Residual cognitive deficits following Major Depression

Associations to symptoms, course of illness, and outcomes from Computerized Working Memory Training.

Eivind Haga Ronold

Thesis for the degree of Philosophiae Doctor (PhD)
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Scientific environment

The thesis was funded by the University of Bergen (UiB) and is a continuation of student grant-funded work in the neuropsychological clinic at the Institute for Biological and Medical Psychology (IBMP) from 2014. I was employed by UiB from 2018-2023, as a lecturer and working in the clinic, both as a part of the PhD and in a 50% temporary position. I earned a specialization in clinical neuropsychology from the Norwegian Psychological Association (NPF) in 2020 and attended NPF conferences yearly during my PhD. I was part of the International Graduate School for Integrated Neuroscience that facilitated national conferences and courses which I attended. The studies in this thesis were initiated by the main supervisor Professor Åsa Hammar heading the Mood and Cognitive Function group, a node of the fMRI group. Study 1 was financed by Helse Vest and the Norwegian Research Council. Study 2 was financed by UiB, in collaboration with the Division of Psychiatry, Haukeland University Hospital, where co-supervisor Professor Ketil J. Ødegaard works, and I hold a 20% position as of 2021. The thesis has been part of international collaborations: The paradigm used in Papers I and III was given to Professor Hammar by co-supervisor Professor Jutta Joormann at Yale University and was translated by me. The Cognitive Affective Remediation Therapy (CART) group initiated by professor Hammar through a Peder Sather grant, consisting of leading international researchers on psychiatric disorders and cognition, met in Bergen at the start of my PhD, where I presented findings from Study 1. I visited Professor Joormann during a research stay in the spring of 2019, during which there was a CART meeting in New York, and I presented my research at McClean Hospital, Harvard University, in the group of a fellow CART member.

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Eivind Haga Ronold

Abstract

Cognitive deficits in Major Depressive Disorder (MDD) have received increased attention in recent decades. Even though cognition generally improves following affective remission, some cognitive deficits and other residual symptoms persist, affecting daily functioning and quality of life, thus contributing to the alarming rate of relapse seen in MDD. This is not well understood, and long-term studies of MDD from first onset into remission are needed. Treatments do not target the remitted phase, nor remediate residual symptoms, although cognitive remission is crucial for a successful recovery, and relapse prevention. This thesis, therefore, investigated how different aspects of cognitive functioning developed following MDD. Specifically, how executive function (EF), processing speed (PS), emotional working memory (e-WM), and other residual symptoms in remitted MDD developed, manifested, and were associated with depressive symptoms, relapse risk, and MDD history (Study 1; Papers I & II). Also, outcomes of Computerized Working Memory Training (CWMT) on residual cognitive symptoms and their associations were investigated in a remitted sample (Study 2; Paper III).

Paper I investigated the development of EF and PS five years following first episode MDD, the clinical course, and associations between cognitive deficits and other residual symptoms. If cognitive deficits improved after symptom remission, deficits could be caused by depressive symptoms as state-dependent. Conversely, if deficits were stable and relatively independent of symptoms, these could be understood as trait related. If deficits are exacerbated over time relative to MDD history, this could be understood as scar related. Twenty-three patients and 20 controls were assessed in the acute phase, one, and five years following the first episode of MDD. Neuropsychological tests assessed aspects of PS, in addition to EF. Five years following MDD, patients, and controls differed on most cognitive tests with the strongest effects for PS, and comorbid disorders had increased. PS was state-dependent. EF was mostly independent of symptoms, suggestive of trait effects. There was limited support for the scar perspective and no indication of worsening cognition during the five years. There were associations between history of

depression, EF, and neurotic rumination that could indicate risk factors for a more severe course of MDD.

Paper II investigated e-WM processing and associations with rumination and risk for relapse five years following MDD. The study was a cross-sectional investigation of differences in e-WM between participants who experienced their first MDD five years earlier compared to a matched control group. Twenty-three patients and 22 controls were compared on the e-WM task where sequences of three different sad- or happy faces were maintained in memory in a forward or manipulated in a backward high effortful WM loading condition. Correct sequential placement of one of these images was then assessed. Groups differed on accuracy for the low effortful positively, and high effortful negatively valenced images. Accuracy in the highly effortful negative condition was inversely correlated to rumination. Rumination predicted relapse. Thus, there was support for deficits in maintaining low WM loading positive stimuli and high WM loading manipulation of negative stimuli, with the latter being associated with rumination. Rumination was a risk factor for relapse and recurrence.

Paper III explored how systematic computerized training of WM influenced e-WM, EF, PS, rumination, and depressive symptoms. Twenty-nine participants remitted from MDD were recruited, and 20 completed the intervention and follow-up assessments. Improvements in cognitive function and residual symptoms, and their associations, were investigated pre- and post-intervention. Associations between depression history and changes in cognition and improved CWMT were explored. Hypotheses and statistical analyses were preregistered before data was analyzed. Accuracy in the negative high effortful WM manipulation condition showed an inverse correlation to rumination pre- but not post-intervention. Associations between PS and depressive symptoms were not found. Cognitive functioning improved in most conditions with the largest effects for EF. Symptoms did not change. Improved CWMT showed an association with improvements in aspects of EF and PS. History of depression was associated with less improvement in EF. The study supported that CWMT improved cognitive functioning.

Sammendrag

Kognitive vansker ved depresjon har fått økt oppmerksomhet de siste tiårene. Selv om kognitiv funksjon bedrer seg etter affektiv remisjon så vedvarer betydelige kognitive residual symptomer. Dette påvirker daglig fungering, livskvalitet og bidrar til den alarmerende tilbakefallsraten ved depresjon. Det er manglende forståelse for prosessene for tilbakefall, og longitudinelle studier som følger pasienter etter sin første depressive episode over i remisjon, over lengre tid, er nødvendige for å øke kunnskapen rundt dette. Tilgjengelig depresjonsbehandling fokuser lite på remisjonsfasen og kurerer ikke alle kognitive residualsymptomer, selv om det kan være avgjørende for å forbli frisk og forebygge tilbakefall. Avhandlingen undersøkte derfor hvordan kognisjon utvikler seg etter første depresjon. Det ble undersøkt hvordan eksekutive funksjoner, prosesseringshastighet, emosjonelt arbeidsminne og andre residualsymptomer og sykdomsutvikling opptrer, endres og korrelerer, i to grupper; en gruppe fem år etter førstegangsdepresjon (Studie 1; Artikkel 1 & 2), og en i remisjon fra depresjon. Effekten av databasert arbeidsminnetrening på residualsymptomer undersøkt i sistnevnte (Studie 2; Artikkel III).

Artikkel I undersøkte utviklingen av eksekutive funksjoner, prosesseringshastighet og symptomer fem år etter første depresjon, og korrelasjon mellom kognitive residualsymptomer og sykdomshistorikk. Teorier rundt utviklingen av kognitive funksjoner ble undersøkt: Funksjoner som bedret seg i samspill med bedring av affektive symptomer kunne forstås som en konsekvens av den depressive tilstanden, vedvarende kognitive vansker som potensielt var med å utløse den, kunne forstås som predisponerende trekk. Dersom vanskene ble verre i samspill med nye episoder og sykdomshistorikk kunne de forstås som depressive forandringer i form av kognitive arr. Tjuetre pasienter og 20 kontrollpersoner skilte seg på de fleste kognitive testene med størst forskjeller på prosesseringshastighet. Forekomst av komorbide tilstander økte. Prosesseringshastighet hang sammen med-, mens eksekutive funksjoner som inhibering fremsto som uavhengige av-, depressive symptomer. Kognitiv funksjon ble ikke dårligere etter fem år. Eksekutive funksjoner hang sammen med

sykdomshistorie og nevrotisk grubling, som indikerte risiko for mer alvorlig sykdomsforløp.

Artikkel II undersøkte emosjonelt arbeidsminne fem år etter førstegangsdepresjon. Korrelasjon mellom gruppeforskjeller i emosjonelt arbeidsminne, ruminering, og tilbakefallsrisiko ble også undersøkt. Artikkelen var en kryss-seksjonal undersøkelse av forskjeller mellom 23 tidligere førstegangsdeprimerte og 22 kontrollpersoner. På oppgaver som målte emosjonelt arbeidsminne skulle en huske sekvenser av tre ansikter som enten var triste eller glade. Sekvensen skulle enten holdes i korttidsminnet forlengs, i en lavt arbeidsminnebelastende betingelse, eller manipuleres, og holdes baklengs i arbeidsminnet, i en høyt arbeidsminnebelastende betingelse. Deretter skulle plassering i sekvensen for et av ansiktene angis. Det var gruppeforskjeller i riktig svar for glade ansikter i den enkle betingelsen, og for triste ansikter i den vanskelige betingelsen. Sistnevnte betingelse viste negativ korrelasjon med ruminering, som predikerte tilbakefall i gruppen. Tidligere førstegangsdeprimerte hadde vansker med arbeidsminneprosessering av negative stimuli, som hang sammen med ruminering, som igjen var assosiert med tilbakefallsrisiko.

Artikkel III undersøkte hvordan arbeidsminnetrening påvirket emosjonelt arbeidsminne, eksekutive funksjoner, prosesseringshastighet, ruminering og depressive symptomer. Tjueni deltakere i remisjon fra depresjon ble rekruttert, hvorav 20 fullførte intervensjonen. Endringer i kognitive residualsymptomer, og samvariasjon dem imellom før og etter trening, ble undersøkt. Hypoteser og statistiske analyser ble preregistrert før data ble analysert. Riktig respons i betingelsen for manipulering triste ansikter viste igjen negativ korrelasjon med ruminering i forkant, men ikke i etterkant av intervensjonen. Det var en bedring i kognitiv funksjon, med størst effekter for tester av eksekutive funksjoner. Symptomer endret seg ikke. Det var samvariasjon mellom forbedret prestasjon for arbeidsminnetrening og kognitive funksjoner. Depresjonshistorikk hang sammen med mindre forbedring av eksekutiv funksjon. Studien fant støtte for forbedring av noen residualsymptomer etter arbeidsminnetrening i remisjon fra depresjon.

List of Publications

I. Ronold, E. H., Schmid, M. T., Oedegaard, K. J., & Hammar, Å. (2020). A Longitudinal 5-Year Follow-Up Study of Cognitive Function After First Episode Major Depressive Disorder: Exploring State, Scar and Trait Effects. *Frontiers in Psychiatry*, Vol. 11, p. 1395. https://doi.org/10.3389/fpsyt.2020.575867

II. Ronold, E. H., Joormann, J., & Hammar, Å. (2020). Facing Recovery: Emotional Bias in Working Memory, Rumination, Relapse, and Recurrence of Major Depression; An Experimental Paradigm Conducted Five Years After First Episode of Major Depression. *Applied neuropsychology. Adult*, *27*(4), 299-310. https://doi.org/10.1080/23279095.2018.1550406

III. Ronold, E. H., Joormann, J., & Hammar, Å. (2022). Computerized Working Memory Training in Remission From Major Depressive Disorder: Effects on Emotional Working Memory, Processing Speed, Executive Functions, and Associations With Symptoms. *Frontiers in Behavioral Neuroscience, 16*, 1–14. https://doi.org/10.3389/fnbeh.2022.887596

Related publications not included in thesis

Hammar, Å., Ronold, E. H., & Rekkedal, G. Å. (2022). Cognitive Impairment and Neurocognitive Profiles in Major Depression—A Clinical Perspective. *Frontiers in Psychiatry*, *13*. https://doi.org/10.3389/fpsyt.2022.764374

Hammar, Å., Semkovska, M., Borgen, I. M. H., Myklebost, S., Ronold, E. H., Sveen, T., Johnson, S. L. (2022). A pilot study of cognitive remediation in remitted major depressive disorder patients. *Applied Neuropsychology: Adult*, *29*(2), 172–182. https://doi.org/10.1080/23279095.2020.1726919

Ronold, E., Schmid, M. T., & Hammar, Å. (2021). Risk Factors and Cognitive Deficits in First Episode Major Depression: A Five-Year Longitudinal Study of Explorative Subgroups. *Biological Psychiatry, 89*(9), S131. https://doi.org/10.1016/j.biopsych.2021.02.338

Abbrevations

(In alphabetical order)

Analysis of variance: ANOVA

Color Word Interference Test: CWIT

Computerized Working Memory Training: CWMT

Delis Kaplan Executive System: D-KEFS

Diagnostic and Statistical Manual of Mental Disorders 5th edition: DSM-5

Dorsolateral Prefrontal Cortex: DLPFC

Emotional Working Memory: e-WM

Executive functions: EF

General cognitive functioning: *g*

General psychopathology factor: *p*

Major Depressive Disorder: MDD

Mini-International Psychiatric Structural Interview: MINI

Processing Speed: PS

Rumination Reflection Questionnaire: RRQ

Ruminative Response Scale: RRS

The International Classification of Diseases 10th edition: ICD-10

The Montgomery Åsberg Depression Rating Scale Self-report: MADRS-S

The Montgomery Åsberg Depression Rating Scale: MADRS

Trail Making Test: TMT

Verbal Fluency Test: VFT

Wechsler Abbreviated Scale of Intelligence: WASI

Working Memory: WM

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1 Introduction

Some are Born to Sweet Delight

Some are Born to Endless Night (William Blake, 1863)

1.1 Purpose and scope of dissertation

Major Depressive Disorder (MDD) is among the most devastating, costly, and prevalent disorders in modern society (Otte et al., 2016). This thesis aimed to investigate the development of residual cognitive symptoms following MDD, their relation to clinical variables, and outcomes from an intervention targeting cognitive functioning (See Table 1 for an overview of the thesis). Improving residual cognitive symptoms following MDD is important given the substantial impact of MDD, and the role of residual cognitive symptoms in the alarming rates of relapse and recurrence seen in the disorder. Residual symptoms include cognitive deficits (Semkovska et al., 2019), emotional regulation difficulties like rumination (Watkins & Roberts, 2020), subthreshold depressive symptoms and subjective cognitive difficulties (Zajecka, 2013), and deficits in the processing of emotional material (Ahern et al., 2019; Miskowiak et al., 2015). Increased understanding of residual symptoms and new interventions are needed. Thus, investigating the development of residual symptoms in a long-term perspective, the effects of novel interventions, and identifying new periods for treatment and prevention is currently vital. The links between cognitive functioning, emotional processing, symptoms, and relapse risk, could be understood through many levels from biology to behavior. Although MDD is associated with lower performance on various neuropsychological tests (cognitive deficits), there are many questions concerning this, including cognitive profile, long-term development and associations to symptoms and course of illness, and outcomes from interventions targeting cognition. The impact of MDD, new perspectives, and a brief history of how cognition became central for understanding the disorder, interacts with emotional processing, and a summary of the literature on cognitive deficits and their relation to symptoms, is useful for understanding the questions the present thesis

addresses. Finally, recent efforts have been made to remediate cognitive deficits in MDD through different interventions, for which an overview is relevant to the aims of the current thesis.

Table 1.
Overview of Thesis and Papers

Title of the thesis	*Residual cognitive deficits following Major Depression: Associations to symptoms, course of illness, and outcomes from Computerized Working Memory Training.*		
Main aims of the thesis	To investigate specific aspects of residual cognitive symptoms following MDD, including: Long-term development. The association to symptoms and course of depression over a long-term perspective. Outcomes of Computerized Working Memory Training (CWMT).		
Studies	**Study 1**		**Study 2**
Title of papers	**Paper I:** *A longitudinal 5-year follow-up study of cognitive function after first episode major depressive disorder: Exploring state, scar and trait effects.*	**Paper II:** *Facing recovery: Emotional bias in working memory, rumination, relapse, and recurrence of major depression; an experimental paradigm conducted five years after first episode of major depression.*	**Paper III:** *Computerized working memory training in remission from major depressive disorder: Effects on emotional working memory, processing speed, executive functions, and associations with symptoms.*
Journal (year)	Frontiers in Psychiatry (2020).	Applied Neuropsychology, Adult (2020).	Frontiers in Behavioral Neuroscience (2022).
Aims of papers	Understand the long-term development of cognitive functioning and symptoms and explore associations to symptoms and course of illness following first episode depression.	Investigate deficits in emotional working memory (e-WM) five years following first episode MDD and how e-WM is associated to rumination and relapse.	Investigate outcomes on residual cognitive symptoms in remission after CWMT, and explore associations between cognition, symptoms, and course of illness pre post intervention.
Research questions	1) Which differences persist between patients and controls in processing speed (PS) and EF five-years following first episode MDD? 2) What associations between PS, EF, and depression supported the state, trait, and scar hypotheses?	1) Do patients and controls differ in e-WM performance? 2) Is rumination associated with e-WM and the rate of relapse?	1) Will there be associations between cognitive functions, rumination, and depressive symptoms pre intervention? 2) Will CWMT effect EF, PS, e-WM, rumination, symptoms, and their associations?
Design	Longitudinal follow up case control study.	Cross-sectional, experimental case control study.	Pre-post exploratory open label effect study.
Participants	**Paper I:** At five-year follow-up patients (n = 23) and controls (n = 20).		**Paper III:** Remitted (MADRS ≤ 12) patients

	Paper II: Same sample, with 2 additional matched controls (n = 22).		pre- (n = 29) post (n = 20) intervention.
Measures	**Cognitive:** WASI, D-KEFS: TMT, CWIT, VFT. **Clinical:** MINI, MADRS, NIMH LCM. **Self-Report*:*** RRS, RRQ.	**Cognitive**: WASI, e-WM (Experimental paradigm). **Clinical:** MINI, MADRS, NIMH LCM. **Self-Report:** RRS.	**Cognitive**: WASI, e-WM, D-KEFS: TMT, CWIT. **Clinical:** MINI, MADRS(-S). **Self-Report:** RRS, RRQ.
Independent variables	Group (Depression vs. Controls), Time, MADRS and course of illness.	Group (Depression vs. Controls), e-WM, RRS.	CWMT, e-WM, Rumination, MADRS and course of illness.
Dependent variables	Change in: EF, PS, comorbid disorders, RRS, RRQ.	e-WM (reaction time, accuracy), MADRS, Relapse.	Change in EF, PS, e-WM, associations, CWMT MADRS, RRS, RRQ.
Statistical Methods	Mixed model- and One way ANOVA, Independent *t*-test, Man Whitney *U*-test, McNemar's test, Bivariate-correlation (Pearson's *r*, Spearman's ρ).	One way-ANOVA, Independent *t*-test, Bivariate-correlation (Pearson's *r*), Linear regression, Logistic regression, Hierarchical logistic regression.	Paired sample *t*-test, Wilcox Signed rank test, Bivariate-correlation (Pearson's *r*, Spearman's ρ).
Main findings	1) Deficits in EF and PS persisted. PS showed largest deficits. 2) PS was associated with depressive symptoms. Some aspects of EF, like Inhibition/Switching showed associations to history of depression/RRQ, while Inhibition was independent of depression.	1) Deficits in e-WM accuracy for low effortful positive and high effortful negative stimuli. 2) Differences in rumination between groups. Associations between rumination and high WM loading negative condition. Rumination predicted relapse.	1) Associations between rumination and high WM loading negative condition before intervention. 2) Improved e-WM, PS, and particularly EF post intervention, and associations between e-WM and rumination disappeared. 3) Improvements in CWMT is associated with improvements in EF and PS. Inhibition/Switching change negatively associated to history of depression.
Conclusion thesis	Cognitive deficits in PS and EF remain, but appear to be stable, five years following MDD. Deficits show different associations to MDD with PS being more state related, and EF more trait related. Relapse and comorbidity are common when following MDD in a long-term perspective. Rumination is a risk factor for relapse in remission from MDD and is associated with effortful WM processing deficits for negative material. This association disappeared following CWMT. In addition, both hot and cold cognitive functions improved following the CWMT. Interventions targeting residual cognitive functions in remission from MDD are needed. However, future research should optimize interventions for remission and relapse prevention following MDD.		

Note. MDD = Major Depressive Disorder, EF = Executive Function, WASI = Wechsler Abbreviated Scale of Intelligence, D-KEFS = Delis-Kaplan Executive Function System, TMT = Trail Making Test, CWIT = Color Word Interference Test, VFT = Verbal Fluency Test, MINI = Psychiatric Structural Interview, NIMH-LCM = National Institute of Mental Health prospective Life Chart Methodology, RRS = Ruminative Responses Scale, RRQ = Rumination Reflection Questionnaire rumination scale, MADRS-*S* = Montgomery Åsberg Depression Rating Scale *Self-report*, ANOVA = Analysis of Variance.

1.2 Major Depressive Disorder

Major Depressive Disorder (MDD) is characterized by reduced mood and energy, and loss of interest and pleasure (American Psychiatric Association, 2013). The disorder affects roughly one in five people (Otte et al., 2016), casting its shadow on the afflicted, their families, and society at large. MDD is rated as a leading cause of burden of disease in global health estimates (Vos et al., 2020), and ranked as the top cause of years lived with disability (World Health Organization, 2017). The costs of depression are considerable and rising (Santomauro et al., 2021), partly due to MDD being related to a diverse range of comorbid disorders, functional decline, and lifestyle issues (Gold et al., 2020; Krishnan & Nestler, 2008), and was recently included as a modifiable risk factor for the development of Alzheimer's (Livingston et al., 2020). A recent study found that the effects of depression on cognitive deficits influence the economic impact of MDD to a considerable degree (Nafilyan et al., 2021). Thus, cognitive deficits are a central mediator of this risk for functional decline in MDD (Knight et al., 2018). The disorder, however, is characterized by many symptoms.

1.2.1 Classification of depression and MDD

The International Classification of Diseases 10th edition (ICD-10; World Health Organization, 2019a), described three core symptoms as central to clinical depression, including: Lowered mood, reduced energy and activity level, and anhedonia, the inability to appreciate things that were formerly enjoyable. The following symptoms support the presence of MDD: Reduced concentration, fatigability, guilt and reduced self-esteem, anxiety, and suicidal ideation. Consequently, MDD could be a fatal disorder. Reduced concentration is explicitly defined by the classification manual, highlighting the importance of cognitive deficits in the etiology of MDD. Symptoms must have been present most days most of the day, for two or more weeks for a depressive episode to have occurred. The manual distinguishes between mild episodes, with two of the central-, and two of the supporting, moderate episodes, with two central and three supporting, and severe depression, with three central and five or more supportive symptoms. The term

MDD, as used in the current thesis, originates from the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM–5; American Psychiatric Association, 2013). The DSM-5 has two core symptoms, namely lowered mood and/or reduced motivation/interest, one of which must be present for the disorder to have occurred, in addition to at least four supporting symptoms comparable to the ones described for ICD-10. MDD is thus equivalent of a mild- to moderate episode in ICD-10. DSM-5 also mentions attention difficulties, in addition to reduced ability to think and make decisions, even more explicitly defining MDD as a disorder characterized by cognitive deficits. Interestingly, the new version of the International Classification of Diseases (11th edition; World Health Organization, 2019b), currently under implementation, requires five symptoms to be present, more like MDD. This illustrates the ongoing development regarding the understanding and classification of depression.

1.2.2 Relapse and recurrence

Relapse- and recurrence rates in MDD are alarming. One early comment suggested that relapse was the rule, rather than the exception "Single episodes are extremely rare if the period of observation is significantly extended" (Angst et al.1973, p. 1000; in Mueller et al., 1999). Ormel and colleagues (2022) however, suggested that 50% of first-episode patients newer experience another episode, but also posit that most of these cases do not seek clinical help, and remit spontaneously. The story is different in clinical samples where relapse rates are estimated over 80% (Mueller et al., 1999). The DSM-5 defines relapse as a return to the depressive state, within a period of symptom remission lasting 8 weeks or less (American Psychiatric Association, 2013). Recurrence, conversely, is defined as a new episode of MDD after symptom remission for more than 8 weeks. Alarmingly studies suggest that economic costs (Touya et al., 2022), symptom load, cognitive decline, and relapse, all show incremental increases (Kessing & Andersen, 2017). A meta-synthesis of the literature by Buckman and colleagues (2018), suggested that relapse risk is influenced by previous episodes, and found strong evidence for childhood maltreatment, in addition to some evidence for cognitive biases, neuroticism (a personality trait related to experiencing negative emotions), as a well as comorbid disorders contributes to

relapse. Notably, the authors found that residual symptoms contribute to the risk of relapse and recurrence. Increased knowledge and prevention strategies targeting risks for relapse and recurrence are thus important to reduce the burden of MDD.

1.2.3 Treatments

Current interventions and treatments for MDD do not work for everyone. In a recent review of several meta-studies, Ormel (2022) and colleagues claimed that despite the increased availability of treatments, rates of MDD have not declined. The authors termed this phenomenon the treatment-prevalence paradox, and suggested amongst other things, that identification of risk factors for relapse and recurrence, and interventions preventing new episodes should be a way forward. Remarkably few improvements in the treatment and prevention of MDD have occurred in the last decades (Buckman et al., 2018; Nestler et al., 2002; Otte et al., 2016). Ormel and colleagues (2022) suggested that the two most common treatments, psychotherapy, and psychopharmacology, showed small- to medium effect sizes for treating MDD. The former was preferred by patients and associated with less relapse and recurrence. Thus, behavioral interventions are sought after. For the more severe forms of MDD, the effects of combining medicines and psychotherapy seem to be slightly larger than either alone. Given the burden of MDD, increased knowledge about residual cognitive symptoms and their mechanisms, and novel interventions preventing MDD are required to improve the state of matters. MDD is a heterogenous disorder, however, which complicates straight answers and interventions.

1.2.4 Heterogenous manifestations of depression

MDD is a complex disorder, with high comorbidity rates (Caspi et al., 2020; Kotov et al., 2017). Several disorders share risk factors commonly seen in residual symptoms following MDD (Ahern et al., 2019; DeYoung et al., 2002; Griffith et al., 2010; Snyder et al., 2015; Watkins & Roberts, 2020). Anxiety is the most common comorbidity in mood disorders (Moffitt et al., 2007), and contributes to relapse and recurrence (Buckman et al., 2018), is associated with cognitive deficits (Abramovitch et al., 2021; Snyder et al., 2015), and might thus have a cumulative effect on the cognitive deficits in depression (Beblo et al., 2011; Lyche et al., 2010). Depressive

symptoms vary (Stein et al., 2020), and sometimes show opposite manifestations like too much or too little sleep. Two persons could thus have two versions of MDD without any overlapping symptoms. Two hundred and twenty-seven different symptom manifestations of MDD were possible with the DSM -IV criteria (Zimmerman et al., 2015). This indicates several causes of MDD, and this heterogeneity could also exist for residual cognitive symptoms (Nestler et al., 2002; Porter et al., 2015). Depression manifests in bipolar disorder types-I and II (Vieta et al., 2018), postnatally (Cooper & Murray, 1998), in late life (Blazer, 2003), vary throughout the year (Otte et al., 2016), show melancholic/somatic features like sleep disturbances, worse depression in the morning, appetite issues, and psychomotor retardation, a slowing of thoughts and movements, potentially causing cognitive deficits (Carroll, 2012; Zaninotto et al., 2016), and as psychotic depression (Otte et al., 2016). This illustrates the complexity when it comes to studying, treating, and preventing depression, and emerging understandings of mental disorders try to model this heterogeneity.

1.3 New perspectives on mental disorders

New perspectives on mental disorders seek to explain symptom overlap, comorbidity, relapse, persisting residual cognitive symptoms, and could expand the window of interventions in disorders like MDD. Investigating symptoms as dimensions rather than in diagnostic categories is proposed (Insel et al., 2010), and symptoms are understood as normally distributed with extremes predisposing for pathology (Cuthbert & Insel, 2013; Cuthbert et al., 2022). The utility of the categorical diagnostic manuals described above has been questioned (Caspi et al., 2014; Lahey et al., 2012). Caspi and Moffitt (2018) postulated that all mental disorders are influenced by a general psychopathology factor (*p*), representing shared risks, with the severity of *p* influencing the development of disorder(s) in a comorbid, concurrent, and sequential way. This has been integrated into hierarchical bifactor models of psychopathology (Kotov et al., 2017; 2021), with *p* on top explaining most of the variance in dysfunction (Caspi et al., 2014), and predicting inverse relationships between concepts like general cognitive ability (*g*) and *p* (Caspi &

Mofitt, 2018). Supporting this, Abramovitch and colleagues (2021) found cognitive deficits across psychiatric disorders in a meta-study of meta-studies, suggesting associations between a cognitive deficit factor (c), and the *p* factor, also supported by studies finding small but significant negative associations between *p* and *g* (Caspi et al., 2014; Littlefield et al., 2020). These relatively new perspectives on psychiatric disorders suggest that conditions share risk factors, outcomes, and predisposing traits, and could be useful for connecting behavior to biology, and future studies of residual cognitive symptoms.

1.3.1 Neurobiological aspects of MDD

The genetic aspects of MDD have been recognized for more than a century (Burmeister, 1999; Otte et al., 2016). Heritability estimates range around 40% (Krishnan & Nestler, 2008). Cognitive abilities like executive functions (EF) and *g*, are also suggested to be polygenic and highly heritable (Friedman & Robbins, 2021; Engelhardt et al., 2016). Genes associated with MDD are implicated in neurochemical processes, and brain function and structure (Wray et al., 2018). Altered homeostatic processes regulating stress- and thyroid hormones, neurotrophic factors, monoamines, and inflammation are also seen in MDD (Stetler & Miller, 2011). Stress hormones like cortisol impair cognitive functions (Sapolsky, 2004), and could worsen cognition through neurotoxicity, particularly in the hippocampi (Hasselbalch, 2015), the brain area most consistently altered in MDD (Schmaal et al., 2016). Lower levels of brain-derived neurotropic factors have been observed in MDD (Otte et al., 2016), that increase with treatments (Sanacora et al., 2021), influencing brain plasticity and thus potentially cognitive functioning. Biochemical systems thus interact to influence dysfunctions (Pasqualetti et al., 2015; Zhao et al., 2018; Belmaker & Agam, 2008), processes that could persist after MDD (Hasselbalch, 2015). Hormones interact with monoamine levels and immune suppression (Otte et al, 2016; Sapolsky, 2004), causing elevated rates of inflammation associated with cognitive deficits (Mac Giollabhui et al., 2021), also persisting in remission (Rosenblat et al., 2014). Monoamines influence cognition (Millan et al., 2012; Roiser & Sahakian, 2013), although deficits are not fully improved by psychopharmacological interventions (Keefe et al., 2014). Brain structures and

functions are influenced by MDD. Goodkind et al. (2015) found similar structural differences across psychiatric disorders, with MDD showing specific differences in amygdala and hippocampus areas. Some report no initial neural changes, but larger changes in recurrent- and early-onset cases (Schmaal et al., 2016). Changes across disorders are also found in functional networks implicated in EF (Goodkind et al., 2015), and neural activation is found to correlate with cognitive deficits (Mcteague et al., 2016). In addition, there is heterogeneity in MDD patients in functional brain connectivity, associated with symptom heterogeneity (Drysdale et al., 2017). Neurobiological aspects have implications for how the development of residual symptoms could be understood, and for how symptoms and deficits develop, and ultimately influence behavior following MDD.

1.3.2 Relating to stress – from biology to psychology

MDD is associated with stressful events. A review by Otte et al. (2016) pointed to research suggesting a dose-response relationship between increased risk for MDD and early aversive events. Stressful events are consistently associated with relapse (Buckman et al., 2018; Chakrabarty et al., 2020). Early stress is related to cognitive deficits (Saleh et al., 2017). However, dealing with stressful events, through emotion regulation strategies like rumination, are central to development of psychiatric disorders (Joormann & Stanton, 2016; Johnson et al., 2020; LeMoult & Gotlib, 2019; Snyder et al., 2019). Rumination has connections to functional brain networks (Hamilton et al., 2015), and is influenced by chronic stress (Sanacora et al., 2021). Dysfunctional emotional regulation strategies could thus be a result of previous stressful events and depressive episodes (Wichers et al., 2010; Watkins & Roberts, 2020), interacting with traits like negative emotionality and neuroticism (Etkin et al., 2021; Griffith et al., 2010), impulsive reactions and lack of control over negative emotions (Johnson et al., 2020), together with bias and cognitive deficits (LeMoult & Gotlib, 2019), resulting in repetitive negative thoughts as emotional regulation strategies (Snyder et al., 2019; Watkins & Roberts, 2020), related to risk for MDD (Buckman et al., 2018). In sum, a trait like vulnerability in personality and cognitive functioning, stress sensitivity, and cognitive deficits could cause residual cognitive symptoms and enhance depressive states, potentially altering neuronal structures

regulating emotions, leading to lasting changes, and decreased cognitive functioning, further increasing vulnerability for repetitive negative thinking thus protracting the viscous circle of MDD. Thus, neurobiology is central for how residual cognitive symptoms are understood as traits, manifest in depressive states, develops as scars, and influence reactions to stressful events.

