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History of Psychosis Matters: Deviation in Age-related Decline of Working Memory Across the Schizo-bipolar Spectrum

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Abstract

Deficits in visuospatial working memory (WM) have been consistently reported in both persons with schizophrenia (PSZ) and bipolar disorder (PBD). In healthy controls (HCS), WM typically declines with age; however, it remains unclear whether a similar age-related decrease in WM performance occurs in PSZ and PBD, or whether a history of psychosis (HPS, meaning at least one psychotic episode) may significantly influence this trajectory. 189 participants, (20 to 61 years old) were separated into two groups based on HPS (HPS+, n = 90; HPS-, n = 99). Two cognitive tasks were employed to measure attentional competition during WM encoding (ACE-WM) and WM capacity (WMC). Linear regression analyses were used to separately investigate ACE-WM and WMC. HPS+ stored significantly less information in both ACE-WM (p = .003) and WMC (p = .005) tasks compared to HPS-. The factor of age was significant in both tasks (both p < .001). A significant effect of psychosis (p = .001) and a psychosis x age interaction (p = .011) were observed only in the ACE-WM task. Although age significantly affected performance in both tasks separately, HPS appears to mainly moderate age-related WM performance of attentional competition and not necessarily of WMC. This suggests different age-related patterns of cognitive functioning across these groups, with higher performance in the HPS- group. Although cross-sectional, our findings further our understanding of cognitive functioning across age and across mental disorders with psychosis.

INTRODUCTION

Transdiagnostic investigations of schizophrenia and bipolar disorder provide valuable insight grounded on shared cognitive impairment (1–3). Deficits in working memory (WM) are a hallmark across the schizo-bipolar spectrum both in persons with schizophrenia (PSZ) (4) and bipolar disorder (PBD) (5), and importantly predict functional outcome and quality of life (6). Psychotic symptoms including delusions and hallucinations are a core clinical feature of schizophrenia and often occur in bipolar disorder (7).

Higher lifetime psychosis scores including the severity and frequency across the schizo-bipolar spectrum have been associated with poorer cognitive performance (8). Specifically, WM impairment has been associated with history of psychosis (9), and significant deficits have been reported in tasks with higher cognitive demand including n-back and long-delay tasks in a transdiagnostic group of persons with a history of psychosis compared to those without (10). Additionally, in a study comparing PBD with and without a history of psychosis, executive control processes appeared to be affected specifically in those with a history of psychosis (11).

Performance in most cognitive domains improves during childhood, peaks in early to late adulthood, and is impacted to varying degrees by aging- at least in neurotypical populations (12). Specifically, WM is known to decline with increasing age in neurotypical individuals (13). Greater overall cognitive decline has been observed in schizophrenia-spectrum disorders compared to healthy controls, with more pronounced deficits after middle age- particularly in domains such as attention, language, visuospatial, and executive functions (14, 15). The findings in PBD are quite mixed, with cross sectional data not in line with very few longitudinal studies, possibly further limited by the heterogeneity of the disorder (16). A decline in visuospatial WM (VWM) and associated gray matter loss was observed in a longitudinal study of a transdiagnostic cohort of adolescents including the diagnoses of schizophrenia, bipolar disorder, depression and other with an onset of psychosis between the age of 7 and 17, two years after illness onset (17).

Previous studies on accelerated brain aging in PSZ and PBD demonstrate neuroimaging deviations in line with premature aging in both conditions, with schizophrenia being more severe than in bipolar disorder (18). In PSZ, accelerated aging of the brain is detectable with neuroimaging in early disease stages and appears to be more strongly associated with cognitive impairment than with clinical symptoms (19). Importantly, older PBD have been shown to

have a higher risk of mild cognitive impairment and dementia, with cognitive impairment being linked to a heightened risk of functional disability (20). Pathophysiological changes associated with accelerated deterioration of gray matter volume across the brain have also been observed in PBD (21, 22). Crucially, history of psychosis has been associated with accelerated aging of the brain (23). Given that psychosis is a common feature in schizophrenia and can occur in bipolar disorder, it raises the possibility that psychosis itself is associated with accelerated (cognitive) aging patterns irrespective of any categorical diagnosis.

VWM and attention are closely interrelated cognitive domains (24–26), and are central to understanding disrupted information processing especially in schizophrenia (27). The encoding of VWM representations is critical, as both behavioral (28–30) and neurophysiological evidence (31, 32) point to a fundamental impairment in this component of VWM in PSZ.

