# Impaired Visuospatial Working Memory but Preserved Attentional Control in Bipolar Disorder

Running Title: Visual Working Memory Dysfunction in Bipolar Disorder

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**ABSTRACT**

**BACKGROUND**

Persistent deficits in working memory (WM) and attention have considerable clinical and functional impact in people with bipolar disorder (PBD). Understanding the neurocognitive underpinnings of these interacting cognitive constructs might facilitate the discovery of more effective pro-cognitive interventions. Therefore, we employed a paradigm designed for jointly studying attentional control and WM encoding.

**METHODS**

We used a visuospatial change-detection task using four Gabor Patches with differing orientations in 63 euthymic PBD and 76 healthy controls (HCS), which investigated attentional competition during WM encoding. To manipulate bottom-up attention using stimulus salience, two Gabor patches flickered, which were designated as either targets or distractors. To manipulate top-down attention, the Gabor patches were preceded by either a predictive or a non-predictive cue for the target locations.

**RESULTS**

Across all task conditions, PBD stored significantly less information in visual WM than HCS (significant effect of group). However, we observed no significant group by salience or group by cue interactions. This indicates that impaired WM was not caused by deficits in attentional control.

**CONCLUSIONS**

Our results imply that while WM is disturbed in PBD, attentional prioritization of salient targets and distractors as well as the utilization of external top-down cues were not compromised. Consequently, the control of attentional selection appears

be intact. These findings provide important constraints for models of WM dysfunction in PBD by indicating that later stages of WM encoding are likely primarily impaired. We also demonstrate that selective attention is not among the main sources of cognitive impairment in PBD.

## INTRODUCTION

Cognitive impairment in persons with bipolar disorder (PBD) is a core feature persisting over all illness phases (Torrent et al., 2012), including euthymia (Goldberg & Roy Chengappa, 2009; Quraishi & Frangou, 2002). It is a key predictor for quality of life (Green, 2006; Mackala, Torres, Kozicky, Michalak, & Yatham, 2014), and for important measures of clinical and functional outcome including recurrence of affective episodes (Bauer, Hautzinger, & Meyer, 2017; Sachs, Berg, Jagsch, Lenz, & Erfurth, 2020), suicidal ideation (Luo, Zhu, Lu, Zong, & Lin, 2020), employment trajectory (Gilbert et al., 2010), and occupational disability (Bauer et al., 2017; Sachs et al., 2020). However, sufficiently effective pro-cognitive interventions for PBD remain elusive (Miskowiak et al., 2022), mainly because we lack a thorough understanding of the underlying neurocognitive architecture.

Impaired information processing in bipolar disorder (BD) has been linked to its neurodevelopmental origins (Bortolato, Miskowiak, Köhler, Vieta, & Carvalho, 2015). Within the proposed neurodevelopmental continuum, which also encompasses intellectual disability, autism spectrum disorders, schizophrenia, and attention-deficit/hyperactivity disorder (ADHD) (Owen & O'Donovan, 2017), BD is considered to have the lowest degree of neurodevelopmental and cognitive disturbances, with a unique cognitive profile (Pearlson, 2015; Valli, Fabbri, & Young, 2019).

Both working memory (WM) and attention are regarded as central cognitive domains for transdiagnostic studies of impaired information processing (Insel et al., 2010). Specifically, WM dysfunction is a crucial deficit in both PBD and schizophrenia (Barch & Smith, 2008; Glahn et al., 2006), with stronger impairment observed in schizophrenia (Barnes-Scheufler et al., 2021). It remains the most

consistently reported cognitive deficit in PBD and correlates most strongly with functional outcome (Keramatian, Torres, & Yatham, 2021), making it a key target for pro-cognitive interventions in PBD (Miskowiak et al., 2018). Based on its presence in unaffected first-degree relatives, WM dysfunction is also regarded as a neurocognitive endophenotype for BD (Glahn et al., 2010). Similar levels of WM impairment have been observed in both type I and type II BD (Bora, 2018; Bora, Yücel, Pantelis, & Berk, 2011; Mayer & Park, 2012), but PBD with a history of psychosis appear to be more affected than other PBD (Bora, 2018). WM capacity is reduced even in euthymic PBD (Barnes-Scheufler et al., 2021; Gold et al., 2018; Mayer & Park, 2012). Importantly, functional neuroimaging studies indicate disturbances during WM encoding in areas closely involved in both WM and attention (Huang et al., 2019; Linden et al., 2003; Mayer et al., 2007; McKenna, Sutherland, Legenkaya, & Eyler, 2014).

Deficits in visual attention are already present in young children at high familial risk for BD (Hemager et al., 2019), as well as in unaffected first-degree relatives (Bora, Yucel, & Pantelis, 2009). Impairments across multiple measures of attention in PBD – particularly sustained attention – have been reported (Dickinson, Becerra, & Coombes, 2017). These have been linked to clinical severity (Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009). Notably, sustained attention has also been implicated as an endophenotype for BD (Guglielmo, Miskowiak, & Hasler, 2021).

While the focus on sustained attention (Patino et al., 2023; Strakowski, Adler, Holland, Mills, & DelBello, 2004; Yatham et al., 2010) is logical considering the link to impulsivity and fluctuating affective phases (Mayberg et al, 1999; Yamasaki et al, 2002), studies investigating bottom-up and top-down attention remain scarce. Yet, these processes are of particular importance given their close connections to WM

(Oberauer, 2019). Top-down attention influences visual WM (VWM) capacity because of its close involvement in selecting relevant information during VWM encoding (Cowan & Morey, 2006; Vogel, McCollough, & Machizawa, 2005). This constitutes an important candidate mechanism for reduced WM capacity in BD, especially given the evidence for impaired WM encoding (Barnes-Scheufler et al., 2021; Huang et al., 2019; McKenna et al., 2014). However, the contribution of attentional dysfunction to impaired WM encoding in BD remains unclear.