1.4 Depression as a cognitive disorder

This thesis does not concern itself directly with the biological causes of MDD, but with how cognition develops following MDD, poses a risk for further episodes, and if this risk can be remediated by enhancing cognition. This focus on cognition in MDD is relatively recent, emerging in the 1960s with the cognitive revolution (Beck, 1967), resulting from a merging of insights from academic psychology and cognitive behavioral therapy (Beck & Bredemeier, 2016). The cognitive perspective proposes that biased processing of emotional material in unison with cognitive deficits results in symptoms of MDD (Matthews & McLeod, 2005; Ahern et al., 2019), and has been utilized in modern treatments and research (Beck & Bredemeier, 2016; Beevers 2005; Watkins & Roberts, 2020). Residual cognitive symptoms exemplify this and contribute to relapse and recurrence rates (Buckman et al., 2018; Hammar, Ronold et al., 2022; Schmid & Hammar, 2013a), and impaired daily functioning (Evans et al., 2014; Hammar & Årdal, 2009; Knight et al, 2018). A recent review of cognitive approaches to MDD proposed that cognitive deficits interact with, and are exacerbated by, biased processing of emotional material (LeMoult & Gotlib, 2019). Specifically, preferential processing of negative material and lack of positive bias, in addition to reduced cognitive control for negative material associated with rumination, is proposed to contribute to depressive symptoms. Traits, most notably neuroticism, are also believed to contribute to emotional processing bias and cognitive deficits (Griffith et al., 2010; Kotov et al., 2021). Residual cognitive symptoms associated with MDD, like cognitive deficits, have been approached from different research traditions, however.

1.4.1 Hot vs. cold cognitive functioning in MDD

Clinical neuropsychological perspectives have traditionally focused on response times, processing speed (PS), attention, EF, memory, *g*, and problem-solving abilities, which could be understood as *cold cognition* (Ahern et al., 2019; Semkovska et al., 2019). A synthesis from the fields of psychometrics and clinical neuropsychology, neuroscience, and cognitive psychology has proposed that deficits in EF (termed cognitive control in the two latter traditions, but referred to as EF in the present thesis) is a risk factor in MDD (Snyder et al., 2015; Friedman & Robbins, 2021). Specifically, deficits in EF for emotional material (LeMoult & Gotlib, 2019; Joormann & Stanton et al., 2016; Mathews & MacLeod, 2005), and impulsive responses to emotional stimuli (Carver & Johnson, 2018; Johnson et al., 2020), are suggested to mediate symptoms across disorders. Furthermore, a lack of control over emotional material is suggested as a trait of MDD (Ahern et al., 2019; Miskowiak et al., 2015). This is described as *hot cognition*, where emotional valence (e.g. positive/negative) is added to cognitive tasks to investigate how valence influences cognitive functions like EF (Ahern et al., 2019). Hot cognition could be defined as processing, manipulating, or remembering emotionally valenced stimuli, in addition to reward and punishment sensitivity (Roiser & Sahakian, 2013; Miskowiak et al., 2015). Studies have found bias for negative material in memory (Mathews & McLeod, 2005), attention (Peckam et al., 2010), and in emotional facial processing (Bourke et al., 2010), in MDD. Thus, combining emotional facial stimuli with tasks measuring functions like WM could shed light on deficits in hot cognition. Deficits in emotional processing are important residual cognitive symptoms in MDD and are associated with another central risk factor, namely rumination.

1.4.2 Rumination resulting from deficits in cognitive control?

Residual cognitive symptoms following MDD involve dysfunctional emotional regulation strategies like rumination. This is the most studied emotional regulation process in depression and a known risk factor for a more severe course of illness (for a recent review see Watkins & Roberts, 2020). Rumination focuses on past events, instead of concerns for the future seen in worry (Zetsche et al., 2018). Adopted from the Greek word *ruminare* meaning to mend in the mind or churn over (Cropley et al.,

2016), rumination shows both overlapping and specific characteristics, relative to other forms of repeated negative thinking like worry (Taylor & Snyder, 2021; Zetsche et al., 2018). Rumination is suspected to be caused by cognitive deficits (Zetsche et al., 2018), but could also cause deficits by taxing limited attentional resources (Beevers, 2005; Roberts et al., 2017). Rumination is theorized to be related to specific cognitive deficits (Joormann & Gotlib, 2010; Koster et al., 2011; LeMoult & Gotlib, 2019; Roberts et al., 2017; Watkins & Roberts, 2020). Theories have in common that a proposed lack of cognitive control, i.e. deficits in EF for negative material influences propensity for rumination (Beevers, 2005; Joormann, 2010; Koster et al., 2011; Whitmer and Gotlib, 2012), and there is support for all the theories (Watkins & Roberts, 2020). Lack of control could be conceptualized and operationalized as an emotional WM (e-WM) deficit associated with rumination and MDD. Several meta-analyses found small associations with some aspects of EF and WM, and rumination (Vălenaș & Szentágotai-Tătar, 2017; Yang et al., 2017). Zetsche et al. (2018) suggested that difficulties in negative discarding from WM could contribute to rumination. Single studies find a relationship between WM manipulation of negative stimuli and rumination (Joormann et al., 2011; Joormann & Gotlib, 2010). Associations between cognitive deficits and rumination in samples in remission from MDD, and consequences for clinical course, thus need to be investigated further. Types of rumination investigated could be important, however.

1.4.3 Measuring rumination

One early and influential conceptualization of depressive rumination (rumination when sad or depressed), the response styles theory (Nolen-Hoeksema, 1991), proposed that rumination is a stable tendency for responding to depressed mood. This is measured by the response styles questionnaire, whereof the 22-item ruminative responses scale (RRS) has been most studied (Watkins & Roberts, 2020; Zetsche et al., 2018). RRS can be separated into reflective- depressive- and brooding rumination, whereof the latter is most pathological (Treynor et al., 2003). However, given the shared variance of repeated negative thinking, depression, and rumination (Taylor & Snyder, 2021), it is unsurprising that meta-analytic studies do not find differences between the subclassifications of the RRS (Zetsche et al., 2018).

Correlations between the subscales of RRS are high (typically >.8) in clinical samples (Zetsche et al., 2018; Taylor & Snyder 2021). Thus, the full RRS score was used in the current thesis. The distinction between reflection and rumination was captured by another measure, the rumination reflection questionnaire (RRQ) by Trapnell and Campbell (1998): Rumination is associated with the personality trait neuroticism, while reflection is related to openness. Since openness is not associated with psychopathology, the rumination scale was most relevant for the current work. The importance of studying different types of rumination (du Pont et al., 2019), relatively independent of sad mood (Trapnell & Campbell, 1999; Watkins & Roberts, 2020), has been emphasized. In sum, rumination is an important residual cognitive symptom that could contribute to impaired cognitive function and relapse in MDD. Still, there are mixed findings on the relationship between rumination and cognitive functioning which should be investigated further.

1.5 Specifying cognitive deficits

The cognitive profile in MDD is still not fully understood. Cognitive approaches to MDD have historically focused on cognition as dysfunctional thoughts, attitudes, and behaviors (Beck, 1967; Beck & Bredemeier, 2016). MDD, however, is also recognized as a disorder with decreased ability to think, concentrate and make decisions, often referred to as cognitive deficits. Cognitive functioning consists of several abilities that are captured by tests to varying degrees, and a distinction could be made between PS and EF. The latter is sometimes conceptualized as cognitive control, sometimes as EF, depending on research tradition and measures (computerized experimental- or clinical neuropsychological tests), that are often applied in cognitive neuroscience or clinical neuropsychological traditions, respectively (Friedman & Robbins, 2021). EF is dependent on lower processes like PS (Semkovska et al., 2019; Snyder, 2013), and thus controlling for speed of processing could elucidate aspects of cognition in MDD (Porter et al., 2015). Thus, both these functions could be crucial to measure following MDD to better identify the neuropsychological profile in the remitted phase of the disorder.

1.5.1 Defining cognitive deficis

Cognitive deficits could be understood as persisting differences between populations with or without a history of MDD on emotional regulation, hot cognition, and cognitive tests. Differences in subjectively experienced cognitive difficulties could also be a part of cognitive deficits but show surprisingly small associations with cognitive tests, and larger associations with mood symptoms (Serra-Blasco et al., 2019). Cognitive deficits refer to underperformance relative to a healthy population on cognitive and neuropsychological tests. Another term sometimes used, cognitive impairment, is commonly understood from a clinical neuropsychological perspective as a low score, in the 16-2. percentile range (Douglas et al., 2018; Iverson et al., 2011), on neuropsychological tests compared to the norm (distributed frequencies in comparable groups), or relative to matched control participants. Meta-studies find small to medium differences between populations with and without a history of MDD, which in standardized scores represent normative underperformance above a 16% cut-off (representing one standard deviation below the norm, roughly comparable to a large effect like Cohen's $d = 1.0$), thus calling this a deficit is more fitting than impairment. Some patients are cognitively impaired to a larger degree. This is a minority, however (Douglas et al., 2018; Iverson et al., 2011). Which aspects of cognition that show deficits are also important with cognitive functions potentially relating to different clinical outcomes.

1.5.2 Structure and relevance of EF

Deficits in EF have been proposed as having a central role in the development and maintenance of MDD. EF is important for daily functions related to MDD (Diamond, 2013; Knight & Baune, 2018), is associated with the pre-frontal cortex (Friedman & Robbins, 2021), important in the cognitive control networks mentioned above (Mcteuge et al., 2016). Some authors have suggested that deficits in EF are a transdiagnostic risk factor associated with several forms of psychopathology (Abramovitch et al., 2021; Friedman & Roberts, 2021; Snyder et al., 2015). EF controls functions central to many other cognitive domains (Snyder et al., 2015), like memory consolidation, problem solving, and reasoning. EF is functionally and foundationally different from *g*, but also related to it (Friedman & Roberts, 2021).

Miyake et al. (2000) proposed the unity diversity model of EF, including one common EF factor, highly correlated to the others including inhibition, mental flexibility (referred to as switching in the current thesis), and updating, with the latter closely related to WM (Friedman & Miyake, 2017). Inhibition is described as a function where suppression of automatic responses is made to perform task-relevant responses and has recently been suggested as more related to/or overlapping with the common EF factor, while the other EFs are more specific functions (Friedman & Miyake, 2017). Abramovitch et al. (2021) found larger deficits in inhibition in MDD compared to all other psychiatric disorders. This is a persisting deficit (Snyder, 2013), present from first episode (Schmid & Hammar 2013b), to 10 years following MDD (Årdal & Hammar, 2011). Thus, both unity and diversity functions show lasting deficits following MDD, impairing functioning in remission. However, the nature of EF deficits is still debated.

1.5.3 PS a basic process influencing cognition

Relatively little attention has been given PS in the literature on cognitive deficits in MDD. PS show some of the largest deficits in first episode MDD (Ahern & Semkovska et al., 2017). Studies suggest that PS is related to cognitive functions like general abilities and EF, but also distinct from them (Friedman et al., 2008; Nigg et al., 2017). In addition, imaging studies find different neuronal structures associated with performance in EF and PS tasks (Goodkind et al., 2015), with the latter showing relatively little gray matter correlation. White matter is associated with deficits in PS (Meinert et al., 2021), suggesting different neurobiological underpinnings than EF, that could be associated with different etiological processes in MDD. PS is by its nature a timed ability, and thus influence performance on all timed tasks. Porter et al. (2015) in a review of meta-studies, suggested that the cognitive deficits in MDD are not well understood partly due to the hierarchical organization of cognitive function implies that deficits in basic tasks like motor- and processing speed influence deficits in higher order processes like EF and memory. The influence of PS on EF tests is controlled for to differing degrees in studies (Snyder, 2013; Snyder et al., 2015). Deficits in PS could influence results in EF (Nigg et al., 2017), and some meta-analyses suggest that basic attentional and PS functions, might account for deficits

found in EF (Henry & Crawford, 2005; Semkovska et al., 2019), sometimes called the motor slowing hypothesis (Snyder, 2013). Cognitive functions are highly intertwined, and separating domains when assessing associations to depression could lead to new insight into deficits and their associations to MDD.

1.5.4 Issues regarding separating EF and PS

The development of cognitive deficits could be clarified by separating EF and PS. A meta-analysis of cognition following MDD suggested that deficits in EF only manifest in timed tasks, and therefore are due to low processing speed and attentional difficulties (Semkovska et al., 2019). Snyder (2013) found deficits in untimed executive tasks (like the Wisconsin Card Sorting Task), as did Semkovska et al. (2019), although deficits were smaller than in timed tasks. A meta-analysis by Rock et al. (2014) found no deficits in simple timed tasks, which indicated that response time alone cannot explain deficits. It is suggested that deficits in EF persist to a larger degree than PS deficits in remission (Ahern & Semkovska, 2017; Douglas & Porter, 2009; Porter et al., 2015; Rock et al., 2014; Snyder, 2013). Examining how both EF and PS develop and are associated with residual cognitive symptoms, from first episode, over five years, could inform on the neuropsychological profile of MDD, and the state, trait, and scar perspectives. There is, however, some debate regarding the measurement of EF. Many cognitive functions are involved in EF tests, a phenomenon termed *the task impurity problem* (Snyder et al., 2015). Deficits in PS could thus influence the deficits in EF reported in the literature. Nuño and colleagues (2021) investigated this by reviewing studies using the trail making test (TMT), and color word interference test (CWIT, a.k.a. the Stroop test) in MDD. They found evidence for deficits in both PS and EF, suggesting both a cognitive effort and processing deficit, and that TMT and CWIT could separate between EF and PS. Snyder et al. (2015) recommended controlling for PS when measuring EF, and suggested using composite scores consisting of several EF tests to best capture the specific function (and minimalize measurement error and task impurity effects). This comes with the risk of precluding deficits in more specific EF tasks, however (Hammar, Ronold et al., 2022). There seems to be some disagreement regarding which deficits persist following MDD. Therefore, examining both EF, and PS, over a

long-term perspective, could be important for understanding the cognitive profile following MDD, the development of deficits, and the association to symptoms and risk factors with regards to the trait state and scar perspectives.

1.6 Questions regarding cognitive deficits in MDD

While there is agreement that cognitive deficits are associated with MDD (Semkovska et al., 2019), the cognitive profile, and the causes and consequences of deficits are less known. Deficits persist in remission and represent risks for exacerbation of functional recovery and course of illness (Hammar & Årdal, 2009; Hammar, Ronold et al., 2022; Knight & Baune, 2018; Knight et al., 2018). Common treatments do not fully remediate cognition (Bernhardt et al., 2019; Groves et al., 2021; Keefe et al., 2014; Miskowiak et al., 2022; Rosenblat et al., 2015), and deficits influence treatment effects (Groves et al., 2018). Thus, interventions improving cognitive deficits in remission are sorely needed.

1.6.1 The cognitive profile in MDD

Not all cognitive functions show the same deficits in MDD. General ability, *g*, especially when measured independently of timed tasks (PS) and WM, seems to be spared (Semkovska et al., 2019), a considerable difference from disorders like schizophrenia (Stefanopoulou et al., 2009; Abramovitch et al., 2021). The first meta-study of cognitive deficits in MDD focused on-, and found, memory problems (Burt et al., 1995), however, deficits are broader than this. The first meta-study on the cognitive *profile* in MDD stated “the neuro-psychological deficits of individuals with major depression are shown to be consistent with a global-diffuse impairment of brain functions with particular involvement of the frontal lobes” (Veiel, 1997, p. 587). This is supported by the most recent meta-analysis on cognitive functions in MDD, reporting small to medium deficits in three-quarters of cognitive tests (Semkovska et al., 2019), persisting in remission. MDD is associated with cognitive deficits in many domains, both acutely- and in remission (Bora et al., 2013; Hasselbalch et al., 2011), with the largest effects in the depressed state (Rock et al., 2014; Semkovska et al., 2019; Snyder, 2013). Considerable heterogeneity

complicates findings on cognitive deficits in MDD (Porter et al., 2015). This will be discussed in the following sections.

1.6.2 Variables moderating and mediating cognitive deficits

Variables associated with cognitive deficits could represent risk factors (Porter et al., 2015). Risk factors for cognitive deficits in MDD pertain to severity, including depressive symptoms (McDermott & Ebmeier, 2009; McClintock et al., 2010), depression status (Bora et al., 2013), number and length of episodes (Haselbalch et a., 2011; Semkovska et al., 2019), and rumination (Zetsche et al., 2018). Comorbid disorders could moderate deficits (Baune et al., 2009; Beblo et al., 2011; Porter et al., 2015), in addition to a family history of mental disorders representing genetic predisposition (Kjærstad et al., 2021; McKenzie et al., 2021). Nigg et al. (2017) suggested a cumulative severity effect of both symptoms and comorbidity on cognitive deficits, as would be predicted from emerging transdiagnostic perspectives on mental disorders described above (Caspi & Moffitt, 2018; Abramovitch et al., 2021). Another risk factor for deficits is older age (Rock et al., 2014; Hasselbach et al., 2011), reducing improvement in cognition after treatment (Bernhardt et al., 2019), and late-life depression is more influenced by variables like comorbidity (Allot et al., 2016; Dotson et al., 2020). Thus, neuropsychological profiles in older groups are not directly comparable to that of younger patients (Bora et al., 2013). Younger age of onset could represent a risk for more severe deficits (Porter et al., 2015), and has been associated with more deficits in memory (Ahern & Semkovska, 2017), and switching (Goodall et al., 2018). Development of both MDD and EF occur early in life and could influence each other (Allott et al., 2016): Thus, following a group from their initial depressive episode, could inform on the development of residual cognitive symptoms relatively unconfounded by the risk of these factors. This could inform on the development of cognitive deficits as state, trait, or scar phenomena.

1.6.3 Deficits as state traits and scars

One way of understanding the development of residual cognitive symptoms is through the state, trait, and scar hypotheses. A seminal review by Hammar and Årdal (2009), stated that cognitive deficits are not mere epiphenomenal state effects caused

by depressive symptoms, a view commonly held earlier, but persist following remission, influencing everyday function, and risk for relapse. State effects are deficits caused by symptoms of MDD like low mood. Alternatively, or in addition, limited cognitive capacity could be taxed by depressive symptoms and rumination (Beevers, 2005). Larger deficits in the depressed state support this perspective (Ahern & Semkovska, 2017; Bora et al., 2013; Rock et al., 2014; Semkovska et al., 2019; Snyder, 2013). Correlations between deficits and symptoms are expected from this perspective, but findings are inconsistent (Dotson et al., 2020; McDermott & Ebmeier, 2009). The fact that deficits remain in remission supports the trait or scar perspectives, however. The former positing deficits before MDD, representing risk factors for the disorder (Allott et al., 2016). Deficits in relatives of patients could support a trait hypothesis, and emerging literature finds some evidence for this (Kjærstad et al., 2021; Mackenzie et al., 2019). The polygenic nature of EF reviewed above, could support it as a trait (Engelhardt et al., 2016; Friedman & Robbins. 2021). Cognition is also influenced by the environment. Scar effects could be one such influence. Here, it would be expected that deficits exacerbate with the length and number of episodes (Ahern et al., 2019; Hammar Ronold, et al., 2022; Peters et al., 2017), which could be caused by stress-induced neurobiological processes (Hasselbalch et al., 2011). Previous MDD severity could influence the size of cognitive deficits (Allott et al., 2016), and is suggestive of scar effects. Also, the number of episodes could represent severity. Semkovska and colleagues (2019) found that the number of episodes negatively influenced global cognition, attention, verbal fluency, and task shifting, but did not find an effect of subsyndromal MDD severity on cognitive function in remission. Interaction effects between age and the number of episodes cannot be ruled out (Bora et al., 2013), and age could mediate associations between depressive symptoms and cognition, as suggested by a meta-analysis by Dotson and colleagues (2020). These hypotheses could be investigated by longitudinal studies and have implications for understanding and treating MDD. In sum, the development of cognitive deficits in MDD is largely unknown, and state, trait, and scar perspectives could be utilized to understand the development of residual deficits.

1.7 Persisting cognitive deficits

The majority of studies on cognitive deficits in MDD have used cross-sectional designs. Longitudinal studies better grasp the development of cognitive functions following MDD and could shed light on the development and stability of deficits. Assessing cognition in remission could further illuminate the relationship between cognition, symptoms, and clinical outcomes. One early review done by Douglas and Porter (2009) investigated studies of patients following treatment of MDD. PS, memory, and verbal fluency improved with declining symptoms, while EFs remained impaired in remission. Hasselbach (2011) found improvements in motor speed to be the most pronounced in remission. A meta-study investigating the effects of psychopharmacological treatments on cognitive deficits found the most support for improved memory and verbal fluency, but little change in EF (Keefe et al., 2014). This was partly supported by a recent meta-analysis by Bernhardt and colleagues (2019), reporting that working- and verbal memory and verbal fluency improved, while PS, nonverbal memory, and EF improved less. Thus, there seem to be heterogenous findings regarding persisting deficits. This could be further clarified by examining a homogenous group from a long-term perspective.

1.7.1 Longitudenal studies of first episode MDD

Risk factors for cognitive deficits and a more severe course of illness could cumulate. Studying MDD from the first episode gives a unique perspective on the development of the disorder. One benefit of studying the population is that several of the risk factors discussed above are more homogeneous at first episode (Allott et al., 2016). The development of deficits and relevance for symptoms and relapse could be studied by following a group longitudinally (Douglas & Porter, 2009). Despite this, few studies have investigated first episode MDD longitudinally for any considerable length of time (Ahern & Semkovska, 2017). Thus, there is a need for longitudinal studies investigating potential risk factors in the remitted phase following first episode (Ahern & Semkovska, 2017; Allott et al., 2016), to enhance understanding of residual cognitive symptoms and identify targets for interventions to reduce the risk for new episodes. Previous studies of first episode MDD found deficits in EF and PS

both acutely (Schmid & Hammar, 2013b), and after one year, with associations between Inhibition/Switching and recurrence/relapse (Schmid & Hammar, 2013a). Thus, investigating first episode MDD over a long-term perspective could inform on the development of risk factors. These could be targeted by interventions, potentially reducing the alarming rate of relapse and recurrence seen in MDD.

1.8 Interventions targeting cognitive residual symptoms

Traditional treatments do not all cognitive residual symptoms. Miskowiak and colleagues (2015) suggested that common treatments improve some functions like emotional processing, but not completely. There seems to be agreement that deficits in hot cognition also persist in remission from MDD (Ahern et al., 2019). This, together with the fact that cold cognitive deficits appear to be undertreated by traditional interventions (Bernhardt et al., 2019; Groves et al., 2021; Keefe et al., 2014; Rosenblat et al., 2015), point to a need to target cognitive residual symptoms in remission from MDD with new interventions. One approach focusing on hot cognition is cognitive bias modification (Jones & Sharpe, 2017), targeting biased processing in MDD. Other approaches include drill and practice training of cognitive functions like WM (Koster et al., 2017), and learning strategies to compensate for deficits or improve cognition, termed cognitive remediation when a combination of these elements is included, and cognitive training when only the former is implemented (Vita et al., 2021). Motter et al. (2016) suggested computerized cognitive training as an intervention well suited for improving cognitive deficits following MDD and their meta-analysis found improvements in cognition and symptoms (but not EF). More recent meta-analyses on interventions targeting cognition have found improvements in both PS and to a lesser extent EF, with smaller effects on symptoms (Legemaat et al., 2021; Thérond et al., 2021. Optimal outcomes could be a consequence of the cognitive functions targeted by interventions. Manipulation of material in the short-term memory span (WM), could be important in this regard, due to its association with MDD (Baddeley, 2013), EF (Friedman & Robbins, 2021), PS, rumination (Zetsche et al., 2018), and daily function (Diamond,

2013). Thus, a standardized comprehensive WM training intervention could improve cognitive residual symptoms following MDD.

1.8.1 Computerized Working Memory Training

Computerized WM training (CWMT) targeting capacity for maintaining and manipulating information could improve cognitive functions, including control for emotional material and rumination (Koster et al., 2017; Launder et al., 2021; Zetsche et al., 2018). Thus, investigating outcomes from CWMT on broad aspects of residual cognitive symptoms in remitted MDD could improve knowledge about how to improve functioning following MDD. Several theories have placed WM as central to EF (Friedman & Miyake, 2017), and emotional regulation processes (Barkus, 2020; Zetsche et al., 2018). The originator of the WM concept suggested that negative feedback from dysfunctional hedonic set points represented in WM causes the symptoms of depression (Baddeley, 2013). Recent work has focused on how networks of EF relate to WM and the prefrontal cortex (Friedman & Robbins, 2021), and how this relates to emotional regulation. Cognitive control networks including the dorsolateral prefrontal cortex (DLPFC) are implicated in emotion regulation (Kohn et al., 2014). Given the DPFC role in MDD it could be targeted for interventions (Pizzagelli & Roberts, 2022). Training interventions targeting WM activate DLPFC (Ferrari et al., 2021; Constantinidis & Klingberg, 2016). Thus, enhancing WM functioning could potentially reduce the deficits in hot and cold cognition, depressive symptoms, rumination, and subjective cognitive deficits in remission from MDD.

2 Aims

The thesis aimed at understanding MDD from a long-term perspective and examining the development, clinical consequences, and associations between residual cognitive symptoms. In addition, outcomes from computerized cognitive training targeting working memory functioning (CWMT), were investigated. The aims were pursued through two studies: Study 1 investigated the long-term development of cognitive residual symptoms five years after the first episode of MDD. Study 2 investigated how CWMT could affect residual cognitive symptoms and associations between these.

2.1 Aims and research questions Paper I

Paper I investigated the development of cognition five years following first episode MDD. Speed of processing (PS) and EF were separated to examine where deficits were most pronounced, and if these functions were differentially related to symptoms and course of depression. Associations between PS, EF, symptoms- and course of depression were explored to investigate if deficits represented independent traits, associated states, or exacerbated as cognitive scars. The aims were to enhance the understanding of the development of cognitive deficits following MDD, from first episode over a long-term perspective, and how residual cognitive symptoms are associated and clinically relevant in remission. The following research questions were posed:

1) Which differences between patients and controls persist in PS, EF, five-years following first episode MDD?

2) Which associations between PS, EF, and depression supported the state, trait, and scar hypotheses?

2.2 Aims and research questions Paper II

Paper II examined WM processing of emotional stimuli (hot-cognition in e-WM). Differences in e-WM between the patient group and a healthy matched control group were examined cross-sectionally five years following the first episode of depression. This was done to examine deficits in hot cognition, and to investigate how e-WM was related to rumination. Associations between e-WM, rumination, and rates of relapse were investigated to examine how residual symptoms related to the course of illness following MDD. The following research questions were investigated:

1) Do patients and controls differ in e-WM performance?

2) Is rumination associated with e-WM and the rate of relapse?

2.3 Aims and research questions Paper III

Paper III investigated outcomes from computerized working memory training on residual cognitive symptoms in remission from MDD in a pre-post intervention design. Associations between cognitive functions and symptoms from Study 1 were pursued in a new population. The effects of working memory training on e-WM, PS, and EF and their associations to symptoms and depression history were investigated, and associations between improvements in CWMT and cognition were explored. This was aimed at informing on how to treat residual cognitive symptoms following MDD, potentially reducing risks for relapse. The following research questions were addressed:

1) Will there be associations between cognitive functions, rumination, and depressive symptoms pre-intervention?

2) Will CWMT effect EF, PS, e-WM, rumination, symptoms, and their associations?

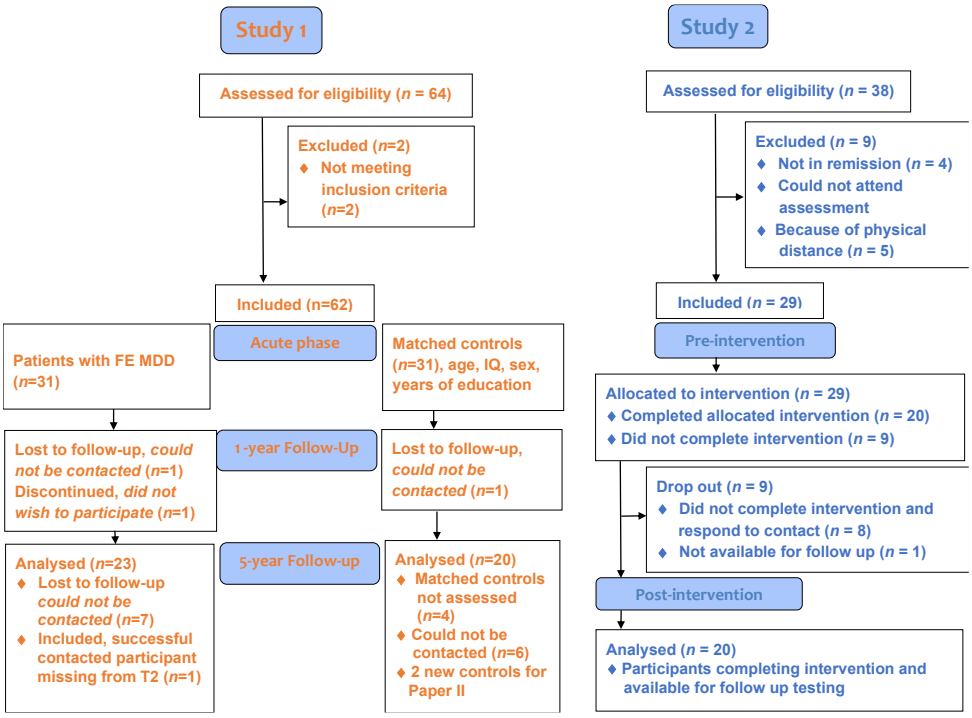
3 Methods

The thesis was based on data from two studies: Study 1 was a five-year longitudinal case-control follow-up study investigating cognitive functioning in patients after their first episode of MDD. After five years, convenience sampling of participants available for follow-up was implemented. The development of cognitive residual symptoms was investigated in the sample both longitudinally in Paper I, and cross-sectionally in Paper II. Study 2 (Paper III) was a pilot study investigating the effects of CWMT in remitted MDD through a pre-post exploratory open-label effect-study design. Hypotheses and statistics in Paper III were preregistered on the Open Science Framework before analyses were conducted (https://osf.io/vpxgw).

3.1 Participant flow

The studies had different participants, drop out, and follow up times (See Figure 1).

Figure 1. Participant flow.



3.1.1 Paritcipants Study 1

Participants in Study 1 were recruited through cooperation with general practitioners, student health care services, and newspaper advertisements (See Table 2 for demographic and clinical variables). Controls were recruited at the University of Bergen and through colleagues at the department where the study was conducted. The inclusion criteria for patients were receiving treatment for MDD for the first time. Exclusion criteria were neurological disorders, electroconvulsive therapy, substance abuse, psychosis, and severe somatic disorders. In addition, controls could not have experienced any psychiatric disorders.

