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The influence of a computerized social cognitive training on the functional connectivity of the brain in major depressive disorder

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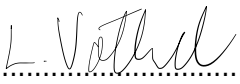
Unterschrift: 

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To my parents, Nina, Luisa and Henning.

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List of abbreviations

AAL *Automated anatomical labeling*
ADS-F/-B *Auditory Digit Span Test - forward and backward version*
AMAP *Adaptive Maximum A Posteriori*
AN *Affective network*
ANCOVA *Analysis of Covariance*
APA *American Psychiatric Association*
BOLD *Blood oxygenation level dependent*
BWT *Brain Wavelet Toolbox*
CAT12 *Computational anatomy toolbox 12*
CBT *Cognitive behavioral therapy*
CCN *Cognitive control network*
CPT-IP *Continuous Performance Test - Identical Pair Version*
CR *Cognitive remediation*
CSF *Cerebrospinal fluid*
DANVA *Diagnostical Analysis of Non-verbal Accuracy Test*
DANVA-2-AF *Diagnostic Analysis of Non-Verbal Accuracy - Adult Face Subtest*
DARTEL *Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra*
dlPFC *Dorsolateral prefrontal cortex*
DMN *Default Mode Network*
DSM-V *Diagnostic and Statistical Manual of Mental Disorders - fifth edition*
DSST *Digit Symbol Substitution Test*
ECT *Electroconvulsive therapy*
EEG *Electroencephalography*
EMT *Emotion matching task*
EPI *Echoplanar imaging*
FC *Functional connectivity*
FD *Framewise displacement*
fMRI *Functional magnetic resonance imaging*
FU *Follow-up*
FWE *Family Wise Error*
GAF Global Assessment of Functioning
GAF-D *Global Assessment of Functioning - Disability score*
GAF-S *Global Assessment of Functioning - Symptoms score*
GDP *Gross domestic product*
GF *General Functioning Score*
GF-R General Role Functioning
GF-S General Social functioning
GM *Gray matter*
HDRS-17 *Hamilton Depression Rating Scale – 17th version*
IQ *Intelligence Quotient*
MCCB *MATRICS Consensus Cognitive Battery*
MDD *Major depressive disorder*
MFL *Medial frontal lobe*
MMN *Mismatch negativity*
MNI *Montreal Neurological Institute*
MPRAGE *Magnetization Prepared - Rapid Gradient Echo*
MRT *Magnetresonanztomographie*
NIMH *National Institute of Mental Health*
PANAS *Positive and Negative Affect Scale*
PFC *Medial prefrontal cortex*
RAVLT *Rey Auditory Verbal Learning Test*

RCT *Randomized controlled trial*
REST *Resting-state fMRI Data Analysis Toolkit*
ROD *Recent-onset depression*
ROI *Regions-of-interest*
rsFC *Resting-state functional connectivity*
rsfMRI *Resting state functional magnetic resonance imaging*
SCID-4 *Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition for Axis I Disorders*
SFL *Superior frontal lobe*
sMRI *Structural magnetic resonance imaging*
SPC *Sensory processing change*
SPM-12 *Statistical Parametric Mapping, version 12*
SSRI *Selective serotonin reuptake inhibitors*
STL *Superior temporal lobe*
T0 *Timepoint 0*
tDCS *Transcranial direct current stimulation*
TE *Time to Echo*
TMT *Trail Making Test*
TMT-A *Trail Making Test - Part A*
TMT-B *Trail Making Test - Part B*
TR *Repetition time*
VFT-P *Verbal Fluency Test - Phonemic Version*
VFT-S *Verbal Fluency Test - Semantic Version*
vmPFC *Ventromedial prefrontal cortex*
WAIS *Wechsler Adult Intelligence Scale*
WAIS-MR *Wechsler Adult Intelligence Scale, Matrices Subtest*
WAIS-V *Wechsler Adult Intelligence Scale, Vocabulary Subtest*
WFU PickAtlas *Wake Forest University PickAtlas*
WM *White matter*

1 Summary

1.1 Deutsche Zusammenfassung

Hintergrund Kognitive Defizite sind ein Kernthema der Major Depression (MDD) [1,2] und wirken sich auf multiple Bereiche des täglichen Lebens wie die Aufrechterhaltung von Beziehungen oder die Bewältigung der Anforderungen am Arbeitsplatz aus [3]. Ein vielversprechender Ansatz bei der Behandlung von kognitiven Defiziten ist computer-basiertes kognitives Training (CCT) [1,4]. Diese Therapieform nutzt die Mechanismen der Neuroplastizität um Gehirnregionen, die der Kognition und den Emotionen unterliegen, umzustrukturieren und damit die kognitiven Einschränkungen von betroffenen Personen zu lindern und die Alltagsfunktionalität wiederherzustellen [1,5,6]. Die Programme von CCT zielen auf frühe Prozesse in der Verarbeitung von Sinneswahrnehmungen ab [6-8], wobei die Verarbeitung von sozial-relevanten Stimuli bei computer-basiertem sozial-kognitivem Training (SCT) im Vordergrund steht [8]. In vorangegangenen Studien variierte jedoch die Ansprechrate auf CCT, sodass die Identifizierung von Indikatoren für die Trainingseffizienz und ein positives Ansprechen auf die Therapie Gegenstand aktueller Forschung ist [6]. Hierbei wiesen erste Ergebnisse daraufhin, dass die Fähigkeit zur Verarbeitung von sensorischen Eindrücken ein potentielles Maß für die Trainingseffizienz und den Therapieerfolg von CCT darstellt [9,10].

Ziele In dieser randomisiert-kontrollierten Studie (RCT) untersuchten wir den Effekt von computer-basiertem SCT auf (1) die Kognition und die Alltagsfunktionalität (2) die spontane funktionelle Konnektivität bestimmter Hirnregionen (dorsolateraler präfrontaler Kortex [dlPFC], Nucleus caudatus und Amygdala) im Ruhezustand des Gehirns (rsFC) und (3) die Beziehung zwischen kognitiven und neuralen Veränderungen im Vergleich zur Standardtherapie (TAU) bei der MDD. Darüber hinaus interessierte uns die Rolle der individuellen Verarbeitung von sensorischen Informationen, sodass wir die Auswirkungen von SCT auf die (1) Kognition und die Alltagsfunktionalität (2) die rsFC bestimmter Hirnregionen (dlPFC, Nucleus caudatus und Amygdala) und (3) die Beziehung zwischen kognitiven und neuralen Veränderungen in Gruppen mit unterschiedlicher sensorischer Sinnesverarbeitung analysierten.

Methodik Die Teilnehmer der Studie wurden mit Hilfe des Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition for Axis I Disorders (SCID-4) auf eine MDD hin gescreent. Eingeschlossene Probanden durchliefen eine klinische und kognitive Testung sowie eine kraniale Magnetresonanztomographie-Untersuchung (MRT) und wurden anschließend per Zufall der SCT- oder der TAU -Gruppe zugeteilt. Die SCT-Gruppe erhielt zusätzlich zur TAU ein computer-gestütztes SCT über einen Zeitraum von vier bis sechs Wochen und einer Gesamtdauer von 10 Stunden. Am Ende der Studie erhielten alle Teilnehmer eine zweite klinische und kognitive Testung sowie eine kraniale MRT-

Untersuchung. Darüber hinaus wurden die Probanden der SCT-Gruppe anhand ihrer Leistung in der „Emotion matching task“ (EMT) in „Maintainers“ (intakte sensorische Verarbeitung) und „Improvers“ (eingeschränkte sensorische Verarbeitung) eingeteilt. Um Gruppenunterschiede zwischen (1) der SCT- und der TAU-Gruppe und (2) Maintainern und Improvern bei der Kognition und der Alltagsfunktionalität über den Studienzeitraum hinweg festzustellen, verwendeten wir eine Kovarianzanalyse. Mit Hilfe der Statistical Parametric Mapping, version 12 (SPM-12) (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) version 6685 Software erstellten wir „Correlationmaps“ der rsFC zwischen den zuvor festgelegten Gehirnregionen (dlPFC, Nucleus caudatus und Amygdala) und dem restlichen Gehirn um (1) den Effekt von SCT auf die rsFC verglichen mit TAU und (2) den Effekt von SCT auf die rsFC von Maintainern und Improvern zu untersuchen. Schließlich berechneten wir den Pearson’s Korrelationsstest zur Überprüfung einer möglichen Assoziation zwischen neuralen und kognitiven Veränderungen.

Ergebnisse Das SCT zeigte in dieser Studie keinen zusätzlichen Nutzen für die Kognition oder die Alltagsfunktionalität von Personen mit einer MDD verglichen mit TAU. Bezogen auf die Fähigkeit zur Verarbeitung von Sinneseindrücken in der SCT-Gruppe, schnitten Maintainers zu Beginn der Studie im Bereich soziale Kognition signifikant besser ab ($F = 1.72$; $p = 0.05$), wohingegen Improvers über den Studienzeitraum die Effizienz der Verarbeitung sensorischer Informationen steigerten und sich im Bereich soziale Kognition signifikant verbesserten ($F = 7.78$; $p = 0.01$; $\eta^2_G = 0.34$). Maintainers profitierten hingegen im Bereich soziale Alltagsfunktionalität von dem SCT (GF-S: $F = 5.42$; $p = 0.03$; $\eta^2_G = 0.27$). Über den Studienzeitraum hinweg zeigten Teilnehmer in der SCT-Gruppe signifikant erhöhte rsFC zwischen dem rechten Nucleus caudatus und dem linken Lobus temporalis superior (STL) (p-corr. = <0.01) im Vergleich zur TAU-Gruppe. Dahingegen fanden wir in der TAU-Gruppe eine signifikant erhöhte rsFC zwischen dem rechten Nucleus caudatus und dem linken und rechten Lobus frontalis superior (SFL) (rechter SFL: p-corr. = 0.04; linker SFL: p-corr. = < 0.01) sowie dem rechten dlPFC und dem linken medialen Cingulum (p-corr. = <0.01) und dem rechten Precuneus (p-corr. = 0.02) im Vergleich zur SCT-Gruppe vom Beginn bis zum Ende der Studie. Bei dem Vergleich der Gruppen mit unterschiedlicher Effizienz der Verarbeitung sensorischer Informationen fanden wir in der Improver-Gruppe einen signifikanten Interaktionseffekt auf die rsFC zwischen der linken Amygdala und dem linken SFL (p-corr. = <0.01) und dem linken Lobus frontalis medialis (MFL) (p-corr.= <0.01) im Vergleich zu Maintainern über den Studienzeitraum hinweg. Auch in der Gruppe der Maintainer stellten wir eine signifikant erhöhte rsFC zwischen der linken Amygdala und dem linken MFL (p-corr. = < 0.01) von Anfang bis Ende der Studie, verglichen mit Improvern, fest. Die Analyse der Beziehung zwischen

kognitiven und neuralen Veränderungen blieb sowohl für den Vergleich zwischen 1) SCT- und TAU-Gruppe und (2) Maintainern and Improvern ohne statistisch signifikante Ergebnisse.

Schlussfolgerung Den Ergebnissen unserer Studie zufolge erfordert die Beurteilung der Effektivität von SCT bei der MDD eine differenzierte Betrachtung der Studienteilnehmer, wobei sich die Verarbeitung von sensorischen Informationen als möglicher Mediator des Therapieansprechens herausstellte. So wirkte sich das SCT insbesondere bei Personen mit eingeschränkten sensorischen Verarbeitungsvermögen, welche ebenfalls schlechtere kognitive Fähigkeiten präsentierten, positiv auf die Verarbeitungseffizienz sowie die soziale Kognition aus. Entsprechend dieser Ergebnisse könnte die Messung der sensorischen Verarbeitungsgeschwindigkeit als Indikator für die Trainingseffizienz und das Therapieansprechen auf SCT hinsichtlich der Kognition und Alltagsfunktionalität dienen. Als mögliches Korrelat trainings-induzierter neuraler Veränderungen stellten wir unter SCT eine Verstärkung der rsFC zwischen Strukturen der emotionalen Informationsverarbeitung im Vergleich zu TAU fest. Da auch unter TAU signifikant erhöhte funktionale Konnektivität zwischen unterschiedlichen neuralen Netzwerken auftrat, sind jedoch weitere Studien zu Erforschung der neuralen Veränderungen unter SCT bei der Depression nötig. Die verstärkte funktionelle Konnektivität zwischen limbischen und frontalen Strukturen im Vergleich der Gruppen mit unterschiedlicher sensorischer Verarbeitungseffizienz unterstreicht dabei die Erkenntnisse vorangegangener Studien zur Rolle der fronto-limbischen neuralen Verbindungen bei der Pathophysiologie der Depression [11], welche ein mögliches Ziel der neuroplastischen Effekte von SCT darstellt. Auch für die Analyse der Beziehung von kognitiven und neuralen Veränderungen unter SCT bei der Depression sind zukünftige Studien nötig.

1.2 English abstract

Background Cognitive impairment is common in major depressive disorder (MDD) [1,2] and influences multiple domains of daily living such as maintaining relationships or work performance [3]. A promising approach that demonstrated an effect on cognitive deficits is computerized cognitive training (CCT) [1,4]. This therapy method induces neuroplastic changes in the brain representational system of cognitive and emotional processes to reduce cognitive impairment and reach functional recovery [1,5,6]. The exercises of CCT focus on early perceptual processes, whereby the processing of socially relevant stimuli is on the forefront in social cognitive training (SCT) interventions [6-8]. However, treatment response to CCT varies between the participants, and current research shifted the attention towards the identification of behavioral and neural markers to measure the target engagement and to predict future outcome [6]. Preliminary results now suggest the individual sensory processing behavior as a potential marker for target engagement and treatment response to CCT [9,10].

Aims In this randomized controlled trial (RCT) we examined the effect of a computerized SCT on (1) the cognitive performance and psychosocial functioning (2) the rsFC of a priori selected brain regions (dorsolateral prefrontal cortex [dlPFC], caudate nucleus and amygdala) and the rest of the brain and (3) the relationship between the change in the cognitive performance and the rsFC as compared to TAU. We were further interested in the role of distinct patterns of sensory processing behavior and therefore analyzed the effect of a SCT on (1) the cognitive performance and psychosocial functioning (2) the rsFC of a priori selected brain regions (dlPFC, caudate nucleus and amygdala) and the rest of the brain and (3) the relationship between the change in the cognitive performance and the rsFC between groups with diverging sensory processing behavior.

Methods Participants were screened for MDD with the SCID-IV. Included subjects (n=40) underwent a standardized clinical and cognitive assessment and a neuroimaging scan and were then randomized to the SCT or the TAU group. Participants in the former received a ten hours computerized SCT over four to six weeks additional to TAU. At the end of the study, both the clinical and the cognitive assessment and the neuroimaging scan were replicated, and participants in the SCT group were additionally classified as Maintainers (perceived baseline sensory processing efficiency) or Improvers (impaired baseline sensory processing efficiency) depending on the individual performance in the EMT. To examine group differences between (1) the SCT and the TAU group and (2) Maintainers and Improvers on the cognitive performance and psychosocial functioning from baseline to follow-up, we used an analysis of covariance (ANCOVA). Correlation maps of the rsFC between the a priori selected brain regions (dlPFC, caudate nucleus and amygdala) and the rest of the brain were further

calculated with SPM-12 to investigate (1) the effect of the SCT on the rsFC of MDD patients as compared to TAU and (2) the effect of the SCT on the rsFC of Maintainers and Improvers across the study. Lastly, Pearsons's correlation tests were performed to analyze the association between the change in the rsFC and the cognitive performance in each group.

Results SCT did not show an additional effect on cognition or psychosocial functioning as compared to TAU in this study. However, Maintainers exhibited significantly higher scores on social cognition at baseline ($F = 1.72$; $p = 0.05$) while Improvers enhanced the sensory processing efficiency and showed significantly increased social cognitive abilities across the study ($F = 7.78$; $p = 0.01$; $\eta^2_G = 0.34$). Moreover, Maintainers showed significantly more benefit on a social functioning score (GF-S: $F = 5.42$; $p = 0.03$; $\eta^2_G = 0.27$). On the neural level, we found a significant increase of the rsFC between the right caudate and the left superior temporal lobe (STL) (p-corr. = <0.01) in the SCT group compared to TAU across the study. On the contrary, participants in the TAU group exhibited a significantly enhanced rsFC between the right caudate and the bilateral superior frontal lobe (SFL) (right SFL: p-corr. = 0.04; left SFL: p-corr. = < 0.01) as well as between the right dlPFC and the left medial cingulum (p-corr. = <0.01) and the right precuneus (p-corr. = 0.02) compared to SCT over the follow-up period. We further identified a significant group by time interaction on the rsFC between the left amygdala and the left SFL (p-corr. = < 0.01) and the left medial frontal lobe (MFL) (p-corr.= <0.01) in the Improvers group compared to Maintainers. Likewise, the rsFC between the left Amygdala and the left MFL (p-corr. = < 0.01) was significantly increased in the Maintainers group compared to Improvers across the study. There was neither a significant correlation between the cognitive and the neural changes in 1) the SCT and the TAU group nor 2) Maintainers and Improvers.

Conclusion The results of our study indicate that the effect of SCT on cognition and psychosocial functioning probably depends on individual characteristics of the participants whereby the sensory processing efficiency might be one of the mediators of therapy response. Consecutively, individuals with reduced sensory processing efficiency, who additionally presented impaired baseline cognitive functions, seem to benefit more clearly from SCT. Hereinafter the individual sensory processing efficiency might serve as a behavioral measure of target engagement to predict the treatment response to SCT. On the neural level, increased rsFC between neural structures that are integrated in the processing of emotional stimuli underline the potential of SCT to induce neuroplastic changes in the brain. Since we additionally identified altered rsFC between distributed brain regions in the TAU group over the follow-up period, further studies are needed to precisely identify the neuroplastic mechanism underlying SCT. However, the reorganization of fronto-limbic pathways, which plays an important role in the pathophysiology of depression [11], might be an appropriate neural target

for cognitive training interventions. Finally, future studies on the relation of cognitive and neural changes after SCT in depression are needed.

2 Introduction

2.1 Major depressive disorder

2.1.1 Definition and epidemiology

MDD is a severe mental disease that affects more than 350 million people worldwide [12,13]. Mean lifetime prevalence is estimated at 13% in western countries with women being affected twice as frequently as men [14,15]. The typical age of onset of the first depressive episode is in the middle 20s, whereby the distribution varies from late adolescence to late adulthood [16]. Affected individuals suffer from a depressed mood and a loss of interest, that are the key features of MDD according to the Diagnostic and Statistical Manual of Mental Disorders - fifth edition (DSM-V) [17].

MDD substantially contributes to the morbidity and mortality in the global society [16]. Thus depression is listed as the main cause of life years lost to premature death and disability in developing countries [18] and counts the highest number of disability adjusted life years in the world [19]. The societal burden of MDD is further emphasized by a study of Kessler, Akiskal [20] who reported on a reduced work productivity and increased work absenteeism of patients affected by MDD which led to an annual mean loss of 27.2 workdays per ill worker and makes depression the most costly brain disorder, causing 33% of the total cost in Europe [21]. Consecutively, the total annual cost of depression in Europe was estimated at 118 billion euros in 2004 which corresponds to 1% of the total economy of Europe (GDP) [22].