The successful encoding of relevant information into VWM is strongly influenced by attentional control. This includes the suppression of irrelevant information and relies on the interplay between bottom-up and top-down attention—guided by stimulus salience and stimulus relevance, respectively. The likelihood that an object will be encoded into VWM relies on attentional competition between bottom-up and top-down attention (33, 34).

Importantly, the amount of information that can be stored into WM- its capacity, is limited (26). An individual's WM capacity has been linked to important cognitive measures including global fluid intelligence, abstract reasoning, language abilities, mathematics, and overall scholastic performance (35–40).

Impairments in both cognitive constructs, i.e. WM capacity and attentional control during encoding into working memory (ACE-WM) have previously been demonstrated to varying degrees in PSZ and PBD (1–3). However, the transdiagnostic impact of psychosis on cognitive aging and WM function in particular remains a rather underexplored field (41).

The current study is a secondary data analysis to investigate the effects of psychosis and age on WM performance across diagnostic categories in a cross-sectional design. Based on our previous findings, we decided to define groups not according to diagnostic categories but to history of psychosis, based on DSM-5 criteria. As a result, our study compares WM impairment in people with a history of psychosis (HPS+) and people without a history of psychosis (HPS-). The HPS+ group included PSZ and PBD with a history of psychosis whereas the HPS- group included healthy controls and PBD without a history of psychosis. Within each of these groups we included participants across the age range.

We expected to observe significant main effects of history of psychosis and age on performance in both tasks, as well as an interaction of psychosis and age. Based on previous studies, we predicted poorer performance on tasks investigating WM capacity and ACE-WM in the HPS+ group compared to the HPS- group. Furthermore, we expected to observe a steeper age-related decrease in WM performance with increasing age in HPS+, as well as significant cognitive impairment present already in early adulthood in HPS+ compared to HPS-.

MATERIALS AND Methods

Participants

In total, 189 participants (62 PSZ, 57 PBD, and 70 HCS) were included in this analysis (Table 1). All participants reported no history of neurological illness, no drug use (excluding nicotine) within the past six months, normal or corrected-to-normal vision, and no color-blindness. We recruited PSZ and PBD from psychiatric outpatient facilities in and around Frankfurt am Main, Germany. We established diagnoses of all patients according to DSM-5 criteria based

on a clinical interview and careful chart review at a consensus conference. The ethics committee of the University Hospital Frankfurt approved all study procedures. Subjects provided written informed consent after receiving a complete description of the study.

Table 1
Participant Characteristics

Demographics	**HPS− (N = 99)**	**HPS+ (n = 90)**	**Statistic**	**df**	***p***
Age, Years	**38 (12.92); range 20–61**	**39.09 (10.17); range 20–57**	***t* = 0.04**	**183**	**.964**
Sex, Male/Female	66 (66.67%) / 33 (33.33%)	42 (46.67%) / 48 (53.33%)	χ^2 = 6.90	1	.008**
Participant Education, Years	16.08 (2.48)	16.36 (2.20)	*t* = − 0.82	183	.415
Parental Education, Years	13.89 (3.93)	15.67 (3.25)	*t* = − 3.65	183	< .001***
Premorbid IQ	115.88 (11.99)	113.15 (13.79)	*t* = 1.44	183	.151
Duration of Illness, Years	3.7 (7.8); range 0–43	12 (10); range 1–35	*t* = 0.27	49.46	.787
Age of Illness Onset, Years	29 (13); range 13–54	28 (9); range 9–52	*t* = 0.46	39.15	.649
Diagnosis Schizophrenia	–	39 (43.3%)			
Schizoaffective disorder	–	23 (25.6%)			
Bipolar Type I	9 (9.1%)	24 (26.7%)			
Bipolar Type II	20 (20.2%)	4 (4.4%)			
Healthy Controls	70 (70.7%)	–			
Psychopathology PANSS Positive	–	10.29 (3.63)			
PANSS Negative	–	11.84 (3.92)			
PANSS General	–	22.97 (5.07)			
PANSS Total	–	44.93 (10.23)			
YMRS	2.00 (2.69)	1.32 (1.91)			
MADRS	3.27 (2.82)	3.25 (2.96)			
Medication	0 (0%)	2 (2.2%)			
FGA					
SGA	13 (13.1%)	78 (86.7%)			
FGA + SGA	13 (13.1%)	4 (4.4%)			
Lithium	15 (15.2%)	15 (16.7%)			
Valproate	4 (4.0%)	7 (7.8%)			
Other mood stabilizers	9 (9.1%)	12 (13.3%)			

Note. Values are mean (SD) or n (%). HPS− = patients without a history of psychosis; HPS + = patients with a history of psychosis. PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale; MADRS = Montgomery˚Asberg Depression Rating Scale; FGA = first-generation antipsychotics; SGA = second-generation antipsychotics. FGA + SGA = receiving both antipsychotics (FGA and SGA). **p < .01. ***p < .001.

