; however, we know that very few had been hospitalized or experienced a severe state of depression. This does not make the sample less relevant from a clinical perspective, considering the heterogeneous nature of MDD and the subjective suffering and impairment to occupational and social functioning found in mild and moderate MDD. Our deviating Stroop results may also be due to different versions of the task. Penner et al. (2012) showed that, despite high test–retest reliability, three versions of Stroop had surprisingly low correlation. Given that Stroop task correlations are low, other versions of the Stroop task may have higher sensitivity to depression-related cognitive impairments.

Only one of the included measures of inhibition differentiated remitted depressed from control participants. This imposes a question about what the two tasks measure. An empirical investigation linked Stroop and SST to a common underlying factor called prepotent response inhibition (Friedman and Miyake, 2004), and Nigg (2000) argued that the Stroop and Stop Signal paradigms are linked conceptually because they both require effortful inhibition as a response to demands from the executive control system. There are, however, some important differences between the tasks. Stroop is invariable and predictable in the sense that all trials are inhibitory trials. The Stop Signal task is unpredictable because the Stop Signal occurs randomly after a minority of go signals. This indicates that the Stop Signal task requires more executive control and more dynamic regulation of the inhibitory process (see Verbruggen and Logan, 2008, for a similar discussion of automatic inhibition in the Go/NoGo task relative to the SST).

Different modes of presentation, i.e. manually presented Stroop vs. computerized SST, may also be a source of different outcomes. Furthermore, the level of stress elicited in the participants may be higher in the Stop Signal task. The Stop Signal task elicits more subjective anxiety, frustration, and unpleasantness in participants than does an identical choice-reaction task without stop trials (Spunt et al., 2012). This is likely due to the frequent experiences of failure to stop. In comparison, Stroop elicits few mistakes. The elevated level of stress may increase the load on executive control functions and therefore differentiate more clearly between individuals with different capacities for inhibitory control.

To our knowledge, only one study had previously investigated behavioral adjustment in remitted MDD. Elliott et al. (1997) used problem solving tasks and found that depressed patients more often reacted to negative feedback by committing another error, and this was specific to depression. The participants improved with recovery, but when in remission, they still showed abnormal response to negative feedback. This, and studies showing that the performance of individuals with symptoms of depression deteriorates after mistakes (Beats et al., 1996; Pizzagalli et al., 2006; Steffens et al., 2001), led us to predict larger post-error adjustment (i.e. slowing) in remitted MDD. This hypothesis was not supported. Obviously, reaction time measures in the SST are not directly comparable to the accuracy measures used by Elliott et al. (1997). Furthermore, a closer inspection of our data suggests that the post-correct and post-error adjustment variables have questionable validity. Although the group means indicate slowing after stop trials, a large minority of individuals in both groups speed up after stop trials. Twenty-two percent of participants responded faster after a failed stop. It is difficult to explain how this strategy corresponds with the notion of post-error adjustment as a measure of response monitoring.

Slowing after error is common in non-clinical groups (Lawrence et al., 2009; Pizzagalli et al., 2006; Rieger and Gauggel, 1999; Steele et al., 2007), but medicated, acutely depressed individuals have been found to lack this “normal” slowing response (Steele et al., 2007). Elliott et al. (1997, 1996) showed that abnormal response to negative feedback was specific to depression and correlated with depression severity, and was still present after clinical recovery, suggesting that it may be a trait-like marker of depression. More recent research has shown inconsistent evidence of how post-error behavior relates to scale measures of depression, such as BDI (Compton et al., 2008; Farrin et al., 2003; Pizzagalli et al., 2006). Changes in response following errors have typically been interpreted as top–down cognitive control (Botvinick et al., 2001; Notebaert et al., 2009), but other explanations have also been proposed. Rieger and Gauggel (1999) observed slowed response after both correct and failed Stop Signal inhibition; they suggested that this may be due to inhibitory after-effects which slow down responses that need to be activated immediately after an inhibitory trial. Others have argued that post-error slowing can be an “oddball” effect. Notebaert et al. (2009) showed that slowing occurred after infrequent events, regardless of correct or failed response. The oddball effect was explained with the orienting account, which states that infrequent events orient attention away from the task and therefore increase response latency on the following trial (Notebaert et al., 2009). Oddball cannot explain the difference between post-correct and post-error adjustments in our data, because these events occurred in similar frequencies.

The most prominent limitation of this study is the correlational design, which cannot reveal whether group differences were present before first onset of depression. We therefore cannot say whether the relative impairments in inhibition caused, or were caused by, previous depression. The presence of residual symptoms may also be considered a limitation. BDI scores varied greatly in the remitted MDD group. Some individuals scored above 20, which may indicate clinical depression. These individuals were not classified as currently depressed because they did not meet diagnostic criteria. BDI and BAI are not diagnostic tools, and scores on these scales alone do not state the presence or absence of depression or anxiety in the diagnostic sense. Other factors than clinical depression or anxiety may lead to elevated scores. Such factors include stress, somatic illness, or lack of sleep. The importance of differentiating between formal diagnoses and the symptom scales is underscored by our results, which showed that a history of clinical depression was related to Stop Signal inhibition, but BDI and BAI were not. Thus, although some may consider the residual symptoms a limitation, these symptoms cannot explain for the differences in SSRT.