2.1.2 Etiology

To date, the exact etiology of MDD is not completely understood [23]. Recent findings suggest a multifactorial genesis of depression and highlight the role of both biological and psychological aspects [24]. From a neurochemical perspective, depressive symptoms seem to arise from a disruption of the interaction between multiple neural circuits [25]. Thus researchers observed that agents targeting the monoamine system by increasing the concentration of monoamine neurotransmitters (serotonin, norepinephrine) in the synaptic gap [3] lead to reduced depressive symptoms [25] and consequently established the monoamine hypothesis [3,26]. This neurochemical hypothesis declares the deficiency of the monoamine system as a biological mechanism underlying depression [3]. Additionally, epidemiological twin studies demonstrated a certain genetic risk for family members of affected individuals [27].

More recently, the focus turned to the diathesis-stress-model which states that the development of depressive symptoms results from stress factors or stimuli (e.g. hormonal disturbances, somatic diseases, personal losses, interpersonal conflicts) that appear additionally to a premorbid personality [28-30]. Abramson, Seligman [31] further established the

hopelessness theory of depression which “posits that repeated exposure to uncontrollable and aversive environmental stimuli leads gradually to the belief that the aversive situation is inescapable and a sense of helplessness ensues regarding the situation. This helplessness, in turn, results in depression” [32]. According to this theory, the individual risk to develop a depression strongly depends on the causal attribution of negative life events in the dimensions of internal to external, stable to unstable and global to specific [32]. Hence the risk to develop a depression significantly increases with an internal, stable and global attribution of negative events [32]. Lastly, the cognitive triad first developed by Beck [33], highlights three components of a person’s belief-system that are: the self-perception, the environment and the future, and states that individuals with a negative attribution of new information to the mentioned domains develop a dysfunctional cognitive system that increases the risk for depression [34].

2.1.3 Diagnosis

According to the DSM-V [17], key features of MDD (a loss of interest and a depressed mood) must persist over a minimum period of two weeks. Other symptoms include:

i. Significant weight loss or decrease or increase in appetite
ii. In- or Hypersomnia
iii. Impaired psychomotor activity
iv. Fatigue or loss of energy
v. Decreased ability to think or concentrate
vi. Recurrent thoughts of death or suicide attempts
vii. Feelings of worthlessness or inadequate guilt.

MDD is primarily diagnosed based on clinical characteristics. Nevertheless, any organic cause must be ruled out by neuroimaging, electroencephalography (EEG) or blood test in the first place. A major depressive episode is diagnosed if a minimum of five of the aforementioned criteria is reached.

2.1.4 Therapy and prognosis

The acute therapy of MDD targets both the reduction or remission of symptoms and the psychosocial and occupational rehabilitation [23]. Depending on the severity and the stage of the disease, the therapeutical approach includes low-intensity interventions (e.g. guided self-help, the strengthening of self-management and psychoeducation), psychotherapy, antidepressant medication, neurostimulation, psychosocial interventions or supplementary therapy (physical exercise therapy, phototherapy, peer support) [23]. Besides psychoeducation and the provision of information about the disease, low-intensity interventions, internet-based approaches or psychotherapy are in the forefront to treat patients with mild depression [23]. In contrast, S3-

guidelines recommend psychotherapy, antidepressant medication or the combination of both for the treatment of moderate to severe depression [23].

The pharmacological mechanism of the majority of antidepressants relies on the neural monoamine system, whereby these agents increase the concentration of monoamine neurotransmitters in the synaptic gap [23]. Selective serotonin reuptake inhibitors (SSRI), that increase the serotonerg neurotransmission of the central neural system by inhibiting the reuptake of serotonin in the synaptic gap, are the most frequently prescribed antidepressants in Germany [23]. However, the actual S3-guidelines prefer the combination of different treatment approaches rather than the sole use of antidepressant medication [23].

Cognitive behavioral therapy (CBT), psychoanalytic approaches and systemic therapy are commonly used for the ambulant treatment of MDD patients [23], whereby CBT is the most frequently examined psychotherapeutic intervention [23]. This therapy method reframes cognitive distortion and behavior, and introduces coping strategies and skills that can be used in challenging situations [23]. With regard to the selection of the best-fitting psychotherapeutic intervention, the S3-guidelines recommend a participative decision depending on the individual characteristics of the patient (e.g. the therapeutic relationship, the motivation and the perception of the patient, the therapy setting and the individual resources) [23].

Despite these well-implemented therapies, MDD counts a chronicity rate of 20% [35] and a mean number of 5 episodes per lifetime [36]. Moreover, patients often experience a relapse of the disease under treatment or do not recover completely [37,38].

2.2 Cognition and psychosocial functioning as a raising topic in MDD

2.2.1 The effect of MDD on psychosocial functioning

Impaired psychosocial functioning is a common feature of MDD[39,40]. Thus IsHak, Mirocha [41] observed that 90% of MDD patients suffer from functional disability while another 20% remain permanently incapacitated even after remission [42]. Additionally, the mean disability score of remitted MDD patients is still above the score of healthy individuals [43] (https://harmresearch.org/product/sheehan-disability-scale-sds-2/).

Psychosocial functioning is defined as “the degree to which individuals successfully interact with their environment across in daily, occupational, and social domains” [44,45] and includes interpersonal relationships [46], everyday functioning [47], home management [48], employment status [46] and occupational productivity [46]. Affected individuals struggle with day-to-day environmental and social tasks which results in problems with maintaining relationships or workforce performance [49,50].

However, depressive symptomatology does not cover the entire magnitude of disability found in depression [51]. Thus, Knight, Air [52] identified cognitive function as a mediator between symptom severity and functional disability. Buist-Bouwman, Ormel [53] further observed that cognitive impairment leads to reduced psychosocial abilities and predicts functional outcome in MDD [54]. Thereby, several cognitive domains influence psychosocial functioning such as attention [51], verbal learning [18] , psychomotor speed [55], memory [56], processing speed [18], executive functioning [18] and social cognition [57].

2.2.2 The role of cognitive deficits in MDD

Cognitive deficits are often present in MDD [1,2]. Nearly two thirds of MDD patients experience cognitive impairment in the acute stage of the illness [58] while deficits can also persist through remission [59]. These deficits include a wide range of domains such as working memory [59], verbal learning [60], psychomotor speed [61], attention [62], executive function [62] and social cognition [63,64]. While some cognitive domains (e.g. “working memory”, “verbal fluency”, “psychomotor speed” and “social cognition”) were strongly associated with depressive symptom severity and the clinical state [58,65-67], other domains showed a permanent decrease in remitted patients (e.g. “attention”, “response inhibition” and “verbal fluency”) [68-71] .

The consequences of cognitive impairment are far-reaching [72] since it leads to an increased chronicity rate [73] and heightens the risk of relapse of depression [74]. However, cognitive impairment remains an unmet need in the conventional therapy of MDD [58]. In a study of Potter, Kittinger [75] verbal perseveration among depressed older adults was associated with a lower remission rate after a pharmacological treatment. Moreover, subtle prefrontal dysfunction in MDD patients predicted poor treatment response to fluoxetine [76], and impaired attention was associated with delayed response to pharmacological treatment [74]. Likewise, a certain number of MDD patients did not successfully respond to cognitive therapy in a study of DeRubeis, Hollon [77].

2.2.3 Cognitive training as a method of treatment in MDD

A promising approach that targets cognitive impairment is cognitive remediation (CR)[78-81]. This therapy method was defined by the Cognitive Remediation Experts Workshop (Florence, Italy, April 2010) as “a behavioral training-based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition or metacognition) with the goal of durability and generalization” [82]. The interventions are specifically designed cognitive learning events that reduce cognitive impairment and improve a broad range of functionally relevant domains to reach functional recovery [1,5,83]. The effectiveness of CR is based on neuroplastic mechanisms that target impaired neural systems underlying cognitive processes and induce neural changes in the brain representational system [6]. The idea of CR is to identify

and target key neural systems that enhance cognition and community functioning with the ultimate goal to develop a personalized cognitive training program that may serve as a preventive intervention [6].

A widely accessible form of the CR technique is CCT [84]. This therapy method uses software to train and improve cognitive functions, whereby one single or an array of cognitive domains can be aimed [85]. The composition of CCT relies on scientific principles of learning and encompasses computerized structured drills and practice-related tasks [84,86]. Thereby, the extent of the conducted CCT varies from target specific exercises to broadly-applied programs with heterogenous activities [84]. Since CCT was the most effective when combined with another treatment, rather than implemented on its own, growing evidence suggests to add CCT to the standard therapy of patients affected by physical or mental illnesses with impaired cognitive processes [84,87-89]. The benefits of CCT are emphasized by its immense potential to overcome specific barriers of conventional therapy "including cost, transportation, lack of available providers or insurance, and long waitlists for services, as well as reduced stigma and more privacy" [84,90].

Recent research demonstrates a significant effect of CCT on cognitive impairment in mental disorders [1,4,91,92]. In a study of Elgamal, McKinnon [4] CCT significantly improved psychomotor speed, verbal learning and executive function. Motter, Pimontel [1] further reported a significant decline of disability in attention, working memory and global functioning. Besides cognitive restoration, CCT additionally improved everyday functioning and depressive symptom severity [92-94]. Mounting evidence now points towards a rather short and frequent form of cognitive training [84,95], although a general consensus on the optimal duration, frequency and degree of individualization of CCT is still missing [58].

The exercises of CCT are adaptive and grounded on basic principles of neuroplasticity [7], that is defined as the change in the dimension of recruited neuronal populations and coherence in response [96]. Neuroplasticity underlies cortical remapping, which is caused by behaviorally important experiences through life and follows alterations of peripheral input [96]. Buonomano and Merzenich [96] further declared that the cortical representational reorganization correlates with the learning process and stated that the ability of the brain to allocate certain areas to selected inputs is crucial for perceptual learning. Consecutively, mental illnesses are suggested to be a result of maladaptive learning about behaviorally important input resulting in a distorted neural representation of cognitive and emotional processes [6]. On a neural level, CCT induces neuroplastic changes related to learning that improve cortical representation and reduce internal brain noise [6]. Thereby, the designed exercises focus on early perceptual processes to refine fundamental processing abilities and improve the speed and accuracy of

task-related information processing [6-8,92]. A relatively new form of cognitive training therapy is computerized SCT [9]. This approach shifts the attention towards the processing of socially relevant stimuli and targets "affect perception, social cue perception, theory of mind and attributable style“ [8].

2.2.4 Sensory processing as potential marker for target engagement in CCT

Recent research in the field of cognitive training therapy shifted the focus towards moderators and mediators of CCT that might account for the variability of treatment response as well as the identification of measurable markers for target engagement [6]. In a study of Biagianti, Fisher [10], the individual “ability to generate and sustain sensory processing efficiency in the auditory system” of participants with schizophrenia was significantly associated with the degree of cognitive improvement after an auditory system training. Thereby, specific patterns of sensory processing behavior (time to reach a plateau of auditory processing speed) were correlated with greater cognitive gains after the training procedure [10]. In line with these findings, Melissa Fisher , Christine Holland [97] et al. observed that the individual psychophysical learning capacity of participants with schizophrenia models the response to cognitive training, whereby subjects with the most progress in basic psychophysical auditory exercises showed the greatest improvement in general cognitive abilities. Consecutively, Biagianti, Fisher [10] suggested that the intrinsic sensory learning behavior (e.g. “auditory processing speed”) could serve as a behavioral measure of target engagement for treatment response to CCT. Kambeitz-Ilankovic, Wenzel [9] was the first study that used different patterns of sensory processing to model target engagement during SCT in patients with psychosis. They observed that participants with perceived pretreatment sensory processing showed improved abilities in emotion recognition after the intervention, while those with impaired sensory processing at baseline could not transfer training engagement into cognitive improvement.

2.3 Using neuroimaging in MDD

2.3.1 Functional magnetic resonance imaging (fMRI)

fMRI measures changes in the blood oxygenation level-dependent (BOLD) signal to reproduce neuronal brain activity [98] and “ is now the method of choice to examine brain behavior relationships” [99]. Thereby, the BOLD signal uses the endogenous deoxyhemoglobin as a source of contrast based on the magnetic properties of ferrous irons that are included in deoxyhemoglobin [99]. The distribution of oxygenated and deoxygenated hemoglobin depends on the local metabolic demand and blood supply, whereas greater demands result in a higher inflow of oxygenated blood and lead to an elevated BOLD signal [99,100]. Assuming that neural activity increases the metabolic demand [99], changes in the BOLD signal reflect neural activity and allow for a regional and global mapping of activated brain regions in different states [100].

An advantage of fMRI is its repeatability which allows a high signal-to-noise-ratio within subjects [99] and the possibility to link the fMRI scans to high resolution structural images acquired in the same session to identify activated regions and facilitate the spatial transformation [99].

2.3.2 Measuring rsFC in MDD

Resting state functional magnetic resonance imaging (rsfMRI) "is a fundamental tool in characterizing brain network alterations in mental disorders" [101,102]. This approach presumes that patients lie still in the scanner with their eyes closed to reach a continuous state of rest [103]. Thus spontaneous low-frequency neural oscillations with spatiotemporal correlation between different brain regions can be detected that define functionally connected networks [98] (see Figure 1). rsfMRI is often used in studies with mentally affected participants that are not able to perform cognitive tasks on a satisfying level [103]. Moreover, rsfMRI is particularly appropriate for depressive disorder due to the omnipresent and persistent nature of depressive symptoms including continuous ruminations throughout the day [104]. A common technique of rsfMRI is the regions-of-interest (ROI)-based approach [105], whereby functional connectivity (FC) maps of the temporal correlation of BOLD time series between a priori selected brain regions (seed regions or regions of interest) and the rest of the brain are extracted. Hence a voxel-wise connectivity map of covariance between the seeds and all other brain regions is created. The ROI-based approach benefits from its simple comparability and its straightforward interpretation [105]. Recent findings in MDD support rsfMRI research since different symptom profiles were associated with varied patterns of brain activation [106,107] and the underlying pathology of MDD was declared to depend on altered functional neural networks rather than on isolated brain regions [108].

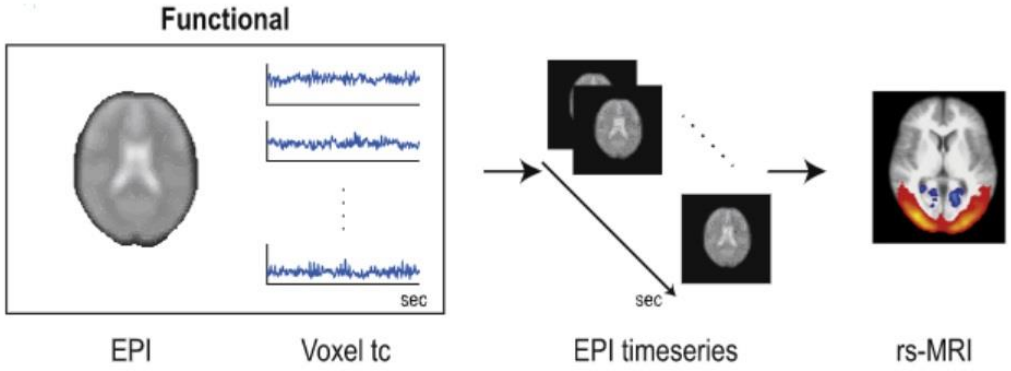

Figure 1 Visualization of the generation of rsfMRI data. Echoplanar imaging (EPI) series map the BOLD time course in each voxel of the brain. Tc = time course. From Deco and Kringelbach [102]

2.3.3 Neural correlates of CCT in MDD

With the help of neuroimaging, recent studies examined the effect of CCT on the neuroplasticity of the brain [109]. In a meta-analysis of Isaac and Januel [109] the majority of included studies showed a significant increase of frontal [110-114] and limbic activity [110,115] after CR therapy in schizophrenia. For example, Subramaniam, Luks [112] found a significantly increased tasked-based fMRI activity of frontal regions in participants with schizophrenia after a CCT intervention that was correlated with improved cognitive abilities. Kral, Schuyler [116] further observed an increased FC between the amygdala and the ventromedial prefrontal cortex (vmPFC) after a short-term cognitive training in healthy adults, while Bor, Brunelin [110] reported on an increased tasked-based activity in both frontal regions and the cingulate gyrus after CR therapy in patients with schizophrenia. Comparable results were observed by Meusel, Hall [117] who detected an increased activity of the lateral and medial prefrontal cortex (PFC) and the superior temporal lobe after a cognitive training intervention in a sample with individuals affected by mood disorders.

The neural prefrontal circuitry of the brain underlies emotional and cognitive processes [72,118-124] and is often summarized to a fronto-parietal control network (cognitive control network [CCN]) that consists mainly of the dlPFC and the inferior parietal lobe [125]. The dlPFC plays a primary role in the pathology of depression [126] and its altered activity is strongly associated with impaired cognition [126-129], whereby especially the right PFC seems to function poorly [130]. In addition, an abnormal connectivity of a prefrontal-amygdala-pallidostriatal-medio-thalamic mood-regulating circuit is proposed, that is associated with reduced emotion processing and response capabilities [121]. The amygdala and the striatum are parts of the affective network (AN) [131] that underlies the processing of emotional and rewarding stimuli [131,132] by shifting the attention away from emotional content [133] and impacts the perception and social behavior [134].

With respect to neuroplastic changes that are associated with the effectiveness of CCT, Hooker, Bruce [135] observed that increased postcentral gyrus activity in task-based fMRI after a combined CCT and SCT predicted the behavioral improvement on a standardized test of emotion processing (MSCEIT: Perceiving Emotions) [136] among patients with schizophrenia. Moreover, greater deficits in Mismatch negativity (MMN), an event-related potential that represents automatic auditory deviance processing, predicted greater improvement in global cognition after an auditory training in patients with schizophrenia-spectrum illness in a study of Biagianti, Roach [137]. Greater MMN amplitudes were additionally associated with a stronger improvement in the auditory processing efficiency after an auditory cognitive training in patients with schizophrenia in a study of Perez, Tarasenko [138] and suggested as a potential biomarker for target engagement during CCT. However, there is still little knowledge about the key neural

systems that can be targeted by CCT to induce broad neural changes and that might even predict treatment outcome in depression [6].

2.4 Aims of the study

In this RCT we examined:

i. The effect of a computerized SCT on cognitive performance and psychosocial functioning as compared to TAU.
ii. The effect of the SCT on the rsFC between a priori selected brain regions (dlPFC, caudate nucleus and amygdala) and all the other voxels of the brain as compared to the TAU group.
iii. The relationship between the change in the cognitive performance and the rsFC in the SCT and the TAU group.

We were additionally interested in the effect of the SCT on participants with distinct patterns of sensory processing. The following aims were:

i. To examine the effect of the SCT on cognitive performance and psychosocial functioning between groups with different patterns of sensory processing.
ii. Further to compare the effect of the SCT on the rsFC between the aforementioned ROIs and all the other voxels of the brain between groups with different patterns of sensory processing.
iii. Lastly, to investigate the relationship between the change in the cognitive performance and the rsFC of the brain of participants with different patterns of sensory processing.