Demographics	HPS− (N = 99)	HPS+ (n = 90)	Statistic	df	*p*
Age, Years	**38 (12.92); range 20–61**	**39.09 (10.17); range 20–57**	***t* = 0.04**	**183**	**.964**
Antidepressants	15 (15.2%)	21 (23.3%)			

Note. Values are mean (SD) or n (%). HPS− = patients without a history of psychosis; HPS + = patients with a history of psychosis. PANSS = Positive and Negative Syndrome Scale; YMRS = Young Mania Rating Scale; MADRS = Montgomery˚Asberg Depression Rating Scale; FGA = first-generation antipsychotics; SGA = second-generation antipsychotics. FGA + SGA = receiving both antipsychotics (FGA and SGA). $^{**}p < .01$. $^{***}p < .001$.

Table 2
Linear Regression Models Predicting Attentional Control during Encoding into Working Memory (ACE-WM) and Working Memory Capacity (WMC)

IQ	**0.005**	**0.002**	**1.95**	**.052**	**[0.000, 0.010]**	**.01**	**0.005**	**0.004**	**1.26**	**.211[−0.003, 0.013]**	**< .01**
Gender	0.062	0.063	0.99	.321	[−0.061, 0.186]	< .01	−0.068	0.103	−0.65	.514[−0.272, 0.136]	.02
Age	−0.016	0.003	−4.77	< .001	[−0.022, −0.009]	.08	−0.019	0.005	−3.44	< .001[−0.029, − 0.008]	.06
Psychosis (HPS+)	−0.725	0.221	−3.28	.001	[−1.161, −0.289]	.05	−0.675	0.365	−1.85	.066[−1.396, 0.045]	.03
Age × Psychosis	0.014	0.005	2.56	.011	[0.003, 0.024]	.03	0.011	0.009	1.20	.231[−0.007, 0.028]	< .01
Model Fit											
R^2 (Adj. R^2)				.156 (.133)						.111 (.087)	
F (df)			6.77*** (5, 183)						4.59*** (5, 183)		

Note $N = 189$. *B* = unstandardized regression coefficient; SE = standard error; CI = confidence interval; η_p^2 = partial eta squared. HPS + = patients with history of psychosis (reference = HPS−). Bold values indicate $p < .05$. $^{***}p < .001$. Models include age, psychosis group, their interaction, and covariates (IQ and sex).

Table 3
Group Differences in Attentional Control during Encoding into Working Memory and Working Memory Capacity

Measure	Group	Mean	SD	*t*	df	*p*	Cohen's *d*
WMC	**HPS**−	3.31	0.72	2.80	187	.006**	0.41
	PBD	3.10	0.93				
	HCS	3.39	0.60				
	HPS+	3.02	0.66				
	PSZ	2.96	0.68				
	PBD	3.16	0.58				
ACE-WM	**HPS**−	1.13	0.43	2.94	186	.004**	0.43
	PBD	0.89	0.56				
	HCS	1.23	0.32				
	HPS+	0.95	0.43				
	PSZ	0.90	0.42				
	PBD	1.06	0.44				

Note. N = 189 (HPS−: n = 99 [PBD: n = 29, HCS: n = 70]; HPS+: n = 90 [PSZ: n = 62, PBD: n = 28]). HPS− = individuals without a history of psychosis; HPS + = individuals with a history of psychosis; PSZ = patients with schizophrenia; PBD = patients with bipolar disorder; HCS = healthy control subjects. SD = standard error. Independent samples t-tests were conducted to compare HPS + and HPS− groups. $^{**}p < .01$.

PSZ

We used the Positive and Negative Syndrome Scale (PANSS) to assess current psychopathology in PSZ (M = 44.93, range: 28–73). Positive symptom scores averaged 10.29 (range: 7–26), negative symptoms averaged 11.84 (range: 7–21), and general psychopathology averaged 22.96 (range: 16–37), therefore no patients were classified as 'markedly ill (42)'. All PSZ receiving antipsychotic medication did not change their dose or medication for at least one month at the time of the study; one PSZ was not on antipsychotic medication.