The strengths of this study include a robust measure of Stop Signal inhibition, the reanalysis showing that the difference in SSRT withstands the exclusion of participants on medication, and larger samples than previous studies. Importantly, all participants were carefully assessed for psychiatric disorders. In a review of the literature on cognitive impairments in remitted depression, Hasselbalch et al. (2011) pointed out that, in most studies, it was unclear whether the control group participants had been properly assessed for current or previous depression and psychiatric disorder. A few of our participants in both groups had one or more current anxiety diagnoses; this is expected in the general population.

Top–down executive control is important for adaptive emotion regulation (Spinella, 2007), which in turn is central to prevent

worsening of depressive symptomatology (Berking et al., 2014; Joormann and Gotlib, 2010). An implication of impaired inhibition is that cognitive training, aiming to strengthen basic executive control, could be a useful supplement in secondary prevention of depression (see Siegle et al., 2007). This study supplements the existing literature on inhibitory control in previously depressed individuals, which was mainly based on Stroop-type inhibition, by showing impaired Stop Signal inhibition. The impairment may be present even when no difference is observed with the Stroop task, demonstrating the need for sensitive methods to detect inhibitory deficiencies in remitted populations.

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Conflicts of interest

Authors MA, RB, TCS, and NIL: None. Author CH: received consultancy fees from Lundbeck, p1vital and Servier, and holds directorship and shares in Oxford Psychologists Ltd.

Ethical standards

The project was approved by the Norwegian Regional Committee for Medical and Health Research Ethics. The authors assert that all procedures contributing to this work comply with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

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More rumination and less effective emotion regulation in previously depressed women with preserved executive functions

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Abstract

Background: Major depressive disorder is associated with very high recurrence rates, and specific vulnerability factors that increase the risk for repeated episodes should be identified. Impaired executive functions have repeatedly been found in remitted populations. The current study included both neutral and emotional executive tasks, and we expected to find impaired performance in unmedicated previously depressed women compared to controls. Furthermore, we hypothesized that the executive functions inhibition and shifting would be related to the ability to apply cognitive reappraisal and to avoid unhealthy rumination.

Methods: Inhibition and shifting data derived from neutral and emotional computerized tasks, and questionnaire data on emotion regulation and trait rumination, were obtained from previously depressed (n = 109) and never-depressed women (n = 64) and analyzed in independent samples t-tests. A logistic regression analysis investigated the ability of emotion regulation and rumination to predict depression vulnerability. The associations of executive functions to emotion regulation and rumination were investigated in a series of linear regression analyses. Participants on psychotropic medication were excluded from all analyses of executive performance.

Results: Previously depressed participants, the majority of which had experienced recurrent episodes, matched control participants on both neutral and emotional executive tasks. However, significantly more rumination and expressive suppression, and less cognitive reappraisal, were found in the previously depressed group. Executive function was unrelated to rumination and emotion regulation in this sample.

Conclusions: Previously depressed women whose executive function was intact were characterized by ruminative tendencies and more frequent use of expressive suppression. Trait rumination and expressive suppression are known to increase depression risk, but were unrelated to executive functions in this population. This indicates that unhealthy emotion regulation strategies may be targeted directly in preventive interventions.

Keywords: Executive function, Emotion regulation, Rumination, Depression, Remitted MDD

Background

Depression is characterized by emotional and cognitive impairments including depressed mood, feelings of worthlessness, and diminished ability to think or concentrate [1]. Of the 15–20% who experience depression during their lifetime [2], 65–75% experience recurrent episodes [3,4]. The National Institute for Health and Clinical Excellence [5] has identified secondary prevention as a key goal in the long-term management of depression. High recurrence rates suggest that specific vulnerability factors increase the risk for developing repeated episodes of the disorder and these factors should be identified. One way to achieve this goal is to compare previously depressed subjects in remission, having a known vulnerability, and never depressed subjects, on relevant cognitive and emotional function dimensions.

Meta-analyses confirm that ongoing unipolar depression is reliably associated with impairments in multiple aspects of executive function [6,7]. Executive functions (EF) also tend to be impaired in participants with remitted Major

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Depressive Disorder (MDD), and the largest impairments are found in inhibitory control [8,9].

Emotional (or "hot") cognition is also affected in depression. In particular, biased attention and perception of negative stimuli in dysphoric and clinically depressed individuals has been reported [10-12]. Importantly, biased attention to negative information has been found in both currently depressed and remitted participants [13,14].

Variations in the use of emotion regulation strategies like cognitive reappraisal, expressive suppression, and rumination play an important role in depression [12,15,16]. Individuals who have experienced depression in the past have been found to employ dysfunctional strategies more frequently (i.e. rumination, catastrophizing), and employ functional strategies less frequently (i.e. putting into perspective) [17]. However, negative findings have also been reported [15,18].

