Cognitive Impairment Along the Course of Depression: Non-Pharmacological Treatment Options

Lena Listunova^a Corinna Roth^a Marina Bartolovic^a Johanna Kienzle^a
Claudia Bach^a Matthias Weisbrod^{a, b} Daniela Roesch-Ely^a

^aDepartment of General Adult Psychiatry, Center for Psychosocial Medicine, Division Neurocognition, University of Heidelberg, Heidelberg, Germany; ^bDepartment of Adult Psychiatry, SRH-Klinik, Karlsbad-Langensteinbach, Germany

Keywords

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Abstract

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders, with a large global impact on both the individual and the society. In this narrative review, we summarize neurocognitive deficits during acute and (partially) remitted states of depression. Furthermore, we outline the potential negative effect of cognitive impairment (CI) on functional recovery, and discuss the role of several variables in the development of CI for MDD patients. Though there is cumulating evidence regarding persistent CI in unipolar depression, research on treatment options specific for this patient group is still scarce. Hence the central aim of our review is to present non-pharmacological interventions, which are thought to reduce CI in affected MDD patients. We discuss cognitive remediation therapy (CRT), physical exercise, yoga, mindfulness-based therapy, and modern neuromodulation approaches like neurostimulation and neurofeedback training. In conclusion, we propose future directions for research on CI in depression. Looking

further ahead, we suggest creative interventional designs that include a direct comparison of different non-pharmacological treatment approaches on neurocognition and functional outcome of MDD. Furthermore, additive and synergistic effects of CRT with other treatment approaches should be examined and compared to create multimodal and even personalized intervention programs.

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Introduction

Major Depressive Disorder (MDD) is one of the most common psychiatric disorders with an estimated lifetime prevalence of 16% [1]. MDD, however, is not solely characterized by its high prevalence but also by its major global impact. In addition to substantial personal consequences of depressive symptomatology, the direct and indirect burden of the disease are associated with considerable socioeconomic costs [2]. Thus, an examination and identification of factors associated with the course of illness and its functional outcome helps in designing treatment interventions, which not only reduce the individual burden but also, in consequence, the entire socioeconomic system.

Cognitive impairment (CI) during depression was identified as one of the factors predicting the relapse or recurrence of MDD [3]. CI, in particular, has emerged as a meaningful predictor of the functional outcome of depression [4]. The longitudinal examination of CI shows that various measurable deficits are found in the acute and remitted states of depression, despite pharmacological and psychotherapy interventions [5].

CI Over the Course of Depression

CI is estimated to occur in around two-thirds of acutely depressed patients [6] and is already present in first-episode depression [7]. Although a consistent neuropsychological pattern of deficits remains to be determined [8], empirical evidence of impaired cognitive capabilities is regularly found in several domains, that is, psychomotor function [7, 9–12], attention [6–8], memory and learning [6–8, 13, 14], and executive functioning [6, 7, 10, 15, 16].

In the remission phase of depression, there is evidence that CI may persist [17]. Therefore, a distinction is made between CI as state-marker (which correlates with mood symptoms and diminishes with recovery) as opposed to persistent CI, which rather could be interpreted as trait-marker of the disease [7]. To evaluate the effect of CI along the course of depression, research is generally conducted in states with varying degrees of depression severity [18–20]. This approach is based on the assumption that a potential association between mood state and cognitive abilities exist, in which improved cognitive performance is found during states of reduced depression severity compared to clinically relevant states. Existing data indicate persisting and significant CI, despite partial remission of depressive symptomatology [6].

It is estimated that CI affects one-third to one-half of previously depressed subjects [6, 21–23]. Moreover, a study by Bhalla et al. [23] revealed that CI persists in an approximate 94% of remitted patients who displayed cognitive difficulties during clinical late-life depression.

Similar to the acute state, a specific pattern of deficits in remission remains to be determined, though evidence of CI is regularly found in domains also emphasized in the context of acute depression, that is, psychomotor function [19, 24, 25], attention [6, 8, 20, 26], memory and learning [6, 8, 19, 27, 28], and executive function [6, 18, 19, 26, 28–30].