We hypothesized that participants in the SCT group would show a stronger improvement in cognitive performance and psychosocial functioning at the follow-up as compared to participants in the TAU group. We further suggested an increase of the rsFC in the SCT group as compared to the TAU group after the intervention, that might be reflected by a strengthening of the FC of fronto-limbic-mesostriatal neural circuits. The increase of rsFC in the SCT group, in turn potentially correlates with changes in the cognitive or functional performance and hence represent a biomarker for training response to SCT in MDD.

Moreover, we expected that participants with preserved pretreatment sensory processing would benefit more clearly from the SCT in terms of cognitive and functional outcome as compared to participants with impaired pretreatment sensory processing, and that these differences in the response to the SCT would be accompanied by distinct patterns of rsFC. Lastly, there might be a relationship between changes in the sensory processing behavior, cognitive performance and rsFC patterns that underlines the role of the sensory processing behavior as a potential marker for target engagement during SCT.

3 Material and Methods

3.1 Study population

Recruitment took place at the Early Detection and Intervention Center at the Department of Psychiatry and Psychotherapy of the Ludwig-Maximilian-University in Munich. All subjects were screened for MDD with the SCID-4 [139,140]. We included all participants who met the criteria of an ongoing first episode of MDD according to DSM-IV [141] with an onset in the past three months. Inclusion and exclusion criteria of the study are listed in Table 1. The study was designed in accordance with the 1964 Helsinki Declaration and approved by the Local Research Ethics Committee of the Ludwig-Maximilian University. All participants signed a written informed consent.

Table 1: General inclusion and exclusion criteria of the study. Adapted from Haas [142]

General Inclusion and Exclusion Criteria

Inclusion criteria

1. Age between 15 and 40 years
2. Good general physical health
3. Sufficient capacity to provide informed consent
4. Sufficient language skills for participation
5. First major depressive episode
    a. Symptoms must persist over a minimum period of two weeks
    b. ≥ 5 symptoms according to the DSM-IV whereby one symptom must be anhedonia or a depressed mood
6. Symptom onset within the past 3 months with a maximal duration of 24 months

Exclusion criteria

1. Intelligence Quotient (IQ) below 70
2. Insufficient hearing for neuropsychological testing
3. Current or past head trauma with a loss of consciousness (> 5 minutes)
4. Current or past neurological brain disorder
5. Current or past somatic disorder potentially affecting the brain structure or functioning
6. Current or past alcohol dependency
7. Current polytoxicomania or polytoxicomania within the past six months
8. > 1 major depressive episode in lifetime
9. Current antipsychotic medication (> 30 cumulative days in life time) or within three months prior to the study at or above the minimum dosage of the ’1st episode psychosis’ recommendations of the DGPPN S3 Guidelines [24]
10. MRI eligibility criteria were not met

3.2 Study design

Participants who were included into the study (n=40) underwent a standardized clinical and cognitive assessment as well as a structural and functional neuroimaging scan. They were then randomized to the intervention group that received a ten hours computerized SCT over four to six weeks (30 minutes per session; 4-5 days per week) additional to TAU (SCT group) (n=23) or to the control group obtaining TAU (TAU group) (n=17). The first three sessions of the SCT were supervised by trained research personnel while the following sessions were continued at the clinic or at home. A quiet room and headphones were provided. To ensure compliance with the training protocol and to provide potential technical support, the pseudo-anonymized training data was monitored on the brain hq platform additionally to the research staff. Six participants did not complete the study and one additional participant was excluded due to not fulfilling criteria for MDD. After five weeks, 33 participants completed the follow-up clinical and neurocognitive assessment alongside a neuroimaging scan. A visualization of the study design can be found in Figure 2.

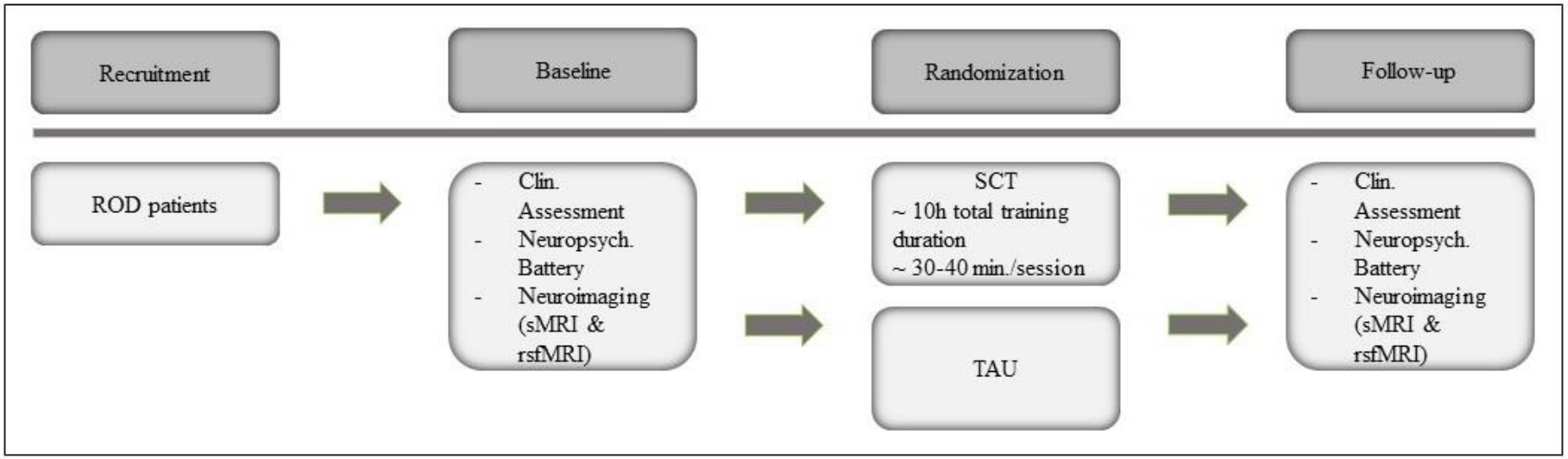

Figure 2: Description of the study design. MRI protocol obtained in addition. ROD = recent-onset depression; sMRI = structural magnetic resonance imaging. Adapted from Haas [142].

Subsequently, we excluded two participants from the analysis because they exceeded the threshold for mean framewise displacement (FD) parameters that were calculated to control for movement artifacts in the scanner. Participants in the SCT group were classified as Improvers (n=7) and Maintainers (n=10) based on the individual pattern of sensory processing change (SPC) after completion of the intervention (see chapter 3.4). A flowchart of the study sample can be found in Figure 3.

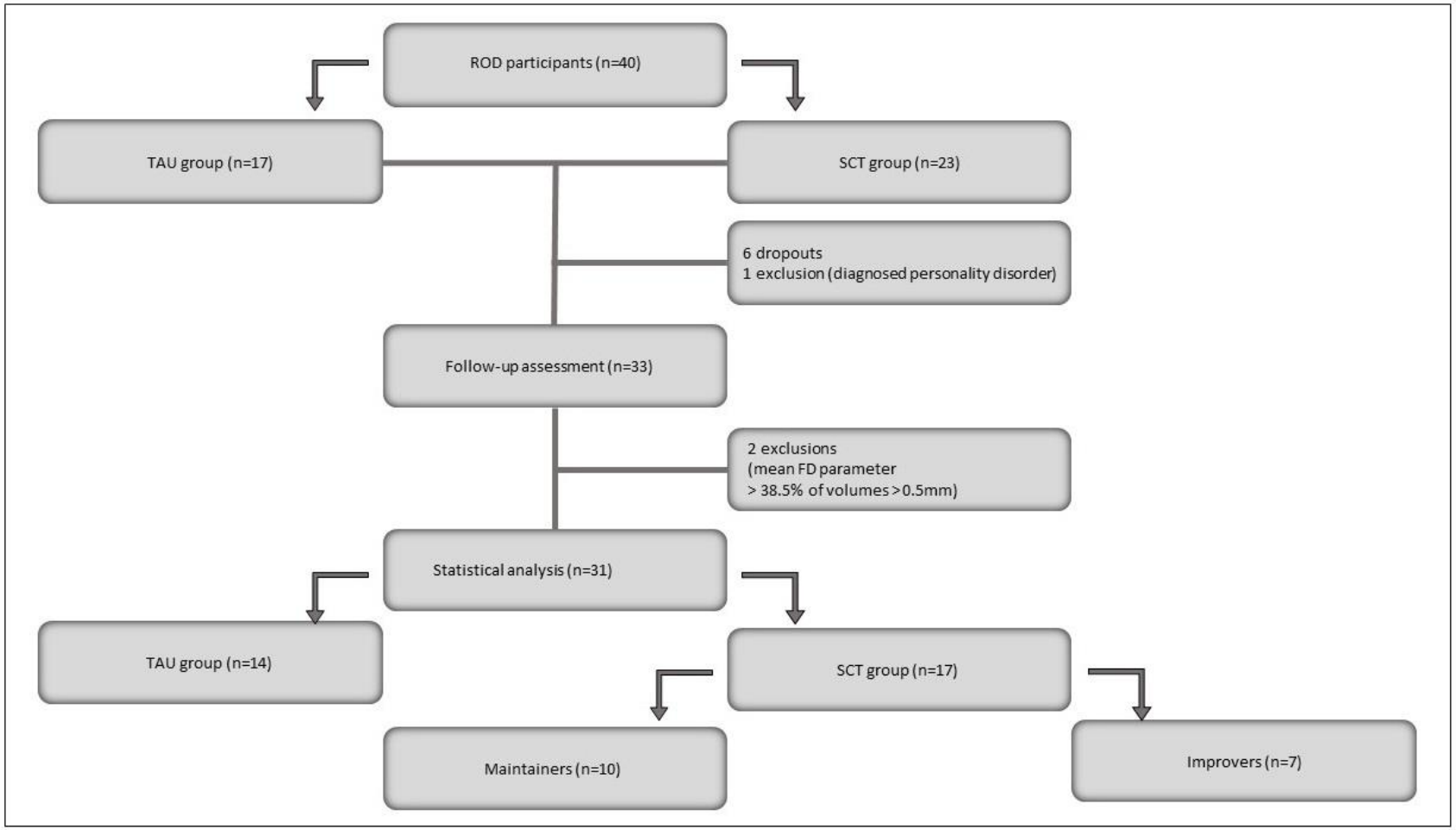

Figure 3: Flowchart of the study sample.

3.3 Training procedure

We used the ‘Social Ville Program’, which was developed by the Posit Science Inc. primarily to improve cognitive deficits in patients with schizophrenia, to conduct the SCT [143]. Training sessions consisted of four computerized exercises aimed to improve the accuracy and speed of neuronal processes that are integrated in the social interaction, especially attention, working memory and the perception of social stimuli (visual and vocal affect perception and social cue perception). Each exercise was structured in blocks (2-4) with 30-60 trials. A description of the exercises can be found in Table 2 (see Figure 4 for a visualization of the program).

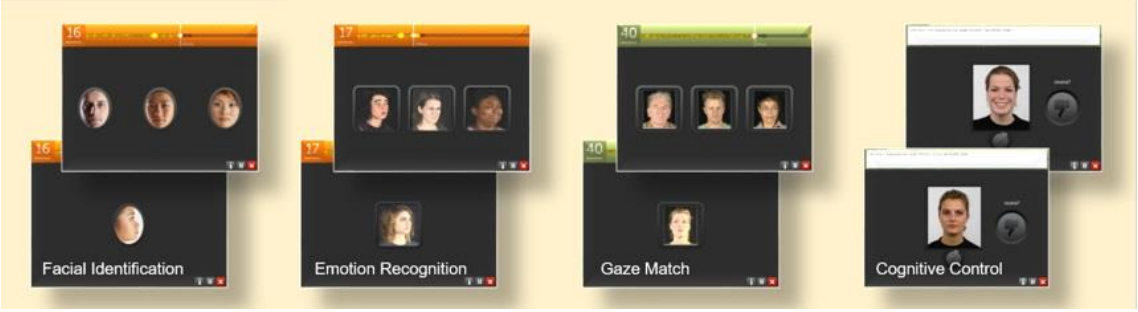

Figure 4: Visualization of the Social Ville Program. Four computerized exercises (“Face recognition”, “Emotion matching task”, “Gaze match”, “Cognitive control task”) were conducted in 30 min. sessions. From Haas [142].

Table 2: Description of the exercises of the Social Ville Program. Adapted from Haas [142].

Exercise	Trials/ iteration	Description	Target
Face recognition	20	Select the matching facial expression to a prior presented face out of a set of possible answers (Speeded face matching task)	Processing of facial characteristics.
Emotion matching task	20	Select the face with the emotion similar to the target face (Speeded facial emotion matching task)	Make implicit speeded decisions about facial emotion features.
Cognitive control task	60	A continuous performance task with facial expressions: inhibiting the response to neutral expressions (10% of trials) while responding only to emotional facial expressions (90% of trials)	Differentiate between emotional and neutral facial expressions.
Gaze Match	40	Recognize the direction of view in a presented face (speeded gaze matching task)	Identification of the eye gaze direction of a counterpart.

Early blocks used more obvious, example-like stimuli to consolidate fundamental processes of encoding by synchronizing brain response, while later blocks presented naturalistic stimuli with increasing difficult discrimination to approximate to the real-world performance. The difficulty was constantly adapted to the individual performance by a statistically optimal Bayesian approach to maintain a performance level of 80-90 percent correct answers. Dimensions used to increase the difficulty were (1) stimulus complexity; (2) number of response alternatives, both altered between blocks, and (3) stimulus and response representation time that could differ within blocks. If the algorithm detected a lack of performance improvement, the block was terminated and switched to a more easy or difficult one. Therefore, each participant completed a different number of blocks depending on the individual performance within the session. We measured two variables for each exercise: (1) baseline performance (score of the first training session) and (2) best performance (best score reached through the total duration of training). Correct answers were rewarded with points and animations. If participants chose incorrect answers, a negative sound and the correct answer were presented. Additionally, the

participants received feedback after each training session. Previous studies describe the training procedure in detail [9,143,144].

3.4 Distinct patterns of the SPC

In order to examine differential patterns of the SPC in the SCT group, we chose to study the EMT as the best fitting proxy to capture the ability of processing basic social information in social circumstances. The exercise is designed to improve the ability to make implicit speeded decisions about facial expressions. To model the SPC, we chose one block that was (1) completed at least once by all participants and (2) provided the largest amount of block repetitions per participant. The SPC on this exercise was calculated by dividing the difference between the subject-specific best and the baseline performance within that block, deviated by the standard deviation of the baseline performance for that block across all study participants (see Figure 5). Participants with a greater delta were those who showed an impaired performance at baseline and improved over training procedure, while a lower delta implied perceived EMT performance. Subjects were then dichotomized into Maintainers (n=10) and Improvers (n=7) by the median split of the SPC score. Improvers are participants who showed an impaired performance at baseline and reached the optimal EMT threshold (~31ms) during the training, while Maintainers showed intact EMT performance at baseline (~31ms) and sustained the optimal psychophysical threshold throughout the training experience.

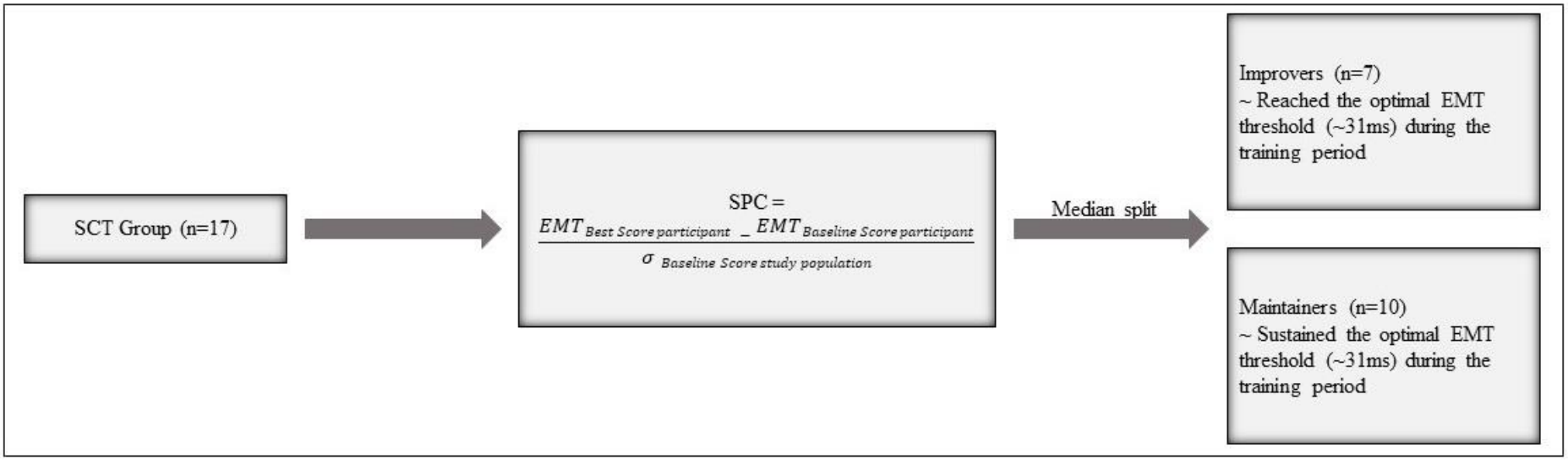

Figure 5: Visualization of the classification of Maintainers and Improvers by the SPC.

3.5 Clinical and cognitive assessment

The standardized clinical and cognitive assessment was provided by trained research personnel.

3.5.1 Clinical assessment

Beck Depression Inventory-II (BDI-II)

In the present study, we used the revised second version of the BDI to test depression severity [145]. The BDI is a self-questionnaire with 21 items representing symptoms or characteristics associated with depression and respectively 4 answer alternatives scored from 0 to 3 points. Depression severity is evaluated by the sum score of all items with a minimum score of 0 points and a maximum score of 63 points. Cutoffs are defined as follows: 0-12 no depression; 13-19 mild depression; 20-28 moderate depression, 29-63 severe depression [24].

Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (SCID)

The SCID [146] is a diagnostic screening instrument for mental disorders that are listed in the DSM-IV and was published by the American Psychiatric Association (APA) [141,147]. The interview starts with a short, less structured exploration of biosocial information and actual symptoms, followed by a well-structured part of 10 sections representing all mental disorders listed in the first axis. Answers are coded from unsure to certainly present. The Interview can be used for stationary and ambulant patients and has a total duration of about 100 minutes.

Global Assessment of Functioning (GAF)

The GAF is a questionnaire that measures the impairment in daily life activities of patients suffering from mental disorders [148]. The questionnaire includes the categories: psychological, social and occupational functioning assessed by a clinician or interviewer. The scale reaches from 0 to 100 points with higher scores going along with less impairment in general functioning and less symptoms. The scale is further divided in ten equal parts categorized by specific characteristics of symptoms and the level of functioning (e.g. 100-91: Superior functioning in a wide range of activities and no symptoms; 10-1: persistent danger of severely hurting self or others or persistent inability to maintain minimal personal hygiene or serious suicidal act with clear expectation of death) [141,149] . In the present study, we subdivided the GAF questionnaire in the categories: GAF-symptoms (GAF-S) and GAF-disability (GAF-D) to differentiate more precisely between effects of SCT on symptom severity and the level of daily functioning.