Compared to men, women have nearly twice the lifetime prevalence of depression [19]. Women tend to ruminate more, and the gender difference in rumination precedes the gender difference in depression, indicating that rumination may contribute to the sex difference in depression [20,21]. In rumination studies both trait and experimentally induced rumination are associated with impaired inhibition and switching in depressed individuals [15,22-25].

It has been reported that depressed patients show a specific failure to inhibit negative information, whereas formerly depressed individuals exhibited impaired inhibition of negative as well as positive information [26]. In another study, executive control functions with emotionally valenced material, and clinical phenomena like emotion regulation and rumination, were investigated in a sample of previously depressed subjects compared to never depressed individuals [15]. In that study a substantial proportion of participants in the clinical groups were taking medications. This is a compromising factor because antidepressant medication influences emotional processing and reduces the negative bias associated with depression [27]. The two aforementioned studies [15,26] used a negative affective priming task to assess inhibition, but negative priming is a controversial paradigm which has been criticized for low reliability [28]. It is weakly related to latent inhibition factors derived from other inhibition tasks, and researchers have questioned whether negative priming reflects active suppression of distracting information [29,30]. It is also a paradox that objectively better performance (faster reaction time to a probe) is interpreted as poorer inhibition, even though faster termination of the inhibitory effect would cause the same result. It was necessary to supplement the findings from J Joormann and IH Gotlib [15] and E Goeleven, R De Raedt, S Baert and EH Koster [26] with an investigation based on other measures of inhibition.

The aim of the current study was to investigate emotion regulation and executive control functions in unmedicated previously depressed and control participants. Inhibition was measured with the traditional Stroop paradigm and a modified version of the Stop-Signal task. Secondly, we also investigated the proposition that executive control in general, and in the processing of emotional material in particular, is related to depressive rumination and the emotion regulation strategy of cognitive reappraisal.

Methods

Ethics statement

The project was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REC South East D, 2011/2593/REK) and conducted in accordance with the Helsinki Declaration. All participants received both written and spoken information about the project, ethical and legal obligations of the researchers, and the rights of voluntary participants. Test administrators ensured that each participant had understood the information before informed consent was obtained by signature.

Participant inclusion

We included female participants because, compared to men, women have nearly twice the lifetime prevalence of depression [19]. Two strategies were used for recruitment. Advertisements in local newspapers and online social media were used to recruit participants, with or without a history of depression, from the general local community. To ensure a sufficient number of participants with a history of depression, people discharged from a public mental health outpatient clinic were contacted and invited to participate. This outpatient clinic offers short-term treatment to patients that have a job and are at risk of long-term disability due to depression or anxiety. Inclusion criteria were female, age 18–65, no known neurological disorder, no history of severe head trauma, and good Norwegian language skills. Exclusion criteria were alcohol or drug abuse, current or previous manic episode or other psychotic disorder, current hypomanic episode, current depression.

Clinical assessment and questionnaires

Diagnostic assessment

Diagnostic interviews were performed based on the MINI International Neuropsychiatric Interview 6.0. Some modules were omitted to reduce total time consumption and strain on the participants. The following modules were administered: major depressive episode, manic and hypomanic episodes, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, psychotic disorders, anorexia, bulimia, and

generalized anxiety disorder. All interviewers had received formal training in diagnostic assessment. With the exception of one case in which the participant declined, all interviews were audiotaped. The audiotaping allowed reviewing when the interviewer experienced any uncertainty about diagnostic decisions. Upon any uncertainty each interview was reviewed by author MA. After all inclusions were finalized, twenty-one cases which were still associated with some doubt were reviewed by a highly experienced clinical psychologist and researcher who was otherwise uninvolved with the project, and final diagnostic decisions were made by MA based on the expert recommendations.

Current symptoms

Symptom levels of depression and anxiety were measured using the Beck Depression Inventory II [31] and the Beck Anxiety Inventory [32].

Alcohol and drug use

Norwegian versions of the Alcohol Use Disorder Identification Test (AUDIT) [33] and Drug Use Disorder Identification Test (DUDIT) [34] were included to identify participants with alcohol or drug abuse. AUDIT and DUDIT are self-report forms consisting of 10 and 11 questions, respectively. Each question is accompanied by graded response alternatives and respondents are asked to check the alternatives that best represent their personal alcohol or drug habits and negative consequences of use.

Rumination

The Ruminative Responses Scale (RRS) is a 22 items self-report assessment of tendency to depressively ruminate. It comprises a three-factor structure that differentiates neutrally valenced and coping-oriented contemplation (reflection, five items) from passive and unproductive focus on problems and unachieved goals (brooding, five items) and depressive symptoms that are similar to BDI items (depression, 12 items) [35]. Respondents were instructed to use a 4-point scale to rate how often they react according to the 22 statements when feeling down, sad or depressed.