PBD

The Young Mania Rating Scale (YMRS) and Montgomery-Åsberg Depression Rating Scale (MADRS) were utilized in PBD to establish euthymic mood state - participants with YMRS values of ≥ 11 or MADRS values of ≥ 11 were excluded from our analysis. Two PBD did not receive psychotropic medication for at least one month prior to their participation in the study. Medicated PBD patients were receiving either antipsychotic (n = 31), mood stabilizer treatment (n = 44), or both (n = 21), and were on stable medication for at least one month at the time of the study.

HCS

Healthy control subjects (HCS) were screened using the German version of the Structural Clinical Interview SCID-I from the Diagnostic and Statistical Manual, Version IV (43). HCS were recruited by online and printed advertisements. They reported no history of any psychiatric illness and no family history of psychiatric illness in first-degree relatives.

HPS grouping

For the current analysis, the cohorts were grouped not according to diagnostic category but rather with respect to history of psychosis. We defined HPS + as having experienced at least one psychotic episode as defined by DSM-5 criteria during the lifetime, confirmed with medical records. The HPS+ group consisted of 90 participants (n = 62 PSZ and n = 28 PBD). The HPS- group consisted of 99 participants (n = 29 PBD and n = 70 HCS).

Both groups (HPS + and HPS-) were matched for age, premorbid IQ, handedness, years of education, and parental years of education (Table 1). Premorbid verbal intelligence was assessed by the German Mehrfachwahl-Wortschatz-Intelligenz Test (44).

Early adulthood subgroup

To test whether cognitive impairment in HPS + is evident in early adulthood, we conducted an additional analysis within the youngest tertile of our sample. The full dataset was divided into three equal age groups based on quantile distribution (n = 63 per tertile: 20–31, 32–46, and 47–61 years). The youngest tertile (20–31 years) was selected to examine whether cognitive deficits are present in early adulthood. Within this age range, HPS+ (n = 25) and HPS- (n = 38) groups did not differ significantly in sex distribution ($\chi^2(1) = 1.81$, $p = .179$) or in age ($M = 27.6$ vs. $M = 26.0$ years; $t(53.6) = -1.95$, $p = .056$).

Working Memory Paradigms

Participants completed two visual WM paradigms during a single testing session, with the ACE-WM task administered first in all cases. Both tasks were implemented on a personal computer in a dimly lit room with a viewing distance of approximately 60 cm using Presentation software version 14.9 (www.neurobs.com). All participants received the same instructions prior to beginning the task, and were asked to perform as accurately as possible, and to keep their eyes fixated constantly on the center of the screen.

Attentional control during encoding into working memory (ACE-WM) paradigm

A visuospatial change detection task was used to assess attentional control during encoding into WM (ACE-WM) (Fig. 1) (3). Four Gabor patches were placed on an imaginary circle around a fixation cross in the middle of the screen. The fixation cross also functioned as either a predictive cue which indicated the future locations of task-relevant stimuli by having turned the corresponding arms of the cross white, or as a non-predictive cue which was entirely white and did not provide any information. At each trial, there were two patches that flickered and two that did not. Before each block started, participants were notified about the task-relevant Gabor patches for the current trial, which indicated which ones would be probed more likely during retrieval. Following a delay, the retrieval phase began where one Gabor patch was probed at one of the locations on the imaginary circle. The participants had to indicate by button press, if the orientation of the highlighted Gabor patch was the same or different from the one that was displayed at the same location during the encoding phase.

Overall, the task included four conditions: flickering/predictive cue, flickering/non-predictive cue, non-flickering/predictive cue, non-flickering/non-predictive cue. The participants were instructed at the beginning of each block to focus either on the two flickering or two non-flickering stimuli out of four items, therefore there was a maximum set size of two (28, 45). 80% of trials were target trials where a task relevant Gabor patch was probed, and the remaining 20% were catch trials in which the stimulus that was probed at retrieval was not task relevant. Inter-individual reliability estimates were moderate to high (0.797–0.900) (2). For more information see (3).

Working memory capacity (WMC) paradigm

We implemented a 'canonical' color change detection task to measure WM capacity (Fig. 2). Throughout the experiment, a black fixation cross was displayed at the center of the screen. An alert phase indicated the start of a trial which lasted 500 ms and the fixation cross turned red. The start signal was followed by a 500 ms preparation period. During the encoding phase, a sample array of four colored circles that were evenly spaced apart was shown on an imaginary circle with 12 alternative locations for 200 ms. The set size of four remained constant. Seven easily distinguishable colors were chosen and they did not repeat within a trial. The black fixation cross stayed on the screen for 1800 ms during the delay phase. During the test phase, participants were given a maximum of 3000 ms to determine whether the test array that was shown was the same as the sample array ('no-change' trials) or if one of the circles had changed color ('change' trials). There were equal numbers of 'change' and 'no-change' trials. Each trial lasted 6000 ms in total, followed by a 3000 ms inter-trial interval. For more information see (Barnes-Scheufler et al., 2021).