Table 2.
Demographic and clinical variables in Studies 1 & 2

Groups (M/F)	Paper I and II: fDG *n* = 23 (11/12)	Paper I: CG *n* = 20 (9/11)	Paper II: CG + 2 *n* = 22 (10/12)	Paper III: rDG *n* = 29 (10/19)
Sample characteristics	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
Age	30.34 (5.74)	30.45 (6.09)	30.14 (6.09)	36.21 (10.9)
Education	15.34 (2.34)	16.6 (2.01)	16.48 (1.94)	16.53 (1.79)
IQ**	118.65 (8.47)	119.7 (8.27)	119.76 (8.32)	115.83 (8.06)
T2 RRS	45.49 (11.89 *n* = 22	***	***	**48.07 (13.48)
T3 RRS*	48.43 (13.31)	30.15 (9.74)	31.05 (9.61)	***
T2 RRQ *	44.90 (8.99) *n* = 20	30.26 (7.26) *n* = 19	***	**40.93(9.6)*n*=28
T3 RRQ *	42.13 (12.52)	32.40 (8.02)	***	***
T1 MADRS**	24.43 (3.8)	***	***	6 (4.35)*n*=28
T2 MADRS	10.27 (5.64) *n* = 22	***	***	***
T3 MADRS	8.87 (8.13)	***	***	***

Note. M = Mean, *SD* = Standard Deviation, M/F = Males/Females, fDG = First episode Depression Group, CG = Control Group, rDG = Remitted Depression Group, *n* = Number of participants, IQ (Wechsler Abbreviated Intelligence Scale at T1), RRS = Ruminative Responses Scale, RRQ = Rumination-Reflection Questionnaire (Rumination subscale), MADRS = Montgomery Åsberg Depression Rating Scale, *Significantly different between groups in Study 1 $p < .05$ ** Measured at inclusion, *** CG/rDG not assessed.

3.1.2 Participants Study 2

Study 2 had a sample of 29 remitted participants (See Table 2 for demographic and clinical variables). Twenty completed the intervention and were available for follow-up assessment. Recruitment was done from an outpatient clinic for mood disorders at Haukeland University Hospital, and through advertisements and previous projects. Exclusion criteria were significant depressive symptoms (>12 on The Montgomery Åsberg Depression Rating Scale), neurological disorders, substance abuse, and severe somatic disorders.

3.2 Overlapping Papers in Study 2

Paper III was based on a secondary analysis of a study by Hammar, Semkovska et al. (2022), with an extended sample. Paper III utilized the whole sample recruited for Study 2 and used different methods and research questions. Hammar, Semkovska et al. (2022) assessed the feasibility and acceptability of the CWMT intervention, before all data was collected (the study was published online in 2020), in addition to effects on cold WM, attention, inhibition, and rumination. In contrast, Paper III analyzed the investigated associations between residual cognitive symptoms, EF, PS, e-WM, and rumination pre-intervention, change post-intervention, and associations between improvements and depression.

3.3 Ethics and funding

Participants gave informed consent before participating in the studies and procedures were in accordance with the Helsinki Declaration of Ethical Research regarding Ethical Principles for Medical Research Involving Human Subjects. Study 1 (REK 2010/982), and Study 2 (REK 2014/1079), were approved by the committee for ethical research in Western Norway. Participants in both studies received a gift card valued at 400 Norwegian Kroner (approximately 50 dollars) after completing the study. Participants in Study 2 got access to the CWMT program free of charge. Study 1 was funded by the Research Council of Norway (NFR-contract 185712/V50) and Helse vest (project 911436). Study 2 was funded by the University of Bergen.

3.4 Measurements, procedure and intervention

Several clinical screening tools, self-report scales, neuropsychological tests, and an experimental paradigm were administered.

3.4.1 Clinical measures

Clinical measures were administered to patients by trained health care personnel for both studies.

Montgomery Åsberg Depression Rating Scale

The Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) was administered at inclusion in both studies, and at one- and five-year follow-up in Study 1. This is a scale for assessing the severity of depressive symptoms and is scored on a seven-point scale from zero to six (range 0-60). High scores indicated a high level of depression, and ≥ 20 were set as an initial inclusion criterion for Study 1, indicating ongoing MDD (Schmid & Hammar 2013b). MADRS ≤ 12 was the inclusion criteria for Study 2 indicating remission. Item 6 on MADRS assessed self-reported cognitive difficulties ("do you have trouble concentrating") and was used to assess subjective cognitive difficulties (Lengvenyte et al., 2020), in Paper III.

MINI International Psychiatric Structural Interview

Both studies used the Norwegian version of the MINI-International Psychiatric Structural Interview (MINI; Sheehan et al., 1998) at inclusion to assess exclusion criteria and comorbid diagnoses. Study 1 also employed this measure at five-year follow-up, allowing for comparisons of comorbidities over the five years. MINI is a structured clinical interview assessing psychiatric disorders according to DSM criteria and takes approximately 30-40 minutes to administer. A trained psychologist administered MINI in Study 1 while a trained psychologist or a psychiatric nurse administered MINI in Study 2.

The National Institute of Mental Health prospective Life Chart Methodology

In Study 1, the National Institute of Mental Health prospective Life Chart Methodology (Denicoff et al., 2000) was used to investigate whether patients had experienced relapse or recurrence since inclusion, in addition to number and length of depressive episodes. This measure was originally developed to assess frequency and polarity of bipolar episodes but was utilized for describing episodes of MDD in the thesis. Years and moths were represented on a horizontal x axis line, and episodes was graphed according to severity and length below the line on the y axis. A trained psychologist administered this measure at five-year follow up.

3.4.2 Self report

Depressive symptoms, depressive rumination and neurotic rumination were assessed by self-report in both the studies. The latter measures were also administered in controls in Study 1.

The Montgomery Åsberg Depression Rating Scale Self-report

The Montgomery Åsberg Depression Rating Scale Self-report (MADRS-S; Svanborg & Åsberg, 2001) was administered post-intervention in Study 2. This measure is comparable to other commonly used self-assessment scales for depression (Cunningham et al., 2011). Depressive symptoms are scored on a seven-point scale from zero to six (range 0-54). Subjective cognitive functioning was assessed by item 5 on this scale (with equal wording as MADRS above). A high score indicates a high level of depression.

Ruminative Response Scale

The RRS was used to measure depressive rumination. This scale was originally developed as a part of the measures in the response style theory (Nolen-Hoeksema, 1991). It was suggested as an automatic trait response to negative emotions associated with depression. The response styles questionnaire measures several aspects of rumination, but the RRS is the most used part of this questionnaire, and the most used measure of rumination overall (Watkins & Roberts, 2020), and in studies investigating rumination and cognitive functioning (Zetsche et al., 2018). Some authors have described that the RRS measure different aspects of rumination (Treynor et al., 2003); depressive-, reflective-, and brooding, with the latter purported to be the most pathological form of rumination (Watkins & Roberts, 2020). Some studies find few differences between the RRS and its subscales, however (Taylor & Snyder, 2021; Zetsche et al., 2018). Thus, the full score of RRS was utilized in both studies. The Norwegian version of the RRS consisted of 22 questions on a four-point likert-scale from 1 “almost never” to 4 “almost always” (22-88 range) and asked participants how much they ruminate when they are “feeling sad or depressed”.

Study 1 used this measure at one- and five-year follow-up, and Study 2 pre and post-intervention.

Rumination Reflection Questionnaire

The RRQ measured neurotic rumination. The RRQ was originally developed to measure how different emotion regulation strategies related to the big-five personality traits of openness to experience and neuroticism (Trapnell & Campbell, 1999). These traits are measured by the reflection and rumination part of the scale, respectively, with the latter being associated with psychopathology (du Pont et al., 2019; Zetsche et al., 2018). The rumination subscale from the Norwegian version of the RRQ (RRQ-rumination; hereafter RRQ) was used to measure neurotic rumination independent of depressive mood, since only the rumination part of the questionnaire is associated with negative outcomes. RRQ consists of 12 items with a five-point likert scale ranging from 1 “strongly disagree” to 5 “strongly agree” (12-60 range). This questionnaire has been surprisingly little investigated concerning associations with cognitive functions (Zetsche et al., 2018). Study 1 used this measure at one and five-year follow-up and Study 2 pre- and post-intervention.

3.4.3 Neuropsychological tests

Both studies employed similar neuropsychological tests of EF and PS. These measures were administered at the neuropsychological clinic at the University of Bergen by a trained psychologist or experienced test technician.

Wechsler Abbreviated Scale of Intelligence

The Norwegian version of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), was used in both studies to estimate IQ. WASI was used to control for differences in general intellectual ability between the first episode MDD group, and controls in Study 2. Study 2 used it to describe the sample and control for the effects of IQ, in addition, to controlling for attrition. WASI consists of two verbal ability tests, Similarities and Vocabulary, in addition to two performance ability tests, Matrices and

Block Design, adapted from Wechsler Adult Intelligence Scale-III. An estimated full scale IQ score was used combining scores from the verbal- and performance scores.

Delis-Kaplan Executive Function System

Clinical neuropsychological tests were used to measure EF and PS. Delis et al. (2001) Delis-Kaplan Executive Function System (D-KEFS) was used to measure EF and PS in both studies. The Color-Word Interference Test (CWIT), the Trail Making Test (TMT), and the Verbal Fluency Test (VFT) were used in Study 1, and the two former tests were used in Study 2.

Color Word Interference Test

CWIT is a reinterpretation of the classical Stroop paradigm (Stroop, 1935). The D-KEFS version of the Stroop paradigm includes four different tasks where participants verbally named (Color Naming) or read (Word Reading)-, named the ink of incongruent colored words (Inhibition), and switched between inhibition and reading (Inhibition/Switching) colors as fast as possible. Raw scores consisting of seconds to complete the task were used for all CWIT conditions, with high scores equaling low performance. The two first conditions of the CWIT measured PS. The Color Naming condition required the naming of red-, green-, and blue patches. The second condition, Word Reading, consisted of reading correspondingly written color words printed in black ink. These two conditions measure how fast different colors can be processed through naming or reading. Lezak (2012) described the word reading- and color naming conditions as sensitive to attentional deficits. PS and attention could thus be understood as closely related concepts and these two conditions could provide sensitive measures of PS deficits in MDD. CWIT also included the classical Stroop task measuring the EF Inhibition. Here, participants were asked to name the color of the ink of printed letters of an incongruent color word (Inhibition). For example, to name the red color of the printed letters used to type blue. Participants inhibited the automatic response of reading the colored word (blue) and instead named the incongruent color of the (red) ink the word was printed in. In the last condition, participants switched back and forth between the word reading and inhibition

condition, alternating between responding to incongruently printed colored words and reading words (Inhibition/Switching), and is a condition introduced by Delis et al. (2001). These two latter conditions measures the EFs inhibition and switching (Snyder et al., 2015). Inhibition is a heterogeneous concept and is sometimes separated into attentional- and response inhibition (Tiego et al., 2018), where the CWIT is conceptualized as the latter category. For the current thesis, inhibition refers to scores in condition 3 of the CWIT, which requires suppression of the automatic tendency to read words. Inhibition/Switching requires switching between reading and suppression and is understood as a measure of both cognitive flexibility/switching and inhibition. This latter condition, tapping into two concepts of EF could possibly be understood as a measure of general EF.

Trail Making Test

The D-KEFS TMT consists of five conditions requiring symbol searching (Visual Scanning), connecting sequential circles based on letters in sequential alphabetical order (Letter Sequencing), in increasing numerical order (Number Sequencing), by switching between connecting alphabetical and numerical circles in incremental order (Number-Letter Switching), and by swift filling of lines (Motor Speed). The tasks should be performed as fast and as accurately as possible, and raw scores consisting of seconds to complete the task were used for all conditions, with high scores equaling low performance. Traditionally, number sequencing has been known as TMT A, and Number- Letter sequencing as TMT B, and are understood as measures of PS and EF respectively. Tests measuring trail-making have long traditions as clinical neuropsychological tests, dating back to the American civil war (Lezak, 2012). The D-KEFS battery added Visual Scanning, Letter Sequencing, and Motor Speed conditions to the TMT, so deficits in subdomains could be assessed. Process scores controlling for either of these conditions are calculated to assess in which domain deficits manifest, potentially explaining deficits in the other conditions by motor slowing or visual difficulties. Visual Scanning, Letter Sequencing, Number Sequencing, and Motor Speed are usually understood as a test of visual scanning-, attention-, processing- and psychomotor speed. These conditions were a used as

measures of PS. The Number-Letter Switching condition of TMT was used to measure EF. More specifically, this condition has been associated with working memory and cognitive flexibility which both are considered EF (Lezak, 2012). Cognitive flexibility has been referred to as shifting or switching ability (Snyder et al., 2015; Friedman & Miyake, 2017), which is the term used in the thesis. Thus, TMT measured both PS and EF.

Verbal Fluency Test

The Verbal Fluency Test (VFT) was used in Study 1, and consists of three fluency tasks: Category, Letter, and Category Switching, where participants were instructed to name as many words as possible in a one-minute interval. Raw scores consisting of the number of words produced in one minute were used to measure performance, with high scores indicating high performance. The Letter Fluency conditions consisted of naming words from phonemes like "S". The Category Fluency conditions consisted of producing words from semantic categories like "animals". Finally, Category Switching involved alternating between generating words from two different categories. The VFT measures word-generating ability, PS, attention, retrieval, simultaneous processing, and verbal ability (Lezak, 2012). Category Switching is considered a measure of cognitive flexibility in addition to the abilities listed above (Delis et al., 2001). According to Snyder et al. (2015) these tests tap into many cognitive functions like semantic memory and verbal abilities, in addition to EF and PS. It is complicated to determine which specific cognitive functions are impaired when deficits manifest in these tasks and to separate EF and PS functions. Thus, this test was not used in Study 2.

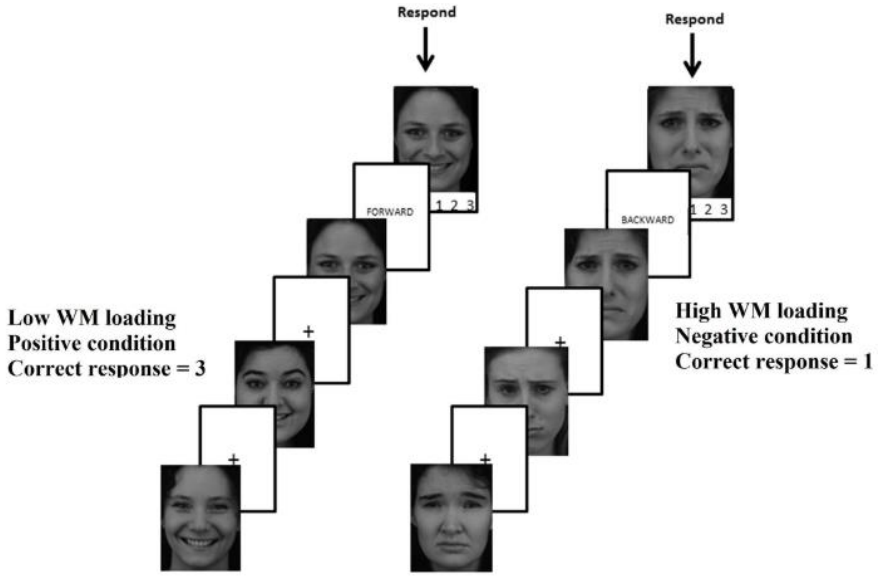
Error scores

The D-KEFS registers errors in each condition. For instance, a misread response to CWIT like reading "blue" instead of "green" result in an error. Similarly, failure to suppress an automatic response in reading a color word instead of naming the printed ink in the Inhibition condition would result in an error. This represented PS and EF errors respectively.

Contrast scores

Contrast scores for EF conditions were made to control for the influence of PS. The D-KEFS manual uses a process-, or contrast scores to control for the effects of cognitive functions like reading ability and motor speed (Delis et al., 2001). However, these scores are calculated by subtracting scaled scores from the normative material for the different conditions. Since the current thesis investigated raw scores in seconds, contrast scores were calculated from raw scores. The purpose of the contrast scores was to separate EF from PS. Thus, averaged lower condition scores were subtracted from the EF conditions to calculate EF contrast scores for TMT and CWIT in Papers I and III.

Figure 2. Illustration of the e-WM paradigm.



3.4.4 Emotional Working Memory paradigm

The e-WM paradigm was used in both studies. The paradigm is a modified version of a lexical task used by Joormann et al. (2011), with sad and happy faces instead of positive and negative words (See Figure 2 for an illustration of the e-WM paradigm). The paradigm used 40 black-and-white pictures of emotional faces retrieved from

The Karolinska Directed Emotional Faces stimuli set (Lundqvist et al., 1998). These consisted of male and female actors displaying sad or happy emotions. All pictures had the same probability of being presented across the conditions, except if they had been presented in earlier trials. The paradigm was administered through a laptop. Pictures were randomly sampled in E-prime (Version 2) from four lists of 10 pictures containing sad and happy male and female actors. In addition to the two valance conditions, there was a working memory manipulation: Picture sequences of three different sad or happy faces were followed by a cue to maintain the sequence in mind in either a forward low effortful (low WM loading) manner, or manipulate the sequence and hold it in mind a high effortful backward (high WM loading) manner. This is roughly comparable to the backward and forward span tasks, considered measures of WM and attention respectively (Snyder et al., 2015). Following maintenance or manipulation, one of the three faces from the sequences was presented, and participants were supposed to respond where in the sequence the face was placed by pressing the "1", "2" or "3" keys, as fast as possible. Thus, accuracy and response time for positive and negative low and high-loading stimuli was obtained. Paper II investigated both accuracy and response time, but only found differences for the former. Therefore, Paper III only investigated accuracy.

3.4.5 Computerized Working Memory Training intervention

Outcomes from CWMT were investigated in Study 2. Paper III investigated the outcomes of cognitive training on residual symptoms in remission from MDD. Cogmed ® working memory training (Pearson, 2022), was employed for this purpose. It is a computer-based program, delivered online, consisting of WM training on various tasks with incremental difficulty depending on past performance. Tasks consisted of number, letter, and spatial span, with forward and backward sequencing of strings of information with increasing length. The intervention consisted of 25 sessions, lasting approximately five weeks, with five weekly 30–40 minute sessions. There was weekly telephone contact between participants and a coach (trained psychologist/nurse, including the candidate), where progress, motivation, and questions related to the training were discussed.

3.5 Statistical analyses

Statistical Package for the Social Sciences (versions 20 and 25) was used for all statistical analyses. The significance level was set at $p \leq .05$ in all studies. Correlations and effect sizes were described as small, medium, and large, according to Cohen (1988). The statistical analyses used in the papers are presented below.

3.5.1 Statistical analyses Paper I

To investigate differences between patients and controls on demographical variables, symptoms, and the different D-KEFS conditions, one way ANOVA tests were used. Mixed-model ANOVA were conducted on the three D-KEFS tests and their conditions to measure differences in cognitive functioning and development of cognition between the patient group and controls over five years: Group was between groups factor, the follow-up time as a within groups factor, and the D-KEFS conditions was within groups factor. Change in cognitive function from one-year to five-year follow up was examined through paired sample *t*-tests. Mann Whitney *U*-test was used as a non-parametric alternative. Effect size measures (η^2) for Man Whitney *U*-tests were calculated through the following formula $Z^2/N-1$. McNemar's test assessed increases in comorbid diagnoses in the first episode group from the five years following MDD. Associations between depression and cognitive functioning were examined through bivariate correlational analyses Pearson's *r*, with Spearman's ρ as a non-parametric alternative. Change scores were calculated subtracting scores at five-year from scores at one-year follow up, so that positive values represented improvements in cognitive function. An EF contrast score was made by averaging and separating the EF and PS conditions of CWIT. Errors were registered in CWIT and sorted by EF and PS conditions and compared between groups. A composite score measuring severity of depression history was calculated from averaging *z*-score computations of the variables number of months depressed and the MADRS scores before the five-year follow up.

3.5.2 Statistical analyses Paper II

Paper II used independent t-tests to investigate differences in demographical variables. One-way ANOVA tests compared groups across the different conditions of

the e-WM paradigm. A linear regression model was used to predict depressive rumination (RRS) score. Pearson's *r* was used to investigate the associations between e-WM, rumination, and depression (MADRS score). Finally, logistic regression was used to predict participants that had relapsed during the five-years since inclusion, and a hierarchical logistic regression was used to compare models predicting relapse.

3.5.3 Statistical analyses Paper III

One-tailed significance levels were used to test pre-registered hypotheses. Bonferroni correction for analyses measuring changes on tests from pre to post intervention were calculated ($p = .05/16 = .003$). For non-parametric tests effect sizes were calculated from the formula $r = Z/\sqrt{}$ total number of observations. Pearson's *r* was used to investigate associations between cognition, symptoms, and CWMT improvements and changes in cognition and symptoms with Spearman's rank order correlation ρ was used as a nonparametric alternative. Changes following CWMT and attrition investigated by paired sample t-tests, with Wilcox Signed Rank Test as a nonparametric alternative. Improvement score for the CWMT intervention was calculated by subtracting starting performance score from highest performance score and dividing this by starting performance score. Change scores for cognitive tests, RRS, RRQ, and MADRS were calculated by subtracting scores from pre to post so that positive values indicated post intervention improvements. A depression history composite was calculated from z-transformed and averaged MADRS, depressive and neurotic rumination pre and post, MDD length in months, and number of MDD episodes.

4 Results

4.1 Results Paper I

A mixed between-within subjects ANOVA found significant main effects of group, on both CWIT $F(1, 40) = 13.55$ $p = .001$, and TMT $F(1, 40) = 6.53$, $p = .016$, while this main effect approached significance on the VFT $F(1, 40) = 3.48$, $p = .069$. A significant interaction effect of time and condition appeared for all tests $F(6, 35) = 3.99$ $p = .004$, $F(8, 33) = 5.12$ $p > .001$, $F(4, 37) = 2.93$ $p < .05$ respectively. There were no significant three-way interactions. Follow up tests revealed no significant changes in D-KEFS performance from one-year to five-year follow-up.

Table 3.
D-KEFS performance

Groups at T3 (M/F)	**Depression Group *n* = 23**		**Control Group *n* = 20**		**Statistics**		
D-KEFS Measure	*M* (*SD*)	Change Score from T2 *n* = 22	*M* (*SD*)	Change Score from T2	*F* (1,41)	*p*	eta sq.
Color Word Interference Test	***						
Color Naming	29.87 (4.68)	-.55	26 (4.63)	.5	7.37	<.01	.152
Word Reading	22.52 (3.3)	.5	18.9 (2.43)	.95	16.37	<.001	.285
Inhibition	48.04 (8.28)	-.95	41 (5.91)	.1	10.02	<.001	.196
Inhibition/Switching	56.13 (7.52)	-.41	48.65 (9.58)	-1.05	8.22	<.001	.167
Inhibition Contrast	21.85 (6.38)	-.52	18.55 (5.57)	-.625	3.13	.084	.071
Inhibition/Switching Contrast	29.93 (5.64)	-.52	26.2 (8.29)	-1.78	3.05	.088	.069
Verbal fluency	***						
Letter Fluency*	50.78 (11.48)	-1.27	55.2 (10.51)	-.4	1.71	.198	.040
Category Fluency*	48.48 (10.18)	.27	51.75 (9.68)	3.1	1.16	.288	.027
Category Switching*	14.96 (2.2)	.32	15.4 (2.32)	.65	0.41	.527	.010
Trail Making Test	***						
Visual Scanning	17.91 (4.5)	.5	15.25 (2.88)	1	5.15	.029	.112
Number Sequencing	24.04 (8.47)	1.95	17.3 (4.92)	2.55	9.78	.003	.193
Letter Sequencing	24.17 (8.95)	-1.5	17.2 (3.37)	2.55	10.78	.002	.203
Number Letter Switching	62.96 (18.95)	.045	50.1 (15.26)	2.65	5.88	.02	.126
Motor Speed	20.13 (9.68)	-.86	16.8 (5.02)	1.45	1.91	.174	.045
Contrast Number Letter Switching	41.39 (15.33)	.02	33.46 (14.43)	.76	3.02	.09	.069

Note. M/F = Males/Females, *n* = Number of participants, *M* = Mean (Seconds to complete task, except for Verbal Fluency), *SD* = Standard Deviation *High score= high performance in these conditions.

Most D-KEFS conditions differed significantly between the groups (See Table 3), except for the TMT motor speed condition, the VFT, and the EF contrast scores for TMT and CWIT. Groups differed in error scores for both the PS and EF conditions of

CWIT (no differences for VFT nor TMT), with largest effects in the latter, with the patient group committing more errors (*Mdn* = 2), compared to controls (*Mdn* = .50), Mann Whitney $U = 92$, $p = 0.001$, $\eta 2 = 0.286$. A composite score consisting of the EF conditions from CWIT also supported a difference in EF with the patient group showing higher (*Mdn* = 27.5) than controls (*Mdn* = 22.75) $U = 146.5$, $p = 0.023$, $\eta 2 = 0.099$. There were stable significant differences between the groups in rumination (See table 2). Comorbid psychiatric disorders increased from 16% at the acute phase to 48 % five years later, a significant increase according to McNemar's test, $p = .039$ (two-tailed). PS showed significant associations to depressive symptoms from $\rho = .341$ (not $p < .05$) to .528 ($p > .01$), for and CWIT Word and Color reading respectively. Category fluency showed a significant medium negative association to depressive symptoms $\rho = -.424$ $n = 23$, ($p < .01$). Inhibition appeared independent of symptoms and course of illness. Neurotic rumination showed medium non-significant associations to Inhibition/Switching $r = 0.34$, $n = 23$, $p = 0.112$ (two-tailed), and somewhat smaller associations to the contrast score. Both these conditions showed medium associations to the scar composite, with the contrast score showing largest associations $r = 0.486$ $n = 23$, p = 0.019 (two-tailed).

4.2 Results Paper II

Patients showed lower accuracy for the low WM loading maintenance positive condition $F(1, 43) = 8.558$, $p = .005$, and lower accuracy for the more effortful high WM loading manipulate condition for negative stimuli $F(1, 43) = 4.577$, $p = .038$, compared to controls. A linear regression model consisting of the two conditions above, explained 9.9% (Adjusted R squared) of the variance in RRS score, $F(2, 41) = 3{,}36$, $p = .044$. The high WM loading negative AC had greatest contribution to the model, approaching significance (beta = -.305 $p = .071$). This was supported by a medium sized negative correlation between RRS and the negative high loading condition $r = -.352$, $n = 45$, $p = .018$. A logistic regression model consisting of e-WM variables and RRS score predicted participants who had relapsed χ^2 (3, $n = 44$) = 24.38. $p < .001$. The model explained between 42.5% Cox and Snell R squared, and 57.7% Nagelkerke R squared of the variance in relapse, correctly classifying 81.8%

of participants. Here, RRS score was the only significant predictor with an odds ratio of 1.16.

Table 4.
Cognitive functions pre post intervention

Pre post groups (m/f)	**Pre** (10/19)	**Post** (8/12)			
	M (*SD*)	*M* (*SD*)	t/Z	*p* (one-tailed)	e. s.
e-WM*	***				
Low WM negative	66.2% (20%)	74.5% (17.5%)	Z = 2.143	*p* = .016	*r* = .378
High WM negative	62% (22.6%)	70.8% (17.9%)	t = 2.202	*p* = .022	*d* = .55
Low WM positive	65.2% (21%)	74.3% (20.9%)	Z = 2.55	*p* = .006	*r* = .45
High WM positive	64.7%(21.9%)	68.3% (13.7%)	Z = 2.045	*p* = .021	*r* = .361
Trail Making Test**	**				
Visual scanning	20.28 (7.755)	17.4 (5.413)	Z = 1.544	*p* = .062	*r* = .244
Number Sequencing	26.07 (8.606)	23.5 (8.935)	Z = 1.941	*p* = .026	*r* = .306
Letter sequencing	24.72 (9.42)	22.50 (10.08)	Z = 2.035	*p* = .021	*r* = .322
Number Letter Switching	69.03 (20.36)	55.8 (18.62)	t = 2.347	*p* = .002[b]	*d* = .748
Contrast LNS Switching	46.47 (17.24)	35.32 (15.69)	t = 2.908	*p* = .005	*d* = .65
Motor speed	19.17 (9.54)	18.50 (7.81)	Z = 1.246	*p* = .105	*r* = .197
Color Word Interference	**				
Color Naming	28.97 (4.45)	27.75 (5.24)	t = 2.666	*p* = .008	*d* = .596
Word Reading	21.45 (3.501)	20.95 (3.65)	t = 2.58	*p* = .009	*d* = .577
Inhibition	50.66 (10.25	44.05 (8.501)	t = 4.25	*p* < .001[b]	*d* = .95
Contrast Inhibition	25.44 (8.805)	19.70 (6.118)	t = 3.16	*p* = .003[b]	*d* = .706
Inhibition/Switching	53.45 (7.822)	49.1 (8.771)	t = 2.102	*p* = .025	*d* = .47
Contrast I/S	19.76 (7.135)	18.183 (5.557)	t = .536	*p* = .299	*d* = .120

*Means for the whole sample, pre n = 28 post n = 17, accuracy in percent ** Means for the whole sample, accuracy in seconds, high score = poor performance, LNS = Number Letter Switching, I/S = Inhibition/Switching. [b] significant after Bonferroni correction.

4.3 Results Paper III

There were no significant differences between participants that had dropped out and completers on demographic and cognitive variables. Pre intervention there was a medium correlation between the negative high WM loading condition and neurotic rumination r = -.381 n = 26 p = .028 (1-sided), while no other significant associations were found. Post intervention, there were large to medium improvements in PS, e-WM, and EF, with largest effects for the latter (See Table 4). Three conditions survived Bonferroni correction: Inhibition improved from pre (M = 49.1 SD = 10.25) to post, with significant improvement remaining in the Inhibition contrast score controlling for PS, from pre (M = 23.325 SD = 8.805) to post intervention. TMT Number Letter Switching, showed large improvements from pre-

(M = 71.75 SD = 20.36) to post intervention. Post intervention there was no longer correlation between e-WM and rumination. However, TMT number letter switching correlated with MADRS ρ = .331, n = 18, p = .090 (one-tailed), with the Switching contrast score showing a significant association ρ = .416, n = 18, p = .043 (one-tailed). Association between improvements in cognition, and improvements in CWMT, appeared for correlations to PS improvement scores on TMT visual scanning ρ = .419, n = 20, p = .033, (one-tailed), and letter sequencing r = .378, n = 20, p = .05 (one-tailed). For EF there was associations to inhibition-switching change score r = .469 n = 20, p = .018 (one-tailed). The depression severity composite showed negative correlations to change in Inhibition/Switching ρ = -.404, n = 16, p =.06 (one-tailed), with significant associations with the change contrast score in this condition ρ = -.499, n = 16, p =.024 (one-tailed).

5 Discussion

The main aim of the thesis was to investigate the long-term development of residual cognitive symptoms, and their associations with MDD, in addition to outcomes from an intervention targeting WM (CWMT). Cognitive functioning, rumination, depressive symptoms, and course of illness were investigated longitudinally, e-WM cross-sectionally, and associations between cognition and symptoms were investigated both longitudinally and pre- post the intervention. Two studies were conducted, resulting in three papers. Findings suggested stable cognitive deficits in both PS and EF, associations between PS and depressive symptoms, EF and course of MDD, and deficits in effortful WM processing of negative material associated with rumination, with rumination predicting relapse. CWMT improved cognitive functioning with the largest effects for EF, but symptoms did not improve. These findings relating to the main aims of the thesis, and to the research questions from the papers will now be discussed.

5.1 Long term development of cognitive functining

Findings suggested stable cognitive deficits following the acute phase of the first episode of MDD, with the largest deficits in PS. Deficits in low effortful maintenance (low WM loading) of positive stimuli, and high effort manipulation (high WM loading) of negative stimuli manifested cross-sectionally after five years.

5.1.1 Which deficits persisted in EF and PS?

Patients showed stable deficits on neuropsychological tests five years following their first depressive episode, as hypothesized. This is in line with previous long-term investigations of cognition following MDD (Årdal & Hammar, 2011), and similar to effects found in meta-studies investigating deficits in remission (Bora et al., 2013; Hasselbalch et al., 2011; Semkovska et al., 2019). Findings converge with the literature on first episode MDD (Ahern & Semkovska, 2017; Lee et al., 2012). Notably, PS has been proposed as explanatory for most cognitive deficits in MDD (Porter et al., 2015; Semkovska et al., 2019). Controlling for PS, small to medium

deficits were found on EF contrast scores, although these were not significantly different, probably due to low power. Notably, significant medium-sized deficits for overall EF and errors in EF (on the CWIT), supported deficits relatively independent of PS. Thus, findings supported both a processing speed- and a cognitive effort perspective (Nuño et al., 2021), and the conclusions in a meta-study on deficits in EF in MDD (Snyder, 2013). Thus, both EF and PS likely influence the cognitive profile following MDD (Porter et al., 2015). Recent studies have suggested that decreased response times (Semkovska et al., 2019), or lack of motivation (Abramovitch et al., 2021), could explain EF deficits in MDD. Psychomotor retardation, a melancholic depressive symptom, could contribute to this. However, there were no significant differences in motor speed in Study 1, suggesting that response time was insufficient in explaining deficits. This is like the meta-analytic findings of Rock et al. (2014), which reported no differences in simple response times in MDD. Thus, results did not support the motor slowing hypothesis (Snyder, 2013), and arguably this condition would be sensitive to motivational difficulties, and results run contrary to the notion that lack of motivation could explain deficits in MDD (Abramovitch et al., 2021), although these hypotheses were not explicitly tested. Consequently, more cognitively demanding tasks were necessary for deficits to manifest. In addition, the verbal fluency test no longer significantly differed between groups at five years follow-up. There is some support in the literature for the normalization of verbal fluency following MDD (Douglas & Porter, 2009; Bernhardt et al., 2019). The complex nature of the tasks (Snyder et al., 2015), made it difficult to determine to what degree EF or PS deficits contributed to this. In sum, differences in cold cognitive functions persisted but did not exacerbate.

