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Improved functioning following computerized working memory training (COGMED®) in euthymic patients with bipolar disorder and cognitive complaints: an exploratory study.

Aiste Lengvenyte[a,d*], Frédéric Coppola[a], Isabelle Jaussent [b], Philippe Courtet[a,b,c], Emilie Olié[a,b,c]

[a] Department of Psychiatric Emergency & Acute Care, Lapeyronie Hospital, CHU Montpellier, Montpellier, France

[b] INSERM U1061, Montpellier, France

[a] University of Montpellier, Montpellier, France

[d] Vilnius University, Faculty of Medicine, Institute of Clinical Medicine, Psychiatric Clinic

***Author for correspondence:**

Aiste Lengvenyte, MD

University of Montpellier, 163 rue Auguste Broussonnet, Montpellier, France;

Phone: +37062679189;

Email address: aistelengvai@gmail.com

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Improved functioning following computerized working memory training (COGMED®) in euthymic patients with bipolar disorder and cognitive complaints: an exploratory study.

1. Introduction

Bipolar disorders (BD) are considered among the top 20 leading causes of disability worldwide. BD global burden is continually increasing (Ferrari et al., 2016), and has been ranked as having the second-highest effect on sick leave days according to a World Mental Health survey (Alonso et al., 2011). Sustained symptomatic remission is generally attainable with the current treatment strategies. However, treatment does not seem to have a major effect on the decline in general functioning, leading to poor quality of life and socio-economic functioning (Tse et al., 2014).

Cognitive dysfunction and residual depressive symptoms have been identified as the main drivers of functional disability in euthymic patients with BD (Roux et al., 2017). Patients with cognitive impairment tend to report poorer quality of life, despite similar mood symptoms as patients without cognitive deficits (Jensen et al., 2016). Memory and executive functions are particularly strong contributors to the occupational functioning outcome in BD, with greater impact than residual mood symptoms (Miskowiak et al., 2018; Tse et al., 2014). Moreover, cognitive impairment is reported by 50-70% of patients during periods of symptomatic remission (Jensen et al., 2016), and could be objectified by neuropsychological tests in 12-30% of patients (Kim et al., 2018). Specifically, it has been hypothesized that working memory (WM) acts as a mediator for subthreshold depressive symptoms in predicting the functional outcome (Ellard et al., 2017). A meta-analysis had demonstrated that all cognitive functions together correlate with the global functioning with an effect size of 0.34, while the working memory alone has an effect size of 0.29 (Depp et al., 2012). These

results underline the critical role of working memory in the global functioning of patients with BD. Another study in community-dwelling older adults found that only the composite of executive function and working memory tasks was a significant predictor of medication adherence (Insel et al., 2006). Working memory has also been demonstrated to be an independent predictor of the quality of life in BD patients (Mackala et al., 2014). However, targeted interventions are lacking.

Cognitive remediation (CR) (Anaya et al., 2012) is a promising strategy to address this deficit. It aims to strengthen cognitive functions by increasing neuronal plasticity, with the final goal of improving everyday function (Kim et al., 2018). CR increases neuroplasticity in the hippocampus, as well as the resting state efficiency in the frontal lobe (Valenzuela and Sachdev, 2009). A recent study in patients with severe mental illnesses showed that CR significantly contributed to their occupational outcome (Ikebuchi et al., 2017). The few studies on CR benefits in BD found that they are comparable to those observed in schizophrenia (Anaya et al., 2012), where much research has focused on this topic. Clinical trials in BD demonstrated a possible association between CR and improvement in cognition, reduction of depressive symptoms and better psychosocial functioning (Deckersbach et al., 2010; Solé et al., 2017). However, studies on CR in BD are characterized by considerable variability in the used software, treatment regimens, and outcome measures. This might explain the inconsistent results among studies, ranging from no effect to significant improvement (Kim et al., 2018).

The diversity in CR modalities may be addressed by using digital approaches (Veeh et al., 2017). The number of studies on the digital transformation of CR is still insufficient (Kim et al., 2018), limiting the applicability of this treatment modality. Interestingly, systematic reviews and meta-analyses found that digital tools for CR are as effective as face-to-face treatments when associated with support by a trained therapist via brief spoken or written guidance and feedback (Andersson et al., 2014). Studies on CR in schizoaffective

disorders showed positive results of computerized CR therapy, with an effect size for neurocognitive improvement ranging from 0.32 to 0.41 (Anaya et al., 2012; Lopez-Fernandez et al., 2018). The efficacy of digital approaches in BD has been demonstrated by several studies (Andersson et al., 2014; Lewandowski et al., 2017; Veeh et al., 2017).