Emotion regulation

The Emotion Regulation Questionnaire (ERQ) was developed by JJ Gross and OP John [36]. It has ten items, each intended to measure one of the regulatory processes cognitive reappraisal or expressive suppression. Respondents were instructed to report how they control their emotions by responding to the ten statements on a 7-point scale, ranging from "strongly disagree" to "strongly agree". The ERQ has six items for reappraisal and four items for suppression, explicitly referring to the regulation of positive as well as negative emotions.

Cognitive measures

Non-emotional executive tasks

The Color-Word Interference Test (CWI) [37] is based on the procedure developed by J Stroop [38]. The CWI has four conditions, of which the first two assess baseline processing speed of color naming and reading. The third condition, Inhibition, is the traditional Stroop paradigm where colors are printed in letters with a different color than the word names, creating interference when the respondent is asked to report the printed color. The fourth condition, Inhibition/switching, has similar non-congruent color words, and requires the respondents to switch between reading and color naming.

The Emotional Picture Sorting Task (EPST)

The EPST was developed by authors MA and NIL [39] and is based on the same task structure as the Wisconsin Card Sorting Test (WCST) [40,41]. The WCST stimuli are comprised of cards depicting figures varying on three features: color, shape, and number. In the EPST, these stimuli have been changed to facial expressions with colored backgrounds, but the structure and procedure of this task was otherwise kept identical to the WCST. The total set of stimuli depicts four different individuals with four different emotional expressions for each individual. From the original WCST each *shape* was interchanged with one individual (i.e., triangle = individual 1, star = individual 2, cross = individual 3, circle = individual 4). *Number* on a WCST card was interchanged with facial expression (one = neutral expression, two = sad, three = happy, four = fearful). The colors red, green, yellow and blue were used as background colors in the pictures.

16 pictures, showing four adult female Caucasian individuals displaying four different expressions, were selected from the Karolinska Directed Emotional Faces database [42]. Graphic adjustments were performed in Adobe Photoshop CS5 software. Pictures were cropped using a 250*297 pixels frame. Eye level was kept center of the picture both horizontally and vertically. Brightness was increased, depending on the original picture, to make it appear similar for all pictures. Finally, background color was manipulated, producing four versions of each of the 16 pictures where the background color for each picture was red, green, yellow or blue. The final set of stimuli consists of 64 different pictures varying on the three dimensions color, person, and expression, and the set of 64 was used twice to allow a maximum of 128 trials. EPST was programmed in C++. See [39] for a more detailed description of this task.

Emotional Stop-Signal Task (ESST)

This task was based on the stop-signal paradigm of inhibitory control developed by GD Logan, WB Cowan and KA Davis [43]. The SST is a choice reaction time

task where the subject makes a motor response by pressing a button corresponding to the direction (right or left) of a visually presented arrow. On a subset of trials, an auditory signal requires inhibition of the predominant motor response. In this emotional version of the SST, a picture of a human face displaying either a neutral or an angry expression was presented for 500 ms immediately before the target stimulus (arrow pointing right or left) on all trials. The test was administered in a blocked procedure with two practice blocks (40 + 20 trials) and four test blocks. The test blocks had 40 trials each, of which 25% were stop trials. Two blocks included only neutral faces (N) and two blocks included only angry faces (A). The sequence of the test blocks were either N-A-N-A or A-N-A-N, randomized between participants. The stop signal delay started on 250 ms and was adjusted in a tracking procedure to converge each participant's performance on 50% successful stopping [44,45]. The main outcome variable was the Stop-Signal Reaction Time (SSRT) which is a time estimate of the inhibitory process. Separate SSRTs were calculated for neutral and angry blocks, based on the integration method [45]. Reaction time to go trials (GoRT) larger than 2.5 SD from mean for each participant were deleted before calculation of SSRT to reduce influence by extreme scores. GoRT and SSRT were found to be higher (i.e. slower) in angry compared to neutral blocks in a similar version of this task [46].

Intellectual functioning

The Wechsler Abbreviated Scale of Intelligence [47] subscales Vocabulary and Matrix reasoning served as indicators of general cognitive functioning.

Procedure

In addition to the assessments described here, Verbal fluency and Digit span tests were administered, and participants provided cells for genetic sampling using buccal swabs. These data will not be presented in the current article. EPST and ESST were administered on a Dell Latitude D610 laptop computer with a 14.1" LCD screen using 1024 × 768 pixels at 32 bit color quality. External mouse and speakers were connected. All other tests were administered manually. After completion participants were compensated with an electronic debit card of 250 NOK (approximately €30). Total duration of the testing session, including MINI interview and questionnaires, was 100–120 minutes.

Statistical analysis

All statistical analyses were performed in IBM SPSS 20. Two groups were defined a-priori based on the criterion history of depression following the research questions. Demographic and symptom characteristics, and all test outcome variables including executive functions and emotion regulation, were analyzed in independent samples *t*-tests between previously depressed and never depressed participants. A logistic regression analysis was performed using the ERQ variables, cognitive reappraisal and expressive suppression, and two RRS factors, brooding and reflection, as predictors of depression. A series of linear regression analyses were performed using executive functions variables as predictors of emotion regulation and rumination.