5.1.2 Did patients and controls differ in e-WM performance?

Deficits in hot cognition manifested cross-sectionally five years following the first episode of MDD. Specifically, groups differed in accuracy for e-WM for low WM-loading positive, and high WM-loading negative stimuli as expected. Deficits could represent a bias in the cognitive processing of emotional material, including a lack of positive processing bias (LeMoult & Gotlib, 2019), and a deficit in cognitive control for negative stimuli (Ahern et al., 2019; Johnson et al., 2020). Findings supported

reduced cognitive control for negative material in WM, which has been proposed as a clinically relevant deficit (Joormann & Stanton, 2016). This was further supported in the present thesis finding associations between e-WM and rumination. In addition, deficits in the processing of emotional facial stimuli could influence social and interpersonal functioning (Bourke et a., 2010), and might have relevance to the deficits in social cognition reported in MDD (Cotter et al., 2018). Thus, bias in processing and cognitive control of emotional facial stimuli warrants further research in relation to depressive symptoms, cognitive and social functioning. In conclusion, deficits in hot cognition contributed to the cognitive profile in MDD.

5.1.3 The cognitive profile in MDD

The thesis supported lasting but relatively stable deficits in both EF and PS, and the presence of deficits in hot cognition five years following first episode of MDD. Thus, the description made by Veiel (1997) in the first meta-analysis of cognitive deficits in MDD was supported: "consistent with a global-diffuse impairment . . . with particular involvement of the frontal lobes" (p. 587). The former could be translated to PS, the latter to EF, and these basic functions likely impact most other cognitive deficits seen in MDD, like memory problems and indecision. This should be taken into consideration when reporting on cognitive functions in psychiatric disorders like MDD (Porter et al., 2015; Snyder et al., 2015). Persisting deficits have consequences for daily functioning (Hammar & Årdal, 2009), relapse (Buckman et al., 2018), and symptom development (Allott et al., 2016). EF and PS deficits likely interact with deficits in hot cognition, which could influence symptoms (Ahern et al., 2019). However, these processes are not well established, and the associations between hot and cold cognition and symptoms should be pursued by future research.

5.2 Associations between cognition, symtoms and course of MDD

Relapse and comorbidity rates following the first episode of MDD were considerable in a long-term perspective. Speed of processing was associated with MDD symptoms, suggestive of state effects. EF showed mixed associations to symptoms and course of illness that could be more associated with trait or scar effects. Deficits in the effortful

processing of negative material were associated with rumination in both studies. There were some inconsistencies in associations between PS and depressive symptoms in the studies, however, that will be discussed below.

5.2.1 Course of illness in a long term perspective

The rates of relapse and comorbid disorders during the five-year follow-up were alarming. Seventy-four percent of patients in Study 1 experienced one or more episodes of relapse or recurrence. This is like other studies (Mueller, 1999), and runs contrary to the notion that only half of the patients will experience relapse after their initial episode (Eaton et al., 2008; Ormel et al., 2022). Findings suggested that MDD is more of a relapsing recurring disorder than not. Increases in comorbid disorders suggested that comorbidity is considerable in MDD and could be the rule rather than the exception (Caspi et al., 2020; Kotov et al., 2017), if follow-up time is sufficient (Moffitt et al., 2007). Findings should be interpreted with caution, however, due to the small size and drop-out rates. Participants with less severe courses of illness could be more unlikely to participate in follow-up assessments. However, arguing for new interventions including prevention strategies with a focus on avoiding relapse and comorbid disorders is feasible following first episode MDD. Targeting cognition should be part of this (Miskowiak et al., 2022), but other residual symptoms like anxiety, worry, and rumination should also be considered (Buckman et al., 2018; Taylor & Snyder, 2021; Zetsche et al., 2018). Findings illustrated that a long-term perspective gives broader insights into how MDD develops and that preventative strategies following the first episode MDD are needed. Associations between cognitive functioning and symptoms in remission could influence the course of illness and represent potential targets for interventions.

5.2.2 Associations between PS, sypmtoms and course of illness

There was some support for state effects on PS. Findings suggested that the deficits seen in the acute phase of first-episode MDD (Schmid & Hammar, 2013b), improved (Schmid & Hammar, 2013a), but remained significantly different from matched controls five years later. Larger deficits in the acute phase are in line with several studies investigating first-episode MDD (Ahern & Semkovska, 2017; Lee et al.,

2012; Liu et al., 2021), and depression in general (Bora et al., 2013; Dotson et al., 2020; Douglas & Porter, 2009), and suggests state effects. There were medium associations between depressive symptoms, PS, and category fluency, in Study 1. This is like other studies finding associations between the depressive state and psychomotor speed in first episode MDD (Ahern & Semkovska, 2017; Lee et al., 2012), and links between symptom severity and PS (Lee et al., 2015; McDermott & Ebemeier, 2009; Nigg et al., 2017; Ronold et al., 2021). Since the association between PS and depressive symptoms did not manifest in Study 2, caution when interpreting results is warranted. The strictly remitted sample in Study 2, and the lack of variance in symptoms, could explain inconsistent findings, however. Associations between PS and depression increase with age (Dotson et al., 2020), and PS shows age-related decline (Salthouse, 2009). Thus, associations with depression could increase later in life due to brain aging (Caspi et al., 2020; Morris et al., 2021), and PS deficits could be mediated by some of the neurobiological state effects described in the introduction. In sum, there was partial support for associations between depressive symptoms and PS suggestive of state effects. However, these might vary with regard to the population being researched, and homogeneous samples with some degree of symptomatology might be needed in future studies of state effects.

5.2.3 Associations between EF, symptoms and course of illness

EF showed trait effects. Following the acute phase, deficits remained stable which supports trait or scar effects. Thus, deficits were apparent from first episode MDD, and could even have manifested before this, as suggested by a trait perspective (Abramovitch et al., 2021; Allott et al., 2016; Hammar, Ronold et al., 2022). There were associations between EF, rumination, and the course of illness. In Paper I, Inhibition/Switching showed associations with both neurotic rumination and a scar composite score. Neurotic rumination was associated with the scar composite, potentially suggesting neurotic trait vulnerability for a more severe course of MDD. Thus, EF deficits could be related to both a more severe course of illness and neurotic rumination. Previous research supported this, where an Inhibition/Switching contrast score predicted relapse at one year follow up in first episode MDD (Schmid & Hammar 2013a). Associations between neuroticism and EF have also been found in

healthy populations (Murdock et al., 2013), and could be larger in samples with MDD. Thus, EF could be associated with MDD through traits like neuroticism, with trait permanence suggested by the high heritability estimates for the latter (DeYoung et al., 2002), and brain structures associated with EF (Friedman & Robbins, 2021). McDermott and Ebmeier (2009) suggested that longitudinal measures of depressive symptoms could show even larger relationships to cognitive functioning. Since inhibition was independent of symptoms and course of illness in both studies, the association between depression and EF could be more related to other specific aspects of EF. Findings were only partly replicated in Study 2, where the association between switching and depressive symptoms emerged only after the intervention for TMT, in addition to less improvement in Inhibition/Switching for participants with more severe MDD history. Recent studies have suggested that deficits in switching could be related to depression severity (Liu et al., 2021), and this should be investigated further. However, prospective studies are needed for clarification of when deficits occur, if they cause MDD (trait), or result from it (state/scar).

5.2.4 Limited support for scar effects

Participants did not show decreased cognitive function, contrary to the scar hypothesis. Since deficits could have manifested through a stressor simultaneous with- or before the onset of MDD, as supported by neurobiological models for stress and cognitive deficits (Hasselbalch, 2015; Sapolsky, 2004), the current study design was unable to disentangle such effects. If deficits are exacerbated by episodes, however, more pronounced deficits in cognition would have been expected in the patient group, especially since the majority of the group had experienced one or more episodes over the five years. Scar effects might take decades not years, however. This is supported by stronger relationships between symptoms and deficits in older individuals (McDermott & Ebemeier, 2009; Dotson et al., 2020), which suggest cumulative effects of depression on cognition. State effects on cognitive function might ultimately become cognitive scars through the inflammation/stress/brain aging processes described previously, and age could be a moderator in this process. Thus, older populations might be more suitable for testing the scar hypothesis. This is important because of the association between MDD and Alzheimer's (Livingston et

al., 2020). Thus, the association between MDD and cognitive decline warrants more research, and interventions to prevent cognitive decline are crucial for future healthcare needs.

5.2.5 Is rumination associated with e-WM and rate of relapse?

Rumination predicted relapse in Study 1, and there were significant associations between rumination and effortful emotional working memory processing of negative stimuli in both studies, as predicted. This is similar to Joormann et al. (2011), where difficulties in WM processing of negative material were related to depressive rumination. Both studies in the thesis found similar negative medium-sized inverse correlations between effortful manipulation of negative material in WM and rumination, suggesting that rumination increases as the accuracy for manipulation of negative stimuli decreases. Thus, a deficit in the manipulation of negative material in WM could contribute to rumination. Recent meta-analyses found no effect on valence on the associations between EF and rumination (Vălenaș & Szentágotai-Tătar, 2017; Yang et al., 2017; Zetsche et al., 2018), however, but heterogeneity was considerable in the analyses. Aspects of cognitive control that are not precisely captured by classical tests of EF could explain some of the mixed findings (Snyder et al., 2015). Neuropsychological tests were designed to detect brain pathology (Lezak, 2012), and not establish relationships between cognitive functioning and symptoms (Snyder et al., 2015). More sensitive, valanced experimental paradigms, could better detect associations between cognition and symptoms. This was supported by a recent meta-study by Zetsche et al. (2018), suggesting that discarding from WM is the cognitive function most related to rumination. The clinical relevance of hot cognition was further supported by a recent meta-analysis suggesting that training hot cognition reduces symptoms to a larger degree than interventions targeting cold cognition (Socially et al., 2022). Thus, there likely exists a complex sequential relationship between hot cognition, cognitive deficits, and the development and maintenance of depressive symptoms (Ahern et al., 2019). Understanding the cognitive mechanisms behind rumination, or how cold deficits become hot, could have implications for preventing rumination and thus relapse and recurrence of MDD. Rumination was a predictor for relapse. The effects were small, but comparable to other studies (Aker et

al., 2014), and supported rumination as a considerable residual symptom with regard to relapse risk following MDD, in concordance with several studies (Buckman et al., 2018; de Klerk-Sluis et al., 2021; Figueroa et al., 2019; Jandric et al., 2021; Nolen-Hoeksema et al., 2008; Taylor & Snyder, 2021; Timm et al., 2017). However, depressive rumination and neurotic rumination could differentially relate to cognitive functions and the course of illness, suggesting that different forms of rumination should be investigated in future research on emotional regulation and relapse risk. Since both types of rumination were persistently relatively high in both studies, interventions reducing rumination after depression are needed.

5.3 Outcomes from computirized WM training in remission from MDD

Improvements in tests of EF, PS, and e-WM were following the intervention. Effects were the largest for EF. Associations between e-WM and ruminations disappeared following the intervention. Depressive symptoms and rumination, however, were unchanged.

5.3.1 Will WM training improve EF, PS and e-WM?

There were improvements in cognitive functioning following CWMT as expected. PS showed small to medium-, e-WM medium-, while EF small to large improvements, similar to effects reported in recent meta-analyses of studies targeting cognition in MDD (Legemaat et al., 2021; Thérond et al., 2021). Inhibition showed the largest improvements following CWMT, and only EF remained significantly improved when adjusting the significance level for multiple comparisons. Interestingly, a recent meta-analysis of meta-analyses by Abramovitch and colleagues (2021), found that inhibition was the most impaired cognitive function in MDD, even more so than in schizophrenia. Thus, improved inhibition could be particularly clinically relevant for MDD (Joormann, 2010; Snyder et al., 2015), albeit this did not manifest in the current sample with regard to self-reported symptoms or rumination. Inhibition is the EF most associated with the common EF factor (Friedman & Miyake, 2017), and improvements might thus generalize to other aspects of functioning. Perhaps more selected samples, longer follow-up times, and broad measures of everyday

functioning could reveal more positive effects of CWMT. Improved outcome measures could shed light on the clinical relevance and ecological validity of improved EF following CWMT, and should be implemented by future research to best capture outcomes from interventions targeting cognition.

5.3.2 Will CWMT effect residual cognitve symptoms and their associations?

There were no changes in depressive symptoms or rumination following CWMT. The former could be because of floor effects, or low initial levels. Several meta-analyses support this and find largest improvements in depressive symptoms are seen in samples with high initial levels (Legemaat et al, 2021; Sociali et al., 2022). Despite the disappearance of associations between e-WM and rumination, and improved e-WM post-intervention, rumination scores did not improve. If there is a causal relationship between e-WM deficits and rumination, it might take a longer time for improvements manifest, however. Hammar, Semkovska et al. (2022) found that depressive rumination improved in a subgroup of participants, that also showed improvements in WM, thus improvements could manifest in subgroups following CWMT. A recent randomized controlled trial of cognitive training as an add-on to depression treatment found no improvements in rumination nor depression (Ferrari et al., 2021). The association between lower improvements in Inhibition/Switching and depression history could imply that intervention in the early course of illness is best for optimal gains from CWMT. It is possible that the Inhibition/Switching capture the common aspects of EF to the largest degree, given that two functions are tapped in this condition, and it is the most cognitively demanding task (longest mean RT; Delis et al., 2001). Thus, the negative association of improvement score on this task, and the composite for depression, could suggest that participants with more depression history show less EF improvement, and might potentially benefit from intervention modification or other interventions like cognitive bias modification. Thus, subgroups could differ in the effectiveness of cognitive remediation interventions, with various timing and implementation, and length or type of intervention as potential moderators of optimal effect (Motter et al., 2016). Targeted treatments, not just for subgroups with MDD, but also for critical periods through the lifespan and course of illness, could probably be important in preventing the development of MDD (Allott et al.,

2016). Thus, timing and finding the individualized/subgroup interventions that are most effective are important for future research on interventions targeting residual cognitive functions.

5.4 Summary of discussion related to main aims and research questions

Cognitive functioning did not decrease five years following the first episode of MDD. Deficits manifested in both EF and PS, and these functions seem to relate differently to symptoms and course of illness, with the former more associated with the depressive state, and the latter as more of a trait. A deficit in hot cognition, namely difficulties in effortful manipulation of negative material in WM, was related to rumination. Rumination was stable and relatively high in remission and represented a risk factor for relapse. Recurring episodes seem to be a norm rather than the exception following the first episode of MDD. Finally, while cognitive deficits in MDD improved following CWMT, other residual symptoms did not change. These findings are not necessarily generalizable to everyone with a history of MDD, however. Thus, several limitations in methods and design could impact the reliability and validity of the findings and will be discussed in the following section.

6 Methodological considerations, strenghts and limitations

Several aspects of the methods used in the studies in the present thesis should be discussed with regard to strengths and limitations of current findings, and their validity.

6.1 Sample characteristics

Samples in both studies were well selected and assessed which is a strength. In addition, matching for Study 1 included a relatively comprehensive measure of intellectual functioning and years of education, which did not significantly differ between the groups. This is a strength compared to other studies where differences in IQ/education between patients and controls could influence results (Vicent-Gil et al., 2018; Ahern & Semkovska, 2017). The samples were also relatively balanced by sex (Study 2 only at posttest), rare in studies of MDD, a disorder that has a higher occurrence in females (Snyder et al., 2013; Aker et al., 2014). There could be differences in test performance related to sex (Semkovska et al., 2019). The first-episode group had lower age of onset compared to other samples investigating first-episode MDD (Roca et al., 2015), and age (of onset) could impact depression severity and cognitive deficits (Allott et al., 2016; Goodall et al., 2018; Porter et al., 2015), and thus contribute to the generalizability of findings. The strengths of clinically relevant, relatively balanced samples with comprehensive assessments, came at the expense of a small sample size, however. Deficits were not used as inclusion criteria in the studies. Both these aspects were limitations. Using some sort of impairment or deficit as an inclusion criterion could be important for the optimal effects of cognitive training (Lengvenyte et al., 2020; Miskowiak et al., 2022), and for identifying associations between symptoms and cognition (Zetsche et al., 2018). The lack of cognitive deficits as inclusion criteria in the studies could thus influence both external and internal validity. Larger deficits and associations between symptoms and cognitive functioning could perhaps have been found, and possibly even larger improvements manifested with different inclusion criteria.

6.1.1 Dropout

Dropout is an issue in all studies of some length and can influence internal and external validity. In Study 1, there was a larger dropout in the control group, suggesting that clinically unrelated factors influenced dropout. Alternatively, participants in the control group could have developed psychiatric disorders. Many participants in both studies were students, and some relocated during the follow-up period, which accounted for some dropouts. No attrition analyses were reported for Study 1 which is a limitation. Attrition analyses in Study 2 suggested that there were no significant differences in demographics, cognitive functioning, or symptom load in dropouts. Some did not have time to complete the five-week intervention during their busy lives. Despite no significant difference, attrition effects cannot be ruled out. However, dropout was comparable to other studies (Douglas & Porter, 2009; Legemaat et al., 2021). Internal validity was influenced by dropout through smaller sample size and statistical power, and external validity could be compromised by potential attrition effects.

6.1.2 Comorbidity

Comorbidity could have influenced results. Comorbidities could be central moderators for a more severe course of illness (Buckman et al., 2018), cognitive and functional deficits (Lyche et al., 2010; Lyche et al., 2011), and studies suggest that a majority with MDD will have anxiety disorders during their lifetime (Caspi et al., 2020; Kessler et al., 2003), as was indicated by the increase in comorbidities in Study 1. This moderator is receiving increased attention through emerging transdiagnostic perspectives (Caspi et al., 2018; Kotov et al., 2020). Study 2 did not report comorbidity, which was a limitation. Sample size and power confounded the degree to which this could be used as a moderator in the present studies, however. Exploratory investigations suggested subgroups with more severe courses of illness showing different cognitive deficits (Ronold et al., 2021). Thus, subgroups could show different cognitive profiles, courses of illness, and treatment responses. A limitation of the present thesis is that moderators and mediators could not be studied further, and this should be pursued by future studies with a larger sample size.

6.1.3 External validity

The investigation of participants experiencing their first episode of MDD could have influenced generalizability to populations with more recurrent depression. The size of deficits (Semkovska et al., 2019), relapse (Mueller, 1999), and comorbidity rates (Caspi et al., 2020), were like those seen in the literature, however. All patients in Study 1, and the majority in Study 2 were outpatients. Thus, generalizability to inpatient populations might be limited. Inpatient status is associated with a more severe course of illness and larger cognitive deficits (Burt et al., 1995; Douglas et al., 2018; Lee et al., 2012; McClintock et al., 2010; Porter et al., 2007). Results in Study 2 could probably not be generalized to populations with ongoing MDD due to the remitted nature of the sample. Thus, participant characteristics must be considered when interpreting the results from the thesis.

6.2 Ecological validity

The clinical relevance of cognitive deficits and improvements were not assessed with regard to measures of everyday functioning. Effect sizes of deficits in MDD are generally small to medium in magnitude (Semkovska et al., 2019), which is like the size of improvements following interventions targeting cognition in populations with histories of depression, as suggested by the most recent meta-analyses (Legemaat et al., 2021; Thérond et al., 2021; Woolf et al., 2021). What clinical relevance does half a standard deviation group difference infer for the individual? The present thesis cannot answer this. One can speculate that a few seconds (roughly equaling the size of deficits in Study 1) subtracted from every 30 seconds while conducting everyday tasks, adds up in the months and years following MDD. Some indication of the ecological validity of improvements from the intervention can be found in other studies. Notably, Hammar, Semkovska et al. (2022) found that all but one participant reached one or more defined goals following training and that the intervention had high acceptability. Self-reported cognition in Study 2 did not show any improvements, however. This is contrary to Lengvenyte et al. (2020), who found improvements in self-reported residual depressive symptoms, daily functioning, and concentration, in a similarly remitted sample, although with bipolar disorder, using

the same intervention. Their study used “cognitive impairment” as inclusion criteria, however. Thus, not establishing clear benefits of training improvements in the daily lives of participants, in addition to associations between cognitive deficits and daily functioning, is a limitation of the current studies, and reduces the ecological validity of the present findings.

6.3 Strengths and limitations of design

Some noteworthy aspects of the design might have influenced the validity of the present results. Firstly, there some noteworthy strengths should be considered. The long-term follow-up time was a considerable strength in Study 1. Five years is the longest follow-up of cognitive functioning in the first episode MDD in the published literature, as far as the author is currently aware of. Thus, at least speaking to the relatively young and educated outpatient sample in the present thesis, cognition does not appear to worsen five years following first episode MDD. Pre-registration was a strength in Paper III and is considered good practice in psychological science. However, preregistration was done after data was collected which is a limitation.

6.3.1 Internal validity

The lack of a control group was perhaps the largest limitation in Study 2. Therefore, training effects (getting better at the tests) cannot be ruled out. Improvements in cognitive functions post-intervention were generally larger than retest or training effects found in the literature (Scharfen et al., 2018), however. There were some associations between improvements in the intervention and improvements in PS and EF suggesting effects of training. Regardless, placebo- or expectancy effects cannot be ruled out, and studies with active control conditions find the smallest effects of cognitive remediation interventions (Legemaat et al., 2021). Small sample sizes and overestimations of effect sizes (von Bastian et al., 2022), partly due to expectancy effects caused by difficulties with blinding of studies (Barkus, 2020), have been suggested as central problems in the cognitive training literature in general. Thus, a small sample and lack of a control group are limitations, and future research should implement procedures controlling for expectancy effects, like randomization and

active control groups when comparing effects when investigating interventions targeting cognition.

6.4 Measures of cognition and contrast scores

Only a limited number of cognitive domains were assessed. Thus, some important deficits and associations with clinical variables could have been missed in the current studies (Hammar, Ronold et al., 2022; Semkovska et al., 2019), which is a potential limitation. Controlling for the effects of PS on EF should be considered a strength, however. Contrast scores have been found to lack reliability and subtracting two scores result in increased measurement error in the final score by combining the error in both scores (Hedge et al., 2018). By averaging the PS scores subtracted from the EF scores, this could have been somewhat mitigated, by averaging out measurement error. Snyder (2013) suggested using a ratio contrast score, while others suggest regressed contrast scores (Hedge et al., 2018). Given the small sample sizes in the studies, more advanced statistical methods were deemed unfeasible, however. Contrast scores used were a limitation but should be considered superior to not dealing with the task impurity effects in EF tasks at all. Snyder et al. (2015) suggested structural equation models as ways to separate different cognitive functions and investigate relationships between symptoms and cognition. This requires large sample sizes, unfeasible for most clinical studies. Future research should pursue large samples with statistical power to separate cognitive functions statistically. The e-WM intervention was a novel measure of hot cognition, and the validity and reliability of the task are not well established, which could be a limitation. Similar results across studies are strengths, however, and diverse paradigms are a limitation in the literature on hot cognition in general. Standardization and repeated administration of paradigms in clinical populations could result in more consistent findings, as evident in the current thesis, which could be considered a strength.

6.4.1 Ratings and self report measures

Several validated measures of psychiatric symptoms were utilized in both studies. Measuring two forms of rumination was a strength of the current studies. Study 2

used MADRS-S at follow-up, which could have influenced the associations between symptoms and cognition. Associations between cognitive measures, self-report- and behavioral ratings are notoriously small (Snyder et al., 2020), however, with some authors suggesting that self-reported difficulties are considerably influenced by depressive symptoms (Serra-Blasco et al., 2019). The extent studies targeting cognitive deficits contribute to everyday functioning has been questioned (Simons et al., 2016). Thus, implementing ecologically valid outcome measures in studies could better assess the effects of interventions targeting cognition and could be important to utilize in future research.

6.5 Statistical validity issues

Several aspects of statistical analyses used could have influenced the internal validity and reliability of findings and their generalizability. A small sample size is mostly responsible for this and could lead to not detecting significant effects (type 2 errors), preventing the utilization of statistical methods that infer causality, and thus the inability to explore important questions regarding associations between cognition and symptoms in remission from MDD. No a-priori power analyses were conducted for the studies, and the studies were underpowered for detecting small effects. In addition, the samples were too small for multivariate designs to be reliably implemented. A minimum of 80% chance of detecting differences has been proposed as an adequate level of power (Cohen, 1992). This can be hard to attain in clinical longitudinal and intervention studies with dropout. Thus, small effects, like for instance cognitive scarring or relationships between EF and rumination could have been missed. However, the clinical relevance of such small associations could also be questioned (Jacobson & Truax, 1991). A small sample size could influence the reliability of correlation coefficients (Schönbrodt & Perugini, 2013), and this could be relevant in the present thesis since state effects from Paper I did not manifest in a new sample in Paper III. Due to multiple comparisons, the current thesis is at risk of making type-1 errors. Correcting for *p*-values was partly implemented, however. Some authors have suggested that this approach might be too strict (Nakagawa, 2004), especially for studies with low power, and conflate the risk for type-2 error

(failing to reject a false null hypothesis). It could be argued that for the first five-year follow-up study of cognitive functioning in first-episode MDD, and when investigating outcomes from a novel intervention for remitted depression, not reporting significant findings is a greater danger than type-1 errors. Novel findings, without support in the literature, should be considered preliminary until replicated, however.

6.5.1 Causation, correlation, mediation and moderation

Given the methodological limitations in the current studies, causality could not be reliably inferred. Thus, the correlations of the studies cannot infer causal relationships. Associations between deficits symptoms and the course of illness could be causally related in either direction. E.g. rumination could lead to increased relapse risk, but relapse could also lead to increased rumination. The change scores in Paper III did not control for the correlated nature of pre- and post-scores, and mediation and moderation analyses would have been more accurate (Hayes & Rockwood, 2017), and should be implemented in future studies investigating the direction of training effects and relationships between cognition and depression. Statistical measures assessing directionality could better assess the causes and consequences for residual cognitive symptoms in remission from MDD (Snyder et al., 2015; Hedge et al., 2018), and should be implemented in future longitudinal studies. Thus, small sample size is a limitation in the present thesis concerning moderators and mediators, and larger samples should pursue subgroup analyses. The ability to assess possible risk factors was limited in the present thesis. However, measuring and reporting on risks like comorbidity could be considered a strength in Study 1.

6.6 Intervention

The choice of intervention could have influenced the results. The thesis implemented a commercial “brain-training” intervention. These have been widely debated, with critics claiming that the producers promise more than they can deliver (Shipstead et al., 2012). Specifically, the degree that improvements in working memory training generalize beyond trained tasks, termed far transfer, has been questioned (Melby-

Lervåg et al., 2016). Despite this, the intervention fulfilled several important aspects of what is thought to optimize effects like length, frequency, and therapist support (Miskowiak et al., 2022; Motter et al., 2016; Vita et al., 2021), and focus on remediating cognitive deficits, which is a considerable strength (Simons et al., 2016). The intervention had potential limitations, however. One possible limitation is that digital interventions could be perceived to come at the expense of getting help in person. While this is a danger in the current environment focusing on reducing costs, there currently are few, if any, interventions available in remission from MDD. As mentioned initially, traditional treatments have limited effects on residual cognitive symptoms. Future studies should continue to develop and test interventions aimed at reducing residual symptoms.

6.7 Ethical considerations

Assessing potentially depressed participants comes with ethical implications. Participants could be suicidal or in need of treatment and excluding participants with depressive symptoms from Study 2 was potentially problematic. Cooperation with health care services and good research procedures, however, facilitated routines for follow-up and referral for participants in need of treatment. Another ethical issue was offering an intervention without established evidence for efficacy following MDD. The intervention and assessments were time-consuming, and the outcomes were not certain. On the other hand, the intervention was one of the most researched working memory training programs available (Simons et al., 2016). Using a commercially available intervention could be ethically problematic if this is proclaimed as being superior to other less costly alternatives, however. Even though participants were compensated, this was small compared to the time used. However, participants got free access to the intervention and could get a neuropsychological assessment and report of their cognitive function by a neuropsychologist if requested. In conclusion, the studies tried to address potential ethical issues and were conducted in concordance with national and international ethical research guidelines.

6.8 Clinical implications and suggestions for future research

Several clinical implications could be drawn from the present thesis. Firstly, cognitive residual symptoms persisted onwards from the first episode of MDD but did not worsen over a five-year period. Cognitive deficits showed different associations with symptoms and course of illness. Secondly, rumination was a considerable residual cognitive symptom related to relapse. Thirdly, the increase in comorbid disorders was of notable concern following the first episode MDD. Thus, targeting residual cognitive symptoms including anxiety and rumination in remission could be important. Residual cognitive symptoms represent risk factors, and some of these were remediated by CWMT, but there are likely individual factors influencing manifestations and treatability of residual cognitive symptoms that warrant further research.

6.8.1 Rumination, a stable residual risk factor

Levels of rumination were comparable between the patients in Study 1 and 2, even though participants in these studies were partly-, and fully remitted, respectively. Levels of rumination were over one and a half standard deviations higher than that seen in the control group in Study 1 (See table 2). Furthermore, the high correlation between rumination and depressive symptoms in Study 1 suggested that there is a considerable association between depression and rumination when the variance in depressive symptoms is higher, which is also supported in meta-studies (Zetsche et al., 2018). Perhaps associations to both symptoms and cognition are dynamic, relative to mood state, and cause and maintain depressive symptoms throughout the course of illness (Watkins & Roberts, 2020). Rumination, and its higher-order component repetitive negative thinking (Taylor & Snyder, 2021), has been suggested as transdiagnostic risk factors for psychopathology in general (Watkins & Roberts, 2020), and depression in particular (Baddeley, 2013; Nolen-Hoeksema, 1991). Rumination shares many risk factors with MDD (Watkins & Roberts, 2020), and is supported as a trait-like residual cognitive symptom and risk factor in the remitted phase of MDD. Thus, rumination is an important function to target with treatments and other interventions before, during, and after depressive episodes.

6.8.2 Optimizing interventions in remission

Some clinical advice related to the present findings could be to screen for and treat residual cognitive functions following MDD, with a particular focus on rumination. Could a poor understanding of psychiatric disorders be the cause of the treatment-prevalence paradox? This thesis suggests that the majority of MDD cases remit and that at least half develop comorbid disorders. This could support some of the notions of transdiagnostic models concerning comorbidity, concurrency, and sequentially manifesting disorders (Caspi et al., 2014). An important implication of this is that remission is a period worthy of treatment and interventions. Cognitive deficits and biases, rumination, and personality traits like neuroticism could be targets for relapse prevention, and interventions effective in altering these variables should be developed and utilized. Social contact and therapeutic interventions like psychoeducation are important mediators for optimizing the effects of interventions. Bridging, strategies for implementing trained skills in everyday life, is important and could enhance the effects of interventions (Woolf et al., 2021; Motter et al, 2016). More knowledge about optimal efficacy and implementation of interventions for residual cognitive symptoms should be pursued. Sequencing treatment interventions and identifying critical periods for prevention could be a way to combat the treatment-prevalence paradox. Studies on how participants experience interventions could increase the understanding of the acceptability and effectiveness of interventions and could be useful for the future development of preventative strategies (Myklebost et al., 2022). Also, studies of subgroups with a higher degree of cognitive deficits might be important to gain more knowledge about how residual cognitive symptoms influence patients in their daily life, uncover knowledge about the nature of deficits and identify potential new avenues for interventions and treatment.