Medication

HPS+

In the HPS+ group, 26 participants were currently being treated with mood stabilizers. Of those, 15 were receiving lithium, 7 valproate, 4 lamotrigine, and 1 pregabalin; 1 person was receiving both lithium and lamotrigine. 80 HPS+ participants were currently being treated with antipsychotics; of those, 2 were receiving an FGA only, 74 an SGA only, and 4 were receiving both an FGA and an SGA. 21 participants were receiving antidepressants.

HPS-

In the HPS− group, 23 participants were currently being treated with mood stabilizers. Of those, 15 were receiving lithium, 4 valproate, and 5 lamotrigine; 1 person was receiving both lithium and lamotrigine. 13 HPS− participants were currently being treated with SGAs, and none received an FGA. 15 were receiving antidepressants. Further details according to diagnosis are listed in Table S1.

Analysis of Behavioral Data

ACE-WM task

The amount of information stored in WM was quantified using Cowan's K, as only a single stimulus was displayed during retrieval, where K = (hit rate + correct rejection rate − 1) × memory set size (26, 46). We based this analysis solely on target trials to study the differential processing of the most relevant information.

WMC task

Our whole-display recognition paradigm required the use of Pashler's K as the appropriate estimate of working memory capacity (47), where K = set size × ((hit rate—false alarm rate) / (1— false alarm rate) (48). Both Cowan's K and Pashler's K were calculated using custom-written Matlab code.

Linear regression models

We conducted linear regression analyses using separate models for ACE-WM and WMC. Both models included psychosis group (HPS + vs HPS-) as a categorical predictor, age as a continuous predictor, the psychosis × age interaction term to assess if HPS moderates age-related WM performance, and the covariates of premorbid IQ and sex. To test whether each group showed significant age-related decline, we calculated group-specific slopes using the emtrends() function from emmeans (Lenth, 2023).

Independent samples t-tests

To test whether cognitive impairment was more pronounced from early adulthood in HPS+, we compared ACE-WM and WMC performance between HPS + and HPS- participants within the youngest age range (20–31 years, n = 63; HPS-: n = 38, HPS+: n = 25) using independent samples t-tests. Cohen's d with 95% confidence intervals was calculated to quantify effect sizes.

Statistical group analyses were conducted using R (Version 2023.12.1, packages: car, multicomp, stats, effectsize, lm.beta, emmeans) and SPSS (IBM) Version 22 for demographic descriptions. Statistical significance was set at α = 0.05 (two-tailed) for all tests. Please see the supplementary materials for more information.

RESULTS

ACE-WM task

Averaged across all target conditions, HPS+ demonstrated significantly lower performance (M = 0.95, SD = 0.43, n = 90) corresponding to an accuracy of 74%, compared to HPS- (M = 1.13, SD = 0.43, n = 99, t(185.6) = 2.94, p = .004), with an accuracy of 78%.

The overall model was statistically significant, F(5, 183) = 6.77, p < .001, with R^2 = .156 (adjusted R^2 = .133). In the interaction model, psychosis displayed a significant main effect (β = -0.725, SE = 0.221, t = -3.28, p = .001, 95% CI [-1.161, -0.289], Cohen's f = 0.22, partial η^2 = .05), with HPS+ participants demonstrating lower performance overall than HPS-. Age displayed a significant negative effect as well (β = -0.016, SE = 0.003, t = -4.77, p < .001, 95% CI [-0.022, -0.009], Cohen's f = 0.30, partial η^2 = .08), indicating age-related decrease in WM performance. The age × psychosis interaction was significant (β = 0.014, SE = 0.005, t = 2.56, p = .011, 95% CI [0.003, 0.024], Cohen's f = 0.19, partial η^2 = .03). Within psychosis groups we observed a significant age-related decline in HPS- (slope = -0.016, SE = 0.003, 95% CI [-0.022, -0.009], t = -4.77, p < .001) but not in HPS+ (slope = -0.002, SE = 0.004, 95% CI [-0.011, 0.007], t = -0.41, p = .681). Premorbid IQ showed a marginal positive effect (β = 0.005, SE = 0.002, t = 1.95, p = .052, 95% CI [0.000, 0.010], Cohen's f = 0.11, partial η^2 = .01), with higher IQ associated with better ACE-WM performance, while sex was not a significant predictor (β = 0.062, SE = 0.063, t = 0.99, p = .321, 95% CI [-0.061, 0.186], Cohen's f = 0.04).