General Role Functioning (GF-R) and General Social Functioning (GF-S)

The General Functioning (GF) questionnaire is an additional measurement for daily life performance that was first developed to examine the prodromal dysfunction in social and occupational domains. Previous studies in patients with an Attenuated Positive Symptom prodromal syndrome observed that role functioning increased over the therapy while social functioning remained relatively stable across the time. They concluded that the level of role functioning could be seen as an indicator of success of the therapy, and the level of social functioning as a predictor of a subsequent mental disorder [150]. Based on these findings we added the GF-R and the GF-S questionnaire to the clinical assessment.

3.5.2 Neuropsychological test battery

The neuropsychological test battery consisted of nine tests that were based on the cognitive domains determined in the MATRICS Consensus Cognitive Battery (MCCB) established by the National Institute of Mental Health (NIMH) initiative [151]. This test battery was shown to measure the key cognitive domains relevant to schizophrenia and related disorders [152]. In the present study, we focused on the cognitive domains: social cognition, verbal learning, working memory, speed of processing, attention and global cognition. These domains were defined as follows: “social cognition” was calculated from the score of correct answers in the Diagnostical Analysis of Non-verbal Accuracy Test (DANVA). The domain “speed of processing” was made up by dividing the difference between the score of the Verbal Fluency Test – Semantic Version (VFT-S) and the sum of the Trail Making Test – Part A (TMT-A) and the Digit Symbol Substitution Test (DSST) by the number of included tests. Next, we divided the sum score of the Auditory Digit Span Test – forward and backward version (ADS-F/-B) by two to receive “working memory”. “Verbal learning” was calculated based on the Rey Auditory Verbal Learning Test (RAVLT) and “attention” was made by subtracting the number of errors from the number of correct answers in the Continuous Performance Test – Identical Pair Version (CPT-IP). Lastly, “global cognition” was calculated by the mean sum of all previous described cognitive domains. Hereinafter the utilized tests are listed in Table 3.

Table 3: The neuropsychological assessment and the composition of the cognitive domains. Adapted from Köhler and Koutsouleris [153]

Cognitive domains	Neuropsychological Test	Appliance
Social Cognition	Diagnostic Analysis of Non-Verbal Accuracy (DANVA)	Tablet-based
Working Memory	Auditory Digit Span (ADS)	
	Forward trials (-F)	Tablet-based
	Backward trials (-B)	Tablet-based
Speed of Processing	Digit Symbol Substitution Test (DSST)	Paper and Pencil
	Verbal Fluency (VF): Semantic trials (-S)	Paper and Pencil
	Trail Making Test- Trial A (TMT-A)	Paper and Pencil
Verbal Learning	Rey Auditory Verbal Learning Test (RAVLT)	Tablet-based
Attention	Continuous Performance Test, Identical Pairs version (CPT-IP)	Tablet-based
Premorbid IQ	Wechsler Adult Intelligence Scale, Vocabulary (WAIS-V)	Paper and Pencil
	Wechsler Adult Intelligence Scale, Matrices (WAIS-MR)	Paper and Pencil

Diagnostical Analysis of Non-verbal Accuracy (DANVA) – 2nd Version

First developed in 1989 by Nowicki and Duke [154], the DANVA is a psychological test instrument that measures emotional processing. We used the Adult Faces-subtest of the second version of the DANVA (DANVA-2-AF) for our study. The test was conducted via tablet and consisted of 24 items presented as images of adult faces. Participants had to evaluate each item on the emotional expression (happiness, sadness, anger or fear).

Digit Symbol Substitution Test (DSST)

The DSST is a part of multiple psychological test batteries used to determine cognitive impairment across a wide range of cognitive domains (e.g. “Wechsler Adult Intelligence Scale”, “MCCB”) [155]. The test is conducted in a paper-and-pencil format whereat participants are asked to register a matching symbol, defined in a key above, to each number in a row. The total duration is restricted to 90 seconds and the participant’s performance is represented in a score calculated by the time and the number of correct matches.

Continuous Performance Test – Identical Pairs Version (CPT-IP)

The CPT measures the ability to sustain selected attention [156]. The identical pairs version of the CPT detects the capacity to attend to a continuous presented stimuli, configured as strings of four digits, that are presented via tablet with a short presentation time [157]. Participants were instructed to press on the left mouse button if two identical digits strings were presented consecutively and to not react to non-identical stimuli. The total amount of stimuli was 300 with 20% target stimuli (two identical consecutive digits strings) and 20% of catch-stimuli (two consecutive strings that were almost identical). All other stimuli were randomly generated by an algorithm (filler-stimuli). The program detected both the number of correct (both reaction to identical strings and no reaction to filler stimuli) and false answers as well as the reaction time for correct answers.

The Semantic/ Phonemic Verbal Fluency Task (VFT-S and VFT-P)

First developed in 1968, the Semantic and Phonemic Verbal Fluency Task measures language production and detects cognitive impairment in participants with a wide range of neurological and psychological diseases [158] [159]. The idea of the test is to let participants associate as many terms as possible to a given task in a predefined time range. For the semantic version, participants were asked to name as many terms as possible in a specific category, which was the category “animals” in our study. In the phonemic task, participants had to tell as many nouns as possible starting with the same letter, in our case it was the letter “S”. The time for

both tasks was set to 60 seconds. Answers were documented twice, once by the examiner and once by a program on the tablet and adjusted after the assessment. We used the amount of correct, repeated and false terms for the evaluation.

The Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT is a commonly used neuropsychological test instrument to evaluate the ability of processing verbal information and working memory [160,161]. Within the test, two lists (list A and list B) with respectively 15 nouns were presented to the participant by an audio file on the tablet computer. At the beginning of the test, the participant listened to list A and directly recalled as many words as possible. The examiner noted the number of correct repeated words without paying attention to the order or repetition of words. After repeating the audio presentation of list A for five times, a second list of 15 nouns (list B) was presented to the participant. This list was used as an interference exercise and the participant had to list as many nouns as possible of list B. Afterwards, the participant was asked to repeat as many terms as possible from list A and then again after a delay of 20 minutes. The number of correct repeated words was again noted for each trial by the examiner.

The Forward and Backward Digit Span Test (F-DST and B-DST)

The F-DST and the B-DST [162] are used as indicators for the efficiency and the capacity of attention and working memory [163]. Starting with the presentation of a sequence of numbers, the participant is then asked to repeat the numbers in the forward (F-DST) or the backward direction (B-DST). In our study, we used an auditory presentation of numbers (recorded male voice) played by a tablet. If the participant responded to two series of numbers correctly, the program automatically added an additional number to the digit span. The test was terminated if the participant gave the wrong sequence of numbers two times consecutively. For the evaluation, we choose two test values (1) the maximum digit string length reminded at least once and (2) the number of correct trials. The test duration was 5 to 10 minutes depending on the individual performance of the participant.

Trail Making Test - Part A (TMT-A) and Part B (TMT-B)

The Trail Making Test (TMT), which is separated into two different parts “TMT-A” and “TMT-B”, serves as a screening instrument for cognitive brain function of children and adults [164]. It especially measures attention and sensory processing in the TMT-A and executive functioning in the TMT-B [163 165]. Both parts were conducted in a paper- and pencil-format with an example and a test exercise for each part. After running through the explanation, the participant was asked to connect 25 circles with numbers in ascending order for part A and alternately 13 circles of numbers and 13 circles of letters in ascending and alphabetical order (e.g. “1-A-2-B-

3-C") for part B. The time was measured for both parts separately and the participant was not allowed to lift the pen or to turn the paper during the task. The examiner had the instruction to directly correct the participant if the circles were connected in the wrong order without stopping the time. The test results were scored by the time needed to finish the exercises, the number of violations and the number of errors. The rating scale reached from "perfectly normal" to "moderately/severely impaired".

Wechsler Adult Intelligence Scale, Vocabulary Subtest (WAIS-V)

In this study, we used the vocabulary subtest of the fourth version of the Wechsler Adult Intelligence Scale (WAIS) which measures verbal intelligence in the domain of verbal comprehension. Within the test, the participant was asked to explain a total of 33 words. The examiner scored the answers of the participant with points from 0 to 2 according to an official manuscript with 2 points as the best score and 66 points as the maximum total score. Results were then adjusted by age according to the official WAIS scores.

Wechsler Adult Intelligence Scale, Matrices Subtest (WAIS-MR)

As a part of the Perceptual Organization Index in the WAIS [166], the matrices subtest is used to measure performance intelligence, especially visual processing, nonverbal abstract problem solving and abstract reasoning. The test was conducted as a paper- and pencil test with 26 trials and the instruction to complete the given matrices or rows with one of five answer alternatives. We used the official WAIS-Matrices charts in our study. For each correct completion, the participant received one point resulting in a maximum total score of 26 points. Results were again adjusted to the participants' age by the official WAIS scores. Premorbid verbal intelligence was measured with the combination of the vocabulary and the matrices subtest of the WAIS.

3.6 Neuroimaging

Structural and functional images were acquired using a 3 Tesla Philips Ingenia scanner with a 32-channel radio-frequency coil located at the radiology department in the clinic of the Ludwig-Maximilian-University in Munich. To receive the rsfMRI images, participants had the instruction to lie still in the scanner with their eyes open while daydreaming and not focusing on any thought in particular.

3.6.1 sMRI acquisition

Structural images were generated with a multi-echo Magnetization Prepared - Rapid Gradient Echo (MPRAGE) sequence. Parameters were set as follows: repetition time (TR) = 9.5 ms, echo time (TE) = 5.5 ms, flip angle = 8°, field of view = 250 x 250 mm, matrix size = 256 x 256;

190 contiguous sagittal slices of 1.0 mm thickness and a 1.0 mm gap, voxel size = .97 mm x .97 mm x 1 mm, pixel band width = 650 Hz.

3.6.2 sMRI preprocessing

We used the Computational Anatomy Toolbox (CAT12) (http://www.neuro.uni-jena.de/cat12/) version r1207 for the preprocessing of the sMRI data. The first step was to denoise the structural images using Spatially Adaptive Non-Local Means filtering to increase the signal-to-noise ratio of the data [167]. Images were then segmented using an Adaptive Maximum A Posteriori (AMAP) approach to reach a homogeneous segmentation across cortical and subcortical structures by modeling the local variations of intensity distributions as slowly varying spatial functions [168]. Next, the Markov Random Field approach was applied for the segmentation estimation which uses spatial prior information of neighboring voxels by AMAP [168]. To account for differences caused by white matter (WM) inhomogeneities and varying gray matter (GM) intensities due to the differential iron content in cortical and subcortical structures, images were harmonized using a Local Adaptive Segmentation step. Therefore, we used a Partial Volume Segmentation algorithm applied to GM, WM and cerebrospinal fluid (CSF) by AMAP technique. Lastly, structural images were registered to the Montreal Neurological Institute (MNI) template using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) algorithm [169].

3.6.3 rsfMRI acquisition

RsfMRI images were generated using an echo planar imaging (EPI) sequence and the intercommissural line (AC-PC) as a reference with the following parameters: number of ascending slices = 53, TR = 3000 ms, TE = 30 ms, flip angle = 90°, field of view = 230 x 230 mm, 3.0 mm thickness and 3.0 mm gap, matrix size = 80x80, voxel size = 2.875 mm x 2.875 mm x 3 mm, total scan time 603 seconds (200 volumes).

3.6.4 rsfMRI preprocessing

The preprocessing was done using SPM-12. The initial 8 volumes were omitted by default because the magnetization equilibrium was not reached. Images were slice-time-corrected and realigned and unwarped to the first volume for head movement correction. To control for further movement artifacts, FD was calculated [170] and subjects with > 38.5 % of volumes with mean FD of > 0.50 mm were excluded [171] from the analysis. Images were then coregistered to the structural images, resliced with 4th-degree B-Spline interpolation and normalized to the standard MNI space. The standard CAT12 template was converted from DARTEL space to MNI space using SPM12's population to the International Consortium for Brain Mapping 152 registration procedure. To generate a GM-, WM- and CSF mask, the image calculator

procedure in SPM12 was used with threshold set to 0.2, 0.2 and 0.5. The variance from the WM and the CSF was eliminated from the mean individual signal estimates and the GM mask was used to margin the space of functional images. The images were then smoothed with 6mm Gaussian kernel to decrease spatial noise. Further denoising steps to remove the effect of systematic drifts in fMRI were: (1) motion correction using the Time Series Despiking Method (Wavelet Despike) of the Brain Wavelet Toolbox (BWT) (http://www.brainwavelet.org/) [172]; (2) regression of confounding signals and residuals of the WM and the CSF with Friston 24 motion parameters [173] to account for physiological artifacts. For this purpose, the 24 motion parameters were deviated from 6 head motion parameters, 6 head motion parameters as of the previous time point and 12 corresponding quadratic terms; (3) background and temporal band-pass filtering (0.01 - 0.08 Hz) to reduce the effects of low-frequency drift and high-frequency noise [174]. We used the Resting State fMRI Data Analysis Toolkit (REST version 1.8; http://www.restfmri.net/) for the preprocessing [174]. For a visualization of the preprocessing pipeline see Figure 6.

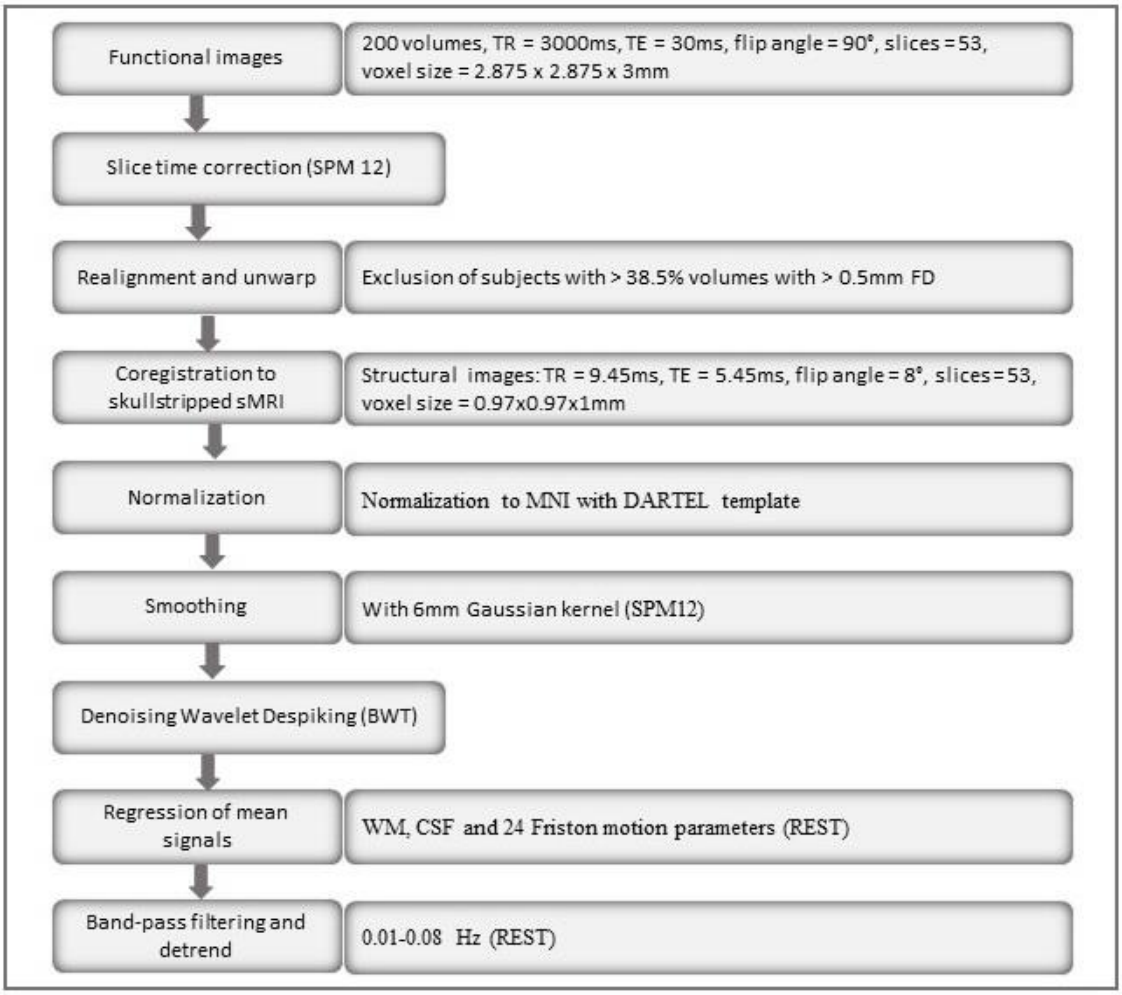

Figure 6: Preprocessing pipeline for rsfMRI data. Adapted from Haas [142].

3.7 Statistical analysis of the behavioral data

R version 3.6.2 (R-Core-Team, 2017) was used for the statistical analysis of the behavioral data. Independent two sample-t-tests for continuous variables (e.g. “age”, “years of education”, “BDI-II”, “GAF”, “GF” and “WAIS”) and Fisher’s chi-square test for categorical variables (e.g. “sex”) were performed to compare baseline characteristics between (1) SCT and TAU group and (2) Maintainers and Improvers. To investigate the change of the neurocognitive and the psychosocial performance across the time, we performed an ANCOVA with the follow-up score as the dependent variable, the baseline performance and sex (only for SCT – TAU) as a covariate and the study group (e.g. “SCT” and “TAU” or “Maintainer” and “Improver”) as a between-subject factor with the “ez”-package (Michael A. Lawrence, 2016) in R 3.6.2. Missing values were imputed by the median of the appropriate variable. The significance level was set to 0.05 (p) with False Discovery Rate (FDR) correction for multiple comparisons [175]. We further controlled for outliers that overstepped the threshold of twice the standard deviation. A description of the primary and the secondary outcome variables can be found in Table 4.

Table 4: Definition of the primary and the secondary outcome variables. T0 = timepoint 0 (at the beginning of the study); FU = follow-up (at the end of the study).

Variable	Timepoint of assessment	
	T0	**FU**
Primary outcome: cognition		
Social cognition	x	x
Working memory	x	x
Speed of processing	x	x
Verbal learning	x	x
Attention	x	x
Global cognition	x	x
Secondary outcome: psychosocial functioning		
GAF-S	x	x
GAF-D	x	x
GF-S	x	x
GF-R	x	x

3.8 Statistical analysis of the neuroimaging data

3.8.1 Generation of seed-based rsFC maps

A ROI-based approach to analyze the rsfMRI data was conducted using the REST software package (http://resting-fmri.sourceforge.net) version 1.8 in SPM12. BOLD time series was extracted from the right dlPFC (23 46 39) [176], the right caudate (12 14 14) [177] and the left amygdala (-22 -6 -24) [178] with 10mm radius sphere. Next, voxel-wise correlation analyses were performed between the seed regions and the remaining voxels of the brain to obtain FC maps. To improve the normality, correlation coefficients of the FC maps were consecutively standardized to z-score by the use of Fisher's r-to-z transformation. See Figure 7 for a visualization of the generation of seed-based FC maps.