WM may represent a particularly attractive therapeutic target due to its strong links with other cognitive domains. WM deficits are present during syndromic remission and can play a crucial role in predicting the functional outcome in bipolar disorder (Del Mar Bonnín et al., 2014; Lima et al., 2018). Moreover, the efficacy of programs that specifically target WM has already been demonstrated in patients with head trauma, attention deficit and hyperactivity disorder (Kim et al., 2018). A randomized clinical trial in patients with head trauma found that WM training significantly improved the general functioning of the patients (Björkdahl et al., 2013). Moreover, it has been demonstrated that WM training has modulatory effects on brain dopaminergic system, decreasing the density of D1 receptors (Klingberg and McNab, 2009).

In a search for the accessible treatment options, it seems necessary to evaluate the efficacy of cognitive remediation programs that have a short duration, little constraints for the patients, are relatively cheap, and are very specific in their targets. The computerized WM remediation could be a good target due to the relatively low need for human interaction, has a limited timeframe and requires minimal restrictions. Therefore, we investigated the effect of computerized WM training using the COGMED® program (Klingberg et al., 2005) in patients with BD and cognitive complaints. Our primary hypothesis was that this intervention would improve global functioning. We also investigated (secondary outcomes) whether this intervention can improve therapeutic compliance and subjective life quality, and explored the association between WM and global functioning.

2. Methods

This was a preliminary naturalistic, prospective, monocentric, open, non-controlled study on the effect of a supervised WM digital intervention in euthymic patients with BD and memory complaints.

2.1 Participants

Participants were recruited at the Department of Psychiatric Emergency and Acute Care, Montpellier University Hospital (France), between May 2014 and November 2015. Subjects were screened for inclusion after confirmation of BD diagnosis by a psychiatrist with expertise in BD. Inclusion criteria were: capacity to provide a written informed consent; ≥18 years of age; primary diagnosis of BD I or II, based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria; presence of subjective or objective cognitive impairment; current euthymia [Montgomery-Asberg Depression Rating Scale (MADRS) score ≤ 12, Young Mania Rating Scale (YMRS) score ≤ 6]; availability at home of a computer with internet access and telephone. Exclusion criteria were: a history of electroconvulsive therapy (ECT) in the past year and psychoactive substance abuse or dependence in the past six months.

2.2. Study design

Clinical and neuropsychological evaluations were done by a psychiatrist and a neuropsychologist, respectively, who received training on the COGMED® program. Two assessment sessions were planned: the first at inclusion (baseline visit) within two weeks before the intervention started, and the second (post-treatment visit) between four and six

weeks after the intervention completion. At both visits, sociodemographic, clinical characteristics, medication use, and neuropsychological performances were recorded.

The study was approved by the Montpellier University Hospital ethics committee (CPP Sud Mediterranée IV) and was registered at clinicaltrials.gov (identifier NCT02988518). All participants gave their written informed consent.

2.2.1. Clinical assessment

Lifetime and current psychopathology were assessed using the Structured Clinical Interview for DSM disorders (SCID-1) (First, 1996). Depression severity was evaluated using the MADRS (Montgomery and Asberg, 1979) and the Quick Inventory of Depressive Symptomatology self-report (QIDS-SR16) (Rush et al., 2003). Manic symptomatology was assessed using the YMRS (Young et al., 1978) and the Altman Self-Rating Mania Scale (ASRM) (Altman et al., 1997). Additional self-questionnaires included the State-Trait Anxiety Inventory (STAI Form Y) (Spielberger et al., 1970) to evaluate anxiety, the Medical Adherence Rating Scale (MARS) (Fialko et al., 2008) to determine treatment adherence, the SF-36 (McHorney et al., 1994) to assess the quality of life, and the Mac Nair questionnaire (McNair and Kahn, 1983) to evaluate memory and attention complaints.

Global functioning was assessed using the Functioning Assessment Short Test (FAST) (Rosa et al., 2007) that is specific for patients with BD. FAST explores six domains of general functioning: autonomy, professional domain, cognitive domain, financial domain, interpersonal relationships, and leisure activities. The total score is the sum of the score of the 24 items that are given 0 to 3 points/each. FAST reliability and validity in patients with BD have already been demonstrated (Rosa et al., 2007). To grade the functional impairment severity, Bonnín et al. proposed to classify patients in four groups according to their baseline

FAST score: absence of, mild (score [12-20]), moderate (score [21-40]), and severe (score >40) functional impairment(Bonnín et al., 2018).