All in all, empirical findings regarding CI in remitted subjects are not conclusive. Improvement of the se-

verity of symptomatology seems to positively impact several neuropsychological processes and the overall cognitive functioning of subjects. Yet, these effects appear to be differential for each domain, with psychomotor functioning and memory showing a stronger association with the mood state than attention and executive function, which tend to persist independent of mood improvement. Consequently, research suggests that CI cannot be completely accounted for by the severity of depressive symptomatology. These results reflect a great uncertainty regarding CI in remitted depression and highlight the importance of further research.

Impact of CI on Functional Recovery

Persistent CI is being discussed as a potential cause for higher functional impairment in MDD patients. CI appears to significantly contribute to the observed poor functional outcome in depression [4, 31]. Longitudinal research by Jaeger et al. [4] linked persistent cognitive deficits in MDD patients at a 6-month follow-up after hospitalization to a poorer functional outcome, with the severity of CI being predictive of the level of recovery. This association remained significant when controlling for residual depressive symptoms, indicating that CI independently impacts functional recovery.

CI was also found to be associated with poor response to antidepressant treatment [32, 33] in late-life depression as well as an unfavorable outcome of Cognitive Behavioral Therapy [34]. Furthermore, MDD patients with neuropsychological deficits experience higher rates of relapse and recurrence [3]. Finally, CI has been shown to be a principal mediator of psychosocial impairment, notably workforce performance, in MDD [35].

Variables Associated with CI in MDD

As described in the previous section, empirical evidence suggests that CI might be an important factor contributing to poorer functional outcome in MDD, and consequently may be referred to as clinically relevant. In consequence, the examination of variables associated with persisting CI in MDD might help to better understand underlying mechanisms as well as identify possible risk groups regarding the development of CI in the course of illness.

A number of variables associated with CI have been thoroughly analyzed and described in literature, for example, various demographic variables like age [17, 36], educational attainment [7, 37, 38], and employment status [8]. Also, variations concerning disease variables and psychopathology, like onset of disorder [17, 36, 39–41], duration of illness [42], number of past hospitalizations [17, 43], and current symptom severity [20, 24, 28] have been found to be associated with the development of CI and the degree to which it presents itself in MDD patients. Some of the inconsistencies in literature regarding the prevalence and profile of CI in depression might be due to complex interactions between these variables.

Age, Onset and Duration of Disorder

It is commonly accepted that geriatric MDD patients are cognitively more impaired than younger subjects [17, 36], due to several somatic risk factors promoting CI [39]. In particular, the impact of vascular lesions has been well established and may account specifically for the persistent CI found among elderly subjects with late onset of depressive disorder [17, 36, 39, 41]. Some authors also described important differences in CI when comparing geriatric early- vs. late-onset MDD patients, in that those with late onset showed stronger impairments in processing speed and executive function than patients with early onset, while both patient groups showed reduced function in all domains compared to healthy controls [40]. Closely related to age at onset is the duration of illness referring to how much time has passed since onset. A longer duration has been linked to poorer cognitive performances [42].

Educational Attainment

Previous research has found education to positively impact cognitive functioning in MDD patients [7, 37, 38]. However, protective effects of educational attainment were mainly examined in older individuals. A meta-analysis by Lee et al. [7] that extended the age-range to samples with younger depressive subjects, found less educated samples to demonstrate more pronounced CI in several domains (visual and verbal memory as well as attentional switching), supporting the protective relevance of educational effects in non-geriatric patients.

Employment Status

The rate of depressed subjects among the unemployed appears to be significantly increased when compared to the employed population [44]. It is hypothesized that

cognitive functioning might be an important factor in the relationship between employment status and depression [8]. Unemployment was shown to be significantly associated with poorer cognitive functioning (memory, attention, and executive function), particularly in remitted MDD patients, with those unemployed performing worse than those employed [8]. The direction of this effect remains unclear due a lack of prospective studies: CI can be interpreted either as cause or consequence of unemployment, or possibly both.

Hospitalization

When separating acute MDD samples by current hospitalization, studies consistently demonstrate more pronounced CI (including psychomotor speed, working memory, as well as verbal and visual memory) in inpatients compared to outpatients, maybe linked to a more severe acute symptomatology and/or to a higher prevalence of the endogenous/melancholic subtype of depression [43, 45]. Furthermore, a history and higher number of hospitalizations have also been found to be associated with more severe CI [43]. The number of past hospitalizations might be an indicator of illness chronicity and severity, which in turn maybe linked to more pronounced CI.