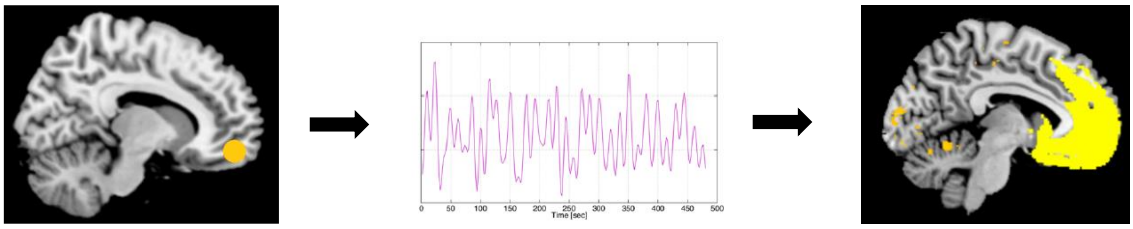

Figure 7: Visualization of the generation of seed-based FC correlation maps. Adapted from Haas [142] and Madeo, Talarico [179].

3.8.2 Statistical analysis of the seed-based rsFC maps

The FC maps of each seed region were added to a second-level group analysis with the REST toolkit in SPM12. To assure image quality, the FC maps were submitted to a one-sample-t-test for each seed separately. Next, we used the CAT12 toolbox (http://www.neuro.uni-jena.de/cat12-html/cat.html) to check for image homogeneity. The FC maps were then added to a 2-by-2 full factorial ANCOVA with time (e.g. "T0" and "FU") as the within-group factor and study group (e.g. "SCT" and "TAU" or "Maintainer" and "Improver") as the between-group factor to examine changes in the rsFC between the seed regions and the rest of the brain across the time with respect to the study group. Mean FD parameters and sex (only for the comparison between SCT and TAU) were added as covariates to the model. The significance level was set to $p < 0.05$ and the Family Wise Error (FWE) was used for multiple comparison correction

to control the false positive rates. Brain regions that showed a significant FC were then localized using the Wake Forest University PickAtlas toolbox (WFU PickAtlas Version 3.0) (https://www.nitrc.org/projects/wfu_pickatlas/) in SPM12 based on the Automated Anatomical Labeling (AAL) atlas.

Lastly, we investigated the relationship between the rsFC patterns and the cognitive performance in the respective study group. Therefore we extracted the z-transformed connectivity values of the global maxima of all regions that showed a significant FC with the seed regions using the Marsbar toolbox [180] in SPM12. These values were imported in R and differences of the connectivity values from T0 to follow-up (FU - T0) were calculated. Next, we performed Pearson's correlation tests between the connectivity values and the cognitive performance scores at the follow-up plus the correlation between the differences of both (FU – T0) for each study group separately. We additionally estimated the Pearson's correlation between the baseline connectivity values and the change in the cognitive performance scores to examine if baseline FC patterns predicted cognitive outcome. The FDR correction was used for multiple comparison correction and the significance level was set to $p < 0.05$.

4 Results

4.1 Baseline demographic and clinical characteristics

4.1.1 SCT and TAU

We recruited 40 participants with both inpatient and outpatient status. The mean age of the study population was 25.05 years (SD= 5.71) with no significant difference between the groups. However, the portion of women was significantly higher in the SCT group ($X2 = 4.19$; $p = 0.04$). Further characteristics of the demographic and clinical variables are described in Table 5.

Table 5: Baseline demographic and clinical characteristics of the SCT and the TAU group. N = Number; SD = standard deviation; F = F-value; X^2 = X^2-value; p = p-value. *Significant at p < 0.05.

	SCT group (n=17)	**TAU group** (n=14)	**F-test**	
	Mean (SD)	Mean (SD)	F/ X^2	p
Male/ Female	6/11	11/3	4.19	**0.04***
Age (years)	26.86 (6.36)	22.71 (5.44)	0.73	0.58
Education (years)	13.33 (4.30)	12.64 (2.85)	0.44	0.22
BDI-II	29.59 (14.31)	26.29 (9.13)	0.41	0.11
WAIS V	11.27 (2.22)	11.25 (2.30)	1.08	0.88
WAIS MR	10.44 (2.37)	11.15 (2.15)	0.83	0.75
GAF-S				
Lifetime	79.47 (7.30)	79.73 (4.86)	0.43	0.19
Past year	63.73 (9.76)	70.73 (8.57)	0.72	0.61
Past month	49 (10.49)	52.09 (8.28)	0.62	0.47
GAF-D				
Lifetime	78.67 (7.38)	76.36 (9.05)	1.47	0.54
Past year	66.33 (9.95)	71.64 (8.73)	1.07	0.91
Past month	51.8 (9.59)	53.45 (7.47)	0.74	0.64
GF				
Social current	5.93 (1.33)	6.64 (1.03)	0.52	0.31
Role current	5 (2.10)	5.64 (1.69)	0.70	0.58

4.1.2 Maintainers and Improvers

Maintainers and Improvers did not differ significantly in age or sex. However, Maintainers exhibited better everyday and social functioning scores in the past month (GAF-S: F = 5.63; p = 0.03; GF-S: F = 5.04; p = 0.04) prior to the baseline assessment (see Figure 8; Figure 9).

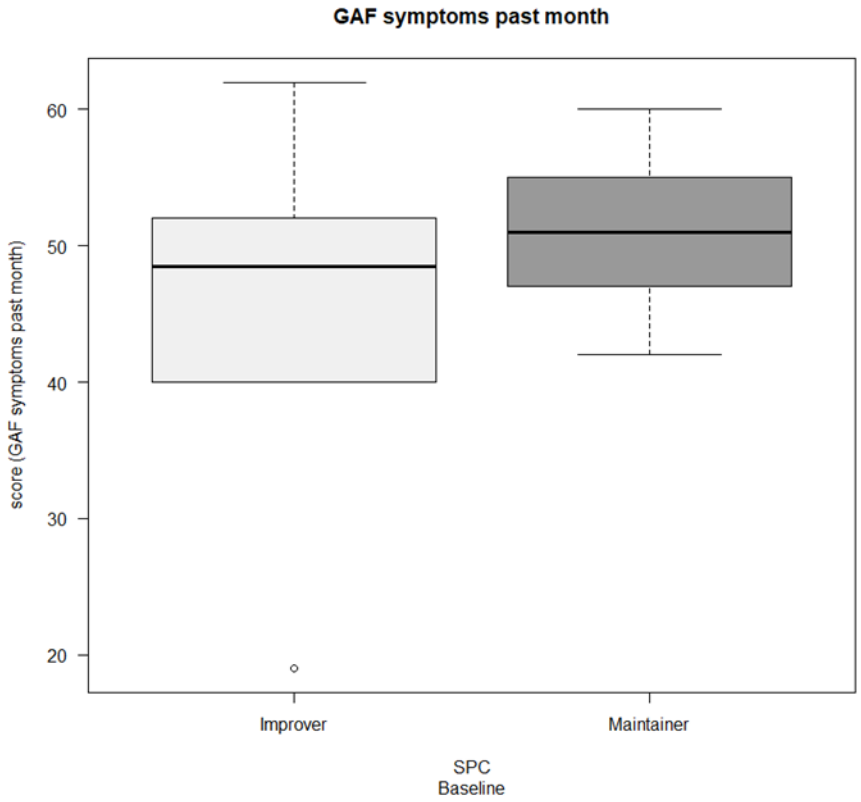

Figure 8: Boxplot of the significant group effect between Maintainers and Improvers on the baseline GAF-S past month score.

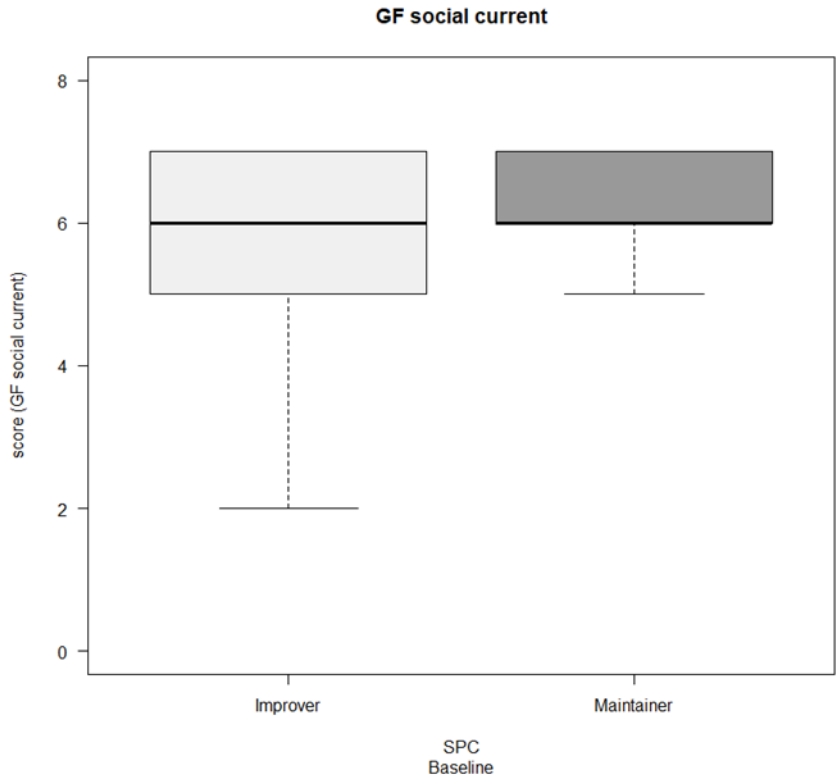

Figure 9: Boxplot of the significant group effect between Maintainers and Improvers on the baseline GF-S score.

Further demographic and clinical characteristics of Maintainers and Improvers can be found in Table 6.

Table 6: Baseline demographic and clinical characteristics of Maintainers and Improvers. *Significant at p < 0.05.

	Maintainers (n=10)	**Improvers** (n=7)	**F-test**	
	Mean (SD)	Mean (SD)	F/ X^2	p
Male/ Female	3/7	3/4	<0.01	0.98
Age (years)	25.44 (6.6)	29.40 (5.64)	0.73	0.81
Education (years)	12.43 (4.43)	16.50 (2.12)	0.23	0.70
BDI-II	34.70 (9.86)	22.29 (17.17)	3.04	0.13
WAIS V	10.78 (2.44)	12.00 (1.79)	0.54	0.51
WAIS MR	10.30 (2.71)	10.67 (1.86)	0.47	0.42
GAF-S				
Lifetime	78.22 (7.16)	81.33 (7.76)	1.18	0.80
Past year	68.33 (7.11)	56.83 (9.52)	1.79	0.44
Past month	51.67 (6.18)	45.0 (14.67)	5.63	**0.03***
GAF-D				
Lifetime	79.33 (6.73)	77.67 (8.85)	1.73	0.47
Past year	70.89 (8.40)	59.5 (8.41)	1.00	0.95
Past month	52.22 (9.26)	51.17 (10.93)	1.39	0.64
GF				
Social current	6.22 (0.83)	5.5 (1.87)	5.04	**0.04***
Role current	5.33 (2.06)	4.5 (2.26)	1.2	0.78

4.2 Effects of the SCT on cognition

4.2.1 SCT and TAU

With respect to cognitive performance, the SCT and the TAU group did not differ significantly at baseline. However, the analysis showed a significant between-group effect on working memory ($F = 4.45$; $p = 0.04$; $\eta^2_G = 0.13$) whereby participants in the TAU group showed a stronger improvement as compared to the SCT group (see Figure 10). This difference did not survive the multiple comparison correction ($p = 0.52$) nor the exclusion of outliers that overstepped the threshold of twice the standard deviation ($n = 3$; $p = 0.166$).

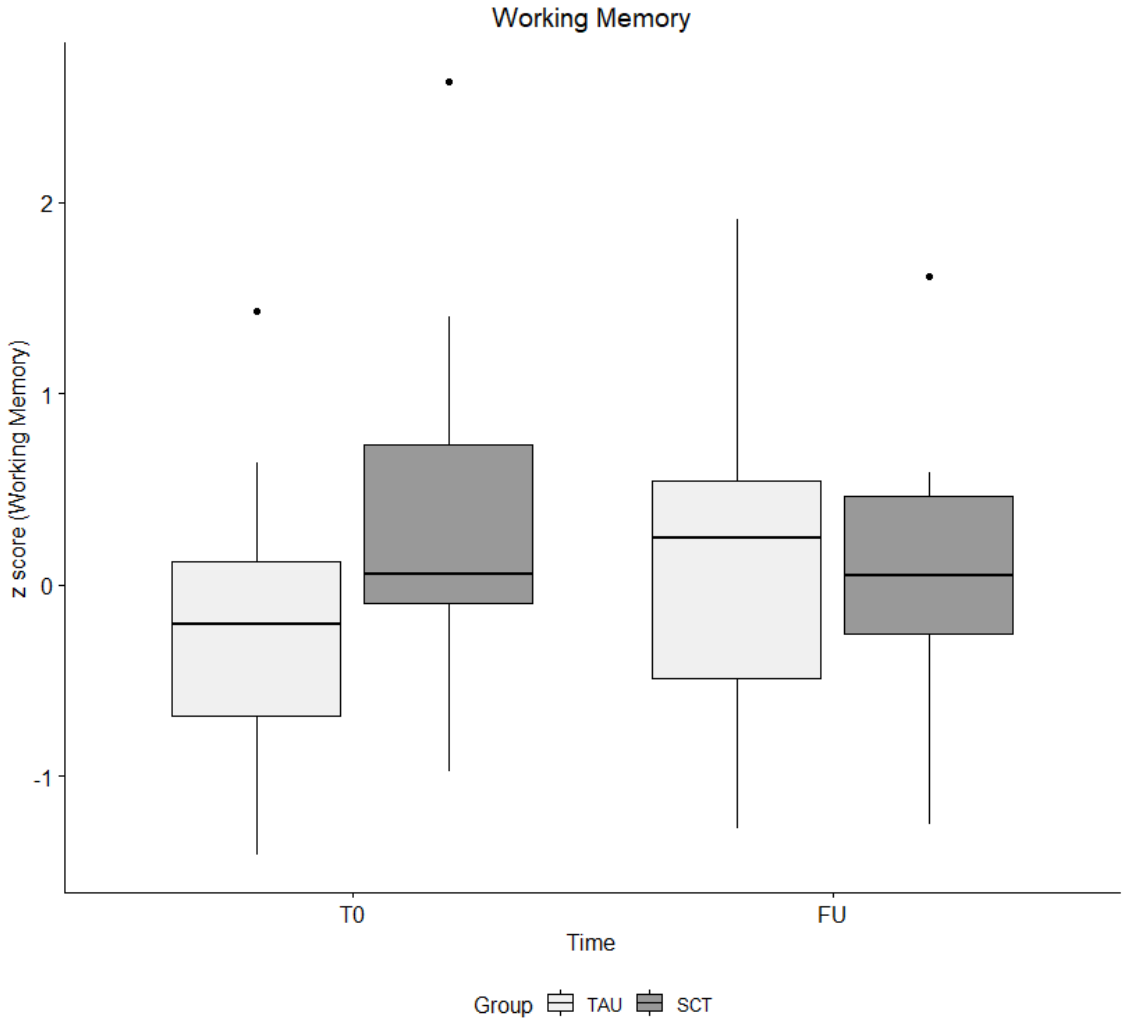

Figure 10: Boxplot of the significant interaction effect between the time and the SCT and the TAU group on working memory.

No significant group effects were found for the remaining cognitive domains. Results of the ANCOVA can be found in Table 7.

Table 7: Baseline and follow-up scores of the cognitive domains and results of the ANCOVA between the SCT and the TAU group. η^2_G = η^2_G-value. *Significant at p < 0.05.

		SCT group (n=17)	**TAU group** (n=14)	**F-test**		**Between-group Comparison (ANCOVA)**		
		Mean (SD)	Mean (SD)	F	p	F	p (p FDR-corrected)	η^2_G
Social cognition	T0	-0.08 (1.21)	0.09 (0.80)	2.11	0.15	2.17	0.15 (0.87)	0.07
	FU	0.24 (0.68)	-0.29 (1.14)	2.78	0.07			
Speed of processing	T0	0.23 (0.48)	-0.12 (0.70)	0.39	0.18	0.83	0.37 (0.87)	0.03
	FU	0.29 (0.63)	-0.14 (0.59)	0.88	0.83			
Working memory	T0	0.28 (0.87)	-0.22 (0.82)	0.53	0.84	4.45	**0.04*** (0.52)	0.13
	FU	0.11 (0.65)	0.11 (0.88)	1.80	0.29			
Verbal learning	T0	0.24 (1.06)	-0.07 (0.77)	0.49	0.27	0.03	0.87 (0.95)	<0.01
	FU	0.19 (0.67)	<0.01 (0.70)	1.09	0.87			
Attention	T0	0.38 (1.49)	0.22 (0.93)	0.88	0.11	0.62	0.44 (0.87)	0.02
	FU	0.19 (0.74)	0.17 (0.67)	0.83	0.75			
Global cognition	T0	0.19 (0.66)	-0.02 (0.46)	2.11	0.21	0.34	0.57 (0.95)	0.01
	FU	0.20 (0.29)	-0.03 (0.39)	1.77	0.30			

4.2.2 Maintainers and Improvers

Participants in the Maintainers group showed significantly higher scores in social cognition (F = 1.72; p = 0.05) at baseline as compared to the Improvers (see Figure 11).