The successful encoding of relevant information into VWM and the suppression of irrelevant information depends on interactions between bottom-up and top-down attention, which are driven by stimulus salience and stimulus relevance respectively. The resolution of attentional competition elicited by both stimulus features determines the probability of encoding an object into VWM (Constant & Liesefeld, 2021; Liesefeld, Liesefeld, Sauseng, Jacob, & Müller, 2020; Lorenc, Mallett, & Lewis-Peacock, 2021). Importantly, two top-down control processes support the selection of relevant information when multiple items compete for attention: the control of selection which assists in the identification of relevant information, and the implementation of selection which differentially processes relevant and irrelevant information (Desimone & Duncan, 1995; Luck & Gold, 2008). Neural computations during attentional competition assign a distinct priority to each stimulus, based on both its salience and its behavioral relevance (Fecteau & Munoz, 2006). An attentional set aids the control of attentional selection by guiding top-attention to the most relevant information based on current goals (Bichot, Rossi, & Desimone, 2005; Corbetta & Shulman, 2002; N. Gaspelin & S. J. Luck, 2018; Wolfe, 1994). According to the signal suppression hypothesis, this mechanism also controls the active suppression of automatic attentional capture by

visually salient distractors via inhibitory mechanisms (Nicholas Gaspelin & Steven J Luck, 2018; Sawaki & Luck, 2010). The parallelized up- and down-weighting of stimuli are essential for the generation of a priority map and the implementation of attentional selection (Nicholas Gaspelin & Steven J Luck, 2018).

We used these findings from cognitive neuroscience as a framework for our investigation of top-down and bottom-up attention during VWM encoding in PBD. To this end, we employed a visuospatial change detection task with an encoding array containing an equal number of salient (flickering) and non-salient (non-flickering) Gabor patches with different orientations. Depending on the specific task condition, either the salient or non-salient Gabor patches would be most relevant and probed preferentially (Nicholas Gaspelin & Steven J Luck, 2018). The encoding array was preceded by either a predictive external cue indicating the location of goal-relevant stimuli, or a non-predictive external cue providing no such information.

Previously, we utilized the same paradigm to study people with schizophrenia (PSZ) (Barnes-Scheufler et al., 2023). We observed a significant VWM deficit in PSZ, with less information encoded by PSZ across all conditions. In addition, we reported significant effects of cue, salience, as well as interactions of group by cue and group by salience indicating group differences in top-down and bottom-up processing. Posthoc results showed that PSZ stored significantly more non-flickering information with the help of a top-down predictive cue, mirroring an earlier report of successful utilization of top-down cues in PSZ (Gold et al., 2006). Furthermore, in the non-predictive cue conditions, PSZ stored significantly more flickering than non-flickering information- indicative of a bottom-up attentional bias in PSZ (Hahn et al., 2010).

In line with the neurodevelopmental continuum model and the clear evidence for overlapping cognitive deficits in schizophrenia and BD (Bora & Pantelis, 2015), we expected to observe a pattern of similar, yet less pronounced disturbances in PBD – including an overall deficit in the amount of information stored in VWM.

## METHODS AND MATERIALS

### PARTICIPANTS

63 PBD and 76 healthy control subjects (HCS) participated in this study. Patients were recruited from outpatient facilities in and surrounding Frankfurt am Main, Germany. HCS were recruited via online and printed advertisements. Diagnoses of all patients were established according to DSM-5 criteria involving a clinical interview and careful chart review of a trained psychiatrist. The Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) and Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery & Åsberg, 1979) were utilized to establish euthymic mood state in PBD - those with YMRS values of ≥ 11 or MADRS total scores of ≥ 11 were excluded from our analysis. All PBD were on stable medication for at least one month at the time of the study.

HCS were screened using the Structural Clinical Interview SCID-I from the Diagnostic and Statistical Manual, Version IV, in German (Saß, Wittchen, Zaudig, & Houben, 2003). No history of any psychiatric disorder or family history of psychiatric disorder in first-degree relatives were reported in HCS. No prior illicit drug use within the past six months and no lifetime history of neurological illness were reported in any participants. All participants reported normal or corrected-to-normal vision, and no color blindness.

Groups did not differ in age, sex, years of education, parental years of education and premorbid IQ (Table 1). Premorbid verbal intelligence was assessed by the German Mehrfachwahl-Wortschatz-Intelligenz Test (Lehrl, Merz, Burkhard, & Fischer, 2005). The ethics committee of the University Hospital Frankfurt approved all study procedures. Participants provided written informed consent after receiving a complete description of the study and adequate time for questions.

## WORKING MEMORY TASK

A visuospatial change detection task utilizing Gabor patches (Figure 1) was implemented on a personal computer using Presentation software version 14.9 (www.neurobs.com). Stimuli were presented on a grey background (RGB values: 191, 191, 191) in a dimly lit room with a viewing distance of approximately 60 cm.

Gabor patches had a visual angle of 0.96° each and were placed at four fixed locations equally spaced on an imaginary circle (visual angle of the diameter: 3.82°). A black fixation cross (visual angle: 0.48°) was presented at the center of the screen throughout the experiment. At the start of each trial, either a predictive or a non-predictive external cue was presented by either partially (predictive cue) or entirely (non-predictive cue) turning white the fixation cross for 300 ms. For predictive cues, the white arms of the fixation cross indicated the future locations of the two most relevant Gabor patches. For non-predictive cues, the entire fixation cross turned white. After a 300 ms preparation interval, the encoding array consisting of four Gabor patches with different orientations was displayed for 400 ms. To manipulate visual salience, two of the four patches flickered at a frequency of 7.5 Hz. To manipulate stimulus relevance, participants received instructions whether the flickering or non-flickering stimuli would be most goal-relevant and thus

probed preferentially, and whether a predictive or non-predictive cue would be displayed, resulting in four conditions: flickering-bias/predictive cue, flickering-bias/non-predictive cue, non-flickering-bias/predictive cue, non-flickering-bias/non-predictive cue.

The delay phase lasted for 2000 ms on average, with a jitter of +/- 250 ms. The retrieval array was displayed for 3000 ms consisting of one Gabor patch surrounded by a white frame at the probed location and three blurred out Gabor patches. Probed locations were randomized but counterbalanced. Participants had to indicate by button press within 3000 ms, if the orientation of the framed Gabor patch was identical to or different from the Gabor patch displayed at the same location in the encoding array. A minimum Gabor patch rotation of 45° indicated a change in orientation.

Both goal-relevant target and goal-irrelevant distractor stimuli were probed during retrieval with 80% and 20% probability, respectively. Probing goal-irrelevant stimuli (catch trials) allowed us to assess the efficiency of attentional prioritization operationalized as the difference of information stored in VWM between target and catch trials. Importantly, predictive cues always indicated the future locations of the target Gabor patches, even in catch trials. A total of 400 trials were presented, 100 for each condition, divided into eight blocks, counterbalanced in order across participants and groups. Each block began with four practice trials to ensure familiarization with the current instructions.