Residual Symptomatology

Depressive symptomatology has been shown to relate to the overall neuropsychological functioning [20]. The majority of findings, however, are based on clinically depressed patients in comparison to those in remission or healthy controls, ignoring the question of how subclinical psychopathology might affect persisting CI. Though there appears to be an overall tendency towards cognitive improvement parallel to symptom remission, the level of subclinical severity has been shown to impact neuropsychological performances (e.g., memory, psychomotor function) [24, 28], indicating the importance of considering residual depressive symptomatology in examining persistent CI.

Treatment Approaches

Since cognitive deficits in MDD may persist beyond routine treatment of depressive symptoms, evaluation of specific treatment options is of critical importance. There is a growing number of studies and reviews concerning the impact of pharmacological strategies on neurocognitive functioning [46–49]. There is limited

evidence for the pro-cognitive effects of conventional antidepressants, also due to lack of clinical trials targeting cognition as a primary outcome. A recent meta-analysis [47] of nine placebo-controlled randomized trials evaluated the cognitive effects of vortioxetine, duloxetine, paroxetine, citalopram, phenelzine, nortryptiline, and sertraline and showed low effect sizes for a positive effect of antidepressants on processing speed (standard mean difference 0.16) and delay recall (0.24) [47]. Among evaluated antidepressant, vortioxetine appeared to have the largest effect size on psychomotor speed (0.34), cognitive control (0.17), and executive function (0.26), while duloxetine had the greatest effect on delayed recall (0.25) [47]. One of the studies in this meta-analysis evaluated the efficacy of vortioxetine on cognitive function in adults with recurrent moderate-to-severe MDD [48]. The study showed a significant improvement of objective and subjective measures of cognitive functions with vortioxetine (standard effect sizes 0.23–0.52), which was largely independent of vortioxetine's effect on improving depressive symptoms [48]. Furthermore, the neurocognitive aspects of N-methyl-D-aspartate glutamate receptor antagonist ketamine was evaluated in addition to its rapid antidepressant effects in treatment-resistant depression [49]. The authors showed a significant improvement in scores of visual memory, simple and complex working memory after the sixth ketamine infusion. However, neurocognitive changes were accounted for by improvement in the depressive severity. It remains uncertain if cognitive improvement was mainly attributed to the improvement of depressive symptomatology and if persistent CI in/after the remission can be improved. Moreover, baseline neurocognition seemed to predict ketamine response.

Beside the pro-cognitive effects, side effects of antidepressant therapies on cognition have to be considered [50], including anticholinergic effects of tricyclic antidepressants [51, 52]. It is important to mention that responders and non-responders to SSRIs could already be distinguished in neuropsychological terms before treatment, with non-responders showing a higher degree of CI [53]. According to Bortolato et al. [46], beside conventional treatment with antidepressants, there are promising pro-cognitive agents like Erythropoietin, S-adenosyl methionine, insulin, N-acetylcysteine, and antidiabetic agents to be further investigated [35].

In all, the cognitive improvement remains an unmet need in the pharmacological treatment of CI. Furthermore, the side effects should be taken into consideration.

Thus, non-pharmacological interventions focusing on CI may be valuable as a treatment element for affected MDD patients. Our review focuses on the growing but still limited body of non-pharmacological treatment approaches. In the following sections, we discuss cognitive remediation therapy (CRT), physical exercise, mind-body Interventions like yoga and mindfulness-based therapies, and neuromodulation approaches.

Literature Search

Studies until April 2017 were identified by searching PubMed and PsychInfo databases, using the following search terms in different combinations: “depression”, “depressive disorder”, “MDD”, “cognition”, “cognitive training”, “cognitive remediation”, “improve cognition”, “neurocognitive training”, “computer-based”, “non-pharmacological interventions”, “physical exercise”, “physical intervention”, “yoga”, “meditation”, “mindfulness-based”, “neuromodulation”, “neurostimulation”, “neurofeedback”, “repetitive transcranial magnetic stimulation (rTMS)”, “transcranial direct current stimulation (tDCS)”. Only studies published in English were considered for this review. After selecting pertinent systematic reviews and meta-analysis, the full text of the studies included in these meta-analyses was reviewed. Outcome measures included global cognition and different cognitive domains (speed of processing, attention, working memory, verbal and visual memory, and executive functioning). The results were limited to participants aged 18 years or more. Reference lists of relevant articles, previous reviews, and Google scholar were examined to identify further relevant articles.