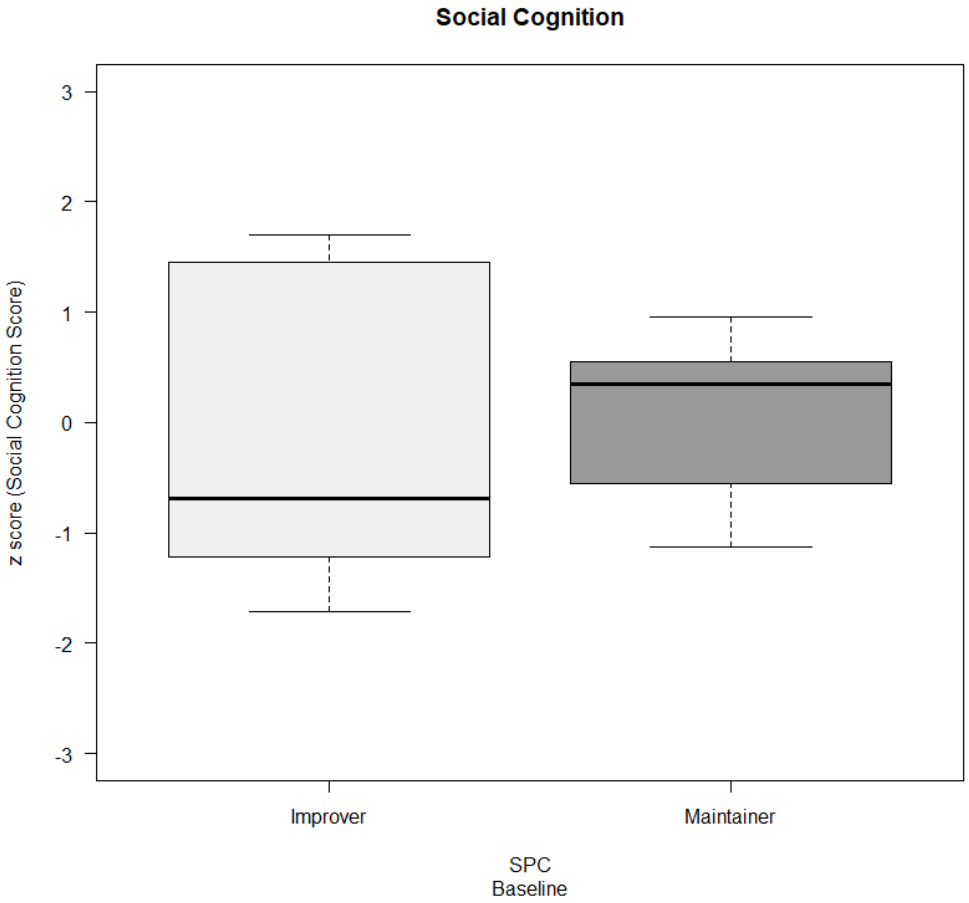

Figure 11: Boxplot of the significant group effect between Maintainers and Improvers on the baseline score of social cognition.

Notwithstanding we observed a significant increase of the social cognitive performance in the Improvers group (F = 7.78; p = 0.01; η^2_G = 0.34) as compared to the Maintainers (see Figure 12). The result did not remain significant after implementing the FDR-correction (p = 0.17) and controlling for outliers (n = 1; p = 0.06).

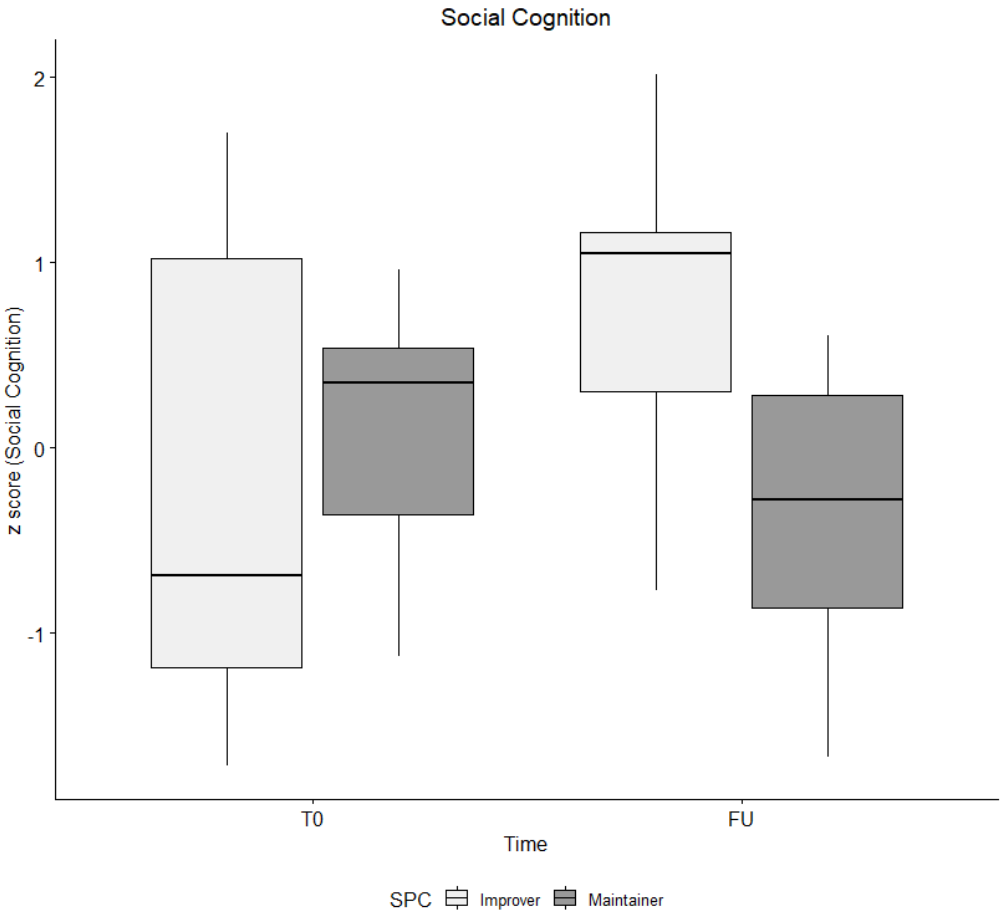

Figure 12: Boxplot of the significant interaction effect between the time and Maintainers and Improvers on social cognition.

Other between-group differences in the cognitive domains were not significant. Results of the ANCOVA are presented in Table 8.

Table 8: Baseline and follow-up scores of the cognitive domains and results of the ANCOVA between Maintainers and Improvers. *Significant at p < 0.05.

		Maintainers (n=10)	**Improvers** (n=7)	**F-test**		**Between-group comparison (ANCOVA)**		
		Mean (SD)	Mean (SD)	F	p	F	p (p FDR-corrected)	η^2_G
Social cognition	T0	0.12 (0.68)	-0.19 (1.45)	1.72	**0.05***			
	FU	-0.38 (0.77)	0.75 (1.05)	1.83	0.42	7.78	**0.01*** (0.17)	0.34
Speed of processing	T0	0.08 (0.55)	0.09 (0.72)	1.58	0.46			
	FU	0.19 (0.82)	-0.37 (0.50)	0.37	0.35	2.01	0.18 (0.45)	0.12
Working memory	T0	-0.00 (0.93)	0.00 (0.90)	0.32	0.98			
	FU	-0.02 (0.66)	0.05 (0.66)	1.00	0.91	0.01	0.91 (0.91)	0.00
Verbal learning	T0	-0.06 (1.19)	0.09 (0.67)	3.45	0.22			
	FU	-0.08 (1.20)	0.18 (0.48)	0.16	0.09	0.27	0.61 (0.82)	0.02
Attention	T0	-0.23 (1.71)	0.39 (2.15)	0.96	0.52			
	FU	-0.12 (1.13)	0.25 (0.70)	0.39	0.37	0.17	0.68 (0.82)	0.01

Global cognition	T0	-0.02 (0.54)	0.03 (1.00)	1.72	0.10			
	FU	-0.09 (0.35)	0.17 (0.29)	0.72	0.80	2.15	0.16 (0.45)	0.13

4.3 Effects of the SCT on psychosocial functioning

4.3.1 SCT and TAU

We found no significant differences in the interaction effect between the time and the SCT and the TAU group on psychosocial functioning. Results of the ANCOVA can be found in Table 9.

Table 9: Results of the ANCOVA of the psychosocial functioning variables between the SCT and the TAU group. *Significant at p < 0.05.

	SCT group (n=17)	**TAU group** (n=14)	**F-test**		**Between-group comparison (ANCOVA)**		
	Mean (SD)	Mean (SD)	F	p	F	p (p FDR-corrected)	η^2_G
GAF-S							
Past year	66.64 (8.12)	69.86 (9.26)	0.89	0.90	0.91	0.35 (0.87)	0.03
Past month	64.21 (8.68)	62.57 (10.36)	1.22	0.79	0.19	0.66 (0.95)	0.01
GAF-D							
Past year	67 (11.73)	69.71 (6.85)	0.49	0.40	0.01	0.93 (0.95)	<0.01
Past month	65.36 (12.31)	65.86 (10.98)	0.97	0.99	0.06	0.81 (0.95)	<0.01
GF							
Social current	7.34 (0.74)	7.57 (0.53)	1.07	0.92	0.67	0.42 (0.87)	0.02
Role current	6.14 (2.11)	5.71 (2.21)	1.11	0.88	<0.01	0.95 (0.95)	<0.01

4.3.2 Maintainers and Improvers

The analysis revealed a significant difference in the GF-S score between the groups whereby participants in the Maintainers group showed more benefit on social functioning as compared to the Improvers group (GF-S: F = 5.42; p = 0.03; η^2_G = 0.27) (see Figure 13). After controlling for outliers, the result was still significant (n = 1; p = 0.02; η^2_G = 0.35). However, the difference did not survive the multiple comparison correction (p = 0.21).

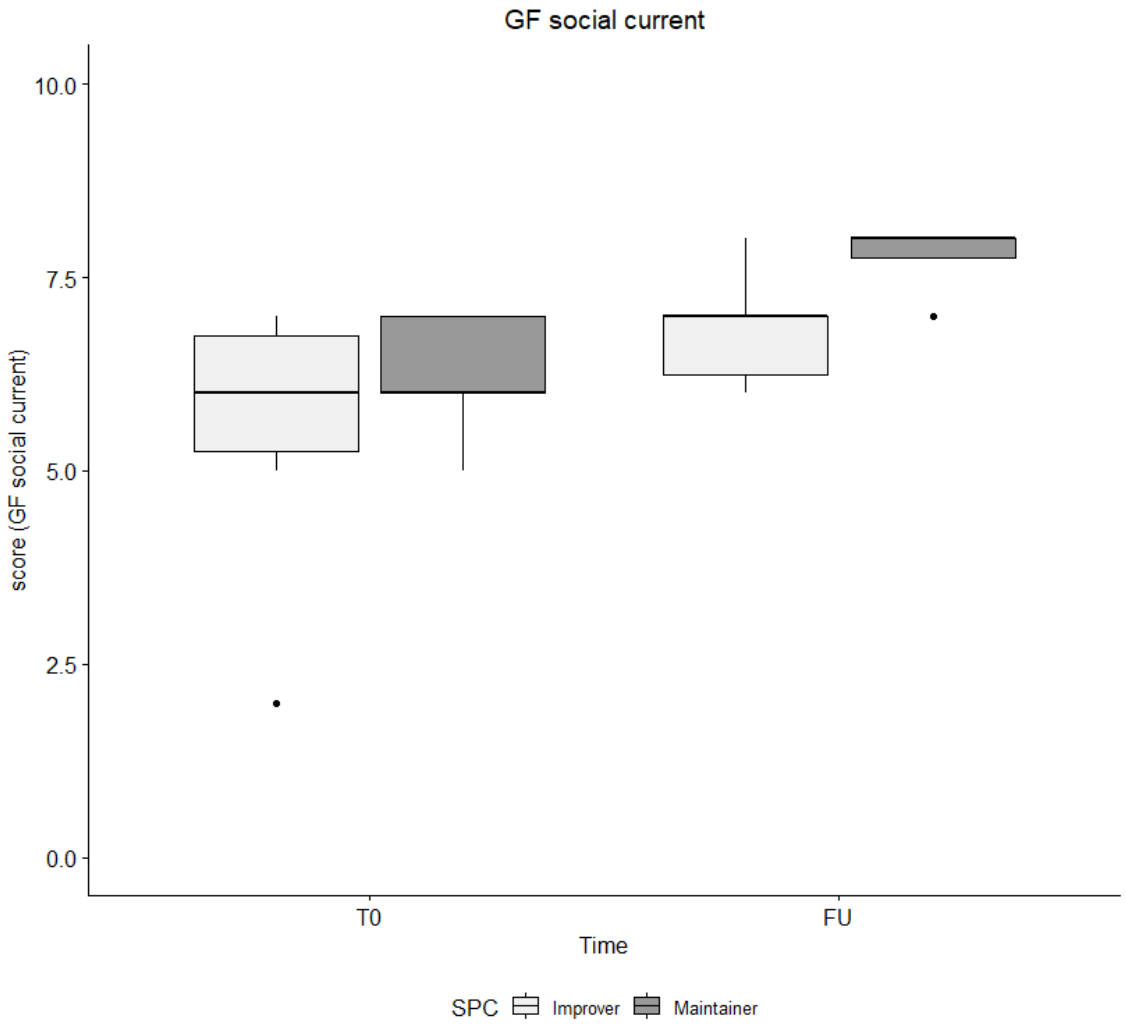

Figure 13: Boxplot of the significant interaction effect between the time and Maintainers and Improvers on the GF-S score.

Other differences in the psychosocial functioning scores between Maintainers and Improvers were not significant. Table 10 presents the results of the ANCOVA.

Table 10: Results of the ANCOVA of the psychosocial functioning variables between Maintainers and Improvers. *Significant at p < 0.05.

	Maintainers (n=10)	**Improvers** (n=7)	**F-test**		**Between-group-comparison (ANCOVA)**		
	Mean (SD)	Mean (SD)	F	p	F	p (p FDR-corrected)	η^2_G
GAF-S							
Past year	70.25 (3.58)	61.83 (10.25)	8.21	0.02	0.36	0.56 (0.82)	0.02
Past month	70.25 (3.58)	61.83 (10.25)	0.61	0.60	0.02	0.90 (0.91)	0.00
GAF-D							
Past year	72.25 (6.92)	60.00 (13.70)	3.91	0.10	0.77	0.39 (0.67)	0.05
Past month	68.88 (11.24)	60.67 (13.08)	1.35	0.69	1.20	0.29 (0.58)	0.07
GF							
Social current	7.75 (0.46)	6.83 (0.75)	2.64	0.24	5.42	**0.03*** (0.21)	0.27
Role current	6.88 (1.36)	5.17 (2.64)	3.79	0.11	1.90	0.19 (0.45)	0.11

4.4 Effects of the SCT on the rsFC

4.4.1 SCT and TAU

Compared to the TAU group, participants in the SCT group exhibited a greater increase of the rsFC between the seed located in the right caudate and the left STL (p-corr. = <0.01) over the follow-up period (see Figure 14). On the contrary, participants in the TAU group showed a significant increase of the rsFC between the right caudate and the bilateral SFL (right SFL: p-corr. = 0.04; left SFL: p-corr. = <0.01) as compared to the SCT group from T0 to follow-up (see Figure 14). There was an additional group by time effect on the rsFC between the seed in the right dlPFC and the left medial cingulum (p-corr. = <0.01) as well as the right precuneus (p-corr. = 0.02) in the TAU group as compared to the SCT group across the study (see Figure 15). We found no significant group by time interaction for the rsFC between the left amygdala and all the other voxels of the brain. Results of the full factorial ANCOVA are presented in Table 11.

Table 11: Results of the full factorial ANCOVA of the rsFC between the SCT and the TAU group. L= Left; R = Right. *Significant at p < 0.05.

Seed region	**Region**	**L/R**	**Cluster size**	**Peak Voxel MNI coordinates**			**Z-score**	**Cluster-level** p (FWE)	**Peak-level** p (FWE)
				X	Y	Z			
Right Caudate									
TAU > SCT	Superior frontal lobe	L	3	0	32	56	6.08	>0.99	**<0.01***
	Superior frontal lobe	R	1	14	17	48	5.22	>0.99	**0.04***
SCT > TAU	Superior temporal lobe	L	258	-51	-20	8	3.93	**<0.01***	>0.99
Right dlPFC									
TAU > SCT	Medial Cingulum	L	261	-12	-24	44	5.63	**<0.01***	**<0.01***
	Medial Cingulum	L	842	0	-45	45	5.54	**<0.01***	**0.01***
	Precuneus	R	2	15	-53	41	5.38	>0.99	**0.02***

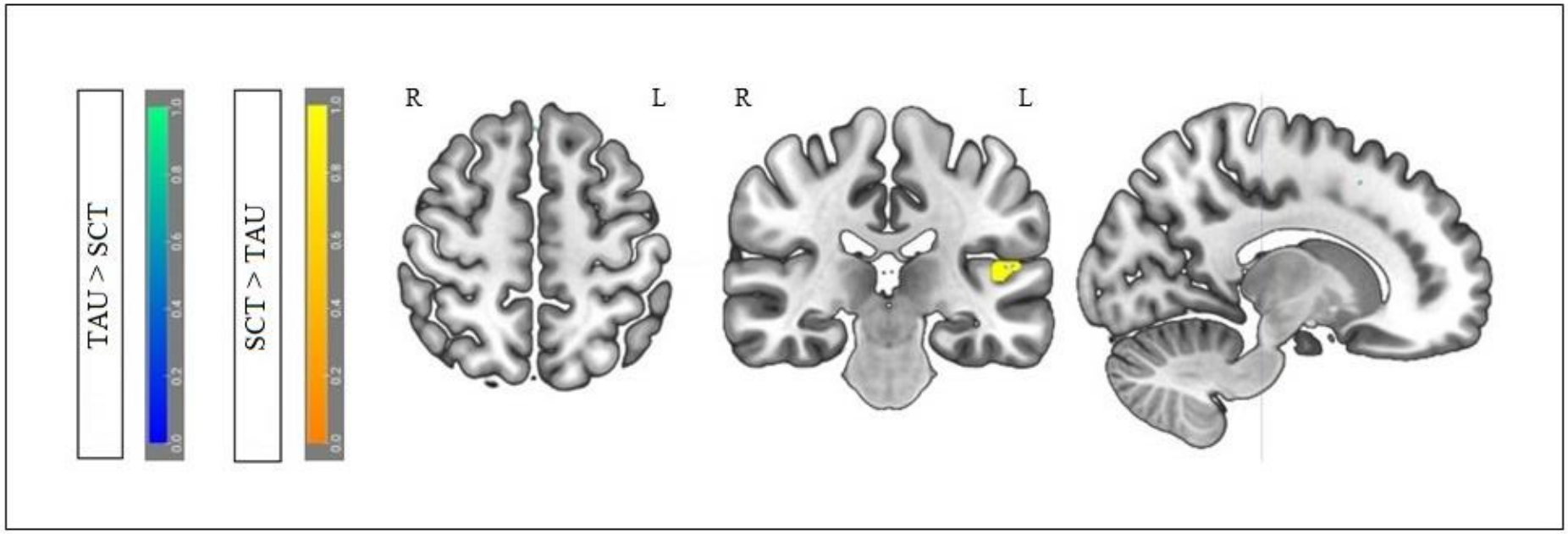

Figure 14: Visualization of the significant interaction effect between the time and the SCT and the TAU group on the rsFC with a 10mm-seed in the right caudate.