For ACE-WM, HPS+ young adult participants showed significantly lower performance than HPS- (M = 0.94, SD = 0.54 vs. M = 1.34, SD = 0.22; t(29.4) = 3.51, p < .001, Cohen's d = 1.05, 95% CI [0.50, 1.60]).

WMC task

Overall, HPS+ stored significantly less information into WM (M = 3.02, SD = 0.66, n = 90) corresponding to an accuracy of 84%, compared to HPS- (M = 3.31, SD = 0.72, n = 99, t(187) = 2.83, p = .005), with an accuracy of 88%.

We conducted a parallel linear regression analysis for WMC, using the same predictors as for the ACE-WM task. The overall model was statistically significant, F(5, 183) = 4.59, p < .001, with R^2 = .111 (adjusted R^2 = .087). HPS+ displayed

a marginal effect (β = -0.675, SE = 0.365, *t* = -1.85, *p* = .066, 95% CI [-1.396, 0.045], Cohen's f = 0.19, partial η² = .03), with HPS+ participants showing lower performance than HPS-, though this did not reach significance. Age displayed a significant negative effect (β = -0.019, SE = 0.005, *t* = -3.44, *p* < .001, 95% CI [-0.029, -0.008], Cohen's f = 0.24, partial η² = .06), indicating age-related decrease in WM performance. The psychosis × age interaction was not significant (β = 0.011, SE = 0.009, *t* = 1.20, *p* = .231, 95% CI [-0.007, 0.028], Cohen's f = 0.09, partial η² < .01). Within each psychosis group, HPS- showed significant age-related decline (slope = -0.019, SE = 0.005, 95% CI [-0.029, -0.008], *t* = -3.44, *p* < .001), while the decline in HPS + did not reach statistical significance (slope = -0.008, SE = 0.007, 95% CI [-0.022, 0.007], *t* = -1.07, *p* = .288). Neither premorbid IQ (β = 0.005, SE = 0.004, *t* = 1.26, *p* = .211, 95% CI [-0.003, 0.013], Cohen's f = 0.06) nor sex (β = -0.068, SE = 0.103, *t* = -0.65, *p* = .514, 95% CI [-0.272, 0.136], Cohen's f = 0.14) were significant predictors.

Young adult HPS+ participants demonstrated significantly lower performance than HPS- (*M* = 3.05, SD = 0.70 vs. *M* = 3.53, SD = 0.62; *t*(46.8) = 2.78, *p* = .004, Cohen's d = 0.74, 95% CI [0.20, 1.27]) for the WMC task.

Discussion

We studied the influence of experiencing at least one psychotic episode during lifetime and age on visual WM performance in a transdiagnostic cohort of PSZ, PBD and HCS stratified by HPS. We hypothesized an interaction between psychosis and age in both the ACE-WM and WMC paradigms, with HPS+ performing worse than HPS-. As expected, HPS- performed significantly better than HPS + in both tasks. We observed a significant interaction of psychosis x age in the ACE-WM task, indicating a significant impact of having experienced at least one psychotic episode in the past on age-related performance of ACE-WM. However, this interaction was not observed in the WMC task. These findings indicate a relevant impact of experiencing a psychosis on age-related performance of ACE-WM encoding, but not necessarily on general WMC.

Furthermore, we expected to observe a steeper decline in WM performance in both tasks in HPS+ compared to HPS-, as well as stronger impairment in the early adult group of HPS+ compared to HPS-. Contrary to our hypothesis of accelerated age-related decrease in WM performance in HPS+, which would be signified by a steeper slope, a rather flat line with a minimal slope was observed in both tasks. This finding refutes our hypothesis and indicates an early, consistent degree of cognitive impairment in HPS+. In line with early impairment, significantly more information was stored in both the WMC and ACE-WM tasks by young adult HPS- than young adult HPS+. This consistent pattern implies an early presence of cognitive impairment in young adulthood in HPS+.

Importantly, we did not observe a significant effect of psychosis in the WMC paradigm, nor an interaction of psychosis and age. However, we did observe a significant effect of psychosis, and an interaction of psychosis and age in the ACE-WM paradigm. While the two tasks differed in several design features including set size, stimulus complexity, encoding and maintenance durations, and retrieval arrays; the most consequential difference likely lies in their differential attentional demands. The ACE-WM paradigm required active distractor suppression, utilization of predictive cues, and selective encoding of only two of the four items presented, whereas the WMC task involved passive encoding of all presented items without selection demands. This pattern suggests that executive control processes during WM encoding, rather than storage capacity per se, show vulnerability to both psychosis and aging.