Cognitive Remediation Therapy

One of the regularly discussed treatments addressing CI is CRT. CRT in general involves two different training approaches: direct restitution of impaired cognitive functions using heterogeneous paper-pencil or computerized cognitive training (CCT) techniques vs. strategy training which rather aims at compensating everyday difficulties associated with CI. However, nowadays most of the programs include both approaches: direct “drill and practice” of cognitive functions in combination with compensatory strategy learning, psycho-education on cognition-related issues, and/or transfer to real-world situations [54].

Up to now, merely a few publications have examined the effect of CRT in affective disorder samples, whereby some included exclusively bipolar [55, 56] or unipolar patients [57–65], while others investigated both groups together [66, 67].

A recent meta-analysis by Motter et al. [68] evaluated the efficacy of CCT in MDD and included nine randomized controlled CCT trials (in one study, patients with a diagnosis of dysthymia were included [63]). The investigation revealed CCT to be associated with improved depressive symptomatology and everyday functioning (significant small to moderate effects). The examination yielded moderate to large effects for attention (Hedge's $g = 0.67$), working memory ($g = 0.72$), and global functioning ($g = 1.05$) on the one hand and small and non-significant effects regarding executive functioning ($g = 0.20$) and verbal memory ($g = 0.08$) on the other hand. Furthermore, slightly lower effects of CCT on age were found. The lack of significant effects for those two domains could either be attributed to methodological issues like highly heterogeneous measures or insufficient assessment. In fact, executive functioning was only targeted in one study during the last 2 weeks of training [57] and only one session of psycho-education in another [62]. However, it could also reflect valid difficulties in improving those two cognitive domains, which need to be theoretically discussed and taken into account when designing specific training approaches.

Regarding the effects on everyday functioning, it must be taken into account that only two studies included in the meta-analysis assessed appropriate transfer measures [57, 62]. Therefore, more studies assessing the effect of the CCT on everyday functioning are needed to confirm the positive findings in this meta-analysis.

However, most of the included studies investigated acute MDD patient groups. Only two clinical trials of this meta-analysis examined the impact of CCT on stable patients with MDD without psychotic symptoms [59, 62]: Elgamal et al. [59], for example, demonstrated improvement under CRT in several neuropsychological tests regarding attention, verbal learning and memory, psychomotor speed, and executive function in $n = 12$ outpatients with long-term illness with stable depressive symptom scores over a time period of ten weeks. Naismith et al. [62] investigated $n = 41$ stabilized outpatients on medication with a lifetime history of major depression and depressive symptoms in the normal to mild range. Patients with the mean age of 64.8 years were randomized either to a wait-list or to an intervention group. The intervention group

underwent a “neuropsychological educational approach to remediation” (NEAR) and multifactorial psycho-education that targeted cognitive strategies, depression, anxiety, sleep, vascular risk factors, diet, and exercise. After 10 weeks of training, patients showed significant improvements in visual and verbal memory (medium to large effect sizes).

Despite the first promising effects of CRT on cognition and functional outcome shown in the meta-analysis, the optimal design of CRT interventions remains a matter of debate. The training designs implemented in the included studies varied substantially, making it impossible to infer general statements or even recommendations regarding the optimal techniques, frequency or duration of CRT. For example, besides using different training software, the duration of CCT intervention among the studies ranged from 5 days [64] to 16 weeks [61]. The training intensity also varied from 3 sessions over 2 weeks [58] to 64 sessions over 16 weeks [61]. Furthermore, only two of the included studies combined CCT with compensatory strategies [57, 62]. Naismith et al. [62] provided the intervention group with a psycho-education training on health and cognitive functioning as already mentioned above, over a period of 10 weeks. Bowie et al. [57], however, supplemented the CCT with strategic self-monitoring training, bridging discussions to facilitate transfer to everyday behavior and 2 homework sessions per day, also over the period of 10 weeks. Thirty-three participants with a diagnosis of MDD and treatment resistance were allocated, either to the intervention or wait list group. The study revealed treatment effects on verbal memory, attention, and processing speed, but not on executive functioning. Although no changes in everyday functional skills and behavior were observed in the intervention group, a significant modest correlation of cognitive improvements with improvements in the ratings of everyday functional behaviors was found.