6.8.3 Improving measurement issues in MDD research

A standardization of cognitive measures used in psychiatric research could be important for clarifying the cognitive profile in MDD. Many studies label tests differently, thus contributing to the mixed findings regarding which cognitive domains are mostly affected by depression (Porter et al., 2015). There is some truth to the discrepancies in labeling however, as different tests measure several cognitive

functions (Snyder et al., 2015). A standardized battery for assessment of cognitive functioning in MDD, like the MATRICS initiative for schizophrenia (Green et al., 2004), could perhaps decrease the variability of reported findings. However, the heterogenous nature of MDD, and the complexities of residual cognitive symptoms, could limit the degree to which this approach would be useful. Standardization of paradigms measuring hot-cognition and the use of selected samples could also result in more consistent findings. Some authors call for more experimental paradigms as more sensitive measures of EF, and hot-cognition-EF paradigms could show larger associations to symptoms or deficits (Friedman & Robbins, 2021; Snyder et al., 2015). Using empirical models for cognitive functions could help organize findings. The Cattell-Horn-Carroll model of cognitive functioning could be one approach for unifying data regarding cognitive deficits in MDD and psychiatric disorders (Jewsbury et al., 2016; Webb et al., 2018). These efforts require large samples, however, that could be hard to muster in single clinical studies. Multisite studies, standardization, and data sharing could facilitate this, and could be necessary to establish the cognitive profiles in MDD.

6.8.4 Residual cognitive symptoms as disorder general or disorder specific

Increasingly, transdiagnostic research suggests that disorder general- rather than disorder-specific effects might account for residual cognitive symptoms (Abramovitch et al., 2021; Friedman & Robbins, 2021; Johnson et al., 2020; Snyder et al., 2015). Thus, future testing of transdiagnostic models could be important for understanding cognitive deficits and developing treatments and prevention strategies. General deficits suggest transdiagnostic causes or consequences, while smaller specific deficits could relate to MDD (Kotov et al., 2017). The heterogeneous nature of MDD allows for both of these possibilities to be true. The link between cognitive deficits and risk factors like hot cognition, neuroticism, rumination (or repeated negative thinking) and relapse risk, should be pursued by further research. Intervention targeting trait deficits and risk factors in MDD, and other psychiatric disorders should be developed and implemented. How persisting cognitive deficits following MDD could represent the *p* factor (Abramovitch et al., 2021), is still largely unknown. Future research should look at cognitive deficits and risk factors

from a trans-diagnostic perspective to infer to what degree these are general or specific for MDD, and tailor interventions and treatments accordingly.

6.8.5 Prospective longitudenal studies of risks for MDD

Prospective longitudinal multilevel transdiagnostic studies could inform on risk factors for who gets MDD, benefit from treatment and interventions, and what the critical periods for the development and efficient targeting of residual symptoms are. This is crucial for future research endeavors. Prospective longitudinal studies could also inform om the trait and scar hypotheses (Allott et al., 2016). Focus on life course outcomes could be important, given that depression at different ages could be associated with different outcomes and risk factors. Lifetime longitudinal investigation might be necessary for scar effects to manifest. Thus, optimizing prevention interventions and cognitive enhancement could be important for healthy aging (Woolf et al., 2021), and preventing potential scar effects should be of the utmost importance, together with preventing relapse and new episodes of MDD.

7 Conclusions

The main findings of the thesis are that cognitive deficits in speed of processing and executive functions remain, but appear to be stable, five years following first episode of MDD. Deficits show different associations with MDD with the former being more state-related and the latter more trait-related. Relapse and comorbidity are common following MDD in a long-term perspective. Rumination is a risk factor for relapse in remission from MDD and is associated with effortful working memory processing deficits for negative material. This association disappeared following a working memory training intervention. In addition, both hot and cold cognitive functions improved following the intervention. Interventions targeting residual cognitive functions in remission from MDD are needed. However, future research should optimize interventions for remission and relapse prevention following MDD.

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9 Papers

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frontiers in Psychiatry

ORIGINAL RESEARCH
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A Longitudinal 5-Year Follow-Up Study of Cognitive Function After First Episode Major Depressive Disorder: Exploring State, Scar and Trait Effects

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Major depression (MDD) is associated with cognitive deficits in processing speed and executive function (EF) following first episode (FE). It is unclear whether deficits are state or trait related. Studies following FE MDD over longer periods are lacking, making it uncertain how cognition and symptoms develop after the initial episode. The present study assessed cognitive function and symptoms 5 years following FE MDD. In addition, the study explored relationships between MDD symptoms, rumination, and cognitive deficits with regards to the trait, state, and scar perspective. Twenty-three participants with previous FE MDD, and 20 matched control participants were compared on Delis-Kaplan Executive Function System measures of processing speed and EF, in a 5-year longitudinal follow-up study. Correlations between current symptoms- and history of MDD, rumination, cognition were investigated. Findings indicated that cognitive deficits persisted with no clear signs of exacerbation after initial episode. Inhibition appeared independent of current and previous symptoms of depression. Processing speed was related to depressive- symptoms and rumination. In conclusion, results indicated persisting, stable deficits in both EFs and processing speed. Findings further suggest that depressive symptoms could be related to deficits in processing speed, indicating state effects. There was limited support for worsening of cognition after initial episode. Some aspects of EF like Inhibition could show persistent deficits independent of depressive symptoms indicating trait effects.

Keywords: major depression and executive dysfunction, first episode major depressive disorder, processing speed, risk factors, rumination, state, trait, scar

INTRODUCTION

Major Depressive Disorder (MDD) is one of the most prevalent and taxing disorders worldwide (1). Recurrence following first episode MDD are of particular concern (2), with estimate rates up to 90% in health care seeking individuals (3). Recurrence leaves patients with higher disability, lower quality of life, affecting everyday functioning (4, 5), and could be incremental (6, 7).

Residual symptoms are important risk factors in recurrent MDD (8). Cognitive deficits persisting in remission (9–11), could contribute to relapse, recurrence, and impaired daily functioning in MDD (12–14). However, the literature is mixed regarding whether deficits in executive- (15–17), or lower cognitive functions persist in remission (11, 18). Hierarchical organization of neuropsychological function implies that lower processing tasks are the foundation of higher cognitive functions like EF (19). Thus, separating EF from processing speed, seems to be important when investigating cognitive deficits following MDD (20, 21). How EF and processing speed relate to other residual symptoms and risk factors in remission from MDD is uncertain (22, 23), however.

Not everyone with MDD shows cognitive deficits (24). Differences in risk factors for cognitive deficits could help explain this, and include: depression status (9, 10, 15, 25), depressive symptoms (26), number- and length of episodes (11, 27), comorbid disorders (19, 20, 28, 29), rumination (30). In addition, comorbidity (31), and rumination [for a recent review see (32)], have been associated with a more severe course of illness. According to Allot et al. (22) development of both MDD and EF occur in parallel in adolescence and early adulthood. Thus, following a group of young adults from FE MDD reduces risk factors and moderators like age (33, 34). Moreover, longitudinal studies investigating FE MDD over longer periods in remission are lacking (23), precluding how cognition develops following FE MDD.

Many central issues regarding the neurocognitive profile in MDD can be illustrated by the state, trait and scar debate [for a discussion see (23, 35)]. *States* can be understood as deficits caused by-, and fluctuating with-, depressive symptoms. There are mixed findings regarding state effects on EF (11, 17, 26). Findings are also mixed regarding processing speed (11, 25), but most authors seem to find a relationship to depressive symptoms or status (15, 26, 36, 37). *Scars* are neurobiological changes due to previous depression or environmental stressors. Scarring could include length, number, and severity of MDD, resulting in exacerbated cognitive impairment (22). Neurobiological changes could also increase risk for further episodes of MDD (7). In addition to this, common treatments could mediate changes and further alter neurocognitive function (25, 38). Scarring effects could be investigated through the relationship between previous MDD duration and symptom severity, and later cognitive function (22). Semkovska et al. (11) found number of episodes negatively influenced attention, processing speed, verbal fluency, and task shifting, supporting scar effects. When manifested as *traits,* impairments are independent of scars and current symptom states, predating FE MDD. There seems to be most agreement on persistent deficits in EFs (15, 25, 36, 39), with mixed findings regarding verbal fluency (15, 25, 36, 39).

The current study was a 5 year longitudinal study, investigating EF, inhibition, working memory/mental flexibility, and verbal fluency, in addition to motor- and processing speed. Previous studies investigating the FE group found deficits in EFs and processing speed in the acute phase- (40), and 1 year following FE MDD (41). (41) found lasting impairments in the EF tasks Inhibition/Switching and verbal fluency. The current study investigated if deficits and symptoms persisted or normalized, after 5-years. In addition, the trait, state, and scar perspective were utilized in exploring the findings. To the authors knowledge, this is the first study to measure cognition in a group with FE MDD over 5 years. Consequently, the study could contribute to an increased understanding of the longitudinal development of cognitive residual symptoms and course of illness following FE MDD. The following hypotheses were investigated:

1) We predict that cognitive deficits persist after 5 years, and that a group with previous FE MDD will differ from a matched control-group, on tests measuring both processing speed and EFs.

2) It is expected that cognitive deficits and rumination related to depressive symptoms at time of assessment could represent state effects. Cognitive deficits and symptoms related previous length and strength of depression, worsening over time, could represent scar effects. Cognitive deficits that are relatively stable and independent of current- and previous symptoms of depression, could represent traits. EF is suspected to be relatively independent of state and scar effects, and a relationship between EF and rumination is expected. Processing- and motor speed are suspected to be influenced by depressive state and scar effects.

MATERIALS AND METHODS

Design

This longitudinal 5-year case control follow-up study examined a group with FE MDD and matched controls. There were three points of assessment: Participants were assessed at baseline in the acute phase of MDD (T1), after 1 year (T2), and after 5 years (T3). For additional information, see **Figure 1**.

Recruitment and Participant Flow

Participants in the depression group (DG) were recruited from primary healthcare and student healthcare services in Bergen, Norway. Participants were informed about the ongoing study through the cooperation of physicians and psychologists in primary- and university healthcare clinics. A study coordinator contacted interested patients that met the inclusion criteria at T1. Initial inclusion criteria were current FE depression of a moderate- to severe degree, indicated by a score of $\geq$20 on the Montgomery Åsberg Depression Rating Scale [MADRS; (42)]. Initial exclusion criteria for the DG were earlier history-, treatment-, or diagnosis of depression. Exclusion criteria for all participants in the DG from T1, T2, and T3 were the following: Psychosis, electroconvulsive treatment, alcohol- or substance abuse, brain damage, neurological- or severe somatic disorder. A trained psychologist assessed exclusion criteria at each time point by a structured questionnaire (T1, T2, and T3), and The Norwegian version of Mini-International Psychiatric structural interview [MINI; (43)] for the DG (T1 and T2). A control group was recruited, individually matched on the following variables: Sex, age, and years of

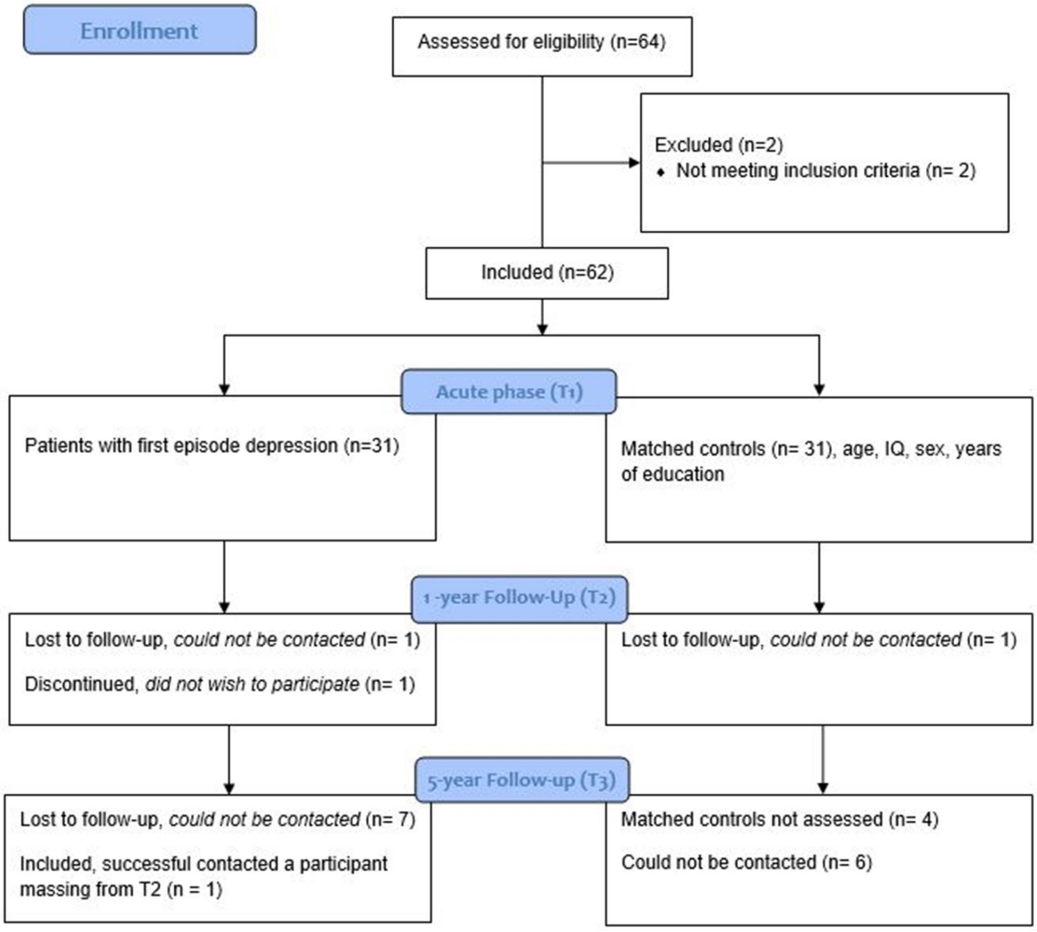

FIGURE 1 | Participant flowchart.

education (±2 years), and the matching was valid at T3 (see **Table 1**). Controls were recruited at the University of Bergen and through colleges at the Department of Biological and Medical Psychology. Exclusion criteria for controls were: History of any mental disorder, alcohol- or substance abuse, brain damage, neurological- or severe somatic disorder, measured by a structured questionnaire designed for the study (at T1, T2, and T3). All participants were invited to a 1-year follow up assessment (T2) at T1. At the 5-year follow up assessment (T3), participants were contacted by mail and invited to take part in the study. Dropouts were largely participants that the study was unable to contact due to expired contact information, and participants that had moved away (see **Figure 1**).

Clinical Assessments and Rumination Measures

Clinical assessments were made by trained psychologists. MINI was used to assess history of psychiatric disorders in the DG at T1 (version 5.0), and at T3 (version 6.0). All in the DG met DSM-IV criteria for MDD as measured by MINI. Depressive symptoms were measured by MADRS at all time points. At T3 a retrospective assessment of relapse-, recurrence, and duration of MDD was done using the National Institute of Mental Health's Life Chart Method [NIMH LCM; (44)]. The LCM was used to measure relapse and asses months of depression in the DG since T2. Relapse was defined as reporting one or more depressive episode since T2. Structured interviews were done in the DG assessing exclusion criteria, the use of psychotropic medication

and psychological treatment. Controls were not assessed by clinical interviews or MADRS, as psychiatric disorders were exclusion criteria in this group.

Both the DG and controls completed self-report assessments of depressive- and neurotic rumination at both T2 and T3. Depressive rumination was measured by the Norwegian version of the Ruminative Responses Scale [RRS; (45)], a 22 item four point likert questionnaire that measures ruminative responses to depressive mood. The Norwegian version of the 12 item five point likert rumination subscale of Rumination-Reflection Questionnaire (RRQ) measured rumination independently of depressive mood. This form of self-rumination is associated with the personality trait neuroticism (46, 47). At T2 RRS was only administered to the DG. RRQ was administered in both groups at T2 and T3 (see **Table 1**).

Clinical Profile

Participants differed in how their course of illness developed following FE MDD. At T3 symptom severity as measure by MADRS ranged from not depressed <12 (n = 16), to mild- 12–22 (n = 5), and moderate symptoms 23–29 (n = 2) as indicated by the Norwegian MADRS manual (48). Seventeen patients had one or more episodes of relapse (74%) between T2 and T3. Almost half of the group (n = 11) had histories of comorbid psychiatric symptoms as assessed by MINI at T1 and T3, hereunder: Generalized Anxiety Disorder, Panic Disorder With- and Without Agoraphobia, Agoraphobia, Obsessive Compulsive Disorder, and Social Phobia. There were no instances of exclusion criteria as assessed by MINI; neither Psychotic Disorder nor Alcohol- or Substance Abuse. At T3 four patients were using psychotropic medication: One was currently using a Selective Serotonin Reuptake Inhibitor medication (SSRI: Escitalopram), while two were using Selective Serotonin-Noradrenalin Reuptake Inhibitors (SNRI: Venlafaxine). Finally, one participant was prescribed a sedative (Chlorprothixene: Truxal). The same patients were also receiving psychological treatment and outpatient psychiatric follow up. One patient was currently in psychotherapy, while three were in contact with the District Psychiatric Center for outpatient follow up of psychotropic mediation and/or psychotherapy (see **Table 1** for more clinical characteristics).

TABLE 1 | Demographics and clinical measures.

Demographics and clinical measures for T3 groups (M/F)	Depression group n = 23 (11/12)	Control group n = 20 (9/11)
	M (SD)	M (SD)
Age	30.34 (5.74)	30.45 (6.09)
Education	15.34 (2.34)	16.6 (2.01)
IQ[a]	118.65 (8.47)	119.7 (8.27)
Age of onset MDD	25.61 (5.73)	
T2 RRS[b]	45.49 (11.89) n = 22	
T3 RRS***	48.43 (13.31)	30.15 (9.74)
T2 RRQ***	44.90 (8.99) n = 20	30.26 (7.26) n = 19
T3 RRQ***	42.13 (12.52)	32.40 (8.02)
T1 MADRS[b]	24.43 (3.8)	
T2 MADRS[b]	10.27 (5.64) n = 22	
T3 MADRS[b]	8.87 (8.13)	
Months depressed since T2	12.60 (14.45) n= 21	

M, Mean; SD, Standard Deviation; M/F, Males/Females; n, Number of participants; IQ, Intelligence Quotient. [a]measured at inclusion [***]Significantly different between groups p < 0.001, RRS, Ruminative Responses Scale; RRQ, Rumination-Reflection Questionnaire (Rumination subscale); MADRS, Montgomery Aasberg Depression Rating Scale; [b]CG were not assessed.

Ethics and Compensation

All participants gave informed consent to participate in the study. Participants received a gift card valued at 400 Norwegian Kroner (∼50 United States Dollars) for their participation. The study was approved by the Regional Committee for Medical and Health Research Ethics and was performed in accordance with the World Medical Associations Declaration of Helsinki regarding Ethical Principles for Medical Research Involving Human Subjects (49).

Neuropsychological Assessment

Neuropsychological testing took place at the University outpatient clinic for neuropsychology at all points of assessment. Experienced test technicians did the neuropsychological assessment. IQ was measured at inclusion (T1) by Wechsler Abbreviated Scale of Intelligence [WASI; (50)]. Participants completed a battery of standardized neuropsychological tests at all time points. EF and processing speed were assessed by Delis et al. (51) Delis-Kaplan Executive Function System (D-KEFS). Three subtests from the battery were investigated: The Color Word Interference Test (CWIT) measuring processing speed, inhibition, switching and general EF (21), the Verbal Fluency Test (VFT), and the Trail Making Test (TMT) measuring motor- and processing speed, as well as switching (52). See **Supplementary Materials 1** for description of tasks.

Contrast-, composite-, and error scores were computed based on descriptions in the D-KEFS manual (51), and previous studies (41). Contrast scores were made to separate EFs from processing speed, subtracting the Color Naming and Word Reading conditions from the Inhibition- [Inhibition Contrast = Inhibition – (Color Naming + Word Reading)/2], and Inhibition/Switching conditions [Inhibition/Switching Contrast = Inhibition/Switching – (Color Naming + Word Reading)/2]. An EF composite score was for the CWIT overall by separating the processing speed- from the EF conditions [CWIT Executive function composite = (Inhibition + Inhibition/Switching)/2 – (Color Naming + Word Reading)/2]. To separate processing speed and lower cognitive processes from EF, contrast scores for TMT Number-Letter Switching were calculated [Contrast Number-Letter Switching = Number-Letter Switching – (Visual Scanning + Letter Sequencing + Number Sequencing + Motor Speed)/4]. Error scores were pooled for the different D-KEFS tests. In addition, CWIT error scores were pooled to represent executive dysfunction in the Inhibition and Inhibition/Switching conditions, and processing deficits in the Color Naming and Word Reading conditions.

Data Scoring and Analysis

All statistical analyses were performed in Statistical Package for the Social Sciences (SPSS version 25). Raw scores, that consisted of seconds to complete task (CWIT, TMT, high score = poor performance), and words generated per minute (VFT, high score = good performance), were used for the neuropsychological tests. Variables were plotted and checked for linearity and outliers. Outliers were inspected and determined to represent real scores and not errors. Normality was assessed using Kolmogorov-Smirnov test of normality and non-parametric tests were used when assumptions were violated. Cohen (53) was used to describe effect sizes as small, medium and large.

Differences Between the DG and Controls in Cognitive Function Over Time

Mixed between-within subjects ANOVA was used to calculate differences between groups in cognitive function and change over the three points of assessment (Group × Time × D-KEFS conditions). Box's test of equality of Error Variance and Mauchly's Test of Sphericity was performed and Multivariate statistics reported when the latter assumption was violated. Levenes test of Equality of Error Variances was performed for all ANOVA analyses, and Welch values given when this assumption is violated. One participant in the DG was only available at T1 and T3 and was thus missing from the Mixed between-within subjects ANOVA, and other analyses containing data from T2 (see **Figure 1**). Groups at T3 were compared by one-way analysis of variance (ANOVA) on matched variables and clinical measures. Mann Whitney *U*-tests were used to assess differences between groups on non-parametric data, and independent samples chi square tested for categorical variables. Change scores were calculated by subtracting D-KEFS scores at T2 from D-KEFS scores at T3. Negative values implied decreased performance over time (with the exception of VFT, were the opposite was the case). Paired sample *t*-tests were used to assess changes on D-KEFS by comparing scores from T2 to scores from T3 in the DG, and the control group.

Separating EF and Processing Speed

One-way ANOVA analyses were used to investigate differences between groups on the different D-KEFS conditions and contrast scores at T3. Man Whitney *U*-tests were used to assess error scores and the CWIT EF composite score. Effect size measures (η^2) for Man Whitney *U*-tests were calculated through the following formula ($\eta^2 = Z^2/N\text{-}1$).

Traits, States, and Scars, Relationships Between Depression, Rumination, and Cognitive Function

Bivariate correlation coefficients were calculated to explore relationships at T3. The relationship between symptoms of MADRS, RRS, RRQ, and D-KEFS scores was investigated. Spearman's Rho was used as a non-parametric alternative to Pearson's correlation coefficients when assumptions for the latter were not met. To separate depressive state (MADRS T3) from scar effects, an explorative composite score consisting of a standardization (Computed in SPSS) of number of months depressed (*Z*-score months depressed), combined with standardized MADRS scores *before* T3 (T1, T2) were calculated: Scar composite = (ZMADRS T1 + ZMADRS T2 + Zmonths depressed)/3.

RESULTS

Matching of Groups

Groups did not differ significantly ($p > 0.05$) on any of the matched variables sex, age, and years of education, nor in IQ (see **Table 1** for means and frequencies).

Differences Between the DG and Controls in Cognitive Function Over Time

Mixed between-within subjects ANOVA found a significant interaction effect for Time × Condition in all D-KEFS tests (see **Table 2**). Means indicated that scores from T1 improved. A lack of a Time × Condition × Group interaction supported that improvements did not differ between groups, and that

TABLE 2 | Cognitive differences between groups over time.

			Main effects			Interaction effects		
		Group	Condition	Time	Time × group	Time × condition	Condition × group	Time × cond. × group
CWIT	Wilk's λ		0.035	0.501	0.918	0.594	0.869	0.910
	$F_{(df)}$	13.55 (1, 40)	347.96 (3, 38)	19.34 (2, 39)	1.75 (2, 39)	3.99 (6, 35)	1.906 (3, 38)	0.58 (6, 35)
	Partial eta-sq.	0.253	0.965	0.131	0.082	0.406	0.131	0.090
	F-sig.	$p = 0.001$	$p < 0.001$	$p < 0.001$	$p = 0.188$	$p = 0.004$	$p = 0.131$	$p = 0.74$
VFT	Wilk's λ		0.035	0.772	0.968	0.759	0.918	0.971
	$F_{(df)}$	3.48 (1, 40)	534.53 (2, 39)	5.57 (2, 39)	0.653 (2, 39)	2.93 (4, 37)	1.751 (2, 39)	0.28 (4, 37)
	Partial eta-sq.	0.08	0.965	0.228	0.032	0.241	0.082	0.029
	F-sig.	$p = 0.069$	$p < 0.001$	$p = 0.006$	$p = 0.526$	$p < 0.05$	$p = 0.19$	$p = 0.89$
TMT	Wilk's λ		0.085	0.559	0.953	0.446	0.791	0.898
	$F_{(df)}$	6.53 (1, 40)	99.53 (4, 37)	15.41 (4, 39)	0.953 (2, 39)	5.12 (8, 33)	2.45 (4, 37)	0.469 (8, 33)
	Partial eta-sq.	0.140	0.915	0.441	0.047	0.554	0.209	0.102
	F-sig.	$p = 0.015$	$p < 0.001$	$p < 0.001$	$p = 0.39$	$p < 0.001$	$p = 0.063$	$p = 0.87$

CWIT, Color Word Interference Test; VFT, Verbal Fluency Test; TMT, Trail Making Test; (df), degrees of freedom; Partial Eta-sq., Partial Eta Squared.

TABLE 3 | Cognitve performance at T3.

Groups at T3 (M/F)	Depression group $n = 23$ (11/12)		Control group $n = 20$ (9/11)		Statistics		
D-KEFS measure	**M (SD)**	**Change score from T2 $n = 22$**	**M (SD)**	**Change score from T2**	$F_{(1,41)}$	p	**eta sq.**
Color word interference test							
Color naming	29.87 (4.68)	−0.55	26 (4.63)	0.5	**7.37	<0.01	0.152
Word reading	22.52 (3.3)	0.5	18.9 (2.43)	0.95	***16.37	<0.000	0.285
Inhibition	48.04 (8.28)	−0.95	41 (5.91)	0.1	***10.02	<0.001	0.196
Inhibition/switching	56.13 (7.52)	−0.41	48.65 (9.58)	−1.05	***8.22	<0.001	0.167
Inhibition contrast	21.85 (6.38)	−0.52	18.55 (5.57)	−0.625	3.13	0.084	0.071
Inhibition/switching contrast	29.93 (5.64)	−0.52	26.2 (8.29)	−1.78	3.05	0.088	0.069
Verbal fluency							
Letter fluency^{hs}	50.78 (11.48)	−1.27	55.2 (10.51)	−0.4	1.71	0.198	0.040
Category fluency^{hs}	48.48 (10.18)	0.27	51.75 (9.68)	3.1	1.16	0.288	0.027
Category switching^{hs}	14.96 (2.2)	0.32	15.4 (2.32)	0.65	0.41	0.527	0.010
Trail making test							
Visual scanning	17.91 (4.5)	0.5	15.25 (2.88)	1	*5.15	0.029	0.112
Number sequencing	24.04 (8.47)	1.95	17.3 (4.92)	2.55*	**9.78	0.003	0.193
Letter sequencing	24.17 (8.95)	−1.5	17.2 (3.37)	2.55	**10.78	0.002	0.203
Number letter switching	62.96 (18.95)	0.045	50.1 (15.26)	2.65	*5.88	0.02	0.126
Motor speed	20.13 (9.68)	−0.86	16.8 (5.02)	1.45	1.91	0.174	0.045
Contrast number letter switching	41.39 (15.33)	0.02	33.46 (14.43)	0.76	3.02	0.09	0.069

M/F, Males/Females; n, Number of participants; M, Mean (seconds to complete task, except for verbal fluency); SD, Standard Deviation; Df, Degrees of freedom $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, ^{hs}*high score indicate high performance in these conditions (words generated).*

both processing speed and EF improved similarly over time. In addition, there was a significant main effect of group on the CWIT and TMT, while the VFT only approached significance, with a medium effect size. Overall, groups showed similar improvements, but differed in test performance.

One-way ANOVA tests indicated no significant differences between groups on change scores from T2 to T3. This was supported by paired sample *t*-tests on D-KEFS scores from T2 to T3, that showed there were no significant improvements in scores, with the exception of controls improving on TMT Number Sequencing from T2 (see **Table 3**). In sum, this supported that the Time × Condition interaction above was due to changes from T1 to T2, not from T2 to T3. Cognitive deficits persisted after 5 years and were relatively stable following the acute phase of FE MDD.

One-way ANOVA tests investigated which of the cognitive functions measured by D-KEFS, processing speed or EF, showed largest differences between groups (see **Table 3**). The DG performed significantly poorer than controls in all the conditions of the CWIT at T3. The contrast scores for Inhibition and Inhibition/Switching were not significantly different, although differences showed moderate effect sizes. There were significant differences in all the conditions of the TMT, except Motor Speed. The Number-Letter Switching contrast score approached significance, with a moderate effect size. There were no significant differences in the VFT conditions with small effect sizes. Groups significantly differed in conditions measuring both EF and processing speed, but not motor speed. Contrast scores were not significantly different.

Separating EF and Processing Speed

A significant difference between the groups was found on a composite score for Inhibition and Inhibition/Switching, with the DG performing poorer ($M = 25.89$, $Mdn = 27.5$, $n = 23$) than controls ($M = 22.38$ $Mdn = 22.75$, $n = 20$) $U = 146.5$, $p = 0.023$, $\eta^2 = 0.099$. Error scores from the two processing speed conditions were also compared to the executive conditions. Errors in the processing speed conditions differed with the DG making more errors ($M = 0.87$, $Mdn = 1$), and controls fewer ($M = 0.25$, $Mdn = 0$), Mann Whitney $U = 150.5$, $p = 0.023$, $\eta^2 = 0.123$. The DG made more errors in the executive conditions ($M = 2.13$, $Mdn = 2$), compared to controls ($M = 0.85$, $Mdn = 0.50$), Mann Whitney $U = 92$, $p = 0.001$, $\eta^2 = 0.286$. No significant differences in error scores appeared in either VFT or TMT. Differences in composite score and errors in the EF conditions of CWIT, supported deficits in EF when controlling for processing speed.

Course of Illness

Overall, symptoms of depression and rumination were relatively stable in the DG after T1 (see **Table 1**). The standard deviation of MADRS and months depressed at T3 suggested increased variance of depression in the DG, however. This could reflect a polarization of depressive symptoms in the group. Comorbid disorders increased in the group. At T1 only (16%) had a history of comorbid disorders (one of these dropped out). At T3 (48%) had a history of comorbid disorders. McNemar's test showed that increased comorbidity was significantly greater than chance from

TABLE 4 | Relationships between depressive symptoms, rumination, and cognitive tests.