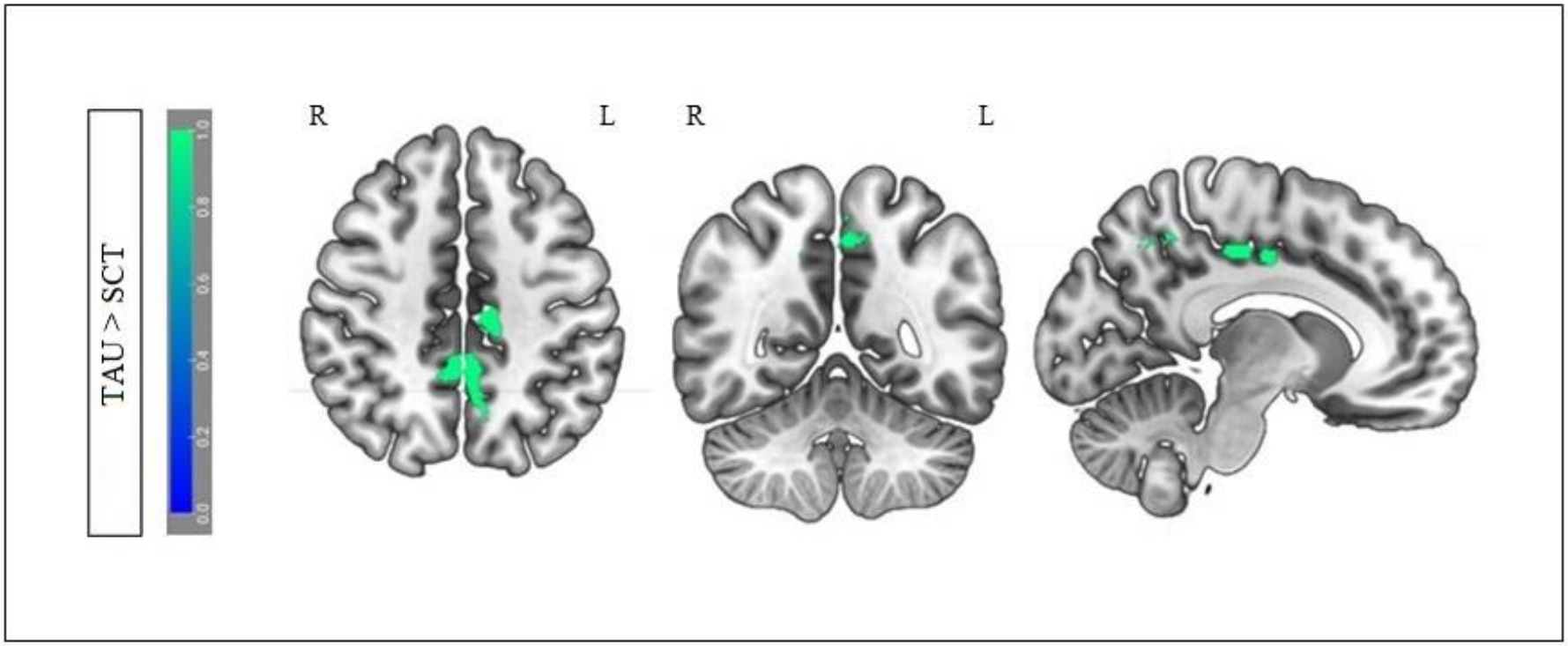

Figure 15: Visualization of the significant interaction effect between the time and the SCT and the TAU group on the rsFC with a 10mm-seed in the right dlPFC.

4.4.2 Maintainers and Improvers

We found a significant interaction effect on the rsFC between the seed region in the left amygdala and the left SFL (p-corr. = <0.01) and the left MFL (p-corr. = <0.01) in the Improvers group as compared to the Maintainers across the study. Likewise, Maintainers showed an increased rsFC between the left amygdala and the left MFL (p-corr. = <0.01) as compared to the Improvers from T0 to follow-up (see Figure 16). There was no significant group by time interaction effect on the rsFC between the seed located in the right dlPFC or the right caudate and all the other voxels of the brain. For the results of the full factorial ANCOVA see Table 12.

Table 12: Results of the full factorial ANCOVA of the rsFC between Maintainers and Improvers. *Significant at p < 0.05.

Seed region	Region	L/R	Cluster size	Peak Voxel MNI coordinates			Z-score	Cluster-level p (FWE)	Peak-level p (FWE)
				X	Y	Z			
Left amygdala									
Improvers > Maintainers	Medial frontal lobe	L	2517	-36	18	45	5.74	**<0.01***	**<0.01***
	Superior frontal lobe	L	117	2	63	18	5.41	**<0.01***	**0.01***
Maintainers > Improvers	Medial frontal lobe	L	121	-35	18	45	5.16	**<0.01***	**0.05***

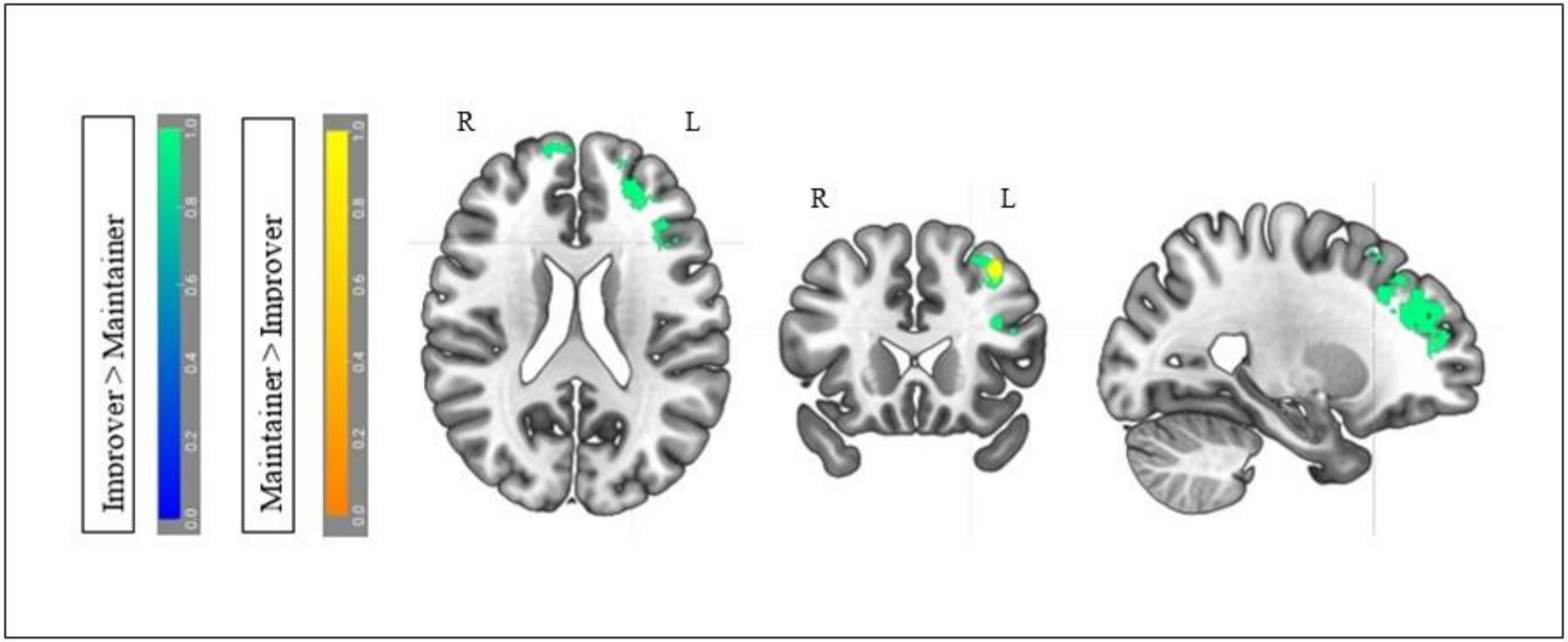

Figure 16: Visualization of the significant interaction effect between the time and Maintainers and Improvers on the rsFC with a 10mm-seed in the left amygdala.

4.5 The relationship between the rsFC and cognition

4.5.1 SCT and TAU

The Pearson's correlation tests did not reveal a significant association between the follow-up scores of the cognitive domains and the follow-up connectivity values of the global maxima of all regions that showed a significant FC with the seed regions of the participants in the SCT group after implementing the multiple comparison correction. There was further no significant correlation between the differences of the both or the baseline connectivity values and the change in the scores of the cognitive domains between baseline and follow-up in the SCT group, after we corrected for multiple comparisons. Results are presented in Table 13.

Similar to the results for the SCT group, we neither found a significant correlation between the follow-up scores of the cognitive domains and the follow-up connectivity values of the regions with a significant rsFC to the seed regions, the differences of the cognitive scores and the baseline connectivity values nor between the differences of the aforementioned variables in the TAU group after we corrected for multiple comparisons. Results of the Pearson's correlation tests can be found in Table 14.

4.5.2 Maintainers and Improvers

There was no significant association between the follow-up scores of the cognitive domains and the follow-up connectivity values of the global maxima of all regions that showed a significant FC with the seed regions in the Maintainers group after correcting for multiple testing. Likewise, we did not find a significant correlation between the differences of the both or the baseline connectivity values and the change in the scores of the cognitive domains between baseline and follow-up in the same group after we corrected for multiple comparisons. The results of the calculated Pearson's correlation tests are presented in Table 15.

With respect to the Improvers group, the correlation tests did not show a significant correlation between the follow-up scores of the cognitive domains and the follow-up connectivity values, the differences of the cognitive scores and the baseline connectivity values or between the differences of the aforementioned variables after we controlled for multiple testing. Results can be seen in Table 16.

5 Discussion

5.1 Effects of the SCT on cognition and psychosocial functioning

5.1.1 SCT and TAU

The SCT showed no significant effect on the cognitive performance or the functional outcome as compared to TAU in this study which is oppositional to our hypothesis that SCT has an additional effect on the neurocognitive performance and daily functioning in MDD. However, previous studies reported similar results including Murthy, Mahncke [181] who did not observe a significant effect of a specific brain fitness program on the cognitive performance in schizophrenia despite a large, significant improvement in a training exercise task (auditory processing speed). Likewise, CR therapy was not associated with a greater cognitive improvement as compared to TAU in schizophrenia and schizoaffective disorders in a study of Lewis, Unkefer [182]. In line with this, Choi, Wang [183] did not observe a significant improvement of memory after a targeted cognitive intervention and concluded that the examined sample had no need of cognitive training therapy due to a greater cognitive reserve. With respect to the functional outcome, the effect size of cognitive training on functional outcome measures was not significant in a meta-analysis of Woolf, Lampit [184] while Bowie, Gupta [185] did not observe a significant improvement in functioning measures after a combined internet-based CR intervention in treatment-resistant depression.

Woolf, Lampit [184] suggested that another possible reason for missing results of cognitive training therapy could be a lack of consensus on the neuropsychological test battery included in the diagnostic of MDD, so that null results may reflect an insufficient cognitive assessment. Moreover, Mowszowski, Lampit [186] highlighted the difficulty of a reliable neuropsychological assessment, since some neurocognitive domains rely on novelty and abstract thinking which hinders the administration of validated tests [184,186]. In this study, we used the MCCB neuropsychological test battery with the resulting cognitive domains (e.g. “social cognition”, “verbal learning”, “working memory”, “speed of processing”, “attention” and “global cognition”) that is designed for schizophrenia and related disorders [152]. However, this battery does not include tests on executive function although previous studies reported significant disturbances in frontal lobe cognitive functioning in depression [187,188].

Executive function is described as the ability to “flexible organize thoughts and actions towards a target behavior and to coordinate and monitor schemas to achieve complex tasks” [129]. It further implies decision making, organization and learning [52,189] as well as inhibitory control and planning [190,191]. The overall effect of cognitive training on executive function was statistically significant in the meta-analysis of Woolf, Lampit [184]. Moreover, further studies

described similar results with improved executive functioning skills after a cognitive training in depression [192,193].

These findings suggest that examining executive function in this study would have brought up additional insights in the effectiveness of the SCT on the cognitive performance. Therefore, we can not exclude that the administered intervention slightly improved basic cognitive domains such as executive function that did not transfer to more distal cognitive domains which might rely on an intact performance of the former [194]. Additionally, as suggested by Choi, Wang [183], the effectiveness of cognitive training probably depends on the individual cognitive reserve, whereby persons with greater cognitive impairment may benefit more clearly from the intervention.

5.1.2 Maintainers and Improvers

We further addressed the effectiveness of the SCT in MDD groups with different patterns of sensory processing. Thereby, we differentiated between participants who already exhibited an optimal processing performance at baseline (Maintainers) and those who showed an impaired baseline performance but reached the optimal processing threshold during the training period (Improvers). According to our results, Maintainers showed significantly higher baseline scores of social cognition while Improvers significantly strengthened social cognitive abilities as compared to Maintainers across the study. Additionally, social functioning was significantly increased in Maintainers as compared to Improvers at the end of the study. These results are in line with previous findings from studies in schizophrenia that demonstrated a significant effect of CCT and SCT on social cognitive functions [195-197] and functional outcome measures [78,195,197]. For example, Nahum, Fisher [198] observed an improved performance on social cognitive tasks and enhanced social functioning after a neuroplasticity-based online SCT program for young adults with schizophrenia. In a study of Sacks, Fisher [199], participants with schizophrenia significantly enhanced social cognitive abilities after a combined computerized SCT and a neuroplasticity-based auditory training. Improvements in activities of daily living after cognitive training interventions were further reported in MDD [1].

With respect to the benefit of the SCT on cognitive performance and psychosocial functioning depending on the intrinsic sensory processing behavior of Maintainers and Improvers, our results are contrary to those of Kambeitz-Ilankovic, Wenzel [9]. They observed that perceived sensory processing was associated with improved emotion recognition in psychosis after a computerized SCT, whereby participants were classified as Maintainers or Improvers similar to this study. Kambeitz-Ilankovic, Wenzel [9] concluded that participants with more cognitive reserve show a greater transfer effect to cognitive performance while Improvers can not translate training improvement into cognitive gains. They further pointed to the possibility that

Improvers might have benefited from an elongated and more diversified CCT program [9]. Differences in the results might originate from a varying responsiveness to CCT depending on the degree of cognitive impairment in MDD and schizophrenia. Thus, more severe neurocognitive impairments were observed in patients with schizophrenia as compared to depression [188,200,201] that might hinder the successful participation in CCT programs and point towards an individual threshold for improvement on the training tasks that is needed to induce a significant strengthening of general cognitive abilities [10,202]. Subsequent, the threshold for training engagement to reach cognitive improvement potentially varies between psychiatric disorders and results in different needs of training duration and intensity.

However, our results concur with Choi, Wang [183] who proposed that participants with less cognitive reserve show more benefit on cognitive outcome measures after cognitive training interventions. Likewise, participants with low baseline cognitive performance showed significantly more benefit from CCT as compared to those with high baseline scores in a sample of patients with MDD, bipolar disorder and schizophrenia in a study of Harvey, Balzer [202]. They suggested that “individuals with psychiatric conditions who do not manifest cognitive impairments at baseline might not be candidates for interventions aimed at cognitive enhancement” [202]. Nonetheless, cognitive disability hinders successful functional recovery [2] and decreases everyday functioning [47,203] that might explain why Maintainers showed more benefit on social functioning measurements as compared to Improvers across the study. Harvey, Balzer [202] further identified training engagement as measured by a self-developed score consisting of the number of levels achieved per training day and the difference of the baseline and the follow-up scores on a cognitive measurement as an independent predictor of cognitive improvement after CCT. In the same line, Fisher, Holland [7] observed that the individual psychophysical learning capacity models the response to cognitive training, whereby subjects with the most progress in basic training exercises (computerized auditory training) showed the most improvement in cognitive abilities. As a conclusion, Harvey, Balzer [202] stated baseline cognitive impairment and training engagement as two appropriate predictors of cognitive improvement after CCT and suggested a standardized assessment of baseline cognitive impairment before and a monitoring of training engagement during CR interventions.

In summary, these findings show that individual characteristics such as the sensory processing efficiency and baseline cognitive performance probably influence the susceptibility to cognitive training in mental health disorders. According to the study results, SCT successfully targets reduced sensory processing efficiency, which co-occurred with impaired baseline cognitive functions, in MDD and leads to an enhanced processing capability and improved social cognition. Consequently, these baseline characteristics of MDD patients probably predict a stronger response to cognitive training interventions with respect to cognitive outcome

measures. Therefore, our results suggest baseline cognitive impairment and the individual sensory processing behavior as potential markers for the treatment response to SCT and might be worth to assess prior to and during an intended CR intervention [7,202].

5.2 Effects of the SCT on rsFC

5.2.1 SCT and TAU

We found an increased FC at rest between the right caudate and the left superior temporal lobe in the SCT group as compared to TAU from T0 to follow-up. The superior temporal gyrus is involved in the perception and processing of auditory stimuli and plays a role in the interpretation of facial affective stimuli. It is further part of an "interconnected system of regions that construct a spatially distributed perceptual representation of different aspects of faces" [204]. Hence, the superior temporal gyrus underlies social cognitive processes especially the perception and judgment of social stimuli and co-actives with multiple parallel processing routes that include the PFC and the amygdala [204]. Additionally, Yang, Tian [205] proposed that reduced rsFC between the caudate and the temporal-parietal cortex is a part of the neural alterations underlying MDD and highlights the role of the superior temporal gyrus as "one of the most identified brain regions linked to the neurobiology of depression" [206]. In line with our findings, Meusel, Hall [117] reported on an increased activity of the superior temporal gyrus in task-based fMRI after 10 weeks of CR therapy in participants with mood disorders which was associated with an improved performance on a neuropsychological test battery.

Contrary to that, participants in the TAU group exhibited an increased rsFC between the bilateral frontal lobe and the right caudate nucleus, the cingulum and the precuneus as compared to the SCT group from T0 to follow-up. The cingulum is an association trajectory of the telencephalon that links regions of the neocortex and the entorhinal cortex. Due to the connection between neocortical and hippocampal structures, the cingulum is attributed to the limbic system which underlies learning, memory and emotion processing. The precuneus is a part of the Default Mode Network (DMN) that consists of neural circuits between cortical and subcortical structures [207] and is integrated in processes of problem-solving and cognitive control [176,208,209]. Previous studies in depression examined alterations of both the frontal lobe and the limbic system [210]. They proposed that cortico-limbic dysregulation is a main contributor to the pathophysiology of depression [131] and suggested that the reorganization of neural cortico-limbic circuits strengthens the cognitive control of prefrontal regions over limbic structures, that leads to an improved emotion regulation in depression [11]. Moreover, previous studies demonstrated an altered FC between structures of the DMN and the frontoparietal network in MDD [211,212] which was correlated with reduced cognitive function in related disorders [213-215].Similar to our results on the effect of TAU on the rsFC of the brain, recent findings

suggest an extensive effect of antidepressant medication on brain networks in depression [216]. For example, Hsu, Lane [217] observed an increased FC between limbic and prefrontal structures after the antidepressant medication with sertraline in a sample of drug-naïve MDD patients. In line with this, Vasavada, Loureiro [218] demonstrated an increased FC between neural correlates of the limbic system and the frontoparietal network after a ketamine infusion therapy in MDD. Likewise, FC was significantly enhanced between the cingulum and the PFC after a CBT monotherapy in patients with current MDD in a study of Pantazatos, Yttredahl [219].

Consecutively, increased rsFC between the caudate nucleus and the superior temporal gyrus in the SCT group as compared to TAU across the follow-up period might represent a training-related strengthening of the FC between brain regions that underlie the encoding of facial affective stimuli [204] and hence underlines the potential of SCT to induce neuroplastic changes in the brain. Consistent with findings from previous studies [131,217-219] , TAU equally showed a significant effect on the rsFC of brain regions that are involved in the pathology of depression, which emphasizes the need of further studies to clarify the additional effect of SCT on the neuroplasticity of the brain in patients with MDD.