Several authors have also emphasized the need to individualize CRT to increase the effects on cognition, motivation, and transfer to real-world situations [54, 69]. This approach contrasts with generalized training programs, which target a broad set of functions in all patients. Our research group currently examines the efficacy of generalized vs. individualized cognitive training (manuscript in preparation), among other important questions. To summarize, there is preliminary evidence for a beneficial effect of CRT on patients with MDD. For future research and clinical practice, there is still need to determine the optimal intensity and frequency, duration and

combination with additional valuable psychosocial treatment approaches. Moreover, the contribution of motivation or expectancy on the differential performance between intervention and control groups should be targeted in future investigations.

Physical Exercise Interventions

Physical exercise has been shown to be effective in improving the cognitive functioning in different groups like healthy subjects [70, 71], individuals suffering from mild CI [72], dementia [73], schizophrenia, and affective disorders [74]. There is a small number of studies, which investigated the effect of physical exercise on neurocognition in MDD. Despite equivocal and inconsistent study results, physical exercise might be a promising intervention to enhance cognition in depression [74]. Until now, physical exercise interventions were mostly investigated among healthy older adults. Physical activity as well as long-term exercise may preserve cognition and prevent or even delay dementia at least at the community level [75, 76]. A meta-analysis of randomized controlled aerobic exercise trials examined the relationship between an aerobic exercise training of at least 1 month on neurocognitive performances in a non-dement sample [71]. Twenty nine studies were included in this meta-analysis, which revealed modest improvements of attention and processing speed, executive function, and memory as well as less consistent effects on working memory. Combined aerobic exercise and strength training interventions improved attention, processing speed, and working memory more than aerobic exercise alone. Furthermore, individuals with mild CI showed a stronger enhancement of memory performance through physical exercise than cognitively unimpaired individuals [71].

A recently published systematic review and meta-analysis of Brondino et al. [77], addressing possible effects of physical exercise on cognitive functioning in depression, including eight randomized controlled trials, showed no improvement of cognition in MDD through physical exercise (one study used yoga as physical exercise intervention [78]). Neither the duration of the intervention, nor the number of sessions per week or the intensity of exercise impacted the outcome significantly. The results of this meta-analysis contradict at the first glance the comprehensive review of Malchow et al. [74], who reported positive effects of physical exercise on schizophrenia and affective disorders,

thereby recommending physical exercise as part of a multimodal intervention program to improve neurocognition and psychopathology. However, the results of Brondino et al. [77] should be taken with caution because of several methodological limitations, already mentioned by authors: None of the included studies recruited patients with subjective cognitive complaints. Patients were only slightly cognitive impaired at baseline, and therefore had a small potential for cognitive improvement. Furthermore, improvement in neurocognition was frequently investigated as a secondary outcome and was not the main focus of investigation. Therefore, studies could be potentially statistically underpowered to find a significant difference in this regard.

In sum, the existing number of randomized controlled trials that systematically investigate the effects of physical exercise on neurocognition in MDD (especially in remission) is promising, albeit still limited and inconsistent. However, taking also into account the described positive findings regarding cognitive improvement through aerobic exercise in other investigated populations [79–81], future research into the impact of physical exercise on persistent CI in MDD is further needed.

Moreover, there is some evidence that the combination of physical exercise and cognitive training can have additive and synergistic effects on neurocognition, possibly by the following path: The potential for neurogenesis and synaptogenesis can be increased through physical exercise, while cognitive training guides it to induce positive plastic change [82]. The effects of combined cognitive and physical interventions on cognition in healthy older adults were examined in a recent meta-analysis, which included twenty studies with older adults without known CI [70]. The meta-analysis revealed greater effects of combined interventions over control group and physical exercise alone, but no significant advantage over cognitive intervention alone. Additionally, the effects were moderated by age, intervention setting, and frequency. The first study in the literature, known to us, that combined cognitive and physical exercise training across two patient groups (29 patients with schizophrenia and 22 patients with MDD) showed the strongest effects on cognitive functioning and psychopathological symptoms across patients groups in subjects undergoing combined cognitive and aerobic physical training. The domains of visual learning, processing speed, and working memory were improved in both patient groups. The combination of cognitive and physical exercise training was superior to the combination of cog-

nitive training and relaxation as well as waiting control group [80]. These findings point to a possible benefit of physical exercise as an add-on therapy to other interventions regarding improvement of cognitive functioning in different patient groups. However, future replication is needed.