We also employed a 60-trial canonical visual change detection task (Barnes-Scheufler et al., 2021) to obtain an independent estimate of VWM capacity (see supplementary materials).

**ANALYSIS OF BEHAVIORAL DATA**

A partial display was used at recall. Accordingly, we quantified the amount of information stored in VWM using Cowan's K, where K = (hit rate + correct rejection rate − 1) × memory set size (Cowan, 2001; Rouder, Morey, Morey, & Cowan, 2011). Because participants were instructed to encode two Gabor patches in VWM, a set size of 2 was assumed (Feldmann-Wustefeld & Vogel, 2018; Gold et al., 2006). Statistical analyses were conducted using SPSS (IBM) Version 22, and R Version 4.3.1 (www.r-project.org). We created a cutoff value of performance by using a binomial expansion on the 400 trials. It was determined that an accuracy of 56% had a cumulative probability of P(X > x) 0.009, i.e., the probability of getting 224 correct responses or more by chance was less than 1%. Accordingly, we excluded the participants with an accuracy below 56% (n = 5, all PBD).

We based our main analysis solely on target trials, to study the differential processing of goal-relevant information. The main analysis consisted of a linear mixed-model (LMM) estimated using ML and nloptwrap optimizer with R to predict Cowan's K with group, salience, cue and age (Formula: score ~ Salience * Cue * Group + Age) and subject as a random effect (formula: ~1 | Subject). This task design was chosen due to the mixed conditions of our study design and therefore repeated measures of the dependent variable. We used an ANOVA function to obtain estimates of the LMM. Post-hoc contrasts of the LMM were obtained with the emmeans package (Russell V Lenth, 2023), and were computed using the Kenward-Roger degrees-of-freedom method with independent sample t-tests adjusted with the Tukey method. The t-tests were adjusted for age, where age was fixed at 40.5 years as determined by the function.

To investigate possible influences of manic and/or depressive symptoms, we correlated overall Cowan's K of target trials across all four conditions with YMRS and MADRS scores in PBD using two-tailed Spearman correlations.

To investigate possible differences in attentional prioritization, independent 2-tailed t-tests were conducted between groups for each condition (Cowan's K for target trials minus Cowan's K for catch trials). For further details, please see the supplementary materials.

We correlated attentional prioritization with WM capacity (Pashler's K), and target Cowan's K measures with WM capacity using two-tailed Spearman correlations in each condition in each group to investigate WM capacity as a possible limiting factor for attentional prioritization.

## RESULTS

### AMOUNT OF INFORMATION STORED IN VWM

We observed a significant main effect of group ($p$ = 0.005; Table 2). For target trials, HCS stored 1.25 items across all conditions, corresponding to a performance accuracy of 81% (Figure 2, Table S1,S2). PBD stored on average 1.05 items, with an accuracy of 76%. HCS stored significantly more information into VWM in all four target conditions: flickering-bias/predictive cue (mean = 1.29), flickering-bias/non-predictive cue (mean = 1.27), non-flickering-bias/predictive cue (mean = 1.26), non-flickering-bias/non-predictive cue (mean = 1.18) than PBD: flickering-bias/predictive cue (mean = 1.10, t(253) = 2.35, $p$ = 0.019), flickering-bias/non-predictive cue (mean = 1.09, t(253) = 2.23, $p$ = 0.027), non-flickering-bias/predictive cue (mean = 1.09, t(253) = 1.99, $p$ = 0.048), non-flickering-bias/non-predictive cue (mean = 0.94, t(253) = 3.10, $p$ = 0.002, Table 3). There were no significant correlations between

YMRS and overall Cowan's K for target trials ($r_s$ = 0.096, $p$ = 0.453), as well as MADRAS and overall target Cowan's K ($r_s$ = -0.014, $p$ = 0.912). Furthermore, there were no effects of medication on Cowan's K (Supplementary Materials). The covariate of age had a significant effect ($p$ < 0.001). Additionally, we observed a significant interaction of salience and cue ($p$ = 0.018). The model's total explanatory power was substantial (conditional $R^2$ = 0.70), and the part related to the fixed effects alone (marginal $R^2$) was 0.17, indicating a better fit when random effects were included (Barton & Barton, 2015). There was no significant group difference for the efficiency of attentional prioritization in any condition. Yet, for the non-flickering/non-predictive cue condition there was a trend-level group difference ($p$ = 0.057)

## EFFECTS OF SALIENCE AND CUE

For both groups we observed significant effects of salience and cue (both $p$ < 0.001), but no significant two-way interactions of either group and salience, or group and cue. Furthermore, we did not observe a significant three-way interaction of group, salience and cue (Table 2). To confirm these findings, we conducted a Bayes factor analysis for the effect of group by cue by salience, and included all three effects in our model. This analysis revealed a Bayes Factor of 0.06 and that it was much more likely that there were no significant effect of group, cue, and salience, refuting a beta error as an explanation of our findings.

## ATTENTIONAL PRIORITIZATION AND VWM CAPACITY

The efficiency of attentional prioritization did not correlate with the independent measure of WM capacity (Pashler's K) in any condition in PBD. It did however,

correlate at a trend level, α = 0.05 in HCS in the non-flickering-bias/non-predictive cue condition (*p* = 0.046). However, the Fisher r to z transformation revealed no group difference for the strength of this correlation (z = 0.533, *p* = 0.297, Table 4).

## CORRELATION BETWEEN TARGET TRIALS AND VWM CAPACITY

VWM capacity correlated with Cowan's K in each condition of target trials in HCS, yet in only three out of four conditions in PBD. There was no significant correlation between the flickering-bias/predictive cue condition and WM capacity. However, the Fisher r to z transformation revealed no group difference for the strength of this correlation (z = 0.453, *p* = 0.325, Table 5).

## DISCUSSION

We investigated the possible contribution of impaired attentional control to VWM dysfunction in BD. We manipulated the visual salience of targets and distractors as well as the predictiveness of external cues to isolate the impact of bottom-up and top-down attentional processing respectively. We observed a significant effect of group with PBD storing less information in VWM across all conditions. Moreover, we observed a significant effect of salience that did not differ between groups, indicating a similar pattern of salience processing across groups. Furthermore, we observed a significant effect of cue that also did not differ between groups. Thus, the ability to utilize external top-down cues appears to be intact in both groups. The Bayes factor analysis revealed that these results were not attributable to a lack of statistical power. Consequently, these findings indicate that both top-down and bottom-up attention are intact during VWM encoding in PBD (Mayer & Park, 2012).