2.2.2. Neuropsychological assessment

Visual attention and task-switching abilities were evaluated using the Trail Making Test (TMT) (Llinàs-Reglà et al., 2017) in which the subject is instructed to connect the items as quickly as possible. Information processing, attention capacity and cognitive inhibition were evaluated with the Stroop test (Van der Elst et al., 2006) that has three different boards with numbers, names of colours in black, and printed in different colours to introduce interference. The patient has 45 seconds to read each board. The number of words and of corrected and uncorrected errors was counted. Three subtests ("codes", "symbols", and "digit span") of the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (Wechsler et al., 2008) were used to evaluate the information processing speed ("codes" and "symbols" subtests), the attention capacity and associative memory ("codes" subtest), and WM verbal component ("digit span" subtest). The WM visuospatial component was assessed with the Corsi block-tapping test of the Wechsler Memory Scale, Third Edition (WMS-III) (Wechsler, 1997). Mental flexibility was assessed using a verbal fluency test.

2.2.3. COGMED® program

After the baseline assessment, patients received information about the importance of WM in everyday life. They were trained to use a computerized WM training program, called COGMED® (Klingberg et al., 2005), and were given individual codes to connect to COGMED® through the web. This web-based program includes a battery of interactive game-like tasks to increase the visuospatial and auditory WM. The program includes 12

different WM tasks (eight per day). Each daily session lasts between 30 and 45 minutes. The typical WM training program included five sessions per week for five weeks (in total, 25 sessions). The difficulty level was adjusted automatically to the patient's maximum capacities in order to stimulate the cognitive effort. A progress index allowed evaluating the progress made by each patient.

At the end of each week, the psychiatrist phoned each patient. Before the conversation, a systematic analysis of each patient's progress was performed, and a personalized feedback content was prepared. At the beginning of the conversations, patients were asked if they had any technical problems with the program and were accordingly advised. Then, the feedback regarding the progress and was given, and an overview of each exercise was done. If patients were experiencing difficulties, additional explanations were provided. Patients were then encouraged to continue their progress and invited to find strategies to increase their efficacy, as well as give themselves small rewards. The conversation ended with an enquiry about the daily mood and attention performance of the patients. Each call lasted approximately ten minutes.

2.3 Statistical analysis

Statistical analysis was carried out using "IBM SPSS STATISTICS version 21". The primary outcome was the change of total FAST score between the baseline and post-treatment visit. Secondary outcomes were changes in the MARS, SF-36, and Mac Nair scores and in neuropsychological functions (executive functions, WM, information processing speed, and attention capacity). The convergent validity of the tests used to evaluate WM was analyzed using the Spearman's rank correlation coefficient (rho). The strength of the correlation was considered high (rho > 0.7), moderate (0.4 to 0.7), or low (<0.4). The assumption of normality was tested before all comparisons. The paired sample Student's *t*-

test was used if data were normally distributed, and the non-parametrical Wilcoxon signed-rank test in all other cases. Univariate analyses with Pearson's correlation coefficient (for continuous variables) and Student's *t*-test (for categorical variables) were used to assess the relationship between the change of FAST total score and sociodemographic, clinical and neuropsychological variables. Then, the repeated-measures ANOVA was performed to adjust for possible covariates for the FAST change. A post-hoc analysis was performed using the four groups of functional impairment according to the FAST score, as proposed by Bonnín and colleagues (Bonnín et al., 2018). The proposed cut-off was used to evaluate the rate of improvement (from severe to moderate), remission (from moderate/severe to mild), and recovery (switch to no impairment).

The p-value threshold for statistical significance was set at <0.05.

3. Results

3.1. Patients' characteristics at baseline

In total, 40 patients with BD were included, and many reported a relatively high delay between the first symptoms and diagnosis. Their main baseline characteristics are presented in Table 1. All patients were taking mood stabilizers, with a high level of treatment adherence according to the MARS scale score. The most recent thymic episode was mainly a depressive episode, with residual depressive symptomatology. No residual manic symptomatology was detected, and the anxiety level was low. Twelve participants had current psychiatric comorbidity, mainly bulimic hyperphagia (N=8).

Functional impairment was severe in 6 patients, moderate in 23, mild in 6, and absent in 5 patients, according to the classification by Bonnín and colleagues (Bonnín et al., 2018). Impairment in the occupational, cognitive, and interpersonal relationship domains was particularly pronounced, as shown by the FAST scores. Subjective memory and attention

complaints were marked (mean score: 68.78, SD 14.77). The baseline neuropsychological evaluation showed that the participants' cognitive profile was relatively preserved.