Yoga

Another approach to enhance neurocognitive functioning is yoga intervention, which involves an active attentional component above its physical activity component and is easily adaptable for most ages and clinical populations. Yoga requires focused effort on breathing, body, and pose control, which can lead to even greater cognitive improvement compared to physical exercise interventions without any attentional component (e.g., [83]). A recent meta-analysis on the effects of long-term yoga interventions and acute (immediate, single session) yoga practice on cognition revealed its potential to improve specific domains of neurocognitive functioning despite the limited number of studies conducted, small sample sizes, and other design weaknesses of the included studies [84]. This meta-analysis, which included 22 studies with diverse sample characteristics, including cognitively unimpaired, healthy, and clinical populations, showed moderate effects of yoga on cognition in randomized controlled trials (long-term yoga interventions), with the strongest effects for attention and processing speed, followed by executive function and memory. The meta-analysis yielded a stronger overall effect of yoga on cognition in counterbalanced repeated-measures acute exposure studies (sessions that lasted between 9 rounds of breathing exercises up to 45 min) than in long-term yoga interventions (ranged from 1 to 6 months in duration). The strongest effect was on memory, followed by attention, processing speed, and executive functioning [84]. Only one study included in the meta-analysis investigated the effect of yoga on neurocognition in a depressive sample. Sharma et al. [78] found an additional improvement in some measures of executive functions in (partially) remitted depressive patients, who were randomly allocated to the yoga meditation group and received conventional antidepressant medication in comparison to the group, which only received conventional antidepressant medication. All in all, although promising there is still research lacking on the efficacy of physical exercises and yoga in MDD patients.

Mindfulness-Based Therapy

As mindfulness is closely related to attentional processes, mindfulness-based therapy is considered as an attention training, and therefore another possible treatment approach of CI in depression. Despite the multitude of studies examining the clinical benefits of mindfulness-based therapy, research on the effects of this approach on neurocognitive functioning is scarce. There are first investigations of mindfulness interventions that revealed improvement in attention and working memory in bipolar depression [85]. Chiesa et al. [86] investigated, in a systematic review of 23 studies, the effects of mindfulness meditation practices on cognitive abilities in healthy, chronic pain, major depression, military personnel, and traumatic brain injury populations. This review revealed an enhancement of working memory capacity and some executive functions. Furthermore, the early stages of mindfulness training were associated with significant improvement of selective and executive attention, whereas the following stages improved unfocused sustained attention abilities. However, these results should be considered with caution because of methodological limitations of the studies included. There is also evidence that mindfulness meditation practices can provide benefits on cognitive abilities, in particular attention, in different psychiatric disorders like Borderline Personality Disorder, MDD, alcohol abuse, and ADHD [87–90]. The purpose of future investigation and clinical practice is to create and modify mindfulness-based therapies for specific psychiatric and neurological disorders. Mindfulness-Based Cognitive Therapy ([91]) and Mindfulness-Based Stress Reduction ([92]) are, for example, already widely incorporated into the treatment of affective disorders but barely examined in their ability to improve cognitive functioning. Taking into account the promising preliminary results of cognitive enhancement in different populations due to mindfulness-based therapy, high quality studies investigating standardized mindfulness-based approaches and comparing them to other interventions are needed.

Neuromodulation Techniques: Neurostimulation and Neurofeedback Training

Novel neuromodulation approaches can also be considered as treatment options of CI in MDD. One possible technique, which evolved in recent years is the non-inva-

sive stimulation of specific brain regions. Especially, brain activity in the dorsolateral prefrontal cortex (DLPFC) areas has been identified as a possible goal for such techniques, trying to enhance associated working memory performances. A systematic review and meta-analysis of non-invasive brain stimulation techniques included 12 studies that used either repetitive rTMS or tDCS to increase DLPFC activity, and therefore working memory performance in healthy and clinical samples [93]. rTMS showed significant improvement of all measures of working memory performance, whereas tDCS improved only the response time. A study by Wolkenstein et al. [94] revealed that anodal tDCS to the DLPFC enhanced working memory performance in 22 MDD patients and 22 healthy controls [94].