Identifying specific cognitive processes that are impaired, and so-called ‘islands’ of preserved cognitive functioning provide important clues about the cognitive and neurophysiological mechanisms underlying attentional and VWM encoding dysfunction in PBD (Gold, Hahn, Strauss, & Waltz, 2009). Importantly, utilizing external cues did not improve performance of PBD up to the level of HCS. Thus, while our results do not implicate attentional control, they do not refute the existence of a primary VWM encoding deficit in PBD. Based on the existing evidence for impairments of WM encoding in PBD (Barnes-Scheufler et al., 2021; Huang et al., 2019; McKenna et al., 2014), other aspects of this component process including VWM consolidation could account for the significant overall reduction in the amount of stored information in PBD. Moreover, disturbances during maintenance or retrieval could make additional contributions to VWM dysfunction.

We observed no group difference in the efficiency attentional prioritization. Analysis of catch trials revealed no significant effect of group (see supplementary materials). Thus, PBD did not store more goal-irrelevant information than HCS in any condition. The efficiency of attentional prioritization did not correlate with our independent measure of WM capacity in PBD and only as a trend in one condition in HCS. Conversely, our independent measure of WM capacity correlated with Cowan’s K in every target condition in HCS, but only in three out of four target conditions in PBD, yet Fisher r to z did not reveal any significant group differences.

Interestingly, the analysis of catch trials revealed a significant effect of cue ($p = 0.001$; Table S4), which we also observed in PSZ (Barnes-Scheufler et al., 2023). This indicates that PBD’s ability to use spatial cues to down-weight both salient and non-salient distractors is preserved. More generally, our results support the interpretation that enhanced inhibitory control during attentional selection with the

use of an external cue increases local inhibition within early visual areas in both PBD and HCS. This interpretation would also be in line with the signal suppression hypothesis (Nicholas Gaspelin & Steven J Luck, 2018).

Abnormal GABAergic inhibitory neurotransmission has been proposed as a substrate of cognitive dysfunction across the schizobipolar spectrum (Volk & Lewis, 2014). Therefore, it is conceivable, that deficits in attention arise partly due to changes in GABAergic neurotransmission. Indeed, GABA levels appear to be reduced in PBD (Romeo, Choucha, Fossati, & Rotge, 2018; Volk, Sampson, Zhang, Edelson, & Lewis, 2016), and in youth with BD cognitive deficits have been associated with GABA levels (Huber et al., 2018). Genetic variants in GABA-A receptor subunits have also been strongly implicated in the genetic architecture of BD (Craddock et al., 2010). However, extensive molecular phenotyping of GABAergic interneuron-related markers revealed that compared to PSZ, GABAergic abnormalities in PBD are less common (Volk et al., 2016). In line with this observation, GABAergic deficits in PBD do not appear to impact the suppression of salient visual distractors to the same extent as in PSZ.

Importantly, our findings differ in crucial ways from our previous results in PSZ (Barnes-Scheufler et al., 2023). Both PSZ and PBD stored significantly less information across all conditions compared to HCS. However, in PBD we did not observe group by salience and group by cue effects as observed in PSZ. Although we did not observe a similar pattern of cognitive impairment in PBD as we did in PSZ, the deficit in information stored indicates intermittent impairment in cognitive processing in PBD compared to schizophrenia, in line with the neurodevelopment continuum hypothesis (Barnes-Scheufler et al., 2021; Owen & O'Donovan, 2017).

Using our paradigm in functional neuroimaging studies will be crucial to elucidate the underlying neurophysiological disturbances and to determine to which degree impairments during encoding, maintenance and retrieval contribute to the overall VWM deficit in PBD. Hypoactivity in the dorsolateral prefrontal cortex in addition to hyperactivity in the default mode network have been associated with impaired WM reported in PBD (Miskowiak & Petersen, 2019; Zarp Petersen et al., 2022). Therefore, it is possible that impairments in downregulating the default mode network perturb the implementation of selection with the correct items being selected, but less information encoded into WM.

To summarize, we observed a significant reduction in the amount of information encoded in PBD across all conditions. We also provide evidence for islands of preserved cognitive function in BD in the form of utilizing external top-down cues and stimulus salience to enhance WM encoding. Our results indicate the importance of using behavioral paradigms geared toward measuring cognitive constructs derived from cognitive neuroscience to identify impaired and preserved component processes of WM and attention in PBD. We believe this to be a valuable approach in the quest to improve our understanding of cognitive deficits in PBD and to identify future therapeutic targets.

## AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. Authors RAB and LR designed the experiment. Authors CVB-S and LR acquired the data. Authors CVB-S, JSM, SM and RAB analyzed the data. Authors CVB-S and RAB undertook the literature

searches and wrote the first draft of the manuscript. All authors contributed to and revised the manuscript. All authors read and approved the final manuscript.

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**ETHICAL STANDARDS**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The ethics committee of the University Hospital Frankfurt approved all study procedures (experiment number 2/15).

**COMPETING INTERESTS**

The author(s) declare none.

## REFERENCES


Barch, D. M., & Smith, E. (2008). The cognitive neuroscience of working memory: relevance to CNTRICS and schizophrenia. *Biol Psychiatry, 64*(1), 11-17. doi: 10.1016/j.biopsych.2008.03.003

Barnes-Scheufler, Catherine V, Passow, Caroline, Rösler, Lara, Mayer, Jutta S, Oertel, Viola, Kittel-Schneider, Sarah, . . . Bittner, Robert A. (2021). Transdiagnostic comparison of visual working memory capacity in bipolar disorder and schizophrenia. *International Journal of Bipolar Disorders, 9*(1), 1-12.

Barnes-Scheufler, Catherine V., Rösler, Lara, Schaum, Michael, Schiweck, Carmen, Peters, Benjamin, Mayer, Jutta S., . . . Bittner, Robert A. (2023). External Cues Improve Visual Working Memory Encoding in the Presence of Salient Distractors in Schizophrenia. *Psychol Med, in press*.

Barton, Kamil, & Barton, Maintainer Kamil. (2015). Package 'mumin'. *Version, 1*(18), 439.