Table 1. Baseline demographic, clinical and neuropsychological characteristics of patients with BD (N=40)

The baseline FAST total score was significantly correlated with the residual depressive symptomatology (r=0.41, p=0.01 for MADRS, and r=0.38, p=0.03 for QIDS-SR16), and positive history of head trauma (r= 0.38, p=0.02). The mean FAST and WM scores did not differ in function of the pharmacological treatment status (current treatment vs absence of current treatment, and one drug vs more than one drug).

3.2. Drop-out

Among the 40 recruited patients, 32 completed the COGMED® program and the post-treatment assessment. One patient abandoned the study before the first COGMED® session due to low motivation. Seven participants withdrew during the intervention after having completed a mean of 13.6 sessions (SD=5.09) in 2.4 weeks (SD=0.98). Following reasons for leaving the study were indicated by these patients: two participants complained of fatigue, one participant indicated that he had difficulties in concentrating in the previous session before leaving the study, and did not want to proceed, one participant expressed low general motivation. Three other patients did not indicate the drop-out reason.

Patients who left the study either before or during the COGMED were younger (mean age 35.63 years, SD 10.68 vs 46.75 years, SD 9.41, p=0.02), had shorter disease duration (mean 13.5 years, SD 10.30 vs 25.38 years, SD 9.57, p<0.01) and fewer of them used anticonvulsants (25% vs 69%, p=0.04) compared with patients who completed the

study. The other clinical characteristics and all neuropsychological performances were not different between leavers and completers. Finally, 50% of leavers (4/8) and 12.1% of completers (4/33) had a lifetime history of substance use disorder (excluding past six months), but the difference was not significant (p=0.06).

3.3 Comparison of clinical variables between baseline and post-treatment visits

The FAST total score was significantly different between baseline and post-treatment visit, with a relative change [(final visit – initial visit)/initial visit] of -0.28 (SD = 0.21), p<0.0001. This difference remained significant after exclusion of patients with head trauma (mean relative change: -0.27, SD = 0.21; p<0.0001). Three FAST sub-scores (cognitive functioning, autonomy and occupational functioning) were significantly different between visits (relative change: -0.49, SD = 0.28; -0.13, SD = 1.16; and -0.09, SD = 0.71, respectively), with the highest decrease in the cognition score (see table 2).

After the exclusion of patients without functional impairment during the post-hoc analysis, the change in FAST score further increased, with a mean change of 7.50 (SD=4.46), from 29.29 (SD 10.77) at inclusion to 20.14 (SD=9.15) at the post-treatment visit, p<0.01. Among the 28 patients who had cognitive impairment at inclusion and completed the study, the general functioning improvement was observed in 3 (10.71%), remission in 9 (32.14%), and recovery in 5 (17.86%). In total, 17 patients (60.71%) showed a favourable clinical change.

Table 2. Comparison of the functioning before and after cognitive remediation

Patients completed a mean of 22.97 (SD=5.23) COGMED® sessions. Compared with baseline, patients reported significantly fewer memory and attention complaints after the

intervention (mean Mac Nair score at the post-treatment visit: 53.50, SD 18.08). The residual depressive symptomatology also significantly decreased, according to the clinician's and patient's evaluations. The difference was particularly significant for the question about concentration (concentration item in the MADRS and QIDS-SR16 scales). However, this change was no longer significant after excluding the concentration item of the MADRS but not of the QIDSR-SR16 scale. Treatment adherence and subjective quality of life did not change between visits.

Treatment (molecules and dosage) did not change between visits in 20 patients, while the changes did not concern the main mood-stabilizing drug in the other 12.

3.4 Comparison of neuropsychological variables between baseline and post-training visits

Verbal and visuospatial WM positively changed after the intervention, as shown by the WAIS-IV digit span and WMS-III Corsi block-tapping test scores (Table 3). A significant change in the WAIS-IV "codes" subtest (attention capacity, associative memory and information processing speed) was identified. The score of the Stroop test, which evaluates information processing speed, attention capacity and cognitive inhibition, also improved. Conversely, the change in the "symbols" test, which reflects the information processing speed, was not significant, as well as the changes in the TMT test scores (visual attention and task switching capacities). Semantic, but not phonemic verbal fluency changed significantly.

Table 3. Comparison of the cognitive functioning tests before and after cognitive remediation

3.5. Global functioning change and working memory

The FAST change did not correlate with the working memory change. However, in repeated measures ANOVA, the difference between two FAST timepoints became not significant after the adjustment for the working memory change ($F(1,29)=1.56$, $p=0.22$). The repeated-measures ANOVA with adjustment for other possible covariates for the FAST change that correlated with the FAST change in the univariate analysis was also performed. After controlling for the number of thymic episodes, history of head trauma, depressive symptomatology at baseline, and decrease of depressive symptomatology according to MADRS, the FAST change remained significant ($F(1,13)=22.12$, $p<0.01$).