Results

Participant characteristics

201 women participated in the project. According to predefined exclusion criteria and based on information that was produced during the interview and testing session, data from 28 participants were excluded from all analyses due to the following reasons. Current or previous manic episode or other psychotic disorder (three participants), current hypomanic episode (two participants), current depression (17 participants). Three participants were excluded due to scores that were high and clearly deviant on AUDIT (one person, score 27) or on DUDIT (two persons, both scores 20). Three participants were excluded because their previous depressions were likely due to hormonal disturbances. These participants reported they had been formally diagnosed with hypothyreosis, they were untreated for hypothyreosis at the time of depression, and had not experienced depressive episodes while taking appropriate hormonal medication. Finally, data from 173 participants was available for analyses.

Twenty-nine currently present diagnoses, most of which were anxiety disorders, were registered in 24 of the remaining participants. These included agoraphobia (10), generalized anxiety disorder (7), bulimia (4), obsessive compulsive disorder (3), social phobia (2), posttraumatic stress disorder (2), and panic disorder (1). With one exception (posttraumatic stress disorder) all current diagnoses were found in previously depressed participants. Twenty-four participants reported using psychotropic medication, of which 18 used antidepressants (SSRI/SNRI), four used mood stabilizers, and two used other psychotropic medication (quetiapine, zopiclone). The participants using psychotropic medication were excluded from the analyses of executive function data because processing of emotional stimuli can be influenced by antidepressants [27] and perseverative behavior can be influenced by manipulation of serotonergic signaling in prefrontal brain areas [48]. Post-hoc analyses showed that these individuals did not perform significantly different from unmedicated participants.

Between-groups comparisons: previously depressed vs. controls

Demographic and clinical characteristics

Descriptive information is presented in Table 1. Compared to the control group, the previously depressed participants

Table 1 Participant characteristics

	All[a]						Without psychotropic medication					
	Controls (*n* = 64)		Prev. depr.[b] (*n* = 109)				Controls (*n* = 62)		Prev. depr. (*n* = 85)			
	M	*SD*	*M*	*SD*	*t*	*p*	*M*	*SD*	*M*	*SD*	*t*	*p*
Age	37.1	12.3	37.5	11.3	−.17	.863	37.2	12.1	38.2	11.6	−.51	.611
Education (years)	16.7	2.5	16.3	2.3	1.11	.268	16.8	2.5	16.4	2.3	.88	.378
Vocabulary[c] (T-score)	61.5	6.5	60.4	6.1	.98	.329	61.6	6.6	60.2	6.6	1.20	.231
Matrix (T-score)	58.5	5.5	57.5	6.3	.97	.333	58.5	5.6	57.6	6.2	.92	.358
BDI-II	4.3	5.2	10.9	7.9	−6.60	.000	4.0	4.8	10.1	7.9	−5.76	.000
BAI	3.2	4.1	5.6	5.0	−3.46	.001	2.9	3.8	5.6	4.9	−3.66	.000
Recurrent depr.			62%						60%			

[a]All participants were female.
[b]Prev. depr. = Previous depression.
[c]Some participants did not complete Vocabulary, primarily because it was not administered to those whose first language was not Norwegian. On a few occasions Vocabulary was skipped because the participant got too tired or because of time constraints. Of the 173 participants in this sample, 151 completed Vocabulary.

reported more than double the symptom load as shown by BDI-II scores. They also reported significantly more anxiety symptoms. There were no differences between groups on age, education, general cognitive functioning, or alcohol and drug use.

Executive functions

Essential outcome data on executive functions are presented in Table 2. In summary there were no significant differences between groups on any of the executive functions measures.

Emotional picture sorting task Two participants did not perform the EPST due to technical issues. Three participants were excluded from analyses because their failure to complete any categories may indicate that these participants did not understand the instructions or chose to not follow the instructions. Furthermore, three scores on the main outcome variable Perseverative responses were excluded as outliers, exceeding 2.5 standard deviations above the mean. Across the remaining 139 participants, the mean number of trials to complete the task was 106.2 (*SD* 21.0), the mean of categories completed was 5.0 (*SD* 1.5); this performance was not significantly different between groups (*t*s <1.4, *p*s > .1). The variable Perseverative responses was log transformed for analyses and was not significantly different between groups.

Table 2 Executive functions

	Controls		Prev. depr.		*t*-test			
	M	*SD*	*M*	*SD*	*df*	*t*	*p*	*d*
CWI[a] Inhibition	11.0	2.2	10.6	2.7	144	.82	.412	−.16
CWI Inhibition/switching	10.5	2.5	10.2	2.5	145	.79	.431	−.12
SSRT[b] neutral	161	53	171	57	144	1.23	.262	.14
SSRT angry	168	48	175	54	144	.84	.405	.18
EPST Perseverative resp.[c]	20.9	14.7	18.6	15.2	137	1.12	.266	−.16

[a]CWI = Color-Word Interference, scaled score of completion time.
[b]SSRT = Stop-Signal Reaction Time, reported in milliseconds.
[c]EPST = Emotional Picture Sorting Task, Perseverative responses. *M*, *SD*, and Cohen's *d* based on actual values, *t*-test was performed with Log transformed values.