Bauer, Isabelle E, Hautzinger, Martin, & Meyer, Thomas D. (2017). Memory performance predicts recurrence of mania in bipolar disorder following psychotherapy: A preliminary study. *J Psychiatr Res, 84*, 207-213.

Bichot, Narcisse P, Rossi, Andrew F, & Desimone, Robert. (2005). Parallel and serial neural mechanisms for visual search in macaque area V4. *Science, 308*(5721), 529-534.

Bora, Emre. (2018). Neurocognitive features in clinical subgroups of bipolar disorder: a meta-analysis. *Journal of affective disorders, 229*, 125-134.

Bora, Emre, & Pantelis, Christos. (2015). Meta-analysis of cognitive impairment in first-episode bipolar disorder: comparison with first-episode schizophrenia and healthy controls. *Schizophr Bull, 41*(5), 1095-1104.

Bora, Emre, Yücel, M, Pantelis, Christos, & Berk, Michael. (2011). Meta-analytic review of neurocognition in bipolar II disorder. *Acta Psychiatr Scand, 123*(3), 165-174.

Bora, Emre, Yucel, Murat, & Pantelis, Christos. (2009). Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. *Journal of affective disorders, 113*(1-2), 1-20.

Bortolato, Beatrice, Miskowiak, Kamilla W, Köhler, Cristiano A, Vieta, Eduard, & Carvalho, André F. (2015). Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatr Dis Treat, 11*, 3111.

Constant, Martin, & Liesefeld, Heinrich R. (2021). Massive effects of saliency on information processing in visual working memory. *Psychological Science, 32*(5), 682-691.

Corbetta, Maurizio, & Shulman, Gordon L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews neuroscience, 3*(3), 201-215.

Cowan, Nelson. (2001). The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behavioral and brain sciences, 24*(1), 87-114.

Cowan, Nelson, & Morey, Candice C. (2006). Visual working memory depends on attentional filtering. *Trends Cogn Sci, 10*(4), 139-141.

Craddock, Nick, Jones, Lisa, Jones, Ian Richard, Kirov, George, Green, Elaine Karen, Grozeva, Detelina, . . . Vukcevic, Damjan. (2010). Strong genetic evidence for a selective influence of GABAA receptors on a component of the bipolar disorder phenotype. *Mol Psychiatry, 15*(2), 146-153.

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annu Rev Neurosci, 18*, 193-222. doi: 10.1146/annurev.ne.18.030195.001205

Dickinson, Tania, Becerra, Rodrigo, & Coombes, Jacqui. (2017). Executive functioning deficits among adults with bipolar disorder (types I and II): a systematic review and meta-analysis. *Journal of affective disorders, 218*, 407-427.

Fecteau, Jillian H, & Munoz, Douglas P. (2006). Salience, relevance, and firing: a priority map for target selection. *Trends Cogn Sci, 10*(8), 382-390.

Feldmann-Wustefeld, T., & Vogel, E. K. (2018). Neural Evidence for the Contribution of Active Suppression During Working Memory Filtering. *Cereb Cortex*. doi: 10.1093/cercor/bhx336

Gaspelin, N., & Luck, S. J. (2018). Combined Electrophysiological and Behavioral Evidence for the Suppression of Salient Distractors. *J Cogn Neurosci, 30*(9), 1265-1280. doi: 10.1162/jocn_a_01279

Gaspelin, Nicholas, & Luck, Steven J. (2018). The role of inhibition in avoiding distraction by salient stimuli. *Trends Cogn Sci, 22*(1), 79-92.

Gilbert, AM, Olino, TM, Houck, P, Fagiolini, A, Kupfer, DJ, & Frank, E. (2010). Self-reported cognitive problems predict employment trajectory in patients with bipolar I disorder. *Journal of affective disorders, 124*(3), 324-328.

Glahn, David C, Almasy, Laura, Barguil, Marcela, Hare, Elizabeth, Peralta, Juan Manuel, Kent, Jack W, . . . Lanzagorta, Nuria. (2010). Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. *Arch Gen Psychiatry, 67*(2), 168-177.

Glahn, David C, Bearden, Carrie E, Cakir, Sibel, Barrett, Jennifer A, Najt, Pablo, Serap Monkul, E, . . . Soares, Jair C. (2006). Differential working memory impairment in bipolar disorder and schizophrenia: effects of lifetime history of psychosis. *Bipolar Disord, 8*(2), 117-123.

Gold, J. M., Barch, D. M., Feuerstahler, L. M., Carter, C. S., MacDonald, A. W., 3rd, Ragland, J. D., . . . Luck, S. J. (2018). Working Memory Impairment Across Psychotic disorders. *Schizophr Bull*. doi: 10.1093/schbul/sby134

Gold, J. M., Hahn, B., Strauss, G. P., & Waltz, J. A. (2009). Turning it upside down: areas of preserved cognitive function in schizophrenia. *Neuropsychol Rev, 19*(3), 294-311. doi: 10.1007/s11065-009-9098-x

Gold, James M, Fuller, Rebecca L, Robinson, Benjamin M, McMahon, Robert P, Braun, Elsie L, & Luck, Steven J. (2006). Intact attentional control of working memory encoding in schizophrenia. *Journal of abnormal psychology, 115*(4), 658.

Goldberg, Joseph F, & Roy Chengappa, KN. (2009). Identifying and treating cognitive impairment in bipolar disorder. *Bipolar Disord, 11*, 123-137.

Green, Michael F. (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry, 67*, 3.

Guglielmo, Riccardo, Miskowiak, Kamilla Woznica, & Hasler, Gregor. (2021). Evaluating endophenotypes for bipolar disorder. *International Journal of Bipolar Disorders, 9*(1), 1-20.

Hahn, B., Robinson, B. M., Kaiser, S. T., Harvey, A. N., Beck, V. M., Leonard, C. J., . . . Gold, J. M. (2010). Failure of schizophrenia patients to overcome salient distractors during working memory encoding. *Biol Psychiatry, 68*(7), 603-609. doi: 10.1016/j.biopsych.2010.04.014

Hemager, Nicoline, Vangkilde, Signe, Thorup, Anne, Christiani, Camilla, Ellersgaard, Ditte, Spang, Katrine Søborg, . . . Mors, Ole. (2019). Visual attention in 7-year-old children at familial high risk of schizophrenia or bipolar disorder: The Danish high risk and resilience study VIA 7. *Journal of affective disorders, 258*, 56-65.