The pharmacological treatment modality, regimen changes, and a number of used drugs were not associated with any of the primary or secondary outcomes.

4. Discussion

To our knowledge, this is the first study exploring the feasibility of a short computerised WM training program in euthymic patients with BD and memory complaints. This is also the first study that applied the functional impairment severity grading to assess the clinical relevance of an intervention. Per our hypothesis, patients' functioning was significantly improved one month after completion of the intervention, with a mean change in the total FAST score of -6.78. These results are comparable with those of longer CR and functional remediation studies (from 21 weeks to 6 months), with an average FAST total score decrease between six and eight points (Kim et al., 2018; Torrent et al., 2013; Veeh et al., 2017). After excluding patients without functional impairment at baseline, the change in FAST score increased to -7.5. Improvement, remission or recovery was observed in two-thirds of completers. Specifically, the FAST cognition sub-score decreased significantly, suggesting that patients experienced fewer difficulties in everyday tasks that required concentration, problem-solving and memory abilities. Less pronounced, but still significant

improvements in occupational functioning and autonomy were observed, suggesting a broad impact of the intervention. Conversely, no change in the financial, interpersonal and leisure domains was detected, possibly due to the short follow-up period, because these functions might take longer to restore. Taken together, our exploratory study demonstrated a functioning increase and provided the basis for future research.

Concerning the secondary outcomes, the subjective quality of life and treatment adherence did not significantly change, differently from some previous CR studies (Deckersbach et al., 2010; Torrent et al., 2013). While the subjective quality of life increased, the change did not reach the level of significance. This could be explained by the insufficient power of the study sample and the short study duration. Indeed, the translation of better functioning to meaningful changes in life quality might take more time. The relative stability of treatment adherence may be due to its already high level at baseline, possibly due to a selection bias. Indeed, most of the patients in our sample had a high level of consciousness about their condition. Half (4/8) of the patients who abandoned the study had lifetime substance use disorder history, while this was the case for only 12.50% of completers (4/32). While this difference was not statistically significant ($p=0.06$), this feature should be explored in future studies.

As expected, both verbal and visuospatial components of WM significantly increased according to the WAIS-IV digit span and Corsi block-tapping scores. Although it is challenging to measure WM precisely, the convergence between the chosen subtests was good. Patients also reported significantly fewer memory and attention complaints after the intervention. While no CR trial has specifically targeted WM, CR trials in BD have shown improvements in neurocognitive performances (Preiss et al., 2013), although the extent of this effect is debated and more evidence-based research is needed (Demant et al., 2015). Besides WM, various other cognitive domains significantly improved, specifically attention

capacity, associative memory, cognitive inhibition, and cognitive flexibility, while changes in information processing speed, visual attention and task-switching were minimal and not significant. Previous studies reported no far-transfer effect of WM on other domains, or a small effect (Lampit et al., 2014). However, these studies included healthy subjects, and their results are not generalizable to patients with BD. Studies on structural brain changes during WM training revealed improvement in prefrontal network efficiency, potentially releasing the resources for compensatory functions in the case of high WM load (Vermeij et al., 2017). One could hypothesize that WM overload might be present in patients with BD. Therefore, WM remediation programs in BD might promote adaptive responses and improve processing efficiency.

In line with previous studies on cognitive and functional remediation (Deckersbach et al., 2010; Kim et al., 2018; Preiss et al., 2013; Veeh et al., 2017), residual depressive symptomatology was significantly decreased at the post-treatment visit. A possible explanation might be that the structure and support offered by the program favoured self-efficacy and empowerment (Veeh et al., 2017). Moreover, BD is associated with impaired emotional regulation, which might be driven by poorer executive function, including WM (Lima et al., 2018). WM remediation could result in emotional and mood improvements via reduction of maladaptive forms of emotional regulation, such as rumination. As residual depressive symptoms are considered to be the strongest predictor of psychosocial functioning (Bonnín et al., 2010), the reduction of depressive symptomatology might represent an additional benefit of this type of intervention.

Some authors suggested that mood and cognitive symptoms are independent sources of variation in the functioning of patients with BD (Roux et al., 2017; Samalin et al., 2017). Other researchers proposed a reciprocal relationship (Bonnín et al., 2010), and hypothesized that the mediation might occur for higher levels of depressive symptoms (Roux et al., 2017).