Stop signal task One person did not complete the SST due to a hearing impairment that affected her perception of the stop signal. Across all remaining 146 participants the mean percent successful stop for the neutral and angry conditions were 52% and 51%, mean go reaction times were 438 ms and 443 ms, respectively. There were no differences between groups on these variables (all *t*s <1.2, all *p*s > .2). *t*-tests also showed no differences between groups on the main outcome variables SSRT neutral and SSRT angry (Table 2).

Color-word interference test Time to complete task was converted to scaled scores based on available norms [37]. *t*-tests showed no differences between groups on CWI Inhibition and Inhibition/switching scaled scores.

Cognitive impairment has been reported to increase with number of depressive episodes [49,50]. We made a post hoc decision to repeat the *t*-tests excluding participants with a history of only one episode, thus comparing the never depressed participants to participants that had two or more previous episodes of depression (n = 51). This procedure did not influence the group means, *t*-values or *p*-values in any noticeable way.

Emotion regulation and rumination

Sum scores for the rumination factors reflection and brooding were calculated based on the factor items identified by W Treynor, R Gonzalez and S Nolen-Hoeksema [35], each factor score comprising five item scores. Sum

scores for the emotion regulation strategies cognitive reappraisal and expressive suppression were calculated from six and four item scores, respectively [36]. *t*-tests confirmed statistically significant differences on all four variables, see Table 3. Previously depressed participants reported more reflection, brooding and expressive suppression, and less cognitive reappraisal.

A logistic regression analysis was performed for further investigation of the ability of ERQ and RRS variables to predict history of depression. The model containing cognitive reappraisal, expressive suppression, brooding and reflection as predictor variables and history of depression as outcome variable was statistically significant, $\chi 2$ (4, N = 173) = 56.90, $p < .001$, indicating that the model was able to predict which individuals had experienced clinical depression. The model explained between 28.2% (Cox & Snell R Square) and 38.4% (Nagelkerke R Square) of the variance in experienced depression, and correctly classified 75% of the cases. As shown in Table 4, brooding was the strongest predictor of previous depression, followed by reflection and expressive suppression. Reappraisal did not significantly contribute to the explanatory power of the logistic regression model.

Our second objective was to investigate the relationships between executive functions and emotion regulation. Data from traditional and emotional EF tests were entered as predictors in linear regression models with cognitive reappraisal, brooding and reflection as outcome variables. As shown in Table 5 none of the executive functions models significantly predicted cognitive reappraisal, brooding or reflection.

Discussion

The previously depressed participants matched never-depressed individuals on all neutral and emotional executive functions tasks. The previously depressed individuals reported that they more often respond to negative emotion with rumination and suppression and more rarely with reappraisal. A logistic regression model including all four factors of rumination and emotion regulation indicated that brooding, reflection, and suppression, but not reappraisal, predicted previous depression. The latter finding coincides with a proposition stating that the use of maladaptive strategies may be more important to psychopathology than the non-use of adaptive strategies [51].

The absence of differences in executive performance between groups was unexpected and calls for a closer inspection. All participants in the current study were carefully assessed for current and previous depression and most other common mental health disorders, and categorized according to history of depression. Marked differences on current depressive and anxiety symptoms as reflected by Beck scales is a further indication of the clinically different characteristics of the groups. We were able to match the groups and avoid potential confounds in age, education, and general cognitive abilities. For the analyses of executive functions we also excluded individuals who were taking psychotropic medication. Whereas executive function, as indicated by the color-word interference test, is only marginally above the general population mean in both our participant groups, education is high and estimated IQ is approximately one standard deviation above the population mean. Although this prevents generalization to subgroups with low education and IQ, it is a strength of this study that the patient and control groups are highly similar in education and general cognitive abilities. Many studies of cognitive correlates of depression include severely impaired inpatients who tend to have high comorbidity, including alcohol or drug abuse, somatic health problems, and lower education. Such comorbidities complicate interpretation of results. Our results indicate that, on group level, previously depressed participants with relatively high education and IQ, and low comorbidity, are unimpaired in both neutral and emotional EF tasks. An alternative interpretation is that our groups were different in executive function, but that the tasks used in this study were not sensitive to the differences. This is an unlikely explanation for the Stroop task, which has been shown to differentiate between euthymic MDD participants and controls [8]. In contrast, this explanation cannot be ruled out for the emotional EF tasks, which were new modifications of established EF paradigms. However, the effect sizes are similarly small for Stroop and the other

Table 3 Emotion regulation and rumination

	Controls		Prev. depr.		*t*-test			
	M	*SD*	*M*	*SD*	*df*	*t*	*p*	*d*
Cognitive reappraisal	30.6	6.5	28.1	6.8	171	−2.49	.014	−.37
Expressive suppression	11.1	3.9	12.9	4.8	171	2.37	.019	.39
Rumination full scale	35.5	8.9	53.6	11.7	165[a]	−10.63	.000	1.31
Brooding	8.0	2.6	11.6	3.5	162[b]	−7.80	.000	.99
Reflection	9.1	3.5	11.8	3.4	171	−5.07	.000	.74

[a]Six cases were excluded due to missing item values.
[b]One case was excluded due to missing item values. Equal variances not assumed.