Huang, Anna S, Rogers, Baxter P, Anticevic, Alan, Blackford, Jennifer Urbano, Heckers, Stephan, & Woodward, Neil D. (2019). Brain function during stages of working memory in schizophrenia and psychotic bipolar disorder. *Neuropsychopharmacology, 44*(12), 2136-2142.

Huber, Rebekah S, Kondo, Douglas G, Shi, Xian-Feng, Prescot, Andrew P, Clark, Elaine, Renshaw, Perry F, & Yurgelun-Todd, Deborah A. (2018). Relationship of executive functioning deficits to N-acetyl aspartate (NAA) and gamma-aminobutyric acid (GABA) in youth with bipolar disorder. *Journal of affective disorders, 225*, 71-78.

Insel, Thomas, Cuthbert, Bruce, Garvey, Marjorie, Heinssen, Robert, Pine, Daniel S, Quinn, Kevin, . . . Wang, Philip. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders: Am Psychiatric Assoc.

Keramatian, Kamyar, Torres, Ivan J, & Yatham, Lakshmi N. (2021). Neurocognitive functioning in bipolar disorder: what we know and what we don't. *Dialogues in clinical neuroscience, 23*(1), 29-38.

Lehrl, Siegfried, Merz, Jürgen, Burkhard, Georg, & Fischer, Bernd. (2005). Mehrfach-wortschatz-intelligenztest MWT-B. *Balingen: Spitta Verlag, 75*.

Liesefeld, Heinrich R, Liesefeld, Anna M, Sauseng, Paul, Jacob, Simon N, & Müller, Hermann J. (2020). How visual working memory handles distraction: cognitive mechanisms and electrophysiological correlates. *Visual Cognition, 28*(5-8), 372-387.

Linden, D. E., Bittner, R. A., Muckli, L., Waltz, J. A., Kriegeskorte, N., Goebel, R., . . . Munk, M. H. (2003). Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network. *Neuroimage, 20*(3), 1518-1530.

Lorenc, Elizabeth S, Mallett, Remington, & Lewis-Peacock, Jarrod A. (2021). Distraction in Visual Working Memory: Resistance is Not Futile. *Trends Cogn Sci*.

Luck, S. J., & Gold, J. M. (2008). The construct of attention in schizophrenia. *Biol Psychiatry, 64*(1), 34-39. doi: 10.1016/j.biopsych.2008.02.014

Luo, Xia, Zhu, Yinghua, Lu, Dali, Zong, Kunlun, & Lin, Xiaoling. (2020). Subjective cognitive dysfunction in patients with bipolar disorder: the prevalence, related factors and effects on predicting psychosocial functioning and suicidal ideation. *Psychiatry Res, 284*, 112669.

Mackala, Sylvia A, Torres, Ivan J, Kozicky, Jan, Michalak, Erin E, & Yatham, Lakshmi N. (2014). Cognitive performance and quality of life early in the course of bipolar disorder. *Journal of affective disorders, 168*, 119-124.

Mayer, J. S., Bittner, R. A., Nikolic, D., Bledowski, C., Goebel, R., & Linden, D. E. (2007). Common neural substrates for visual working memory and attention. *Neuroimage, 36*(2), 441-453. doi: 10.1016/j.neuroimage.2007.03.007

Mayer, Jutta S, & Park, Sohee. (2012). Working memory encoding and false memory in schizophrenia and bipolar disorder in a spatial delayed response task. *Journal of abnormal psychology, 121*(3), 784.

McKenna, Benjamin S, Sutherland, Ashley N, Legenkaya, Anna P, & Eyler, Lisa T. (2014). Abnormalities of brain response during encoding into verbal working memory among euthymic patients with bipolar disorder. *Bipolar disorders, 16*(3), 289-299.

Miskowiak, Kamilla W, & Petersen, Cecilia S. (2019). Neuronal underpinnings of cognitive impairment and-improvement in mood disorders. *CNS spectrums, 24*(1), 30-53.

Miskowiak, Kamilla W, Seeberg, Ida, Jensen, Mette B, Balanzá-Martínez, Vicent, del Mar Bonnin, Caterina, Bowie, Christopher R, . . . Gallagher, Peter. (2022). Randomised controlled cognition trials in remitted patients with mood disorders published between 2015 and 2021: A systematic review by the International Society for Bipolar Disorders Targeting Cognition Task Force. *Bipolar Disord*.

Miskowiak, Kamilla Woznica, Burdick, KE, Martinez-Aran, A, Bonnin, CM, Bowie, CR, Carvalho, AF, . . . Sumiyoshi, T. (2018). Assessing and addressing cognitive impairment in bipolar disorder: the International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians. *Bipolar Disord, 20*(3), 184-194.

Montgomery, Stuart A, & Åsberg, MARIE. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry, 134*(4), 382-389.

Oberauer, Klaus. (2019). Working memory and attention—A conceptual analysis and review. *Journal of cognition*.

Owen, Michael J, & O'Donovan, Michael C. (2017). Schizophrenia and the neurodevelopmental continuum: evidence from genomics. *World Psychiatry, 16*(3), 227-235.

Patino, Luis R, Tallman, Maxwell J, Wen, Hongbo, Adler, Caleb M, Welge, Jeffrey A, & DelBello, Melissa P. (2023). Deficits in sustained attention in adolescents with bipolar disorder during their first manic episode. *Journal of affective disorders*.

Pearlson, Godfrey D. (2015). Etiologic, phenomenologic, and endophenotypic overlap of schizophrenia and bipolar disorder. *Annual review of clinical psychology, 11*, 251-281.

Quraishi, Seema, & Frangou, Sophia. (2002). Neuropsychology of bipolar disorder: a review. *Journal of affective disorders, 72*(3), 209-226.

Romeo, Bruno, Choucha, Walid, Fossati, Philippe, & Rotge, Jean-Yves. (2018). Meta-analysis of central and peripheral γ-aminobutyric acid levels in patients with unipolar and bipolar depression. *Journal of Psychiatry and Neuroscience, 43*(1), 58-66.

Rouder, Jeffrey N, Morey, Richard D, Morey, Candice C, & Cowan, Nelson. (2011). How to measure working memory capacity in the change detection paradigm. *Psychonomic bulletin & review, 18*(2), 324-330.