Interestingly, despite the relatively high baseline MADRS score in our group (7.7 points on average, compared with less pronounced depressive symptomatology in previous studies (Bonnín et al., 2010; Roux et al., 2017; Samalin et al., 2017)), all three domains (cognitive functions, depressive symptomatology and general functioning) were improved at the end of the intervention, but only depressive symptomatology and general functioning correlated with each other. The residual thymic symptom improvement could correlate with short-term changes in general functioning due to the high subjectivity of its measurement. The patients just feel better about their life and frame it more positively. Conversely, changes in the cognitive domains take longer to apply in real life because learning new skills, engaging in professional and personal activities require cognitive capacity and also self-confidence, especially at the beginning.

Though working memory improvement did not correlate significantly with the general functioning and depressive symptomatology improvement, the general functioning change became not significant after the adjustment for the working memory change. Meanwhile, the global functioning change remained significant after controlling for the depressive symptomatology change. This emphasizes the possibility that, though the effect was small in the short term and was not sufficient to reach the statistically significant correlation, working memory change nevertheless, at least partly, drove the improvement in general functioning following the COGMED intervention.

History of head trauma and the number of previous manic, hypomanic or mixed episodes also were associated with the functioning improvement. This result should be interpreted with caution because only half of the patients indicated the number of previous episodes, and only six had a history of head trauma. However, this finding is intriguing. Indeed, it was previously demonstrated that patients with a history of head trauma benefit from WM remediation (Kim et al., 2018), and comorbidity with BD seems to be common.

The exploratory study design allowed using less restrictive inclusion criteria and investigating this patients group. Our data indicate that they benefited from the intervention more than other patients in terms of functioning. Moreover, it has been proposed that the effect of interventions for cognitive dysfunction differs in function of the disease stage (Vieta, 2015). Some studies found a negative correlation between the number of manic, hypomanic and mixed episodes and the efficacy of treatment (Berk et al., 2017), while our study found a positive correlation. Similar to our results, the chance of treatment efficacy on cognition was increased by 16% for every year of illness in patients with mood disorders treated with erythropoietin for cognitive impairment (Miskowiak et al., 2016). While previous longitudinal studies found no association between cognition and the number of thymic episodes (Schouws et al., 2016), a recent study reported that patients with more manic or hypomanic episodes were more cognitively impaired and had poorer functioning (Solé et al., 2018). Moreover, neuroimaging studies in BD have shown progressive structural abnormalities (Hibar et al., 2018), related to the number of manic episodes. It could be hypothesized that patients with a higher number of manic, hypomanic and mixed episodes are characterized by progressive neurocognitive impairments, lower cognitive reserve and better treatment response to WM remediation.

Though the drop-out rate was as expected, and similar to what was previously reported in functional remediation studies (Torrent et al., 2013), it raises concern that some patients lose their motivation to undergo such interventions despite their relative convenience, continuous active motivating, and relatively short duration. An aspect of self-motivation, inherent to such interventions (one has to actively find time during the day to sit in front of a computer), could be one reason for the drop-out. Bipolar disorder patients are proven to have marked impairment in their ability to delay gratification, resulting in their choice of faster, but smaller rewards compared to healthy controls (Ahn et al., 2011). In addition, though we did not find significant differences in cognitive measures between study

completers and non-completers, younger individuals and those with a shorter disease duration were more likely to drop-out. This is following findings from a study with anorexia nervosa patients, that found that younger patients had a lower motivation to change (Hillen et al., 2015).

4.1. Limitations and strengths

Some limitations should be noted. First, the naturalistic open-label, non-controlled design of this study precludes the assessment of causality with any degree of confidence. Second, the small sample size and short study duration resulted in limited power to look at interaction effects among the domains and long-term effects. Even among this relatively small sample, eight patients did not complete the study. Moreover, the pharmacological treatment regimen was flexible, and this could have influenced the treatment response. Some patients were treated with benzodiazepines and had a history of head trauma, two conditions that should preclude their inclusion in cognition trials (Miskowiak et al., 2018). However, drugs did not have any effect on the study outcomes. While the history of head trauma was correlated with a better response to intervention, the response remained significant even after the exclusion of these patients, and their inclusion increased the outreach and generalizability to real-life patients' populations because this comorbidity is common. Another limitation was the absence of screening for physical comorbidities, sleep disorders and ADHD that have been associated with cognitive decline in BD (Berk et al., 2017). Another limitation is that this was a single-centre study, and therefore, a site effect on the outcome cannot be excluded. Finally, the population was recruited in a psychiatric department where patients with more complex/severe disease and longer duration are followed, and this may limit the result generalizability to all patients with BD.