Table 4 Logistic regression: predicting likelihood of previous depression

	B	S.E.	Wald	*df*	*p*	Odds ratio	95% C.I. for Odds ratio	
							Lower	Upper
Cogn. Reappraisal	−.02	.03	.24	1	.623	.98	.92	1.05
Exp. Suppression	.09	.05	3.92	1	.048	1.10	1.00	1.20
Brooding	.30	.07	18.53	1	.000	1.35	1.18	1.55
Reflection	.15	.06	6.14	1	.013	1.16	1.03	1.31
Constant	−4.53	1.48	9.40	1	.002	.01		

executive tasks in our study. We therefore believe that the absence of significant differences between the groups on the executive tasks reflects the true state of our participants, at least in terms of non-emotional executive functioning. But the intensity of emotional stimuli in our tasks may have been too low to induce a significant effect. A comparison of stop-signal reaction time for the conditions neutral and angry suggests that the emotional effect was small.

Consistent with previous research we found more trait rumination among the previously depressed individuals [15,52]. Thus, correlational data suggests that both brooding and reflection may have negative effects on mood and depression risk. Reflection was initially described as an adaptive form of rumination [35], and this proposition gained some further support [53], although J Joormann, DE Nee, MG Berman, J Jonides and IH Gotlib [54] found that more reflection (but not brooding) was associated with working memory interference. Correlational data cannot rule out non-causal explanations, e.g. that reflection does not in itself confer depression risk but is an attempt to cope with the noxious effects of brooding. However, a meta-analysis indicates that both factors are related to symptoms of depression, although the association is stronger for brooding [55]. Whether reflection leads to increased depressive symptoms depends on the interaction with other coping strategies [56]. Importantly, in a prospective study, I Demeyer, E De Lissnyder, EH Koster and R De Raedt [57] found that impaired cognitive control for emotional information influenced depressive symptoms one year later, and that this was fully mediated by rumination.

Contrary to some other studies we found more suppression and less reappraisal in the previously depressed group, and inclusion criteria may explain the differences. Whereas T Ehring, B Tuschen-Caffier, J Schnülle, S Fischer and JJ Gross [18] included only participants whose BDI score was smaller than 10, and J Joormann and IH Gotlib [15] used specified criteria to ensure full remission, we included participants who were currently not depressed according to diagnostic criteria, regardless of their current BDI scores or sub-clinical symptoms. Depending on the research question, excluding participants with negative emotions from studies of emotion

Table 5 Multiple regression analyses for executive functions and emotion regulation

	Predictors	Dependent	R^2	*df*	*F*	*p*
Model 1	CWI Inhibition	Cognitive reappraisal	.021	2,143	1.15	.223
	CWI Inhibition/switching					
Model 2	CWI Inhibition	Brooding	.031	2,143	2.32	.102
	CWI Inhibition/switching					
Model 3	CWI Inhibition	Reflection	.007	2,143	.50	.606
	CWI Inhibition/switching					
Model 4	Log Persev. responses	Cognitive reappraisal	.024	3,140	1.15	.332
	SSRT neutral					
	SSRT angry					
Model 5	Log Persev. responses	Brooding	.031	3,140	1.50	.217
	SSRT neutral					
	SSRT angry					
Model 6	Log Persev. responses	Reflection	.016	3,140	.77	.511
	SSRT neutral					
	SSRT angry					

regulation may imply excluding an important part of the topic. Emotion regulation tendencies are relatively stable [58] whereas mood and symptoms of depression naturally vary with time within individuals. By definition the purpose of emotion regulation is to influence emotion, and our rationale for studying emotion regulation is that it may, over time, influence psychological well-being. Given that individual differences in emotion regulation makes some individuals more vulnerable to depression [12,15] it can be expected that differences in emotion regulation may lead to differences in symptoms as reflected by BDI scores. In this context, strict inclusion criteria based on BDI or similar symptom assessments may eliminate important natural variance in the phenomena that are studied.