Sachs, Gabriele, Berg, Andrea, Jagsch, Reinhold, Lenz, Gerhard, & Erfurth, Andreas. (2020). Predictors of functional outcome in patients with bipolar disorder: effects of cognitive psychoeducational group therapy after 12 months. *Frontiers in psychiatry, 11*, 530026.

Saß, Henning, Wittchen, Hans-Ulrich, Zaudig, Michael, & Houben, Isabel. (2003). Dsm-iv-tr. *Diagnostische Kriterien. Hogrefe, Göttingen*.

Sawaki, Risa, & Luck, Steven J. (2010). Capture versus suppression of attention by salient singletons: Electrophysiological evidence for an automatic attend-to-me signal. *Attention, Perception, & Psychophysics, 72*(6), 1455-1470.

Strakowski, Stephen M, Adler, Caleb M, Holland, Scott K, Mills, Neil, & DelBello, Melissa P. (2004). A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharmacology, 29*(9), 1734-1740.

Swann, Alan C, Lijffijt, Marijn, Lane, Scott D, Steinberg, Joel L, & Moeller, F Gerard. (2009). Severity of bipolar disorder is associated with impairment of response inhibition. *Journal of affective disorders, 116*(1-2), 30-36.

Torrent, Carla, Martinez-Arán, Anabel, del Mar Bonnin, Caterina, Reinares, Maria, Daban, Claire, Solé, Brisa, . . . Salamero, Manel. (2012). Long-term outcome of cognitive impairment in bipolar disorder. *The Journal of clinical psychiatry*.

Valli, Isabel, Fabbri, Chiara, & Young, Allan H. (2019). Uncovering neurodevelopmental features in bipolar affective disorder. *The British Journal of Psychiatry, 215*(1), 383-385.

Vogel, Edward K, McCollough, Andrew W, & Machizawa, Maro G. (2005). Neural measures reveal individual differences in controlling access to working memory. *Nature, 438*(7067), 500.

Volk, David W, & Lewis, David A. (2014). Early developmental disturbances of cortical inhibitory neurons: contribution to cognitive deficits in schizophrenia. *Schizophr Bull, 40*(5), 952-957.

Volk, DW, Sampson, AR, Zhang, Y, Edelson, JR, & Lewis, DA. (2016). Cortical GABA markers identify a molecular subtype of psychotic and bipolar disorders. *Psychol Med, 46*(12), 2501.

Wolfe, Jeremy M. (1994). Guided search 2.0 a revised model of visual search. *Psychonomic bulletin & review, 1*(2), 202-238.

Yatham, Lakshmi N, Torres, Ivan J, Malhi, Gin S, Frangou, Sophia, Glahn, David C, Bearden, Carrie E, . . . Goldberg, Joseph F. (2010). The International society for bipolar disorders–battery for assessment of neurocognition (ISBD-BANC). *Bipolar Disord, 12*(4), 351-363.

Young, Robert C, Biggs, Jeffery T, Ziegler, Veronika E, & Meyer, Dolores A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry, 133*(5), 429-435.

Zarp Petersen, Jeff, Varo, Cristina, Skovsen, Cecilie F, Ott, Caroline V, Kjærstad, Hanne L, Vieta, Eduard, . . . Macoveanu, Julian. (2022). Neuronal underpinnings of cognitive impairment in bipolar disorder: A large data-driven functional magnetic resonance imaging study. *Bipolar Disord, 24*(1), 69-81.

## FIGURE LEGENDS

Figure 1. Visual change detection task with four conditions; flickering/predictive cue, flickering/non-predictive cue, non-flickering/predictive cue, non-flickering/non-predictive cue. Flickering is indicated by white dashes around stimuli. The set size of four items was kept constant.

In 80% of trials, a designated target stimulus was probed during retrieval (target trials). In 20% of trials, a distractor was probed during retrieval (catch trials). Only target trials are depicted in the figure.

Figure 2. Amount of information stored in VWM in target trials, estimated with Cowan's K in healthy control subjects = HCS and people with bipolar disorder = PBD. F/PC = flickering/predictive cue, NF/PC = non-flickering/predictive cue, F/NPC = flickering/non-predictive cue, NF/NPC = non-flickering/non-predictive cue. The between group contrast is displayed. *** indicates $p < 0.001$. Error bars indicate standard deviation.

## TABLE LEGENDS

Table 1. Values are mean (SD), or n. All statistics reported are 2-tailed.

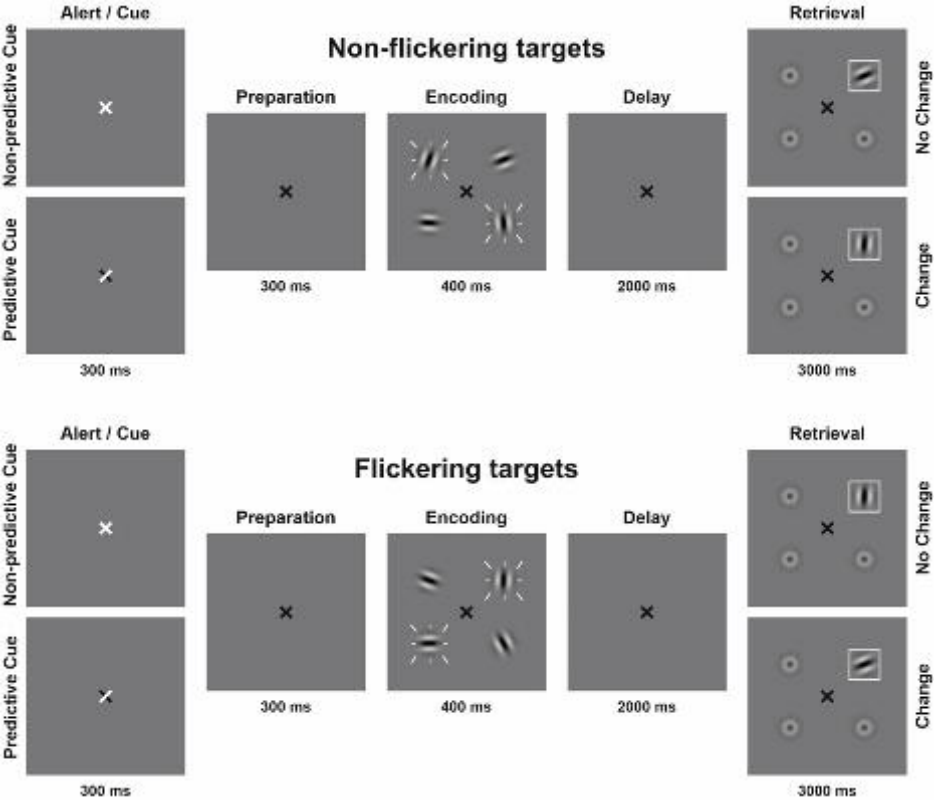
Abbreviations: HCS = healthy control subjects, PBD = people with bipolar disorder, PBD I = type 1, PBD II = type 2, HPS+= with a history of psychosis, HPS-= without a history of psychosis, YMRS = Young Mania Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, SGA = second-generation antipsychotics, df = degrees of freedom.