5.2.2 Maintainers and Improvers

We found an increased rsFC between the left amygdala and the left frontal regions in both groups as compared to the respective other from T0 to follow-up. As mentioned above, the connectivity between limbic and prefrontal structures plays an important role in the pathophysiology of depression, whereby dysregulated fronto-limbic pathways are associated with reduced cognitive functions [131,220]. In addition, previous studies found a reduced connectivity between the amygdala and the PFC in MDD that might reflect an inadequate inhibition of the limbic system [101,131,221,222]. With respect to treatment-induced neuroplastic changes, our results are in line with Cullen, Klimes-Dougan [223] who observed that the treatment response to an antidepressant medication was associated with an increased connectivity between limbic and frontal structures in MDD. Furthermore, recent studies showed an increased activity in frontal regions after a CR therapy in a broad range of mental disorders [110-114] while Kral, Schuyler [116] reported on an increased FC between the amygdala and frontal regions in a tasked-based fMRI study after a short-term cognitive training as compared to the control group in healthy adults.

Consequently, our results provide additional evidence that computerized SCT induces neuroplastic changes in the brain of patients with MDD. These changes potentially include the reorganization of neural connectivity between frontal and limbic networks that play an important role in the pathophysiology of depression [11]. Although future studies should examine the replicability and the long-term effect of the presented results, the connectivity between

these neural structures might represent an appropriate neural target for cognitive training therapy.

5.3 The Relationship between the rsFC and cognition

5.3.1 SCT and TAU

We did not observe a significant association between the change of the cognitive performance and the rsFC patterns from baseline to follow-up neither in the SCT nor the TAU group. Comparable results were reported by Meusel, Hall [117] who could not relate behavioral and neural alterations though they found an increased activity of the lateral and medial prefrontal cortex and the superior temporal cortex and a significant improvement of working memory measured with the backward digit span test in patients with mood disorders after cognitive remediation. Moreover, Bulubas, Padberg [224] did not find a significant association between the baseline rsFC of the PFC and the response to transcranial direct current stimulation (tDCS) measured with the Hamilton Depression Rating Scale – 17th version (HDRS-17) and the Positive and Negative Affect Scale (PANAS) in MDD patients.

On the other side, Subramaniam, Luks [225] detected an increased activity of the left middle and inferior frontal lobe after a combined SCT and CCT in a tasked-based fMRI study in schizophrenia that was associated with improved social functioning over the follow-up period. In line with this, Bor, Brunelin [110] observed an increased activity of the left inferior and middle frontal gyrus that was correlated with improved attention and reasoning capacities after CR therapy in patients with schizophrenia in a tasked-based fMRI study. Furthermore, improved emotion regulation after cognitive training was related to an enhanced FC of the frontoparietal network in a study of Schweizer, Grahn [226].

Due to the varying study results for the association between behavioral and neural alterations undergoing treatment in mental disorders, Meusel, Hall [117] underlined the need of future studies to investigate the relation of the former. Taylor, Kurt [227] further pointed towards the identification of the key neural systems underlying antidepressant therapy approaches that can be used as neural biomarkers for treatment response in depression.

5.3.2 Maintainers and Improvers

In line with results for the SCT and the TAU group, there was no significant association between behavioral and neural alterations from baseline to follow-up in the Maintainers or the Improvers group. Previous studies in electroconvulsive therapy (ECT) reported similar results whereby significantly decreased rsFC between the amygdala and the medial PFC and the right dlPFC in patients with schizophrenia and MDD was not associated with improved depressive symptoms after ECT [228].

However, Straub, Metzger [229] observed that the increased rsFC between the amygdala and the left dlPFC after a CBT intervention correlated with a significant improvement of depressive symptomology. Additionally, baseline rsFC of the amygdala predicted the response to CBT in this study [229]. Hooker, Bruce [230] further measured an increased activity of the amygdala after a combined SCT and CCT in schizophrenia that predicted the improvement of the performance in a face emotion recognition task.

Consequently, Taylor, Kurt [227] claimed that the lack of consensus on the neural processes of the amygdala that are related to antidepressant treatment response might be accounted by a varying sample size and methodological differences. Hereinafter findings support the demand of further studies in the field of neural biomarkers of treatment response in depression [117].

5.4 Conclusion

This study showed that the effect of SCT on cognition and psychosocial functioning in MDD patients probably depends on individual characteristics such as the sensory processing efficiency and the baseline cognitive performance that might mediate the response to SCT. Thus, impaired sensory processing ability that co-occurred with reduced baseline cognitive performance can be successfully targeted with SCT to induce an enhanced sensory processing behavior and improved social cognitive abilities in MDD. Moreover, the individual sensory processing efficiency represent a potential measures of target engagement to predict the treatment response to SCT. On the neural level, SCT might induce a strengthening of the FC between neural structures integrated in the encoding of facial affective stimuli and therefore underline the potential of SCT to induce neuroplastic changes in the brain. Nonetheless, further studies should clarify the effect of SCT on the neuroplasticity of the brain whereby the reorganization of fronto-limbic pathways might be an appropriate target for SCT.

5.5 Limitations and future directions

5.5.1 Limitations

One limitation of the present study is the relatively small sample size accompanied by a dropout rate of 6 participants as compared to a total number of 40 participants included in the study. The relatively small sample size may result from the complex study design with an elaborated assessment, high adherence to training procedure and long overall duration. Since persons suffering from mental disorders struggle with everyday functioning [41,42] and cognitive disability [1,2], these deficits may also lead to difficulties in attending arrangements or maintain training routine. However, further studies with a bigger sample size are needed to replicate our results and test the validity. We also did not assess individual and clinical characteristics such

as employment status [69] or the type of antidepressant treatment [231,232] of the participants that probably mediated the response to SCT. Additionally, we did not include a group of healthy controls in our study that would have given insights into the effect of SCT on the cognitive performance, psychosocial functioning and the FC of the brain of healthy persons as compared to MDD patients. It would have been of further interest to compare different patterns of sensory processing behavior between MDD patients and healthy controls to clarify the role of the individual processing ability in the diagnostic and treatment of MDD. In line with this, Woolf, Lampit [184] emphasized the importance of an optimal control condition in clinical studies to precisely differentiate between effects induced by the intervention or practice and prior exposure. Finally, the ROI-based approach used for the analysis of the fMRI data in this study, contracts the identification of functional networks since we predefined brain regions prior to the analysis. Although we interpreted the identified clusters of significant rsFC in the framework of neural networks, we can not fulfill the demand of a network-based approach [233]. This well-known disadvantage of seed-based rsfMRI analysis may lead to an overrating of the maintained results and emphasizes the role of alternative approaches in rsfMRI analysis [108].

5.5.2 Future directions

Further studies with a larger sample size are needed to clarify the short- and long-term effect of computerized SCT on the behavioral and biological characteristics (e.g. “cognition”, “psychosocial functioning”, “rsFC of the brain”) of MDD [184]. Moreover, future studies might seek a consensus on the optimal training design of SCT (e.g., “frequency”, “overall duration”) [58] as well as the way of integration in the conventional therapy of depression [78,89,184] with the focus on the accessibility and feasibility of cognitive training to the general public [184]. Since our results suggest the individual sensory processing behavior as a potential marker of target engagement to predict the treatment response to SCT, it might be possible to assess the individual need of cognitive training prior to an intervention. Future studies should additionally focus on the identification of neural correlates of target engagement and treatment response to SCT that could direct the treatment of MDD towards an individualized medicine.

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7 Appendix

7.1 List of figures

7.2 List of tables

7.3 Tables of results of the Pearson's correlation tests.

Table 13: Results of the Pearson's correlation test (SCT group). The correlation between the scores of the cognitive domains and the connectivity values of the global maxima of all regions that showed a significant FC with the seed regions was calculated.

		Social Cognition		Speed of Processing		Working Memory		Attention		Verbal Learning		Global Cognition	
		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)	
		FU	FU – T0	FU	FU – T0	FU	FU – T0	FU	FU – T0	FU	FU – T0	FU	FU – T0
Superior frontal lobe (14 17 48)	T0		0.0 (0.99)		-0.4 (0.49)		0.06 (0.96)		-0.04 (0.96)		0.15 (0.96)		-0.01 (0.97)
	FU	0.4 (0.55)		-0.22 (0.72)		-0.49 (0.47)		-0.11 (0.82)		-0.07 (0.87)		-0.22 (0.72)	
	FU – T0		-0.03 (0.94)		-0.09 (0.91)		-0.23 (0.78)		0.17 (0.80)		-0.42 (0.53)		-0.17 (0.80)
Superior medial frontal lobe	T0		-0.1 (0.96)		-0.35 (0.60)		-0.04 (0.96)		-0.1 (0.96)		0.09 (0.96)		-0.14 (0.96)
	FU	0.23 (0.72)		-0.4 (0.55)		-0.16 (0.80)		0.26 (0.72)		-0.29 (0.72)		-0.14 (0.82)	

(0 32 56)	FU – T0		-0.03 (0.94)		0.0 (>0.99)		-0.24 (0.78)		0.08 (0.91)		-0.36 (0.63)		-0.17 (0.80)
Superior temporal lobe (-51 -20 8)	T0		0.19 (0.89)		-0.2 (0.89)		0.19 (0.89)		-0.32 (0.65)		0.08 (0.96)		-0.04 (0.96)
	FU	-0.21 (0.72)		0.26 (0.72)		-0.11 (0.82)		-0.16 (0.81)		0.19 (0.73)		-0.03 (0.93)	
	FU – T0		-0.32 (0.68)		0.29 (0.74)		-0.23 (0.78)		0.3 (0.74)		0.05 (0.91)		0.02 (0.96)
Medial Cingulum (0 45 45)	T0		-0.04 (0.96)		-0.1 (0.96)		-0.23 (0.86)		-0.03 (0.96)		0.09 (0.96)		-0.02 (0.96)
	FU	-0.13 (0.82)		0.02 (0.95)		0.06 (0.87)		0.23 (0.72)		0.06 (0.87)		0.11 (0.82)	
	FU – T0		-0.24 (0.78)		0.15 (0.80)		0.05 (0.91)		-0.05 (0.91)		-0.2 (0.80)		-0.21 (0.80)
Medial Cingulum (12 24 44)	T0		0.03 (0.96)		0.44 (0.48)		-0.34 (0.60)		0.49 (0.31)		-0.14 (0.96)		0.21 (0.88)
	FU	-0.06 (0.87)		-0.22 (0.72)		-0.2 (0.72)		-0.01 (0.96)		0.2 (0.72)		-0.14 (0.82)	
	FU – T0		-0.2 (0.80)		-0.5 (0.28)		0.05 (0.91)		-0.56 (0.21)		-0.13 (0.85)		-0.51 (0.28)

Precuneus (15 -53 41)	T0		-0.1 (0.96)		-0.37 (0.58)		-0.11 (0.96)		-0.21 (0.88)		0.06 (0.96)		-0.18 (0.89)
	FU	-0.06 (0.87)		0.33 (0.72)		0.25 (0.72)		0.37 (0.62)		-0.26 (0.72)		0.28 (0.72)	
	FU – T0		-0.17 (0.80)		0.16 (0.80)		-0.32 (0.68)		0.24 (0.78)		-0.34 (0.63)		-0.17 (0.80)

Table 14: Results of the Pearson's correlation test (TAU group). The correlation between the scores of cognitive domains and the connectivity values of the global maxima of all regions that showed a significant FC with the seed regions was calculated.

		Social Cognition		Speed of Processing		Working memory		Attention		Verbal learning		Global Cognition	
		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)	
		FU	FU-T0	FU	FU-T0	FU	FU-T0	FU	FU-T0	FU	FU-T0	FU	FU-T0
Superior frontal lobe	T0		0.21 (0.99)		0.0 (0.99)		0.34 (0.99)		-0.13 (0.99)		-0.35 (0.99)		0.03 (0.99)
(14 17 48)	FU	0.03 (0.95)		-0.16 (0.84)		-0.37 (0.60)		-0.29 (0.71)		0.16 (0.84)		-0.24 (0.75)	
	FU-T0		-0.11 (0.98)		0.08 (0.98)		-0.07 (0.98)		0.43 (0.69)		0.14 (0.98)		0.22 (0.96)
Superior medial frontal lobe	T0		-0.16 (0.99)		0.15 (0.99)		0.22 (0.99)		-0.01 (0.99)		-0.26 (0.99)		-0.08 (0.99)
(0 32 56)	FU	-0.26 (0.75)		-0.03 (0.95)		-0.36 (0.60)		0.03 (0.95)		0.21 (0.79)		-0.24 (0.75)	
	FU-T0		-0.04 (0.98)		-0.04 (0.98)		-0.07 (0.98)		0.5 (0.53)		0.28 (0.89)		0.3 (0.87)

Superior temporal lobe (-51 -20 8)	T0		-0.23 (0.99)		0.46 (0.89)		0.06 (0.99)		-0.13 (0.99)		-0.11 (0.99)		-0.03 (0.99)
	FU	-0.35 (0.60)		0.15 (0.86)		-0.12 (0.86)		0.19 (0.80)		0.14 (0.86)		-0.1 (0.88)	
	FU-T0		-0.02 (0.99)		-0.09 (0.98)		-0.11 (0.98)		0.21 (0.96)		-0.04 (0.98)		0.0 (>0.99)
Medial Cingulum (0 45 45)	T0		-0.65 (0.40)		0.0 (0.99)		0.09 (0.99)		0.08 (0.99)		0.14 (0.99)		-0.3 (0.99)
	FU	-0.09 (0.88)		-0.13 (0.86)		-0.55 (0.36)		-0.13 (0.86)		-0.07 (0.92)		-0.41 (0.60)	
	FU-T0		0.33 (0.76)		-0.12 (0.98)		-0.53 (0.41)		0.2 (0.96)		-0.18 (0.98)		0.05 (0.98)
Medial Cingulum (12 24 44)	T0		-0.24 (0.99)		-0.02 (0.99)		-0.08 (0.99)		0.34 (0.99)		0.17 (0.99)		0.04 (0.99)
	FU	-0.36 (0.60)		-0.07 (0.92)		-0.53 (0.36)		-0.29 (0.71)		0.06 (0.92)		-0.56 (0.36)	
	FU-T0		-0.36 (0.76)		0.36 (0.76)		0.04 (0.98)		-0.43 (0.69)		-0.21 (0.96)		-0.35 (0.76)
Precuneus	T0		0.02 (0.99)		0.07 (0.99)		0.38 (0.99)		-0.17 (0.99)		0.13 (0.99)		0.12 (0.99)

(15 -53 41)	FU	0.23		-0.35		-0.44		-0.39		-0.01		-0.32	
		(0.78)		(0.60)		(0.60)		(0.60)		(0.98)		(0.69)	
	FU-T0		0.04		-0.13		-0.46		0.53		-0.16		0.07
			(0.98)		(0.98)		(0.66)		(0.41)		(0.98)		(0.98)

Table 15: Results of the Pearson's correlation test (Maintainers). The correlation between the scores of cognitive domains and the connectivity values of the global maxima of all regions that showed a significant FC with the seed regions was calculated.

		Social Cognition		Speed of Processing		Working memory		Attention		Verbal learning		Global Cognition	
		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)	
		FU	FU-T0	FU	FU-T0	FU	FU-T0	FU	FU-T0	FU	FU-T0	FU	FU-T0
Medial frontal lobe	T0		-0.28 (0.70)		-0.24 (0.75)		-0.4 (0.53)		-0.23 (0.75)		-0.05 (0.91)		-0.35 (0.61)
(-36 18 45)	FU	0.44 (0.38)		-0.46 (0.38)		-0.66 (0.22)		-0.57 (0.33)		0.16 (0.78)		-0.53 (0.38)	
	FU-T0		0.65 (0.23)		0.14 (0.81)		0.59 (0.28)		-0.32 (0.56)		0.49 (0.42)		0.43 (0.44)
Superior frontal lobe	T0		-0.32 (0.62)		0.1 (0.91)		-0.63 (0.27)		-0.08 (0.91)		-0.51 (0.53)		-0.49 (0.53)
(2 63 18)	FU	-0.08 (0.85)		-0.56 (0.33)		-0.18 (0.76)		0.1 (0.85)		0.08 (0.85)		-0.25 (0.63)	
	FU-T0		0.1 (0.85)		-0.36 (0.50)		0.34 (0.53)		-0.29 (0.59)		0.45 (0.43)		0.09 (0.85)

Medial frontal lobe	T0		0.04 (0.91)		0.42 (0.53)		0.19 (0.78)		0.44 (0.53)		-0.41 (0.53)		0.15 (0.84)
(-35 18 45)	FU	0.33 (0.53)		-0.68 (0.22)		-0.64 (0.22)		-0.15 (0.78)		-0.26 (0.63)		-0.7 (0.22)	
	FU-T0		0.24 (0.68)		-0.43 (0.44)		-0.08 (0.85)		-0.75 (0.17)		0.38 (0.47)		-0.22 (0.68)

Table 16: Results of the Pearson's correlation test (Improvers). The correlation between the scores of cognitive domains and the connectivity values of the global maxima of all regions that showed a significant FC with the seed regions was calculated.

		Social Cognition		Speed of Processing		Working memory		Attention		Verbal learning		Global Cognition	
		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)		r (p FDR-corr.)	
		FU	FU-T0	FU	FU-T0	FU	FU-T0	FU	FU-T0	FU	FU-T0	FU	FU-T0
Medial frontal lobe	T0		-0.38 (0.65)		-0.34 (0.70)		-0.01 (0.98)		-0.48 (0.53)		0.13 (0.85)		-0.39 (0.65)
(-36 18 45)	FU	-0.48 (0.64)		0.19 (0.86)		-0.45 (0.64)		-0.24 (0.80)		0.4 (0.64)		-0.47 (0.64)	
	FU-T0		0.25 (0.66)		0.42 (0.52)		0.47 (0.49)		0.2 (0.70)		0.37 (0.57)		0.32 (0.63)
Superior frontal lobe	T0		-0.33 (0.70)		-0.65 (0.33)		-0.49 (0.53)		-0.65 (0.33)		-0.15 (0.83)		-0.59 (0.37)
(2 63 18)	FU	-0.62 (0.64)		-0.04 (>0.99)		-0.38 (0.64)		-0.57 (0.64)		0.42 (0.64)		-0.77 (0.37)	
	FU-T0		0.37 (0.57)		0.63 (0.35)		0.48 (0.49)		0.27 (0.66)		0.24 (0.66)		0.44 (0.50)

Medial frontal lobe (-35 18 45)	T0		-0.25 (0.82)		0.32 (0.70)		-0.19 (0.83)		0.16 (0.83)		0.19 (0.83)		0.08 (0.92)
	FU	-0.39 (0.64)		-0.33 (0.70)		-0.09 (0.96)		0.19 (0.86)		0.58 (0.64)		-0.17 (0.87)	
	FU-T0		-0.35 (0.58)		-0.47 (0.49)		-0.24 (0.66)		-0.62 (0.35)		-0.26 (0.66)		-0.56 (0.40)

8 Publication of results

To date, none of the results of this study have been published.