Executive performance did not significantly predict cognitive reappraisal or rumination. The CWI scaled scores show that executive performance is slightly above the general population average in this sample. The absence of executive dysfunction may explain why executive function was unrelated to rumination and reappraisal, and does not exclude the possibility of such correlations in samples with executive dysfunction. Another possible explanation relates to the complexity of executive processes. Inhibition is not strictly a unitary construct: inhibition of external distractors, internal distractors, and prepotent responses are partially separable components [29,59]. Both Stop-Signal and Stroop have been classified as response inhibition tasks [29,59]. In our understanding the involvement of inhibitory subcomponents is rather uncertain for the Stroop task, which may also rely on inhibition of cognitively prepotent irrelevant information. Different aspects of inhibition are likely to contribute differentially to the control of rumination and reappraisal, and the observed correlations will depend on the choice of tasks. J Joormann and IH Gotlib [15] used a Negative Affective Priming tasks to show that reduced inhibition of negative material was associated with less use of reappraisal and more use of suppression in currently depressed, previously depressed, and never depressed participants. Reduced inhibition of negative material was associated with increased rumination only in currently depressed participants [15]. However, the use of negative priming to indicate inhibitory control is controversial.

The fact that we used non-verbal material in the emotional tasks is another possible explanation, as previous studies have indicated that rumination may be associated with performance in tasks using verbal [22], but not facial [26], stimuli in depressed participants. It is also a reasonable assumption that rumination is primarily a verbal process [26,54] and that it consequently should be closer related to performance in verbal, as opposed to non-verbal, tasks. On the other hand, the visual perception of facial expressions is deeply rooted in humans by evolution and not dependent on language or reading skills. Faces are also relevant in the current context because depression seems to be characterized by a disruption in the interpersonal domain [60]. Furthermore, executive functions are typically defined as general high-level control mechanisms that operate on various other processes [61,62]. In this perspective, the contribution from executive inhibitory mechanisms should be the same regardless of whether the task is presented with words or faces, and variance in performance between verbal and non-verbal tasks must be attributed to non-executive processes.

The majority of our previously depressed participants had received cognitively oriented psychotherapy, and we cannot rule out the possibility that this may have had some impact on our main outcome variables. Cognitive therapy for depression will typically attempt to promote antecedent-focused emotion regulation, including reappraisal, and reduce depressive rumination, and may possibly also change executive performance [63]. However, based on the observation that our previously depressed participants are clearly different from controls on rumination and emotion regulation we find it unlikely that initial executive impairments in at-risk individuals have been eliminated by psychotherapy in the current sample.

Limitations and future directions

This study included only female participants. Participant gender has previously proven to not affect executive functions in remitted MDD compared to controls [8], so including male participants would most likely not influence this aspect of our results. By contrast, the observed group differences in rumination and emotion regulation cannot necessarily be generalized to male populations because men and women process emotional events differently [64]. Men and women use partially different strategies to cope with emotional distress in everyday life [65-67], and the relation between rumination and depression is stronger in women [55]. According to Thayer and colleagues, women rely more heavily on inhibitory processes for normal social and emotional functioning, and perseverative thinking and rumination may partly be caused by deficient inhibition [66]. Different aspects of inhibition and their relation to emotion regulation and rumination in men, both in remission from depression and in never-depressed controls, require attention in future studies.

The correlational nature of our data calls for cautious interpretation, but there is reason to trust the proposition that the differences in rumination and emotion regulation constitute vulnerability to depression in our sample. According to a meta-study, the relationship between rumination and depression is equivalent in longitudinal and cross-sectional data [55].

Stronger neural activation may in some instances compensate for the impaired performance otherwise associated with trait rumination. In an fMRI study of healthy, never-depressed individuals, M-A Vanderhasselt, S Kuhn and R De Raedt [68] found that brooding was associated with increased activation in right dorsolateral prefrontal cortex when successfully disengaging from negative material. This indicates that healthy high-brooders need more attentional control to disengage from negative information [68]. BCY Lo, S Lau, S-h Cheung and NB Allen [69] found increased late positive potential on medial scalp sites (Fz, Cz and Pz electrodes) among high ruminators when shifting between emotional material while in an induced sad mood state. An interesting continuation of the current research would be to use ERP data to investigate whether increased activation may explain why the previously depressed perform similar to control participants on executive tasks.

Conclusions

The previously depressed participants did not exhibit impaired executive functions as compared to never depressed subjects, but they more often respond to negative emotion with rumination and suppression and more rarely with reappraisal. Trait rumination is not related to executive functions in this population, which indicates that rumination may be targeted directly in preventive interventions.

Abbreviations

EF: Executive functions; AUDIT: Alcohol Use Disorder Identification Test; DUDIT: Drug Use Disorders Identification Test; CWI: Color-Word Interference test; ESST: Emotional Stop-Signal Task; EPST: Emotional Picture Sorting Task; ERQ: Emotion Regulation Questionnaire; RRS: Ruminative responses scale.

Competing interests

Author MA: Declares no competing interest.
Author CH: Consultancy fees received from Lundbeck, p1vital and Servier. Directorship and shareholder of Oxford Psychologists Ltd.
Author NIL: Declares no competing interest.

Authors' contributions

MA participated in study design, collected the data, performed the analyses, and drafted the manuscript. CH participated in data interpretation and manuscript preparation. NIL participated in study design, data interpretation and manuscript preparation. All authors read and approved the final manuscript.

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