The main strength of our study is that it is the first of its kind and includes a sample of patients with a careful diagnosis of BD. Moreover, it is the first study to address the clinical meaningfulness of WM remediation using functional impairment grading. Although our sample was relatively small, it was congruent with previous studies. The mean level of functioning was in the range found in previous studies on the relationship between cognition and functioning in euthymic patients with BD (Samalin et al., 2017; Tse et al., 2014). Moreover, subjective and objective measures were included, as recommended by the ISBD taskforce (Miskowiak et al., 2018), to investigate the clinical significance and of the intervention and for research purposes.

Conclusions and future directions

The present study demonstrated a significant improvement of global functioning in patients with BD after computerized WM training. This intervention may represent an additional strategy to improve the general functioning in euthymic patients with BD and memory complaints. These preliminary results might direct future research in this area. A pertinent study approach could be a randomized controlled trial with a longer follow-up time, including multimodal approaches to combine pharmacological agents and WM remediation. Although it was not the purpose of the present study, any adverse effects need to be assessed in future trials. Cost-effectiveness studies should be the next step to evaluate the applicability of this short treatment format.

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Table 1. Baseline demographic, clinical and neuropsychological characteristics of patients with bipolar disorder (N=40)

Variable	Mean (SD); median (min - max) or N (%)
Age (years), mean (SD)	44.53 (10.54)
Female gender	30 (70%)
Professional situation: active or in training	21 (52.50%)
Education, years *(n=38)*	14.5 (2.30); 14.5 (9 - 19)
DSM IV diagnosis	
Bipolar I	28 (70%)
Bipolar II	12 (30%)
Disease duration	23 (10.73); 24 (1 - 41)
Duration of untreated disease	14.23 (11.18); 14 (0 - 40)
Number of depressive episodes *(n=35)*	5.34 (3.31); 5 (1 - 15)
Number of manic, mixed and hypomanic episodes *(n=19)*	3.84 (3.06); (1 - 14)
The most recent episode: depressive	26 (65%)
Number of suicide attempts	1.38 (1.75); 1 (0 - 6)
Previous treatment with ECT	3 (7.50%)
History of epilepsy or cerebrovascular events	1 (2.50%)
History of head trauma	7 (15.70%)
History of drug/alcohol abuse/dependence	13 (32.50%)
History of anxiety disorders	14 (35%)
History of eating disorders	12 (30%)
Current psychiatric comorbidity	12 (30%)
Psychiatric medications	
Lithium	21 (52.50%)
Antipsychotics	18 (45%)
Anticonvulsants	24 (60%)
Antidepressants	12 (30%)
Benzodiazepines	10 (25%)
Monotherapy	12 (30%)
MADRS total	7.68 (3.75); 8 (0 - 12)
MADRS concentration	2.58 (1.38); 3 (0 - 4)
YMRS total	1.63 (1.94); 1 (0 - 6)
FAST total	26.8 (12.07); 25.5 (7 - 64)
FAST autonomy	2.33 (2.79); 2 (0 - 11)
FAST	9.45 (5.97); 12.5 (0 - 15)
FAST cognitive functioning	8.23 (3.03); 8 (2 - 14)
FAST financial issues	0.73 (1.63); 0 (0 - 6)
FAST interpersonal relationships	4.75 (3.85); 5 (0 - 13)
FAST leisure time	1.25 (1.81); 0 (0 - 5)
QIDS-SR16 total score	8.65 (5.92); 6 (2 - 22)
QIDS-SR16 concentration	1.28 (1.99); 1 (0 - 3)
ASRM total	1.20 (1.64); 0 (0 - 6)
MARS total	7.78 (1.78); 8 (2 - 10)
STAI form Y total	40.48 (13.71); 36.5 (20 - 68)
SF-36 physical	68.26 (19.66); 70.6 (19.7 - 95.8)
SF-36 mental	54.70 (21.61); 56.4 (19.8 - 90.5)
MAC NAIR total	68.78 (14.77); 70 (37 - 97)
TMT A	36.40 (11.97); 35 (18 - 74)
TMT B	91.70 (58.61); 76.5 (0 - 340)
Verbal fluency	28.13 (7.00); 29.0 (12.5 - 42)
WAIS-IV Forward digit span	8.25 (2.10); 8 (5 -13)
WAIS-IV Backward digit span	6.93 (1.59); 7 (4 - 10)
WAIS-IV Sequential digit span	6.98 (1.90); 7 (2 - 11)
WAIS-IV Coding	62.95 (14.61); 63 (30-97)
WAIS-IV Symbol search	33.78 (10.65); 33 (13 - 82)
Information processing speed	55.30 (52.70); 40 (-26 - 299)
Corsi block-tapping test forward	7.13 (1.65); 7 (3 - 11)
Corsi block-tapping test backward	6.65 (1.46); 7 (2 - 9)
Stroop color item	37.03 (9.28); 37.50 (14 - 57)