	Relationships between symptoms and cognitive tests	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1	MADRS	1																	
2	RRS	**0.541****	1																
3	RRQ	0.305	0.810**	1															
4	CWIT: color naming	0.341	0.174	0.141	1														
5	CWIT: word reading	**0.528****	**0.426***	0.155	0.512*	1													
6	CWIT: inhibition	0.049	0.037	0.217	0.671**	0.313	1												
7	CWIT: inhibition/switching	0.363	0.241	0.242	0.656**	0.581**	0.357	1											
8	CWIT: inhibition contrast	−0.164	−0.076	0.223	0.398	−0.003	0.877**	0.014	1										
9	CWIT: Inh/switching contrast	0.182	0.104	0.169	0.266	0.222	0.044	0.847**	−0.224	1									
10	VFT: letter fluency	−0.063	0.203	0.252	0.135	−0.236	0.147	0.09	0.227	0.152	1								
11	VFT: category fluency	**−0.424***	−0.362	−0.101	−0.022	−0.500*	0.058	−0.02	0.204	0.09	0.578**	1							
12	VFT: category switching	−0.26	−0.231	0.164	0.03	−0.285	0.35	−0.127	0.518*	−0.159	0.144	0.591**	1						
13	TMT: visual scanning	**0.551****	0.137	0.053	0.548**	0.464*	0.388	0.649**	0.088	0.430*	−0.243	−0.247	−0.168	1					
14	TMT: number sequencing	**0.521***	0.264	0.088	0.509*	0.457*	0.335	0.591**	0.032	0.420*	0.183	−0.121	−0.167	0.667**	1				
15	TMT: letter sequencing	**0.545****	0.171	0.034	0.560**	0.387	0.15	0.443*	−0.025	0.199	0.002	−0.029	0.119	0.550**	0.457*	1			
16	TMT: number-letter switching	**0.489***	−0.088	−0.246	0.580**	0.244	0.331	0.376	0.1	0.221	0.055	0.025	0.024	0.538**	0.662**	0.681**	1		
17	TMT: motor speed	0.239	0.096	0.009	0.369	0.539**	0.178	0.550**	−0.165	0.434*	−0.292	−0.275	−0.357	0.470*	0.402	0.186	0.31	1	
18	TMT: N-L switching contrast	0.308	−0.192	−0.344	0.487*	0.09	0.301	0.157	0.154	0.031	0.079	0.097	0.083	0.34	0.472*	0.566**	0.946**	0.124	1

$^{*}p < 0.05$ (2-sided), $^{**}p < 0.01$ (2-sided), MADRS, Montgomery Aasberg Depression Rating Scale; RRS, Ruminative Responses Scale; RRQ, Rumination-Reflection Questionnaire (Rumination subscale); CWIT, Color word interference test; VFT, Verbal Fluency Test; TMT, Trail Making Test.
Bold values represent potential state effects.

T1 to T3, $p = 0.039$ (2-sided), in the DG. This could indicate considerable heterogeneity regarding course of illness after T1.

Relationships Between Symptoms and Cognitive Function

Spearman's Rho was calculated to explore the relationship between depressive symptoms and D-KEFS scores at T3 (see **Table 4**). MADRS showed small to large correlations with CWIT scores. Word Reading showed the largest relationship to MADRS. Relationships between EF (CWIT contrast and composite scores) and T3 MADRS score was small. There were small to medium relationships between CWIT and depressive rumination, showing similar, but smaller relationships than MADRS. MADRS showed a large relationship to depressive rumination supporting this. The CWIT processing speed measures showed small correlations to neurotic rumination. RRQ showed a moderate relationship to Inhibition/Switching, $r = 0.34$ $n = 23$ $p = 0.112$ (2-sided), although this relationship was smaller on the contrast score $r = 0.303$ $n = 23$ $p = 0.116$ (2-sided). CWIT processing speed measures showed the largest relationships to depressive- symptoms and rumination. Neurotic rumination differed, showing only a moderate relationship to Inhibition/Switching.

State Effects VFT and TMT

T3 MADRS showed small to medium relationships to VFT. Category Fluency showed the largest correlation (see **Table 4**). There were similar but smaller relationships to RRS, and only small relationships to neurotic rumination. MADRS showed small to large correlations with TMT. Most of the processing speed measures showed large relationships to MADRS. TMT Letter Sequencing showed the largest association with MADRS. TMT showed mostly small relationships to both types of rumination. One exception was for the TMT Number-Letter Switching contrast score, that showed a negative moderate relationship with RRQ $r = -0.3$ $n = 23$ $p = 0.108$ (2-sided). Category fluency and the processing speed measures of TMT showed strongest relationships to depressive symptoms. Neurotic rumination showed a moderate negative relationship to Number-Letter Switching contrast score.

Scar and Trait Effects

The scar composite score was used to investigate how previous history of depression related to D-KEFS scores and rumination at T3. The scar composite showed small correlations to all of the CWIT scores except for the CWIT Inhibition/Switching condition, with a moderate correlation $r = 0.439$ $n = 23$, $p = 0.036$ (2-sided), and an even stronger relationship to the Inhibition/Switching contrast score $r = 0.486$ $n = 23$, $p = 0.019$ (2-sided), indicating that this relationship could not be explained by processing speed. The scar composite showed a large correlation to RRQ at T3 $r = 0.562$, $n = 23$, $p = 0.005$ (2-sided), higher than to current depressive symptoms (see **Table 4**), which could suggest that neurotic rumination show larger relationship to MDD over time than current depressive symptoms. Differences between the DG and controls in CWIT error scores were new, and could thus represent a scar effect. Error scores on the CWIT, especially errors in the EF conditions, showed weak relationships to the scar composite, $rho = -0.064$ $n = 23$, $p = 0.773$ (2-sided) in addition to MADRS at T3 $rho = -0.073$ $n = 23$, $p = 0.742$ (2-sided), however. The scar composite was related to Inhibition/Switching and neurotic rumination at T3, but not new differences between groups CWIT error scores.

Traits, Stable Differences Between DG and Controls That Are Unrelated to State and Scar Measures

The CWIT Inhibition contrast score showed small correlations to both state- $rho = -0.164$, $n = 23$, $p = 0.454$ (2-sided), and scar measures of depression, $rho = -0.069$ $n = 23$, $p = 0.753$ (2-sided). It did, however, show a medium correlation to error scores in the executive condition, $rho = 0.451$, $n = 23$, $p = 0.031$, thus EF errors could be related to a trait EF/Inhibition impairment independent of state- and scar effects. CWIT Inhibition score differed between the DG and controls at both T1, T2 and T3, and show negligible relationships to both the scar composite $r = 0.059$ $n = 23$, $p = 0.788$, and MADRS at T3 $rho = 0.049$ $n = 23$, $p = 0.825$ (2-sided), and a comparable relationship to error scores in the EF conditions $rho = 0.382$ $n = 23$, $p = 0.072$ (2-sided). In conclusion, there is some support for stable deficits in CWIT Inhibition that could be independent of state- and scar effects, which thus could represent a cognitive trait deficit in MDD.

DISCUSSION

The main aim of the present study was to investigate cognitive residual symptoms in the first longitudinal 5-year follow up study of FE MDD. In addition, relationships between current- and previous depression, current rumination, and cognitive deficits were also explored. It was expected that stable deficits, unrelated to current and previous MDD history, could represent traits.

Persisting Deficits

The first hypothesis predicted that cognitive deficits would persist after 5 years. This hypothesis was supported. Results suggested that there are broad, relatively stable deficits on most of the cognitive measures. Stable differences are in line with several reviews and meta-analyses showing that cognitive deficits persist in remission (9, 11, 15, 36). However, this is the first study to show deficits 5 years following FE MDD. Importantly, there were no indication of significant cognitive decline after initial episode, and therefore little support for a worsening of cognition during the 5 years, although the study could be underpowered to detect small changes.

Deficits in EF and Processing Speed

Current findings support cognitive deficits in *both* EF and processing speed, in line with the first hypothesis. Although there were larger effect sizes for differences in the latter, there was also moderate effects for differences in EF contrast scores controlling for processing speed. The lack of significant differences in motor speed, also suggest that motor slowing is not sufficient to explain differences on the tests (16, 21). Persisting deficits in EF, even when controlling for processing speed, is mostly supported. This could be contrary to Semkovska et al. (11), were the authors suggest that executive dysfunction is due to deficits in processing speed. Deficits in processing speed showed the largest effects, however.

Course of Illness and Cognition

Table 1 indicated that the DG differed in their rate of depression following first episode (large standard deviations), which could influence results. In addition, the increase in comorbidity could influence cognitive function and has been shown to have a relationship to processing speed (20), but not inhibition (54). Of note, there was no indication of significant worsening in cognitive functions after T1, and therefore limited evidence to support cognitive exacerbation from the increase in comorbidity. The study could be underpowered to detect this, however. The increase could illustrate the need for longer follow up times in clinical studies, as comorbidity commonly increase with increasing follow up time (31). The relatively high depressive rumination could indicate that rumination represent risk factor in remission from MDD (32, 55, 56). Residual symptoms like rumination, and risk factors like comorbid disorders, could thus be of importance when planning treatment and prevention strategies. The majority of patients had undergone psychological- and/or pharmaceutical treatments, that could have influenced neurocognitive function (25, 38). However, some authors have suggested that at least some cognitive deficits persist despite "successful" treatment (39), as indicated the current study, and thus new interventions targeting cognitive functions seem warranted.

Are Deficits Associated With Depressive Symptoms States, Scars, or Traits?

There was mixed support for the hypothesized state, scar, and trait effects. Preliminary results supported the hypothesis that processing speed deficits are influenced by state effects. In addition, this finding is in accordance with meta-analyses and reviews showing relationships between MDD and processing speed deficits (26, 37). Similar, albeit weaker, relationships were found between depressive symptoms, depressive rumination, and cognitive tests. This could suggest that the relationship

between depressive rumination and cognitive function is due to depressive symptoms in the current sample. The small relationships between depressive rumination and EF went contrary to our expectations. Recent meta-analyses, however, support small relationships between EF and rumination (57–59). Of note, neurotic rumination at T3 showed different associations to cognitive tests, and stronger relationships to EF, compared to depressive rumination. Inhibition and switching were related to neurotic rumination, in support of our hypothesis. Switching, an EF, somewhat unexpectedly showed a moderate negative relationship to neurotic rumination, although some studies have found relationships between rumination and better scores on some aspects of EF (60). Alternatively, this could be a spurious relationship. In conclusion, measuring different forms of rumination (61), like neurotic rumination, could probably further elucidate on the relationship between rumination and cognition.

The exploratory scar composite score showed a relationship to Inhibition/Switching. There was no relationship between the scar composite and contrast score for Inhibition. This could indicate a scar effect on mental flexibility, although this finding must be taken with caution, as there was no clear indication for a worsening of cognitive functions over time. Thus, there is limited support for the scar hypothesis in the present study. Age and follow-up time could explain this however: 5-years might be too short, and participants to young, for a scaring effect to appear. Neuropsychological exacerbation caused by depression could probably be more apparent with increasing age (33). Semkovska et al. (11) found evidence for exacerbation of cognition with number of depressive episodes, although this finding could be influenced by age as well. However, it is hard to conclude about scar effects without measuring cognitive functions before onset of FE MDD.

Of note, neurotic rumination correlated with both the scar composite and Inhibition/Switching. Surprisingly, the relationship between neurotic rumination and history of depression, was higher than that to current depressive symptoms. This could suggest that neurotic rumination is a risk factor for-, or at least associated with MDD history. It could be that neuroticism/rumination and Inhibition/Switching are a part of risk factors for MDD over time. The former could support emerging perspectives for understanding mental illness that focus on neuroticism like the p-factor model (62), while the latter is supported by Schmid and Hammar (41), that found relationships between Inhibition/Switching and relapse and recurrence in a FE sample. Differences between the DG and controls in CWIT error scores are new and could thus represent a scar effect, but was not related to the scar composite. The scar composite is a novel construct based on theoretical assumptions [see Figure 1 in (22)], and might imperfectly capture the nature of the depressive history in our sample, however. In conclusion, there is insufficient evidence in the current paper to conclude regarding the scar hypothesis. Finally, neurotic rumination and Inhibition/Switching could be related to history of depression.

Inhibition, although significantly different between the DG and controls during the 5 years, did not show any sizable or significant relationships to history- or symptoms of depression nor rumination. All this could indicate that inhibition represent a trait and a cognitive risk factor in a group with recurrent depression. The EF function of Inhibition is recognized in other longitudinal studies as a stable deficit in MDD (63–65), in addition to several meta-analyses (9, 17, 36, 37). Inhibition is also the function most strongly associated with the unity EF factor (66), which could point toward a general persisting EF impairment as a trait associated with recurrent MDD.

Strengths and Limitations

This was the first study to investigate cognition in FE MDD after 5 years. Thus, the study could contribute with a unique perspective on the development of MDD. The current study is important due to the considerable length of follow-up time making it able to assess change and stability in cognitive function in relation to symptoms and course of illness. The thorough neuropsychological testing enabled differentiation between processing speed and EF. In addition, symptoms were measured at different time points, making it possible to investigate longitudinal relationships between cognition and symptoms. Furthermore, the study points to several variables which are relevant for further research, like persisting cognitive deficits (neurotic) rumination, and increased rate of comorbidity following the FE MDD. The increase in comorbidity, however, entails that the study did not asses MDD alone, but also comorbid disorders. This might more accurately reflect the common courses of illness and thus enhance the ecological validity of the current study, but also potentially confound results as discussed above and below. Future studies with larger samples should investigate how risk factors like comorbidity, rumination, relapse, and different treatments mediate and moderate cognition and course of illness in MDD.

Despite some strengths, the study also had major limitations. The results were from a small sample, and a selected group. All participants in the DG were outpatients. IQ was in the average to above average range which could mask deficits. However, the DG and controls showed comparable IQ scores and the groups did not differ on matched variables. MINI does not measure personality pathology (other than antisocial personality disorder) which could have been present- and influenced results. In addition, comorbidity, depressive symptoms, and treatment effects, could have confounded results. Dropout was also considerable. Interestingly, dropout was higher in the control group, which could suggest that clinically unrelated factors played a part in this. Many participants were students that moved away after completing university. The lack of clinical assessments of the controls could be viewed as a major limitation. Symptoms in the control group could have influenced results, but the relatively low rumination scores at T3 (see **Table 1**) suggested that this was not a major issue, however. There were also issues regarding measurements and sample size. Given the long follow up time, the assessments of months depressed could be influenced by subjective memory and is probably not completely accurate, which could have influenced the novel scar composite. Due to increased type II error rate Bonferroni adjustments were not made to significance levels. This could

have increased false positive findings. In addition, the study could be underpowered to detect small changes over the 5 years, which could have resulted in the lack of support for scarring effects. In addition, correlations and other effect sizes might be unstable and inflated due to the small sample (67), and should be interpreted with caution. Results should be considered preliminary and should be replicated in larger samples [for a discussion see (68)]. Also, importantly, correlation does not imply causation, thus the current study cannot say anything about the direction of the relationship between symptoms and cognition. Future studies should longitudinally investigate risk factors in larger samples, making it possible to use more complex statistics to causally model relationships between variables, like in structural equation models. Furthermore, several measures of EFs should be included to facilitate composite scores to more accurately capture the diversity functions of EF and their relationships to symptoms, risk factors, and treatments. Finally, to best inform on the state, trait, and scar debate, prospective longitudinal studies should be done, measuring cognition before the onset of MDD, and thus asses predisposing traits, and potentially scarring effects of FE MDD not captured by the current study.

CONCLUSION

The present study indicated that a group of former FE MDD patients showed lasting, stable, deficits in cognition compared to a healthy matched control group after 5 years. There were deficits in both processing speed and EF. Findings suggest that processing speed are related to depressive symptoms indicating state effects. There was no clear worsening of cognitive function. Some aspects of EF like Inhibition showed persistent deficits independent of depressive symptom state, indicating trait effects. The study underscores the importance of persisting cognitive residual symptoms following FE MDD, and the need to adapt treatments and prevention strategies targeting cognitive functioning.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate approved the study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ER: collection and analysis of data, writing manuscript draft, tables, and figures. KO: writing and editing. ÅH: study PI, writing and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.575867/full#supplementary-material

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Computerized Working Memory Training in Remission From Major Depressive Disorder: Effects on Emotional Working Memory, Processing Speed, Executive Functions, and Associations With Symptoms

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Introduction: Remission from major depressive disorder (MDD) is associated with residual symptoms related to reduced functioning, quality of life, and relapse risk. Previous studies have raised questions about mechanisms involved-in and affected by cognitive training. This study investigated the associations and changes among depressive symptoms, rumination, processing speed (PS), executive functioning (EF), and emotional working memory (e-WM) pre- post computerized working memory training (CWMT).

Method: Twenty-nine remitted participants were included in a pre- post pilot study of within-subject effects of online CWMT. A total of 20 participants completed the intervention and pre- post tests of EF and PS, e-WM, in addition to symptom and rumination measures. Associations between changes in symptoms and cognition were investigated pre- post. Associations between improvements in CWMT, depression history, and changes in cognition were explored. Hypotheses and statistics were preregistered before data were analyzed.

Results: Manipulation of negatively valanced stimuli in e-WM showed an inverse association with rumination pre-intervention, but the association disappeared post-intervention. Cognitive functioning improved in most conditions with largest effects in EF. Symptoms did not change in the remitted sample. CWMT improvements were related to improvements in some aspects of EF and PS, but also to worse self-reported attention. Depression history was related to less improvement in EF.

Limitations: Sample size was small and there was dropout from the study. There was no control group, thus precluding practice and placebo effects and causal relationships.

Conclusions: Computerized WM training improves cognitive functions and could influence associations between e-WM and rumination. This could counteract functional impairment following MDD.

Keywords: computerized working memory training, remission, executive functioning, processing speed, emotional WM, rumination

INTRODUCTION

Major depression (MDD) is associated with lower performance in executive functions (EFs) and processing speed (PS). EFs are the collection of interrelated, but distinct cognitive abilities including *switching* between tasks, *updating*, and *inhibition* of proponent responses and distractions (Friedman and Miyake, 2017), integrated with working memory (WM) and abilities such as planning (Diamond, 2013). Lower performance in tests of EF and PS associated with MDD is referred to as cognitive deficits, which are moderate to large in size (Lee et al., 2012; Snyder, 2013; Parkinson et al., 2020), persist in remission (Hasselbalch et al., 2011; Rock et al., 2014; Semkovska et al., 2019), last for years (Årdal and Hammar, 2011; Ronold et al., 2020b), impair everyday functioning (McIntyre et al., 2013; Evans et al., 2014; Nafilyan et al., 2021; Sumiyoshi et al., 2021), and contribute to relapse and new episodes of MDD (Majer et al., 2004; Schmid and Hammar, 2013; Zajecka, 2013). Evidence-based treatments such as psycho- and pharmacotherapy do not normalize cognitive deficits in remission (Keefe et al., 2014; Rosenblat et al., 2015; Bernhardt et al., 2019; Groves et al., 2021), and deficits can reduce the effects of treatments (McLennan and Mathias, 2010; Groves et al., 2018). Although treatments such as psychopharmacology improve cognition in acute states of MDD (Gorlyn et al., 2015), there is need for interventions for the remitted phase of MDD. Promising new interventions are being investigated with regard to cognitive function (Miskowiak et al., 2022), but knowledge on how and for whom these interventions work is important. In sum, interventions improving cognition in remission from MDD are urgently needed.

The trajectory of cognitive deficits is still being investigated. Deficits are larger during an active episode of MDD, compared to when in remission (Douglas and Porter, 2009; Snyder, 2013; Bernhardt et al., 2019; Semkovska et al., 2019), suggesting *state effects* from depressive symptoms on cognitive functioning. Another perspective is that deficits could exist as a vulnerability before the onset, of MDD, as *traits*. Also, deficits could be a result of depression history or significant stress, through neurotoxic effects and thus exacerbate, as suggested by the *scar hypothesis* (for reviews refer to Hasselbalch et al., 2011; Allott et al., 2016; Ahern et al., 2019). A recent review by Hammar et al. (2022) found support for all these perspectives, relative to the cognitive functions measured. PS could be more state- or scar-related, whereas some EFs could be traits. However, the literature is inconclusive. Cognitive deficits are a major health challenge (Nafilyan et al., 2021), partly on account of the high (Mueller et al., 2013), cumulative relapse rate in MDD (Kessing and Andersen, 2017), and the link between MDD and dementia (Woolf et al., 2021; Hammar et al., 2022). Thus, it is paramount to investigate interventions to improve cognitive deficits for future healthcare needs.

The interrelations between mood symptoms and cognitive functions could vary relative to the domain assessed, as shown above. PS entails how rapidly various tasks can be performed, is associated with current or previous MDD, and is foundational for higher functions such as EF (Salthouse, 1996; Porter et al., 2015). EF is a collection of abilities that show more persistent deficits following symptom remission (Snyder, 2013). According to Nigg et al. (2017), PS and EF relate differently to psychopathology. Supporting this, PS is suggested to be more state-related, whereas EF is more trait-related, in *young* patients with MDD (Douglas and Porter, 2009; Lee et al., 2012). The EF *Inhibition* is sometimes seen as relatively independent of symptoms, whereas *switching* seems to show more associations to MDD (Schmid and Hammar, 2013; Ronold et al., 2020b; Liu et al., 2021). Thus, deficits in EF and PS could have different etiological implications. Tests, however, capture common and distinct EF to a varying degree, a concept commonly conceptualized as task impurity (Snyder et al., 2015), precluding associations between EF and symptoms in the literature. Recently, different conditions of the Stroop and Trail Making Test (TMT) were used in a systematic review investigating PS and EF in MDD, with evidence for deficits in *both functions* (Nuño et al., 2021). Stroop and TMT differentiate between EF and PS and could inform on associations between symptoms and cognitive functions before and following cognitive training (Motter et al., 2019), establishing potential targets for cognitive remediation interventions.

Since recurrence and relapse are more common than single episodes of MDD (Solomon et al., 2000), identifying causes and cures for relapse are vital. Rumination is an emotion regulation strategy which involves self-related, repeated negative thinking about past events (Watkins and Roberts, 2020; Taylor and Snyder, 2021). Rumination related to MDD is measured in several ways, with many studies using the Ruminative Responses Scale (Watkins and Roberts, 2020), measuring general tendency for rumination *in response to depressive mood*. This *depressive rumination* shows large associations with other depressive symptoms (Zetsche et al., 2018) and could contribute to depressive state effects on cognition. Neurotic rumination, measured by the Rumination Reflection Questionnaire (Trapnell and Campbell, 1999), is less studied, measures general tendency for *rumination independent of depressive mood*, and has shown different associations with cognitive functions than the Ruminative Responses Scale (Gustavson et al., 2020; Ronold et al., 2020b). Rumination is consistently associated with relapse, increased symptoms, recurrence, and new episodes of MDD (Nolen-Hoeksema et al., 2008; Aker et al., 2014; Timm et al., 2017; Figueroa et al., 2019; Ronold et al., 2020a; Jandric et al., 2021; Taylor and Snyder, 2021). Deficits in EF, particularly inhibition of negative material, are suggested to contribute to this (Joormann and Gotlib, 2010; Ahern et al., 2019). However, meta-studies find small associations between rumination and shifting, inhibition, and WM discarding (Vălenaș and Szentágotai-Tătar, 2017; Yang et al., 2017; Zetsche et al., 2018). Associations between different forms of rumination, depressive symptoms, EF, and PS have not been studied extensively (Schwert et al., 2017; Gustavson et al., 2020) and could inform on the profile of residual cognitive functions following MDD, and how these can be remediated.

Different cognitive functions could influence the tendency to ruminate. Cognitive processing of emotional material (hot cognition) could show stronger associations with rumination (Roiser and Sahakian, 2013; Joormann and Stanton, 2016; Ahern et al., 2019). Meta-studies find limited effects of emotional valence on associations between EF tests and rumination

(Vălenaş and Szentágotai-Tătar, 2017; Yang et al., 2017), but there is evidence for persisting emotional bias in remission (Semkovska et al., 2019). One meta-study concluded that discarding of negative information from emotional working memory (e-WM) could be related to rumination (Zetsche et al., 2018). Diverse methodology could preclude associations between (hot) EF and rumination in the literature. Deficits in manipulation of negative stimuli in e-WM have shown associations with rumination (Joormann et al., 2011; Ronold et al., 2020a). In addition, one study found that rumination was associated with both PS *and* EF (Schwert et al., 2017). Thus, it is important to measure associations among symptoms, rumination, and e-WM, PS, EF, how interventions influence associations, and thus potentially improve functions.

Subjectively reported cognitive functions could be important residual symptoms in remission from MDD. Self-reported, subjective deficits persist in remission following first episode MDD (Schmid and Hammar, 2021) and appear to be largely independent of objective cognitive tests (Snyder et al., 2020). Subjective cognition has been found to be a potential predictor of quality of life, functioning, and relapse, following MDD (Sumiyoshi et al., 2021). Thus, intervention targeting subjective cognition is important. One recent study by Lengvenyte et al. (2020) found the improvements in depressive symptoms, particularly self-rated attention, in a remitted bipolar group following computerized WM training (CWMT). Thus, it is important to further assess whether new interventions such as CWMT could improve self-rated aspects of cognition and residual MDD symptoms.

Given the persisting residual symptoms described above, research on new interventions targeting residual cognitive symptoms during MDD remission is needed. Computerized cognitive training paradigms, such as CWMT, have been suggested as an intervention in remission from MDD (Motter et al., 2016; Koster et al., 2017). Such interventions have the advantages of being relatively cost efficient, engaging, and can be performed from home. WM is a function closely related to the EF updating and entails manipulation of material in short-term memory (Miyake et al., 2000). WM has been suggested as a target for enhancing cognition through CWMT (Webb et al., 2018; Motter et al., 2019). Recent studies indicate that the improvements appear in depressive symptoms, EF, and PS, following training (Barkus, 2020; Launder et al., 2021; Woolf et al., 2021), but results are mixed with studies including higher symptom levels showing most symptom improvement (Legemaat et al., 2021), and the underlying mechanisms in improvements are largely unknown (Webb et al., 2018; Motter et al., 2019; Ferrari et al., 2021). Given these mixed results (Lengvenyte et al., 2020; Legemaat et al., 2021), investigating depressive symptoms following CWMT with particular focus on subjective cognition seem important. Since emotional processing, subjective difficulties, cognitive deficits, and rumination all contribute to relapse and recurrence of MDD, studies exploring how CWMT influences these processes are warranted.

The aim of this study was to investigate how residual cognitive symptoms in remission from MDD are effected by CWMT. Previous research on most of the current sample concluded that CWMT was well accepted and improved EF and PS (Hammar et al., 2020). Given the clinical significance of residual cognitive symptoms outlined above, it is crucial to study how interventions affect such symptoms in remission from MDD. Improvements and altered associations among cognitive functions, symptoms, following CWMT could support the clinical significance of such interventions and suggest targets with future treatments.

Pre-Intervention: it was expected that emotional working memory for negative stimuli would show negative associations with rumination (Joormann et al., 2011; Ronold et al., 2020a). Processing speed and switching were expected to be associated with depressive symptoms (state/scar) whereas inhibition was expected to be independent (trait) of depressive symptoms (Ronold et al., 2020b).

Post-Intervention: cognitive functioning and symptoms of depression and rumination were expected to improve, while the associations between cognitive functioning and symptoms of depression and rumination, were expected to decrease.

In addition, associations between the CWMT intervention improvement, cognitive functions, and clinical variables were explored.

MATERIALS AND METHODS

The current data were collected as a part of a pilot study on the feasibility of CWMT in remission from depression (Hammar et al., 2020) and are a pre–post-study of how CWMT influences e-WM, EF, PS, and associations with depressive symptoms. Hypotheses and methods were preregistered on Open Science Framework (https://osf.io/vpxgw) before analysis, but after data collection was completed.

Participants and Procedure

Participants were recruited through an outpatient clinic for affective disorders at the Psychiatric unit of Haukeland University Hospital and through advertisements and previous research projects. A total of 29 participants were included in the study, and of these, 20 completed the intervention and retest. Inclusion criteria were age (20–60), previous treatment of MDD, currently remission, or recovery as indicated by $\leq$12 on The Montgomery Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979). Exclusion criteria were brain damage/pathology, severe somatic disorders, alcohol, or substance abuse. The Mini-International Psychiatric Structural Interview (Sheehan et al., 1998) was used to confirm diagnosis and history of MDD, and screen for exclusion criteria. Other clinical data were assessed by a structured form developed for the study. A psychologist or a psychiatric nurse assessed inclusion criteria at the outpatient clinic for affective disorders or the neuropsychological clinic at the University of Bergen. Neuropsychological and experimental assessment was performed at the neuropsychological clinic, both preceding (T1) and following the intervention (T2). The CWMT intervention was delivered at home online on a computer or tablet. Participants started training within 2 weeks following assessment. After the intervention participants were invited to a posttest assessment of e-WM, EF, and PS, depressive symptoms, and rumination.

Missing Data and Participant Flow

Due to technical difficulties, T1 data for e-WM were missing for two participants at T1, and three participants at T2, thus resulting in pre–post-data for 16 participants. One participant was missing MADRS at T1, and four missed the item measuring self rated attention. A total of two participants were missing MADRS at T2, thus resulting in pre–post-data for 18. For demographical characteristics, refer to **Table 1**. For more information about participant flow, refer to **Figure 1**.

Computerized Working Memory Training Intervention

Cogmed™ (Pearson, 2022) was chosen as the CWMT intervention. It is a commercial CWMT program that has several advantages: It is performed online, so participants can use it at home, it has a considerable duration, with incremental difficulty depending on past performance (successfully completed tasks), both aspects that are considered important for successful CWMT (Koster et al., 2017; Launder et al., 2021). Cogmed targets "cold cognition," i.e., working memory span. The program consisted of several different number, letter, and spatial, forward and backward sequencing tasks. For example, Letters are read out loud, while one of several rotating bubbles lights up on screen, participants remember the sequence of the lighted bubbles, clicking on the corresponding bubbles sequentially following presentation. In another task, participants attend to a sequence of numbers read out and then click on the numbers in reverse sequence on screen. In a different task, participants remember the sequence of panels on a cube that light up one by one, then clicking on the panels in the correct sequence after presentation. The intervention consisted of 25 sessions, lasting ∼5 weeks, with five weekly 30–40-min sessions. In addition, there was weekly telephone contact between participants and a trained Cogmed coach, discussing progress, motivation, and questions related to the training.

Neuropsychological Assessment

All participants completed a neuropsychological test battery pre- and post-intervention measuring general intellectual ability, EF, and PS. General intellectual ability was measured by the Norwegian version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999), to better describe the sample and potentially explain dropout (refer to **Table 1**). The Delis–Kaplan Executive Function System (Delis et al., 2001) subtests TMT, and the Color Word Interference Test (CWIT), an updated version of the Stroop task, was used to measure PS and EF. The TMT is a paper and pencil task consisting of five conditions. The CWIT consists of four conditions with verbal responding to visual stimuli.

Measurements of PS

The first condition of TMT, *visual scanning*, consists of marking out symbols. The following two conditions, *number* and *letter* sequencing, require sequential marking of numbers and letters, respectively. These three conditions measure PS. Finally, the fifth condition, *motor speed*, consists of swiftly marking a line and is a measure of motor speed. The first conditions of the CWIT, *color* and *word reading*, measure PS.

Measurements of EF

Color Word Interference Test and TMT measure inhibition and switching. In the fourth condition of the TMT, participants switch between marking letters and numbers in rising alphabetical and sequential order, measuring the EF *switching*. The third condition of CWIT consists of naming the printed color of an incongruently spelled color word, modeled on the classical Stroop effect (Stroop, 1935), and measure the EF inhibition. The last condition of CWIT alternates between condition three and condition two and thus measures both EFs inhibition *and* switching (Inhibition Switching), or arguably more of the common than specific aspects of EF.

Emotional WM Paradigm

Emotional working memory was measured by a computerized paradigm pre–post-intervention (refer to **Figure 2**). Participants were presented with a series of three happy or sad faces (Lundqvist et al., 1998) and then instructed to hold the sequence in mind in either a forward- (low WM loading) or *manipulate* in a backward (high WM loading) sequence. Finally, participants were shown one of the three faces and asked to specify where in the (rotated) picture sequence, the face was presented by pressing

TABLE 1 | Demographic characteristics and symptoms.

	T1 n = (m/f)	T2 n = (m/f)			
Mean (SD)	$n = 29$ (10/19)	$n = 20$ (8/12)			
Age	36.207 (10.896)	37.3 (12.27)			
Education	16.53 (1.792)	16.55 (1.731)			
IQ	115.828 (8.06)	*	*t/Z*	*p* (one-tailed)	E. s.
MADRS	6 (4.35) $n = 28$	8.78 (8.742) $n = 18$	$Z = 0.971$	$p = 0.166$	$r = 0.161$
MADRS SCI	1.292 (1.97) $n = 24$	1.54 (1.33) $n = 18$	$Z = 0.79$	$p = 0.215$	$r = 0.13$
RRS	48.07 (13.48)	46.75 (14.664)	$t = 0.38$	$p = 0.355$	$d = 0.085$
RRQ-r	40.928 (9.561) $n = 28$	40.8 (9.638)	$t = 0.763$	$p = 0.226$	$d = 0.171$

m/f, Male/Female; MADRS, Montgomery Åsberg Depression Rating Scale; SCI, Subjective cognition item; RRS, Ruminative Responses Scale; RRQ-r, Rumination Reflection Questionnaire rumination.