Another treatment approach, neurofeedback, aims at teaching patients to self-regulate their brain activity with the help of real-time feedback to achieve specific goals. One possible goal is enhancement of neurocognitive performances. A first study comparing the cognitive performances of a neurofeedback training group to a non-interventional control group in a sample of MDD patients ($n = 60$) showed significant improvement in working memory and processing speed with medium to large effect sizes [95]. However, there are some limitations that need to be considered, like the lacking of randomization and mixed depressive states of patients. In sum, future research is required.

Future Directions

Evidence shows that one-third to one-half of depressive patients continue suffering from CI even into remission. Research on the underlying factors causing and maintaining CI in MDD is recent but growing considerably. Up to now, it is still not clear for how long CI may persist, and a clear pattern of cognitive deficits could not yet be elucidated. Various demographic and psychopathological characteristics are being investigated in relation to the level of cognitive functioning during depression. However, a more comprehensive understanding of relevant factors is still lacking. Preliminary research on CI associated variables suggest that treatment of CI in MDD patients might be useful early on, namely when a patient shows cognitive risk factors. As the number of past hospitalizations is associated with more severe CI, an initiation of cognitive treatment immediately at first-time hospitalization would be beneficial for the patients. It may also be beneficial

to provide additional compensatory strategy for learning and psycho-education on cognition-related issues offering background information, especially for less educated patients. Furthermore, the different possible cognitive profiles of patients with late-onset of depressive disorder (stronger impairments in processing speed and executive function than patients with early onset) should be investigated, to provide tailored interventions to this group of patients. CI can be interpreted either as a cause or consequence of unemployment, or possibly both. Home-based cognitive treatment could be useful for employed (partially) remitted patients with MDD, and persisting CI for better compatibility with work responsibilities. Research on the impact of persistent CI on general everyday functioning and clinical aspects in MDD patients is currently emerging and is a promising field.

There is some evidence regarding the treatment of CI in MDD, such as in the field of schizophrenia, for positive CRT effects on cognition and functional outcomes. Interventional studies evaluating the effect of other specific treatment approaches for persistent cognitive deficits and its impact on functional outcome are of growing interest. Promising findings of cognitive improvement through physical exercise in healthy elderly populations, individuals suffering from mild CI, dementia, schizophrenia and affective disorders, and through yoga in healthy and clinical cognitively *unimpaired* populations already exist. However, research on the efficacy of physical exercise and yoga in (subjectively) cognitively impaired (remitted) depressive populations is still lacking. Novel investigations of the mindfulness-based therapy and neuromodulation techniques like neurostimulation (rTMS, tDCS) and neurofeedback training also show positive results in healthy as well as clinical populations and require further research in the sample of MDD patients.

There is also a need to provide a consensus on the appropriate screening, measurement, and monitoring tools. Due to the high level of heterogeneity of neurocognitive testing, comparing cognitive clinical trials becomes complex. Thus, standardization of cognitive testing is required. In Schizophrenia research, this has already been accomplished with the MATRICS Battery [96]. A combination of both self-report and objective cognitive testing may lead to a better understanding of subjective complaints in MDD [47].

Looking further ahead, creative interventional designs may include a direct comparison of different non-pharmacological treatment approaches on neurocognitive

functioning and functional outcome of MDD. Furthermore, additive and synergistic effects of CRT with other treatment approaches (physical exercise, yoga, mindfulness-based therapy, and neuromodulation techniques) should be examined and compared to create multimodal and even personalized intervention programs to improve neurocognition and psychosocial functioning of patients with MDD. In our opinion, a combination of different interventions, for example, of physical exercise with subsequent cognitive training sessions may be promising as well as superior to a single-intervention design. Reasons behind this assumption are neuroplasticity effects of physical exercise serving as a basis for improved learning through cognitive remediation. Furthermore, various treatment options should be considered, and cognitive

treatment customized to patients' needs and wishes while considering available resources (e.g., computer access) or physical functioning.

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