Sample size N=40, unless otherwise specified. Values are n (%) or mean (standard deviation) and median (min-max). ECT, electroconvulsive therapy; History of drug/alcohol abuse/dependence, anxiety and eating disorders was measured with the Structured Clinical Interview for the DSM-IV (SCID-1) scale; MADRS, Montgomery-Asberg Depression Rating Scale; YMRS, Young Mania Rating Scale; FAST, Functional Assessment Staging Test; QIDS-SR16, Quick Inventory of Depressive Symptomatology; ASRM, Altman Self-Rating Mania Scale; MARS, Medical Adherence Rating Scale; STAI Form Y, State-Trait Anxiety Inventory, form Y; SF-36, Medical Outcome Study *Short Form 36* health survey; Mac Nair, questionnaire to evaluate memory and attention complaints; TMT, Trail Making Test; Average of verbal fluency "p" and "animals" subtests is presented; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition; Information processing speed was measured with the WAIS-IV Coding and Symbol search subscale ; the Corsi block-tapping test is a part of the Wechsler Memory Scale, Third Edition, and was used to evaluate visuospatial memory; Stroop color item score – part of the Stroop Color-Word test with colors.

Table 2. Comparison of the functioning before and after cognitive remediation

Variable	Initial visit (N=40) Mean (SD)	Final visit (N=32) Mean (SD)	Change, Mean (SD)	p-value‡
FAST total	26.80 (12.07)	18.53 (9.63)	-6.78 (4.65)	<0.0001*
FAST total, without head trauma	23.73 (10.95)	18.00 (10.24)	-5.73 (3.87)	<0.0001*
FAST autonomy†	2.33 (2.79)	1.72 (3.12)	-0.31 (2.60)	0.03*
FAST occupational functioning†	9.45 (5.67)	7.63 (6.21)	-1.53 (3.35)	0.006*
FAST cognitive functioning†	8.23 (3.03)	4.19 (2.66)	-3.97 (2.04)	<0.0001*
FAST financial issues†	0.73 (1.63)	0.41 (1.29)	-0.09 (0.69)	0.63
FAST interpersonal relationships†	4.75 (3.85)	3.94 (3.39)	-0.47 (1.95)	0.14
FAST leisure time†	1.25 (1.81)	0.66 (1.18)	-0.31 (1.47)	0.31

†Normality hypothesis not respected;
‡ Student's t test if the hypothesis of normality is respected, or Wilcoxon signed-rank test if the hypothesis of normality not respected;
FAST, Functional Assessment Staging Test.

Table 3. Comparison of the cognitive functioning tests before and after cognitive remediation

Variable	Initial visit (N=40) Mean (SD)	Final visit (N=32) Mean (SD)	Change, Mean (SD)	p-value‡
WAIS-IV coding†	62.95 (14.61)	70.52 (16.96)	7.55 (9.94)	<0.0001*
WAIS-IV symbol searching†	33.78 (10.65)	34.87 (8.93)	0.32 (11.19)	0.09
TMT A	36.40 (11.97)	32.97 (17.48)	-3.06 (12.42)	0.18
TMT B†	91.70 (58.61)	87.23 (76.91)	-4.42 (64.92)	0.25
Information processing speed†	55.30 (52.70)	54.26 (62.11)	-1.35 (61.48)	0.96
Verbal fluency total	28.13 (7.00)	31.47 (5.80)	2.27 (4.12)	0.006*
WAIS-IV forward digit span	8.25 (2.10)	9.61 (2.16)	1.35 (1.72)	0.0001*
WAIS-IV backward digit span†	6.93 (1.59)	8.84 (2.41)	1.81 (1.94)	<0.0001*
WAIS-IV sequential digit span†	6.98 (1.90)	8.19 (1.97)	1.29 (1.79)	0.0002*
Corsi block-tapping test forward	7.13 (1.65)	8.81 (2.06)	1.77 (1.65)	<0.0001*
Corsi block-tapping backward	6.65 (1.46)	7.68 (1.64)	1.10 (1.35)	<0.0001*
Stroop color item	37.03 (9.28)	40.83 (8.35)	4.00 (5.40)	0.0003*

†Normality hypothesis not respected;
‡ Student's t test if the hypothesis of normality is respected, or Wilcoxon signed-rank test if the hypothesis of normality not respected; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition; TMT, Trail Making Test; Information processing speed was measured using the WAIS-IV Coding and Symbol search subscales; Average of verbal fluency results for the "p" and "animals" subtests is presented; Corsi block-tapping test is part of Wechsler Memory Scale, Third Edition, used to evaluate visuospatial memory; Stroop color item score is part of the Stroop test.