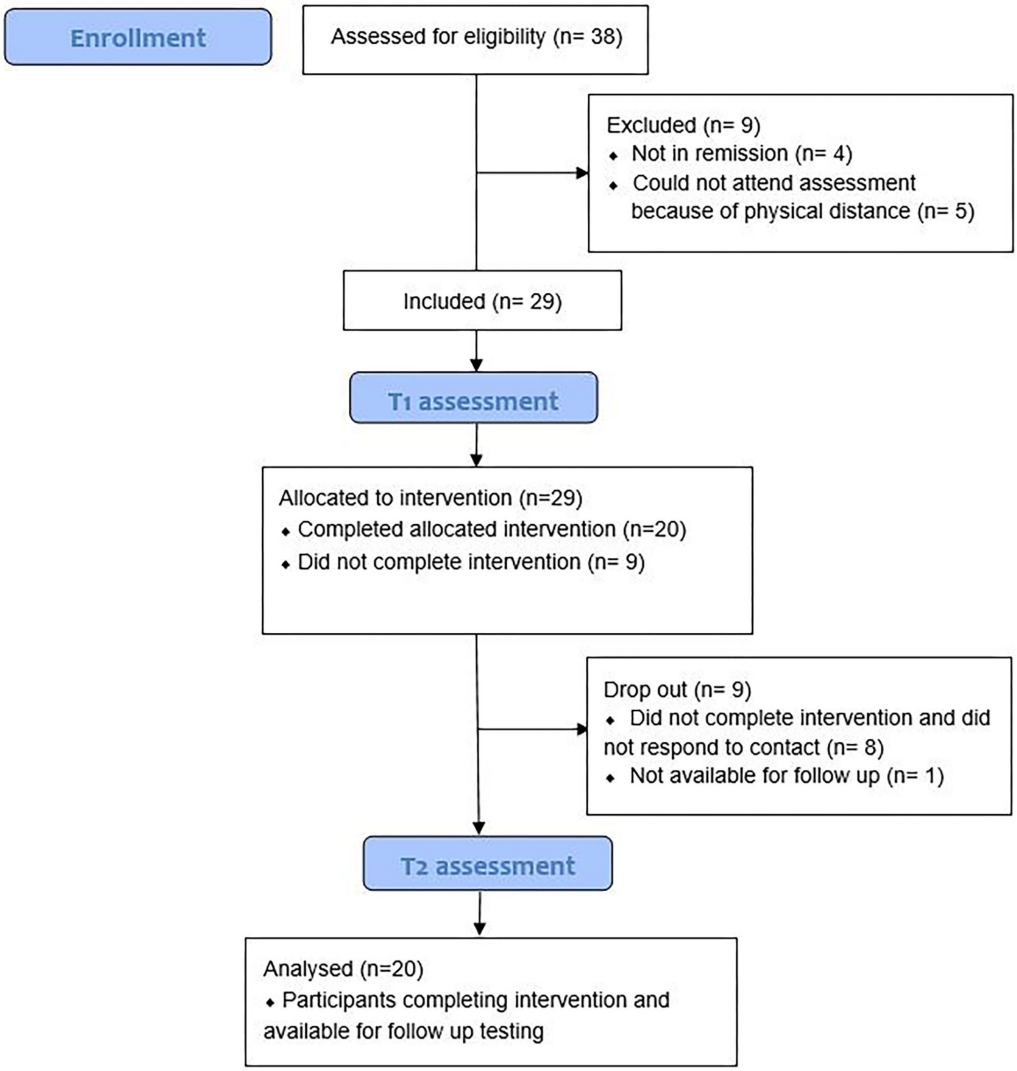

FIGURE 1 | Flow chart of participants.

key "1," "2," or "3." The experiment was run in E-prime (version 2), and percent accuracy was used as an outcome measure. For further description of the paradigm, refer to Ronold et al. (2020a).

Self-Report Scales

Several self-report measures were administered pre- and post-intervention. The Ruminative Responses Scale (RRS) and Rumination Reflection Questionnaire (RRQ) measured depressive and neurotic rumination, respectively. Depression was measured post-test by MADRS self-report.

Ruminative Responses Scale

The Norwegian version of the form RRS (Treynor et al., 2003) was administered pre- and post-intervention. It consisted of 22 questions in a four-point scale from 1 "almost never" to 4 "almost always" (22–88 range) and asked participants lifetime proclivity

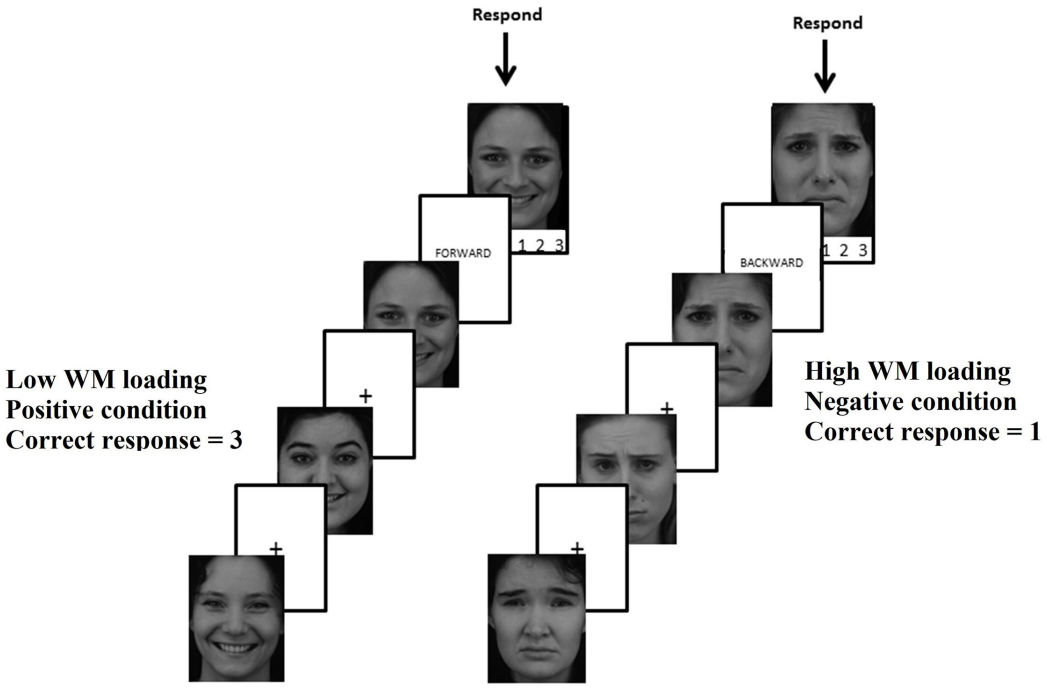

FIGURE 2 | Emotional working memory paradigm using pictures from the Karolinska Directed Emotional Faces.

for rumination when "feeling sad or depressed," e.g., "think about how sad you feel."

Rumination Reflection Questionnaire – Rumination Subscale

The rumination subscale from the Norwegian version of the RRQ was used to measure lifetime proclivity for self- ruminative though, independent of depressive mood, e.g., "My attention is often focused on aspects of myself I wish I'd stop thinking about." Here, 12 items are rated on a five-point scale ranging from 1 "strongly disagree" to 5 "strongly agree" (12–60 range). The scale has been shown to correlate with the personality trait neuroticism and could thus measure *neurotic rumination* relatively independent of mood (Trapnell and Campbell, 1999).

The Montgomery Åsberg Depression Rating, and Self-Report Scale

Clinician administered MADRS was used to assess depression pre-intervention. Following the intervention, the Montgomery Åsberg Depression Rating Scale Self-report (Svanborg and Åsberg, 2001) was used to assess depression. This measure is comparable to the MADRS with the exception of one item (item 1) that assess apparent sadness. Depressive symptoms are scored on a seven-point scale from zero to six (range 0–54 relative to MADRS 0–60) and have proven to be useful and sensitive to change in depressive symptoms in clinical trials (Cunningham et al., 2011). Items 6 and 5 measure self-subjectively experienced difficulties with attention on MADRS and MADRS Scale Self-report, respectively.

Ethics and Compensation

All participants provided informed signed consent prior to participating in the study. The study was conducted in accordance with the Helsinki Declaration of Ethical Research regarding Ethical Principles for Medical Research Involving Human Subjects (World Medical Association, 2013) and was approved by the committee for ethical research in Western Norway (2014/1079), in addition to the Norwegian Data Inspectorate. Participants were awarded with a gift card valued at 400 Norwegian Kroner (∼50 dollars), for their participation. In addition, participants were given access to the CWMT program free of charge.

Data Scoring and Statistical Analysis

E-Data aid (version 2) was used to calculate accuracy in the e-WM paradigm and exported to a statistical program used for all analyses (version 25). For the neuropsychological tests, raw scores consisting of seconds to complete tasks were used. Data were screened for outliers using boxplots and histograms.

Normality was assessed by Kolmogorov–Smirnov test, and non-parametric tests were used when assumptions were violated. To investigate the pre-intervention hypotheses, associations between cognition and symptoms post-intervention, in addition to the explorative analyses, the bivariate correlation coefficient, Pearson's *r* was used. To investigate post-intervention hypothesis and attrition, paired sample *t*-tests were used, with Wilcox signed rank test as a non-parametric alternative. Spearman's rank-order correlation ρ was calculated for non-parametric data. To avoid risk for type 2 errors, Bonferroni correction was not strictly implemented (Nakagawa, 2004), but it has been noted which improvements remained significant after this correction (refer to **Table 2**). Significance level was set at $p = 0.05$ (Bonferroni correction for **Table 2** $= 0.05/16 = 0.003$), and one-tailed significance levels were used to assess pre-registered hypotheses. Effect sizes (Cohen's *d*), where reported, for non-parametric tests *r,* were calculated from the following formula $r = Z/\sqrt{}$ total number of observations. Effect sizes were reported as small ($d =$ 0.2, $r/\rho =$0.1), moderate ($d = 0.5$, $r/\rho = 0.3$), and large ($d = 0.8$, $r/\rho = 0.5$) according to Cohen (1988).

Z-Transformations, Contrast, Improvement, Composite, and Change Scores

Z-score transformation of MADRS pre- and post-intervention was calculated to compare the change in depression from pre- to post-test. *A depression history composite* was computed from the following Z-transformed depression and rumination measures (T1 MADRS + T2 MADRS + MDD length in months + number of MDD episodes + T1 RRS + T2 RRS + T1 RRQ + T2 RRQ)/8. *Change scores* for neuropsychological tests, RRS, RRQ, and MADRS were calculated by subtracting T2 scores from T1 scores. *Change scores* in e-WM were calculated by subtracting scores at T1 from scores at T2. Thus, positive values indicated post-intervention improvements. *Separating EF from PS:* Contrast scores were calculated to separate EF from PS: TMT Switching (TMT Switching contrast = Number-Letter Switching – (Visual Scanning + Letter Sequencing + Number Sequencing + Motor Speed)/4), Inhibition (Inhibition Contrast = Inhibition – (Color Naming + Word Reading)/2) CWIT Switching condition (CWIT Switching Contrast = Inhibition/Switching – (Color Naming + Word Reading + Inhibition)/3). *CWMT improvement score:* Improvement in CWMT was calculated through the formula: highest performance score (i.e., session with most completed tasks) – starting performance score/starting performance score.

RESULTS

Attrition Analysis

There were no significant differences in demographic characteristics in **Table 1**, depressive symptoms, EF, PS, e-WM, with small effect sizes, between participants who completed the intervention and participants that dropped out, suggesting that attrition effects were limited.

Pre-Intervention Hypotheses

Rumination and e-WM

Negative moderate correlations between depressive rumination (RRS total score) and e-WM in the high WM load negative condition did not appear ($r = -0.076$ $n = 27$ $p = 0.354$, one-sided). Exploring this further, the expected moderate negative association appeared between neurotic rumination (RRQ rumination) and e-WM in the high WM loading negative condition $r = -0.381$ $n = 26$ $p = 0.028$ (one-sided). There was no association between MADRS and depressive rumination $\rho = 0.052$ $n = 28$ $p =$0.396 (one-sided). In sum, there was no association between depressive, but a moderate negative relationship between e-WM and neurotic rumination. Depressive symptoms did not correlate with rumination.

Depressive Symptoms and PS

Depressive symptoms (MADRS) showed small negative associations with the Color Naming and Word Reading conditions of CWIT ($\rho = -0.290$ and -0.234), and Visual Scanning, Letter and Number Sequencing, and Motor Speed conditions of the TMT (ranging from $\rho = -0.134$ to -0.250). In sum, positive associations between depressive symptoms and PS did not appear.

Depressive Symptoms and EF

Color Word Interference Test inhibition was independent of depressive symptoms $\rho = -0.038$ $n = 28$ $p = 0.424$ (one-tailed). Opposite associations were also found for EF and depressive symptoms with moderate negative association between CWIT Inhibition Switching, a small negative association between TMT switching ($\rho = -0.385$ and $\rho = -0.256$, respectively), and smaller associations with contrast scores ($\rho = -0.194$ and $\rho = -0.038$, respectively). In sum, positive associations between depressive symptoms and switching did not appear. Inhibition was independent of depressive symptoms.

Post-Intervention Findings

Improvements in e-WM

Participants showed significant moderate e-WM improvements (refer to **Table 2**). The negative (sad faces) low WM loading condition showed improvements, from pre- ($Md = 62.25\%$) to post- ($Md = 75\%$), and the high WM loading maintain condition, improvements from pre- ($M = 60.38\%$) to post- ($M = 69.56\%$) intervention. In the positive conditions (happy faces), improvements appeared in the low WM loading condition, changing from pre- ($Md = 71\%$) to post- ($Md = 79\%$) intervention and in the high WM loading condition from pre- ($Md = 58\%$), to post- ($Md = 67\%$) intervention. Thus, participants improved across all e-WM conditions following CWMT.

Improvements in PS

Trail Making Test scores showed small to moderate improvements in PS following CWMT (refer to **Table 2**). TMT Number and Letter Sequencing showed significant moderate improvements from pre- ($Md = 24$) to post- ($Md =$ 22), and pre- ($Md = 23.5$) to post- ($Md = 21$) intervention,

TABLE 2 | Changes in e-WM, PS and EF from T1 to T2.

	T1 $n = 29$	T2 $n = 20$	*t*/*Z*	*p* (one-tailed)	E. s.
e-WM*	*M (SD)*	*M (SD)*			
Low WM negative	66.2% (20%)	74.5% (17.5%)	$Z = 2.143$	$p = 0.016$	$r = 0.378$
High WM negative	62% (22.6%)	70.8% (17.9%)	$t = 2.202$	$p = 0.022$	$d = 0.55$
Low WM positive	65.2% (21%)	74.3% (20.9%)	$Z = 2.55$	$p = 0.006$	$r = 0.45$
High WM positive	64.7%(21.9%)	68.3% (13.7%)	$Z = 2.045$	$p = 0.021$	$r = 0.361$
Trail Making Test**					
Visual scanning	20.28 (7.755)	17.4 (5.413)	$Z = 1.544$	$p = 0.062$	$r = 0.244$
Number Sequencing	26.07 (8.606)	23.5 (8.935)	$Z = 1.941$	$p = 0.026$	$r = 0.306$
Letter sequencing	24.72 (9.42)	22.50 (10.08)	$Z = 2.035$	$p = 0.021$	$r = 0.322$
Number Letter Switching	69.03 (20.36)	55.8 (18.62)	$t = 2.347$	$p = 0.002$[b]	$d = 0.748$
Contrast LNS Switching	46.47 (17.24)	35.32 (15.69)	$t = 2.908$	$p = 0.005$	$d = 0.65$
Motor speed	19.17 (9.54)	18.50 (7.81)	$Z = 1.246$	$p = 0.105$	$r = 0.197$
Color Word Interference	**				
Color Naming	28.97 (4.45)	27.75 (5.24)	$t = 2.666$	$p = 0.008$	$d = 0.596$
Word Reading	21.45 (3.501)	20.95 (3.65)	$t = 2.58$	$p = 0.009$	$d = 0.577$
Inhibition	50.66 (10.25	44.05 (8.501)	$t = 4.25$	$p < 0.001$[b]	$d = 0.95$
Contrast Inhibition	25.44 (8.805)	19.70 (6.118)	$t = 3.16$	$p = 0.003$[b]	$d = 0.706$
Inhibition/Switching	53.45 (7.822)	49.1 (8.771)	$t = 2.102$	$p = 0.025$	$d = 0.47$
Contrast I/S	19.76 (7.135)	18.183 (5.557)	$t = 0.536$	$p = 0.299$	$d = 0.120$

*Means for the whole sample, pre- n = 28 post- n = 17, accuracy in percent. **Means for the whole sample, accuracy in seconds, high score = poor performance, LNS = Number Letter Switching I/S = Inhibition/Switching.
[b]Significant after Bonferroni correction.

respectively. TMT Visual Scanning showed small non-significant changes pre- ($Md = 19$) to post- ($Md = 16.5$) intervention, and Motor Speed showed small non-significant changes pre- ($Md = 16$) to post- ($Md = 16$) intervention. Moderate significant improvements in PS appeared for the CWIT scores, with improvements in both Color Naming pre- ($M = 29.5$) to post- ($M = 27.75$) intervention, and Word Reading pre- ($M = 22$) to post- ($M = 20.95$) intervention. Thus, participants showed moderate significant improvements in PS, except in Visual Scanning and Motor Speed.

Improvements in EF

Trail Making Test showed moderate to large improvements in switching. The Number Letter Switching condition showed a moderate to large improvement pre- ($M = 71.75$), to post- ($M = 55.8$) intervention, and this effect was also moderate in the contrast score controlling for processing speed, pre- ($M = 48.613$) to post- ($M = 35.33$) intervention. Large improvements in inhibition appeared on the CWIT pre- ($M = 49.1$) to post- ($M = 44.05$)intervention. A significant moderate to large effect remained in a contrast score controlling for processing speed pre- ($M = 23.325$) to post-($M = 19.7$)intervention. In the CWIT condition, measuring inhibition and switching showed small to moderate significant improvement pre- ($M = 52.7$) to post- ($M = 49.1$) intervention. This effect, however, was non-significant, and small, in a contrast score controlling for processing speed. Thus, participants improved across most EF conditions following CWMT, with largest improvements in inhibition.

Change in Depressive Symptoms and Rumination

There were no significant improvements in depressive symptoms measured by MADRS, MADRS subjective attention, RRS, and RRQ rumination scores, pre–post-intervention (refer to **Table 1**). Overall, participants did not show significant improvements in symptoms following CWMT, although initial values on MADRS were low with low variance.

Associations Between Symptoms and Cognitive Functioning Post-Intervention

The association between neurotic rumination and the negative high WM loading condition was small and no longer significant $r = 0.052$ $n = 17$ $p = 0.421$ (one-tailed) post-CWMT. TMT Number Letter Switching showed positive associations with depressive symptoms at T2, with moderate non-significant correlations between TMT Number Letter Switching and MADRS at T2 $\rho = 0.331$ $n = 18$ $p = 0.090$ (one-tailed), and significant correlations with the switching contrast score $\rho = 0.416$ $n = 18$ $p = 0.043$ (one-tailed). In addition, MADRS and depressive rumination (RRS) showed large correlations post-intervention $\rho = 0.732$ $n = 18$ $p < 0.001$ (one-tailed). Thus, associations between e-WM and rumination decreased following the intervention, whereas associations between depression symptom load and EF, and depressive rumination, appeared post-intervention.

Explorative Hypotheses

Associations Between CWMT Improvement and Improvements in PS

The CWMT improvement score was associated with improvements in PS change scores; TMT- Visual Scanning $\rho = 0.419$ $n = 20$ $p = 0.033$ (one-tailed) and Letter Sequencing $r = 0.378$ $n = 20$ $p = 0.05$ (one-tailed). Thus, there were moderate associations between CWMT improvement and some tests of PS.

Associations Between CWMT Improvement and Improvements in EF

The CWMT improvement score was associated with the Inhibition Switching change score $r = 0.469$ $n = 20$ $p = 0.018$ (one-tailed), and the change contrast score in this condition $\rho = 0.407$ $n = 20$ $p = 0.037$ (one-tailed). Thus, there were moderate associations between inhibition switching and improvements in CWMT.

Associations Between CWMT Improvement and Improvements in Symptoms

The CWMT improvement score was not related to changes in symptoms, except for a negative association with change in MADRS self-assessed cognition $\rho = -0.406$ $n = 18$ $p = 0.048$ (one-tailed). Thus, there were a moderate negative associations between improvement in CWMT and self-assessed attention change score, suggesting exacerbation, from pre- to post-intervention.

Associations Between Duration and Strength of MDD, Change in EF, Rumination, and e-WM

A depression load composite score consisting of all symptoms, number, and length of depressive episodes was calculated. The composite score was related to changes in EF: A moderate negative correlation to change score Inhibition Switching $\rho = -0.404$ $n = 16$, $p = 0.06$ (one-tailed), with greater significant associations with the change in contrast score in this condition $\rho = -0.499$ $n = 16$, $p = 0.024$ (one-tailed). Thus, participants with longer and more severe episodes of MDD showed less improvement in EF.

DISCUSSION

The aim of this study was to investigate how a computerized working memory training intervention affected residual cognitive symptoms in remission from MDD. This study investigated association among depressive symptoms and rumination, processing speed, executive functions, and emotional WM, and how these are affected by computerized working memory training. The results show both broad and specific effects of computerized working memory training. Broadly, main findings support the successful implementation of computerized working memory training for improving processing speed, executive functions, and emotional working memory. Specifically, associations between rumination and negative high loading working memory deficits could be altered by the intervention, and improvements appear larger in executive functions. Depression history could influence the effects of working memory training on executive functions.

Pre-Intervention Hypotheses

There was partial support for an association between rumination and e-WM. Neurotic rumination showed a moderate negative association with negative high WM loading material in e-WM, supporting associations between rumination and difficulties in manipulation of negative material in WM (Joormann et al., 2011; Ronold et al., 2020a). Inhibition was independent of depressive symptoms as expected (Snyder, 2013; Ronold et al., 2020b). The lack of association between depressive rumination measured by RRS and e-WM could be due to the low level of depressive symptoms in the group at T1 (remission as inclusion criteria) and could help explain the lack of depressive state effects on cognitive functions such as PS and switching. The direction of associations between depressive symptoms and cognition went opposite of predictions, and from what is usually reported in the literature (McDermott and Ebmeier, 2009; Snyder, 2013; Semkovska et al., 2019). It is thus likely that participants must show higher levels of depressive symptoms for state effects to appear (Dotson et al., 2020), which is noteworthy given the current remitted sample with low levels of depressive symptoms. Supporting this were the findings at T2 when symptoms and variance were higher. Here, some of the expected associations between depressive symptoms and switching and rumination were more evident. This could indicate that some associations between symptoms and cognition remain following CWMT and thus are impacted to a limited degree by improvements in cognition, suggestive of trait or scar effects. Thus, e-WM showed expected associations with rumination, whereas EF and PS did not show expected associations with depressive symptoms. Limited support for state effects on cognition in remitted MDD appeared, and inhibition emerged as a possible trait, independent of variations in current depression symptoms, but state effects were probably difficult to detect due to low variance and score of depression in the current sample initially.

Post-Intervention Hypotheses

Hypotheses about improvements in e-WM, PS, and EF following CWMT were supported. Participants improved across all e-WM conditions, most PS conditions, and most EF conditions, following CWMT. Effects were largest for CWIT Inhibition and TMT Number Letter Switching, and these were the only conditions statistically significant after Bonferroni correction, supporting larger effects for CWMT in EF tasks, and potential for the remediation of trait deficits associated with psychiatric disorders such as MDD. This is in line with stronger associations between EF and WM, relative to PS (McCabe et al., 2010), supporting transfer between CWMT and EF improvements. This could be important since EF deficits are of particular clinical significance (Snyder et al., 2015; Groves et al., 2018). However, the improvements compared to normative data indicated that that only inhibition improved descriptively, i.e., from "low average" to "average" (Delis et al., 2001). Other studies, in contrast, find superior improvements in PS following training (Webb et al., 2018). Of note, improvements were larger than

retest effects reported in the literature (Scharfen et al., 2018), which support causal effects of CWMT on both PS and EF. An association between the EF switching, measured by TMT, and depressive symptoms, emerged following CWMT, suggesting that some associations between symptoms and EF does not disappear following CWMT.

Post-intervention, e-WM showed improvements with similar effects across conditions. The correlation between negative high loading WM condition and rumination disappeared following CWMT, as expected. This suggests that improvements in manipulation of negative material in WM, suspected of contributing to rumination (Ronold et al., 2020a), could improve ruminative tendencies. Improvements in hot cognition following CWMT were found, which could improve the clinical course of remission from MDD (Ahern et al., 2019). Processing of emotional faces could be of particular interest due to its implications for social interaction, and improvements could have positive consequences for interpersonal function (Bourke et al., 2010). This study did not find improvements in symptoms, however, precluding the clinical implications of the reduced associations between e-WM and rumination. Thus, the clinical importance of cognitive improvements remains unclear. In addition, improvements in objective cognitive functions did not transfer to subjective ratings of attention, and there were suggestions that CWMT improvements exacerbated self-rated attention. Objective and subjective cognition are largely distinct (Snyder et al., 2020) however, and findings regarding CWMT and symptomatic improvements are mixed (Barkus, 2020; Legemaat et al., 2021). This could suggest that broader interventions (Myklebost et al., 2021), selection, and personalized interventions for individuals and subgroups with varying degrees of residual symptoms are necessary for optimal effects to appear.

Hypothesis about improvements in symptoms was not supported. Thus, transfer effects, beyond cognition, were not found (Grinberg et al., 2021). This is contrary to the findings of Lengvenyte et al. (2020), where the authors found improvements in depressive symptoms including subjective attention, using similar methods and interventions as this study. However, the authors used subjective cognitive complaints as an inclusion criterion. In addition, it is not evident that MADRS is an optimal measure of subjective cognition (Russo et al., 2015). A recent meta-analysis found that improvements in symptoms following cognitive remediation were related to higher baseline symptomatology (Legemaat et al., 2021), which could help explain our findings. This study had low initial depressive symptoms that could have resulted floor effects in improvement, also influencing sensitivity to state effects. However, the main aim of the study was to investigate CWMT effect on residual cognitive symptoms and not mood symptoms *per se*, resulting in the low mood symptom load in the fully remitted sample at inclusion. Sample size also probably affected results. Meta-studies generally find small associations between EF and rumination (Vălenaș and Szentágotai-Tătar, 2017; Yang et al., 2017; Zetsche et al., 2018), and thus, associations might be too small to detect with the current sample. Rumination did not improve, which could suggest that CWMT does not target this function in remission from MDD. Supporting this, a recent randomized controlled trial did not find effects of cognitive control training on rumination (Ferrari et al., 2021). Possibly, effects could only be evident for a subsample of remitted individuals (Hammar et al., 2020; Woolf et al., 2021), with differing degrees of residual symptomatology and cognitive deficits (Paelecke-Habermann et al., 2005; Pu et al., 2018; Ronold et al., 2021). Thus, inclusion through some sort of objective or subjective deficit or criteria could be essential for optimal effects of CWMT to manifest. The CWMT intervention targeted cold cognition. Targeting hot cognition instead might show larger effects on symptoms as suggested by a recent meta-analysis (Sociali et al., 2022). Future research should compare the effects on interventions targeting hot and cold cognition on several clinically relevant residual symptoms to examine utility for relapse prevention.

Explorative Hypotheses

Explorative analyses found associations between improvements in CWMT and improvements in EF and PS from T1 to T2. Some of the changes in PS and EF showed moderate associations to improvements in CWMT. EF also showed moderate associations to improvements in CWMT, even when controlling for PS. This supports that improvements are related to CWMT and not merely retest effects, and that CWMT improves both EF and PS. In addition, the depression history composite score showed negative associations to the CWIT Inhibition Switching change score, thus supporting an EF deficit associated with depression that could also impair EF improvements from CWMT. This could partly explain the relatively small improvement in this condition and suggests that previous history of illness could impair improvements in parts of the EF domain. These findings could have implications for the timing of interventions and could suggest that some patients may show better training effects for some domains, by utilizing CWMT *early* in their illness (Ahern and Semkovska, 2017). Perhaps, other interventions such as attention bias modification training (Koster and Hoorelbeke, 2015) or interventions targeting hot cognition are more useful than CWMT in later MDD. The CWMT improvement score also showed somewhat paradoxical associations to self-reported attention deficits, with gains being associated with poorer self-assessed cognition. Potential negative effects from CWMT underscore the importance of therapist-assisted interventions, psychoeducation, and/or broader interventions targeting functions beyond WM alone, in interventions targeting residual symptoms in remission from MDD. However, the small, strictly remitted sample, cautions firm conclusion regarding this.

Strengths and Limitations

This is the first study to investigate how CWMT effects e-WM, PS, EF, and symptoms and different forms of rumination combined. Pre-registration of hypotheses was done before analysis. In addition, the sample was selected and the intervention comprehensive. Demand characteristics could have resulted in underreporting of symptoms and could thus have influenced expected associations between MADRS and PS. In addition, dropout was considerable, but not higher than comparable studies. To reduce the chance of type 2

errors, correction of multiple comparisons was not strictly implemented, increasing risk for type 1 errors. The small sample size makes correlation estimates unstable (Schönbrodt and Perugini, 2013), and novel findings in this study should be considered preliminary before being replicated in larger samples. However, it should be noted that this study has higher sample size than 75% of the studies in a recent meta-analysis of cognitive remediation in MDD (Legemaat et al., 2021).

This study shows some overlap with a pilot study on the acceptability and feasibility of CWMT (Hammar et al., 2020). Hammar et al. (2020) investigated some cognitive outcomes of CWMT, namely, WM, inhibition, and rumination, with the two latter similar to this study. However, analyses in the pilot study were done *before all the data were collected* on these measures. In addition, this study investigated several other relevant aspects of cognitive function: e-WM, EF, PS, and depressive symptoms, in a complete dataset. This study focused on the clinically relevant distinctions of hot cognition, PS, and EF, in addition to the differing perspective of investigating the mechanisms of interrelationships between cognitive function and symptoms pre- and post-CWMT. To the best of the authors knowledge, this study is the first CWMT study to do to so, supporting some previous findings (Joormann et al., 2011; Ronold et al., 2020a), while not others (Ronold et al., 2020b), regarding the association between cognitive functioning and depressive symptoms and rumination.

This study design, lacking control group and randomization, makes it hard to control for placebo effects/demand characteristics and retest effects in the sample. However, given the size of improvements, and associations between improvements in CWMT and cognition, it is suggested that both PS and EF are improved by this intervention. Large longitudinal double-blinded randomized controlled studies should replicate and improve on the findings, investigate to what degree effects are *clinically significant* beyond placebo effects, *transfer* to daily functioning, should investigate how long effects last, and what clinical implications they have for relapse, recurrence, quality of life and daily functioning in the remitted phase of MDD. In addition, the change scores utilized in the explorative hypotheses do not correct for the correlated nature of the pre- and post-measures and must be interpreted with caution (Hayes and Rockwood, 2017). Larger samples should thus investigate mediating effects of MDD history on the effects of CWMT, and the associations between EF PS and CWMT.