Table 2. Overall significance estimates of the linear mixed model were obtained post-hoc with an ANOVA function using Satterthwaite's method. Asterisks indicate significance $p < 0.001$ = ***, $p < 0.01$ = **, $p < 0.05$ = *.

Table 3. Two-tailed independent sample t-tests. Asterisks indicate significance $p < 0.001$ = ***, $p < 0.01$ = **, $p < 0.05$ = *. Abbreviations: df = degrees of freedom. Comparisons were adjusted for age.

Table 4. Results of Spearman correlations (two-tailed) of independent WM capacity estimate (Pashler's K) and attentional prioritization efficiency (target Cowan's K – catch Cowan's K) within each condition. Abbreviations: HCS = healthy control subjects, PBD = people with bipolar disorder. The non-significant z-scores indicate no significant differences between groups of the correlations of VWM capacity and attentional prioritization in each condition.

Table 5. Results of Spearman correlations (two-tailed) correlations between visual working memory capacity (Pashler's K) and mean Cowan's K of each target condition. Asterisks indicate significance $p < 0.001$ = ***, $p < 0.01$ = **, $p < 0.05$ = *. Abbreviations: HCS = healthy control subjects, PBD = people with bipolar disorder. The non-significant z-scores indicate no significant differences between groups of the correlations of VWM capacity and mean target Cowan's K in each condition.


Non-flickering targets
Alert / Cue
Non-predictive Cue
Predictive Cue
300 ms
Preparation
300 ms
Encoding
400 ms
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2000 ms
Retrieval
No Change
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Flickering targets
Alert / Cue
Non-predictive Cue
Predictive Cue
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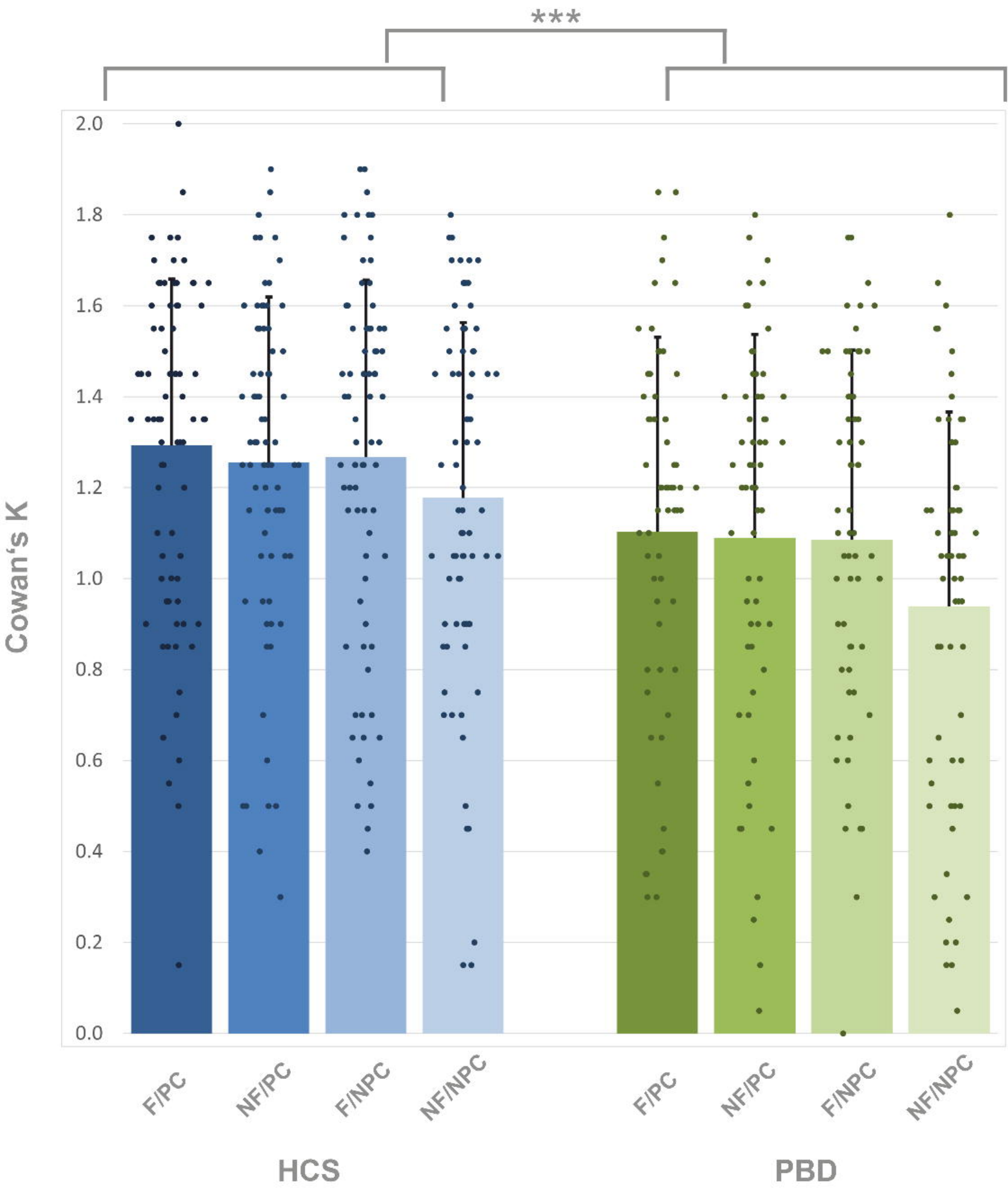
***
Cowan's K
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
F/PC
NF/PC
F/NPC
NF/NPC
F/PC
NF/PC
F/NPC
NF/NPC
HCS
PBD