Supplementary analyses, as described in the supplementary materials, support the interpretation that attentional control impairment emerges early and remains stable in HPS+, rather than progressively deteriorating with age. First, young adult HPS+ participants (ages 20–31) demonstrated substantial impairment relative to HPS- (d = 1.05, *p* < .001), indicating deficits present from early adulthood. Secondly, we examined illness duration effects within HPS+ using linear regression (controlling for age) and compared recent onset cases (HPS+ with ≤ 2 years illness duration) to all

HPS- participants using Welch's t-test. Illness duration showed no relationship with ACE-WM performance when controlling for age (p = .248), and individuals with recent illness onset (≤ 2 years) were already significantly impaired (p = .047).

Additionally, the relatively flat age-related trajectory observed in HPS+ could have two potential explanations. First, it may partly reflect positive selection bias in our recruitment, (49). Despite having a history of psychosis, older HPS+ individuals in our sample were on average highly educated (M = 16.4 years, SD = 2.2) and cognitively able comparable to HPS- individuals (M = 16.1 years, SD = 2.5); with parental education (M = 15.7 years, SD = 3.3) even exceeding that of HPS- participants (M = 13.9 years, SD = 3.9). This suggests that our HPS+ sample may represent a cognitively resilient subset with high cognitive reserve and socioeconomic advantage rather than the broader clinical population. Second, there may be a functional floor effect as HPS+ participants performed near the lower limit of measurable performance, leaving limited room for further age-related deterioration.

This interpretation aligns with evidence that selective attention, WM, and executive function represent potentially independent sources of cognitive dysfunction in schizophrenia, with WM and executive function making separable contributions to cognitive impairment (50). Indeed, attentional filtering deficits are well-documented in psychosis and may underlie positive symptoms such as hallucinations and delusions, where irrelevant sensory information fails to be appropriately gated (51).

Substantial genetic overlap has been observed in schizophrenia and bipolar disorder (52). The common occurrence of psychosis in PSZ and PBD points to psychosis being an unspecific, transdiagnostic syndrome which may be rooted in shared genetic susceptibility (53, 54). Importantly, a gradient of polygenic risk across schizophrenia and bipolar disorder is indexed by the occurrence of psychosis, such that PBD with HPS+ score higher on the shared polygenic risk score value (55). Evidence of cognitive impairment among individuals at familial and/or clinical risk for psychosis and among first-degree relatives of PBD taken together with our findings indicate that early neurodevelopmental processes, rather than the experience of psychosis itself, likely play a role in the development of the cognitive deficits evident in our study (56). This is in line with similar neurodevelopmental trajectories shared between early-onset schizophrenia and pediatric-onset psychotic bipolar disorder (57). Crucially, it is still unclear if accelerated cognitive decline in psychotic disorders is due to neurodevelopmental and/or neurodegenerative aspects (15).

In addition, the majority of our patients were medicated at the time of study or were previously treated with second-generation antipsychotic medication. Therefore, we cannot rule out possible confounding anti-dopaminergic effects related to the anticholinergic burden of antipsychotic medications (58, 59), which is exacerbated in the elderly. Importantly however, an indicator of advanced brain aging in 5,000 PSZ based on structural properties was not associated with antipsychotic use and dose (60), and cognitive impairment has been observed in drug-naive PSZ as well as PBD in a multitude of studies (61, 62).

A crucial limitation for this study is that cross-sectional data were used and not longitudinal. This investigation served as a first insight into this topic, and we highly recommend collecting and evaluating longitudinal data in affected persons to thoroughly investigate the trajectories of cognitive performance across age. Furthermore, it would be possible to study other impacting factors such as changes in antipsychotic medication, efficacy of cognitive remediation strategies, illness stage etc. Other moderators that we did not include in the dataset could have been influential including the lifetime amount, frequency, duration of time since last and severity of psychotic episodes (8), as well as the functional capacity (63).

Due to possible similar underlying neural constructs, our results support the notion that certain pro-cognitive interventions to prevent aging of the brain in neurotypical individuals could also be helpful for patients at an earlier age.

For example, physical exercise has been shown to have positive effects for neurotypical populations as well as in PSZ (64–67). This is especially relevant, since to date findings of certain strategies are highly heterogeneous regarding efficacy in PBD and PSZ (68, 69). Another promising approach is transcranial direct current stimulation tDCS, which has been shown to improve WMC in older adults as well as PSZ (70, 71). Functional neuroimaging would also further elucidate the crucial brain regions and neurophysiological processes that are affected during different phases of aging.