SUMMARY OF FINDINGS AND CONCLUSIONS

The study supports that computerized working memory training improves cognition in remission from MDD. There was evidence for improvements in *some*, but not *all*, residual symptoms following MDD. Executive functions and processing speed improved, with largest effect for the former. Associations between emotional working memory for negative stimuli and rumination manifested initially but disappeared following the intervention. However, there was no significant decrease in rumination, nor depressive symptoms, but the sample showed low initial mood symptom load. Care should be taken in selection and personalization of interventions for optimal effects in studies and clinical settings. Interventions in remission should probably target a broad range of symptoms for optimal relapse prevention. Computerized working memory training appears to improve cognitive functions in remission from MDD and could thus potentially prevent new episodes and functional decline following MDD. Results suggest that computerized working memory training could be useful for improving processing speed, executive functions, and emotional working memory in MDD, but also that other interventions targeting symptoms could be implemented. Cognitive training targeting hot cognition could potentially remediate symptoms to a larger degree than CWMT. Future studies should investigate which individuals benefit from computerized working memory training and implement personalized interventions for residual symptoms and relapse prevention following MDD. Larger studies identifying subgroups that show different cognitive and symptomatic profiles could identify individuals who benefit from computerized working memory training, and should, together with larger, more controlled effect studies, be pursued by future research.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Committee for Ethical Research in Western Norway (REK 2014/1079), in addition to the Norwegian Data Inspectorate. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ER wrote the current manuscript, collected data, and did statistical analyses. JJ designed the paradigm used to measure e-WM, contributed with ideas for design and analyses, and edited the manuscript. ÅH was PI of the study and contributed with, design, ideas and facilitated data collection, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Doctoral Theses at The Faculty of Psychology, University of Bergen

1980	Allen, Hugh M., Dr. philos.	Parent-offspring interactions in willow grouse (Lagopus L. Lagopus).
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1982	Svebak, Sven, Dr. philos.	The significance of motivation for task-induced tonic physiological changes.
1983	Myhre, Grete, Dr. philos.	The Biopsychology of behavior in captive Willow ptarmigan.
	Eide, Rolf, Dr. philos.	PSYCHOSOCIAL FACTORS AND INDICES OF HEALTH RISKS. The relationship of psychosocial conditions to subjective complaints, arterial blood pressure, serum cholesterol, serum triglycerides and urinary catecholamines in middle aged populations in Western Norway.
	Værnes, Ragnar J., Dr. philos.	Neuropsychological effects of diving.
1984	Kolstad, Arnulf, Dr. philos.	Til diskusjonen om sammenhengen mellom sosiale forhold og psykiske strukturer. En epidemiologisk undersøkelse blant barn og unge.
	Løberg, Tor, Dr. philos.	Neuropsychological assessment in alcohol dependence.
1985	Hellesnes, Tore, Dr. philos.	Læring og problemløsning. En studie av den perseptuelle analysens betydning for verbal læring.
	Håland, Wenche, Dr. philos.	Psykoterapi: relasjon, utviklingsprosess og effekt.
1986	Hagtvet, Knut A., Dr. philos.	The construct of test anxiety: Conceptual and methodological issues.
	Jellestad, Finn K., Dr. philos.	Effects of neuron specific amygdala lesions on fear-motivated behavior in rats.
1987	Aarø, Leif E., Dr. philos.	Health behaviour and sosioeconomic Status. A survey among the adult population in Norway.
	Underlid, Kjell, Dr. philos.	Arbeidsløyse i psykososialt perspektiv.
	Laberg, Jon C., Dr. philos.	Expectancy and classical conditioning in alcoholics' craving.
	Vollmer, Fred, Dr. philos.	Essays on explanation in psychology.
	Ellertsen, Bjørn, Dr. philos.	Migraine and tension headache: Psychophysiology, personality and therapy.
1988	Kaufmann, Astrid, Dr. philos.	Antisosial atferd hos ungdom. En studie av psykologiske determinanter.

	Mykletun, Reidar J., Dr. philos.	Teacher stress: personality, work-load and health.
	Havik, Odd E., Dr. philos.	After the myocardial infarction: A medical and psychological study with special emphasis on perceived illness.
1989	Bråten, Stein, Dr. philos.	Menneskedyaden. En teoretisk tese om sinnets dialogiske natur med informasjons- og utviklingspsykologiske implikasjoner sammenholdt med utvalgte spedbarnsstudier.
	Wold, Bente, Dr. psychol.	Lifestyles and physical activity. A theoretical and empirical analysis of socialization among children and adolescents.
1990	Flaten, Magne A., Dr. psychol.	The role of habituation and learning in reflex modification.
1991	Alsaker, Françoise D., Dr. philos.	Global negative self-evaluations in early adolescence.
	Kraft, Pål, Dr. philos.	AIDS prevention in Norway. Empirical studies on diffusion of knowledge, public opinion, and sexual behaviour.
	Endresen, Inger M., Dr. philos.	Psychoimmuniological stress markers in working life.
	Faleide, Asbjørn O., Dr. philos.	Asthma and allergy in childhood. Psychosocial and psychotherapeutic problems.
1992	Dalen, Knut, Dr. philos.	Hemispheric asymmetry and the Dual-Task Paradigm: An experimental approach.
	Bø, Inge B., Dr. philos.	Ungdoms sosiale økologi. En undersøkelse av 14-16 åringers sosiale nettverk.
	Nivison, Mary E., Dr. philos.	The relationship between noise as an experimental and environmental stressor, physiological changes and psychological factors.
	Torgersen, Anne M., Dr. philos.	Genetic and environmental influence on temperamental behaviour. A longitudinal study of twins from infancy to adolescence.
1993	Larsen, Svein, Dr. philos.	Cultural background and problem drinking.
	Nordhus, Inger Hilde, Dr. philos.	Family caregiving. A community psychological study with special emphasis on clinical interventions.
	Thuen, Frode, Dr. psychol.	Accident-related behaviour among children and young adolescents: Prediction and prevention.
	Solheim, Ragnar, Dr. philos.	Spesifikke lærevansker. Diskrepanskriteriet anvendt i seleksjonsmetodikk.
	Johnsen, Bjørn Helge, Dr. psychol.	Brain assymetry and facial emotional expressions: Conditioning experiments.
1994	Tønnessen, Finn E., Dr. philos.	The etiology of Dyslexia.
	Kvale, Gerd, Dr. psychol.	Psychological factors in anticipatory nausea and vomiting in cancer chemotherapy.
	Asbjørnsen, Arve E., Dr. psychol.	Structural and dynamic factors in dichotic listening: An interactional model.

	Bru, Edvin, Dr. philos.	The role of psychological factors in neck, shoulder and low back pain among female hospitale staff.
	Braathen, Eli T., Dr. psychol.	Prediction of exellence and discontinuation in different types of sport: The significance of motivation and EMG.
	Johannessen, Birte F., Dr. philos.	Det flytende kjønnet. Om lederskap, politikk og identitet.
1995	Sam, David L., Dr. psychol.	Acculturation of young immigrants in Norway: A psychological and socio-cultural adaptation.
	Bjaalid, Inger-Kristin, Dr. philos.	Component processes in word recognition.
	Martinsen, Øyvind, Dr. philos.	Cognitive style and insight.
	Nordby, Helge, Dr. philos.	Processing of auditory deviant events: Mismatch negativity of event-related brain potentials.
	Raaheim, Arild, Dr. philos.	Health perception and health behaviour, theoretical considerations, empirical studies, and practical implications.
	Seltzer, Wencke J., Dr. philos.	Studies of Psychocultural Approach to Families in Therapy.
	Brun, Wibecke, Dr. philos.	Subjective conceptions of uncertainty and risk.
	Aas, Henrik N., Dr. psychol.	Alcohol expectancies and socialization: Adolescents learning to drink.
	Bjørkly, Stål, Dr. psychol.	Diagnosis and prediction of intra-institutional aggressive behaviour in psychotic patients
1996	Anderssen, Norman, Dr. psychol.	Physical activity of young people in a health perspective: Stability, change and social influences.
	Sandal, Gro Mjeldheim, Dr. psychol.	Coping in extreme environments: The role of personality.
	Strumse, Einar, Dr. philos.	The psychology of aesthetics: explaining visual preferences for agrarian landscapes in Western Norway.
	Hestad, Knut, Dr. philos.	Neuropsychological deficits in HIV-1 infection.
	Lugoe, L.Wycliffe, Dr. philos.	Prediction of Tanzanian students' HIV risk and preventive behaviours
	Sandvik, B. Gunnhild, Dr. philos.	Fra distriktsjordmor til institusjonsjordmor. Fremveksten av en profesjon og en profesjonsutdanning
	Lie, Gro Therese, Dr. psychol.	The disease that dares not speak its name: Studies on factors of importance for coping with HIV/AIDS in Northern Tanzania
	Øygard, Lisbet, Dr. philos.	Health behaviors among young adults. A psychological and sociological approach
	Stormark, Kjell Morten, Dr. psychol.	Emotional modulation of selective attention: Experimental and clinical evidence.
	Einarsen, Ståle, Dr. psychol.	Bullying and harassment at work: epidemiological and psychosocial aspects.

1997	Knivsberg, Ann-Mari, Dr. philos.	Behavioural abnormalities and childhood psychopathology: Urinary peptide patterns as a potential tool in diagnosis and remediation.
	Eide, Arne H., Dr. philos.	Adolescent drug use in Zimbabwe. Cultural orientation in a global-local perspective and use of psychoactive substances among secondary school students.
	Sørensen, Marit, Dr. philos.	The psychology of initiating and maintaining exercise and diet behaviour.
	Skjæveland, Oddvar, Dr. psychol.	Relationships between spatial-physical neighborhood attributes and social relations among neighbors.
	Zewdie, Teka, Dr. philos.	Mother-child relational patterns in Ethiopia. Issues of developmental theories and intervention programs.
	Wilhelmsen, Britt Unni, Dr. philos.	Development and evaluation of two educational programmes designed to prevent alcohol use among adolescents.
	Manger, Terje, Dr. philos.	Gender differences in mathematical achievement among Norwegian elementary school students.
1998 V	Lindstrøm, Torill Christine, Dr. philos.	«Good Grief»: Adapting to Bereavement.
	Skogstad, Anders, Dr. philos.	Effects of leadership behaviour on job satisfaction, health and efficiency.
	Haldorsen, Ellen M. Håland, Dr. psychol.	Return to work in low back pain patients.
	Besemer, Susan P., Dr. philos.	Creative Product Analysis: The Search for a Valid Model for Understanding Creativity in Products.
H	Winje, Dagfinn, Dr. psychol.	Psychological adjustment after severe trauma. A longitudinal study of adults' and children's posttraumatic reactions and coping after the bus accident in Måbødalen, Norway 1988.
	Vosburg, Suzanne K., Dr. philos.	The effects of mood on creative problem solving.
	Eriksen, Hege R., Dr. philos.	Stress and coping: Does it really matter for subjective health complaints?
	Jakobsen, Reidar, Dr. psychol.	Empiriske studier av kunnskap og holdninger om hiv/aids og den normative seksuelle utvikling i ungdomsårene.
1999 V	Mikkelsen, Aslaug, Dr. philos.	Effects of learning opportunities and learning climate on occupational health.
	Samdal, Oddrun, Dr. philos.	The school environment as a risk or resource for students' health-related behaviours and subjective well-being.
	Friestad, Christine, Dr. philos.	Social psychological approaches to smoking.
	Ekeland, Tor-Johan, Dr. philos.	Meining som medisin. Ein analyse av placebofenomenet og implikasjoner for terapi og terapeutiske teoriar.
H	Saban, Sara, Dr. psychol.	Brain Asymmetry and Attention: Classical Conditioning Experiments.

	Carlsten, Carl Thomas, Dr. philos.	God lesing – God læring. En aksjonsrettet studie av undervisning i fagtekstlesing.
	Dundas, Ingrid, Dr. psychol.	Functional and dysfunctional closeness. Family interaction and children's adjustment.
	Engen, Liv, Dr. philos.	Kartlegging av leseferdighet på småskoletrinnet og vurdering av faktorer som kan være av betydning for optimal leseutvikling.
2000 V	Hovland, Ole Johan, Dr. philos.	Transforming a self-preserving "alarm" reaction into a self-defeating emotional response: Toward an integrative approach to anxiety as a human phenomenon.
	Lillejord, Sølvi, Dr. philos.	Handlingsrasjonalitet og spesialundervisning. En analyse av aktørperspektiver.
	Sandell, Ove, Dr. philos.	Den varme kunnskapen.
	Oftedal, Marit Petersen, Dr. philos.	Diagnostisering av ordavkodingsvansker: En prosessanalytisk tilnærmingsmåte.
H	Sandbak, Tone, Dr. psychol.	Alcohol consumption and preference in the rat: The significance of individual differences and relationships to stress pathology
	Eid, Jarle, Dr. psychol.	Early predictors of PTSD symptom reporting; The significance of contextual and individual factors.
2001 V	Skinstad, Anne Helene, Dr. philos.	Substance dependence and borderline personality disorders.
	Binder, Per-Einar, Dr. psychol.	Individet og den meningsbærende andre. En teoretisk undersøkelse av de mellommenneskelige forutsetningene for psykisk liv og utvikling med utgangspunkt i Donald Winnicotts teori.
	Roald, Ingvild K., Dr. philos.	Building of concepts. A study of Physics concepts of Norwegian deaf students.
H	Fekadu, Zelalem W., Dr. philos.	Predicting contraceptive use and intention among a sample of adolescent girls. An application of the theory of planned behaviour in Ethiopian context.
	Melesse, Fantu, Dr. philos.	The more intelligent and sensitive child (MISC) mediational intervention in an Ethiopian context: An evaluation study.
	Råheim, Målfrid, Dr. philos.	Kvinners kroppserfaring og livssammenheng. En fenomenologisk – hermeneutisk studie av friske kvinner og kvinner med kroniske muskelsmerter.
	Engelsen, Birthe Kari, Dr. psychol.	Measurement of the eating problem construct.
	Lau, Bjørn, Dr. philos.	Weight and eating concerns in adolescence.
2002 V	Ihlebæk, Camilla, Dr. philos.	Epidemiological studies of subjective health complaints.
	Rosén, Gunnar O. R., Dr. philos.	The phantom limb experience. Models for understanding and treatment of pain with hypnosis.

	Høines, Marit Johnsen, Dr. philos.	Fleksible språkrom. Matematikklæring som tekstutvikling.
	Anthun, Roald Andor, Dr. philos.	School psychology service quality. Consumer appraisal, quality dimensions, and collaborative improvement potential
	Pallesen, Ståle, Dr. psychol.	Insomnia in the elderly. Epidemiology, psychological characteristics and treatment.
	Midthassel, Unni Vere, Dr. philos.	Teacher involvement in school development activity. A study of teachers in Norwegian compulsory schools
	Kallestad, Jan Helge, Dr. philos.	Teachers, schools and implementation of the Olweus Bullying Prevention Program.
H	Ofte, Sonja Helgesen, Dr. psychol.	Right-left discrimination in adults and children.
	Netland, Marit, Dr. psychol.	Exposure to political violence. The need to estimate our estimations.
	Diseth, Åge, Dr. psychol.	Approaches to learning: Validity and prediction of academic performance.
	Bjuland, Raymond, Dr. philos.	Problem solving in geometry. Reasoning processes of student teachers working in small groups: A dialogical approach.
2003 V	Arefjord, Kjersti, Dr. psychol.	After the myocardial infarction – the wives' view. Short- and long-term adjustment in wives of myocardial infarction patients.
	Ingjaldsson, Jón Þorvaldur, Dr. psychol.	Unconscious Processes and Vagal Activity in Alcohol Dependency.
	Holden, Børge, Dr. philos.	Følger av atferdsanalytiske forklaringer for atferdsanalysens tilnærming til utforming av behandling.
	Holsen, Ingrid, Dr. philos.	Depressed mood from adolescence to 'emerging adulthood'. Course and longitudinal influences of body image and parent-adolescent relationship.
	Hammar, Åsa Karin, Dr. psychol.	Major depression and cognitive dysfunction- An experimental study of the cognitive effort hypothesis.
	Sprugevica, Ieva, Dr. philos.	The impact of enabling skills on early reading acquisition.
	Gabrielsen, Egil, Dr. philos.	LESE FOR LIVET. Lesekompetansen i den norske voksenbefolkningen sett i lys av visjonen om en enhetsskole.
H	Hansen, Anita Lill, Dr. psychol.	The influence of heart rate variability in the regulation of attentional and memory processes.
	Dyregrov, Kari, Dr. philos.	The loss of child by suicide, SIDS, and accidents: Consequences, needs and provisions of help.
2004 V	Torsheim, Torbjørn, Dr. psychol.	Student role strain and subjective health complaints: Individual, contextual, and longitudinal perspectives.
	Haugland, Bente Storm Mowatt Dr. psychol.	Parental alcohol abuse. Family functioning and child adjustment.

	Milde, Anne Marita, Dr. psychol.	Ulcerative colitis and the role of stress. Animal studies of psychobiological factors in relationship to experimentally induced colitis.
	Stornes, Tor, Dr. philos.	Socio-moral behaviour in sport. An investigation of perceptions of sportspersonship in handball related to important factors of socio-moral influence.
	Mæhle, Magne, Dr. philos.	Re-inventing the child in family therapy: An investigation of the relevance and applicability of theory and research in child development for family therapy involving children.
	Kobbeltvedt, Therese, Dr. psychol.	Risk and feelings: A field approach.
2004 H	Thomsen, Tormod, Dr. psychol.	Localization of attention in the brain.
	Løberg, Else-Marie, Dr. psychol.	Functional laterality and attention modulation in schizophrenia: Effects of clinical variables.
	Kyrkjebø, Jane Mikkelsen, Dr. philos.	Learning to improve: Integrating continuous quality improvement learning into nursing education.
	Laumann, Karin, Dr. psychol.	Restorative and stress-reducing effects of natural environments: Experiencal, behavioural and cardiovascular indices.
	Holgersen, Helge, PhD	Mellom oss - Essay i relasjonell psykoanalyse.
2005 V	Hetland, Hilde, Dr. psychol.	Leading to the extraordinary? Antecedents and outcomes of transformational leadership.
	Iversen, Anette Christine, Dr. philos.	Social differences in health behaviour: the motivational role of perceived control and coping.
2005 H	Mathisen, Gro Ellen, PhD	Climates for creativity and innovation: Definitions, measurement, predictors and consequences.
	Sævi, Tone, Dr. philos.	Seeing disability pedagogically – The lived experience of disability in the pedagogical encounter.
	Wiium, Nora, PhD	Intrapersonal factors, family and school norms: combined and interactive influence on adolescent smoking behaviour.
	Kanagaratnam, Pushpa, PhD	Subjective and objective correlates of Posttraumatic Stress in immigrants/refugees exposed to political violence.
	Larsen, Torill M. B. , PhD	Evaluating principals` and teachers` implementation of Second Step. A case study of four Norwegian primary schools.
	Bancila, Delia, PhD	Psychosocial stress and distress among Romanian adolescents and adults.
2006 V	Hillestad, Torgeir Martin, Dr. philos.	Normalitet og avvik. Forutsetninger for et objektivt psykopatologisk avviksbegrep. En psykologisk, sosial, erkjennelsesteoretisk og teorihistorisk framstilling.
	Nordanger, Dag Øystein, Dr. psychol.	Psychosocial discourses and responses to political violence in post-war Tigray, Ethiopia.

	Rimol, Lars Morten, PhD	Behavioral and fMRI studies of auditory laterality and speech sound processing.
	Krumsvik, Rune Johan, Dr. philos.	ICT in the school. ICT-initiated school development in lower secondary school.
	Norman, Elisabeth, Dr. psychol.	Gut feelings and unconscious thought: An exploration of fringe consiousness in implicit cognition.
	Israel, K Pravin, Dr. psychol.	Parent involvement in the mental health care of children and adolescents. Emperical studies from clinical care setting.
	Glasø, Lars, PhD	Affects and emotional regulation in leader-subordinate relationships.
	Knutsen, Ketil, Dr. philos.	HISTORIER UNGDOM LEVER – En studie av hvordan ungdommer bruker historie for å gjøre livet meningsfullt.
	Matthiesen, Stig Berge, PhD	Bullying at work. Antecedents and outcomes.
2006 H	Gramstad, Arne, PhD	Neuropsychological assessment of cognitive and emotional functioning in patients with epilepsy.
	Bendixen, Mons, PhD	Antisocial behaviour in early adolescence: Methodological and substantive issues.
	Mrumbi, Khalifa Maulid, PhD	Parental illness and loss to HIV/AIDS as experienced by AIDS orphans aged between 12-17 years from Temeke District, Dar es Salaam, Tanzania: A study of the children's psychosocial health and coping responses.
	Hetland, Jørn, Dr. psychol.	The nature of subjective health complaints in adolescence: Dimensionality, stability, and psychosocial predictors
	Kakoko, Deodatus Conatus Vitalis, PhD	Voluntary HIV counselling and testing service uptake among primary school teachers in Mwanza, Tanzania: assessment of socio-demographic, psychosocial and socio-cognitive aspects
	Mykletun, Arnstein, Dr. psychol.	Mortality and work-related disability as long-term consequences of anxiety and depression: Historical cohort designs based on the HUNT-2 study
	Sivertsen, Børge, PhD	Insomnia in older adults. Consequences, assessment and treatment.
2007 V	Singhammer, John, Dr. philos.	Social conditions from before birth to early adulthood – the influence on health and health behaviour
	Janvin, Carmen Ani Cristea, PhD	Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis
	Braarud, Hanne Cecilie, Dr.psychol.	Infant regulation of distress: A longitudinal study of transactions between mothers and infants
	Tveito, Torill Helene, PhD	Sick Leave and Subjective Health Complaints
	Magnussen, Liv Heide, PhD	Returning disability pensioners with back pain to work

	Thuen, Elin Marie, Dr.philos.	Learning environment, students' coping styles and emotional and behavioural problems. A study of Norwegian secondary school students.
	Solberg, Ole Asbjørn, PhD	Peacekeeping warriors – A longitudinal study of Norwegian peacekeepers in Kosovo
2007 H	Søreide, Gunn Elisabeth, Dr.philos.	Narrative construction of teacher identity
	Svensen, Erling, PhD	WORK & HEALTH. Cognitive Activation Theory of Stress applied in an organisational setting.
	Øverland, Simon Nygaard, PhD	Mental health and impairment in disability benefits. Studies applying linkages between health surveys and administrative registries.
	Eichele, Tom, PhD	Electrophysiological and Hemodynamic Correlates of Expectancy in Target Processing
	Børhaug, Kjetil, Dr.philos.	Oppseding til demokrati. Ein studie av politisk oppseding i norsk skule.
	Eikeland, Thorleif, Dr.philos.	Om å vokse opp på barnehjem og på sykehus. En undersøkelse av barnehjemsbarns opplevelser på barnehjem sammenholdt med sanatoriebarns beskrivelse av langvarige sykehusopphold – og et forsøk på forklaring.
	Wadel, Carl Cato, Dr.philos.	Medarbeidersamhandling og medarbeiderledelse i en lagbasert organisasjon
	Vinje, Hege Forbech, PhD	Thriving despite adversity: Job engagement and self-care among community nurses
	Noort, Maurits van den, PhD	Working memory capacity and foreign language acquisition
2008 V	Breivik, Kyrre, Dr.psychol.	The Adjustment of Children and Adolescents in Different Post-Divorce Family Structures. A Norwegian Study of Risks and Mechanisms.
	Johnsen, Grethe E., PhD	Memory impairment in patients with posttraumatic stress disorder
	Sætrevik, Bjørn, PhD	Cognitive Control in Auditory Processing
	Carvalhosa, Susana Fonseca, PhD	Prevention of bullying in schools: an ecological model
2008 H	Brønnick, Kolbjørn Selvåg	Attentional dysfunction in dementia associated with Parkinson's disease.
	Posserud, Maj-Britt Rocio	Epidemiology of autism spectrum disorders
	Haug, Ellen	Multilevel correlates of physical activity in the school setting
	Skjerve, Arvid	Assessing mild dementia – a study of brief cognitive tests.

	Kjønniksen, Lise	The association between adolescent experiences in physical activity and leisure time physical activity in adulthood: a ten year longitudinal study
	Gundersen, Hilde	The effects of alcohol and expectancy on brain function
	Omvik, Siri	Insomnia – a night and day problem
2009 V	Molde, Helge	Pathological gambling: prevalence, mechanisms and treatment outcome.
	Foss, Else	Den omsorgsfulle væremåte. En studie av voksnes væremåte i forhold til barn i barnehagen.
	Westrheim, Kariane	Education in a Political Context: A study of Konwledge Processes and Learning Sites in the PKK.
	Wehling, Eike	Cognitive and olfactory changes in aging
	Wangberg, Silje C.	Internet based interventions to support health behaviours: The role of self-efficacy.
	Nielsen, Morten B.	Methodological issues in research on workplace bullying. Operationalisations, measurements and samples.
	Sandu, Anca Larisa	MRI measures of brain volume and cortical complexity in clinical groups and during development.
	Guribye, Eugene	Refugees and mental health interventions
	Sørensen, Lin	Emotional problems in inattentive children – effects on cognitive control functions.
	Tjomsland, Hege E.	Health promotion with teachers. Evaluation of the Norwegian Network of Health Promoting Schools: Quantitative and qualitative analyses of predisposing, reinforcing and enabling conditions related to teacher participation and program sustainability.
	Helleve, Ingrid	Productive interactions in ICT supported communities of learners
2009 H	Skorpen, Aina Øye, Christine	Dagliglivet i en psykiatrisk institusjon: En analyse av miljøterapeutiske praksiser
	Andreassen, Cecilie Schou	WORKAHOLISM – Antecedents and Outcomes
	Stang, Ingun	Being in the same boat: An empowerment intervention in breast cancer self-help groups
	Sequeira, Sarah Dorothee Dos Santos	The effects of background noise on asymmetrical speech perception
	Kleiven, Jo, dr.philos.	The Lillehammer scales: Measuring common motives for vacation and leisure behavior
	Jónsdóttir, Guðrún	Dubito ergo sum? Ni jenter møter naturfaglig kunnskap.
	Hove, Oddbjørn	Mental health disorders in adults with intellectual disabilities - Methods of assessment and prevalence of mental health disorders and problem behaviour
	Wageningen, Heidi Karin van	The role of glutamate on brain function

	Bjørkvik, Jofrid	God nok? Selvaktelse og interpersonlig fungering hos pasienter innen psykisk helsevern: Forholdet til diagnoser, symptomer og behandlingsutbytte
	Andersson, Martin	A study of attention control in children and elderly using a forced-attention dichotic listening paradigm
	Almås, Aslaug Grov	Teachers in the Digital Network Society: Visions and Realities. A study of teachers' experiences with the use of ICT in teaching and learning.
	Ulvik, Marit	Lærerutdanning som danning? Tre stemmer i diskusjonen
2010 V	Skår, Randi	Læringsprosesser i sykepleieres profesjonsutøvelse. En studie av sykepleieres læringserfaringer.
	Roald, Knut	Kvalitetsvurdering som organisasjonslæring mellom skole og skoleeigar
	Lunde, Linn-Heidi	Chronic pain in older adults. Consequences, assessment and treatment.
	Danielsen, Anne Grete	Perceived psychosocial support, students' self-reported academic initiative and perceived life satisfaction
	Hysing, Mari	Mental health in children with chronic illness
	Olsen, Olav Kjellevold	Are good leaders moral leaders? The relationship between effective military operational leadership and morals
	Riese, Hanne	Friendship and learning. Entrepreneurship education through mini-enterprises.
	Holthe, Asle	Evaluating the implementation of the Norwegian guidelines for healthy school meals: A case study involving three secondary schools
H	Hauge, Lars Johan	Environmental antecedents of workplace bullying: A multi-design approach
	Bjørkelo, Brita	Whistleblowing at work: Antecedents and consequences
	Reme, Silje Endresen	Common Complaints – Common Cure? Psychiatric comorbidity and predictors of treatment outcome in low back pain and irritable bowel syndrome
	Helland, Wenche Andersen	Communication difficulties in children identified with psychiatric problems
	Beneventi, Harald	Neuronal correlates of working memory in dyslexia
	Thygesen, Elin	Subjective health and coping in care-dependent old persons living at home
	Aanes, Mette Marthinussen	Poor social relationships as a threat to belongingness needs. Interpersonal stress and subjective health complaints: Mediating and moderating factors.
	Anker, Morten Gustav	Client directed outcome informed couple therapy

	Bull, Torill	Combining employment and child care: The subjective well-being of single women in Scandinavia and in Southern Europe
	Viig, Nina Grieg	Tilrettelegging for læreres deltakelse i helsefremmende arbeid. En kvalitativ og kvantitativ analyse av sammenhengen mellom organisatoriske forhold og læreres deltakelse i utvikling og implementering av Europeisk Nettverk av Helsefremmende Skoler i Norge
	Wolff, Katharina	To know or not to know? Attitudes towards receiving genetic information among patients and the general public.
	Ogden, Terje, dr.philos.	Familiebasert behandling av alvorlige atferdsproblemer blant barn og ungdom. Evaluering og implementering av evidensbaserte behandlingsprogrammer i Norge.
	Solberg, Mona Elin	Self-reported bullying and victimisation at school: Prevalence, overlap and psychosocial adjustment.
2011 V	Bye, Hege Høivik	Self-presentation in job interviews. Individual and cultural differences in applicant self-presentation during job interviews and hiring managers' evaluation
	Notelaers, Guy	Workplace bullying. A risk control perspective.
	Moltu, Christian	Being a therapist in difficult therapeutic impasses. A hermeneutic phenomenological analysis of skilled psychotherapists' experiences, needs, and strategies in difficult therapies ending well.
	Myrseth, Helga	Pathological Gambling - Treatment and Personality Factors
	Schanche, Elisabeth	From self-criticism to self-compassion. An empirical investigation of hypothesized change prosesses in the Affect Phobia Treatment Model of short-term dynamic psychotherapy for patients with Cluster C personality disorders.
	Våpenstad, Eystein Victor, dr.philos.	Det tempererte nærvær. En teoretisk undersøkelse av psykoterapautens subjektivitet i psykoanalyse og psykoanalytisk psykoterapi.
	Haukebø, Kristin	Cognitive, behavioral and neural correlates of dental and intra-oral injection phobia. Results from one treatment and one fMRI study of randomized, controlled design.
	Harris, Anette	Adaptation and health in extreme and isolated environments. From 78°N to 75°S.
	Bjørknes, Ragnhild	Parent Management Training-Oregon Model: intervention effects on maternal practice and child behavior in ethnic minority families
	Mamen, Asgeir	Aspects of using physical training in patients with substance dependence and additional mental distress
	Espevik, Roar	Expert teams: Do shared mental models of team members make a difference
	Haara, Frode Olav	Unveiling teachers' reasons for choosing practical activities in mathematics teaching

2011 H	Hauge, Hans Abraham	How can employee empowerment be made conducive to both employee health and organisation performance? An empirical investigation of a tailor-made approach to organisation learning in a municipal public service organisation.
	Melkevik, Ole Rogstad	Screen-based sedentary behaviours: pastimes for the poor, inactive and overweight? A cross-national survey of children and adolescents in 39 countries.
	Vøllestad, Jon	Mindfulness-based treatment for anxiety disorders. A quantitative review of the evidence, results from a randomized controlled trial, and a qualitative exploration of patient experiences.
	Tolo, Astrid	Hvordan blir lærerkompetanse konstruert? En kvalitativ studie av PPU-studenters kunnskapsutvikling.
	Saus, Evelyn-Rose	Training effectiveness: Situation awareness training in simulators
	Nordgreen, Tine	Internet-based self-help for social anxiety disorder and panic disorder. Factors associated with effect and use of self-help.
	Munkvold, Linda Helen	Oppositional Defiant Disorder: Informant discrepancies, gender differences, co-occuring mental health problems and neurocognitive function.
	Christiansen, Øivin	Når barn plasseres utenfor hjemmet: beslutninger, forløp og relasjoner. Under barnevernets (ved)tak.
	Brunborg, Geir Scott	Conditionability and Reinforcement Sensitivity in Gambling Behaviour
	Hystad, Sigurd William	Measuring Psychological Resiliency: Validation of an Adapted Norwegian Hardiness Scale
2012 V	Roness, Dag	Hvorfor bli lærer? Motivasjon for utdanning og utøving.
	Fjermestad, Krister Westlye	The therapeutic alliance in cognitive behavioural therapy for youth anxiety disorders
	Jenssen, Eirik Sørnes	Tilpasset opplæring i norsk skole: politikeres, skoleledereres og læreres handlingsvalg
	Saksvik-Lehouillier, Ingvild	Shift work tolerance and adaptation to shift work among offshore workers and nurses
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