In summary, our findings are indicative of lifetime history of psychosis altering the typical trajectory of cognitive aging across the schizo-bipolar spectrum, impacting specifically ACE-WM in younger adulthood. Shared genetic susceptibility specifically for psychosis could be underlying these findings. These results underscore the importance of further investigating cognitive processes transdiagnostically in order to implement treatment strategies to improve functional outcome across the lifespan in affected persons.

Declarations

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Conflict of Interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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Figures

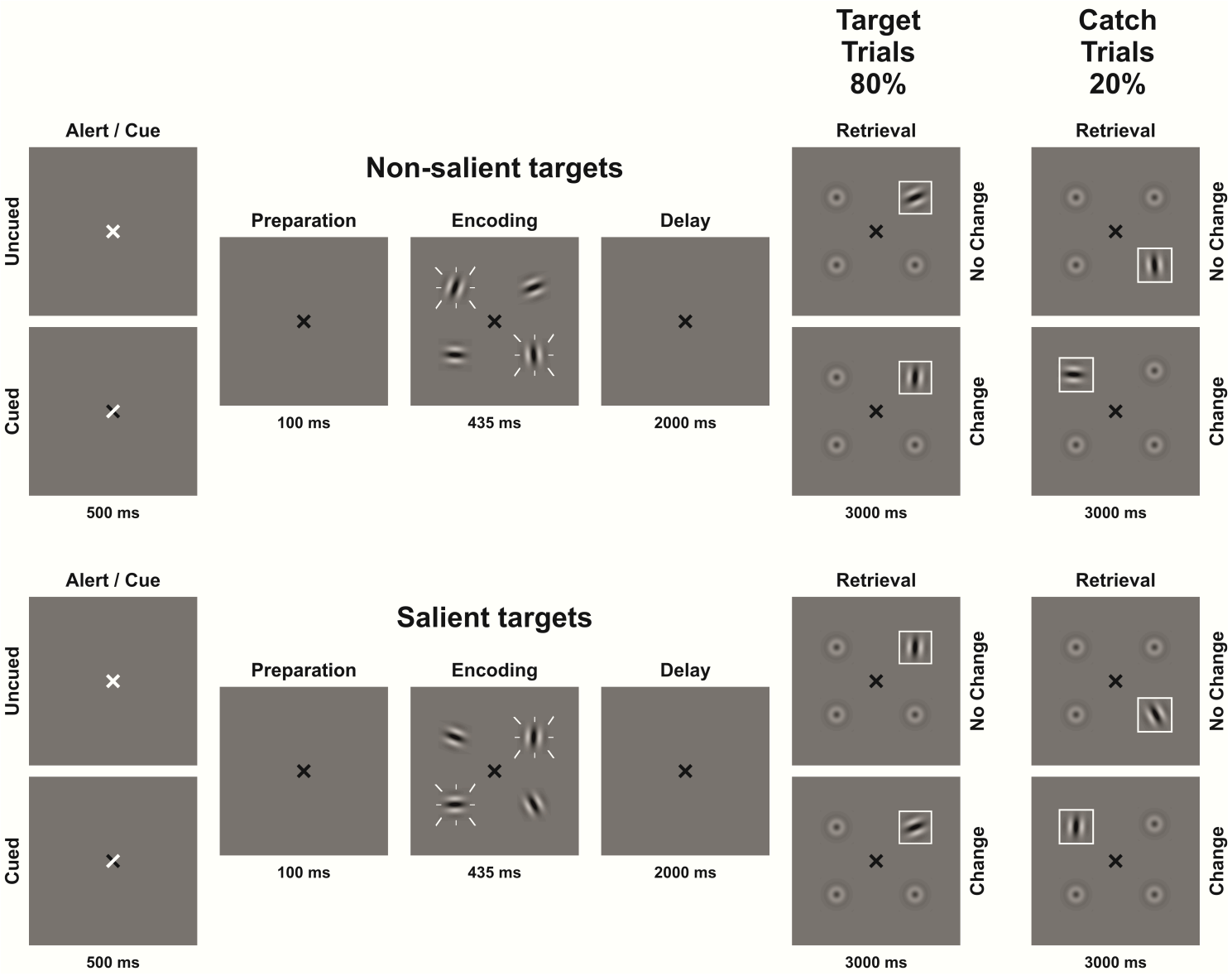


Figure 1

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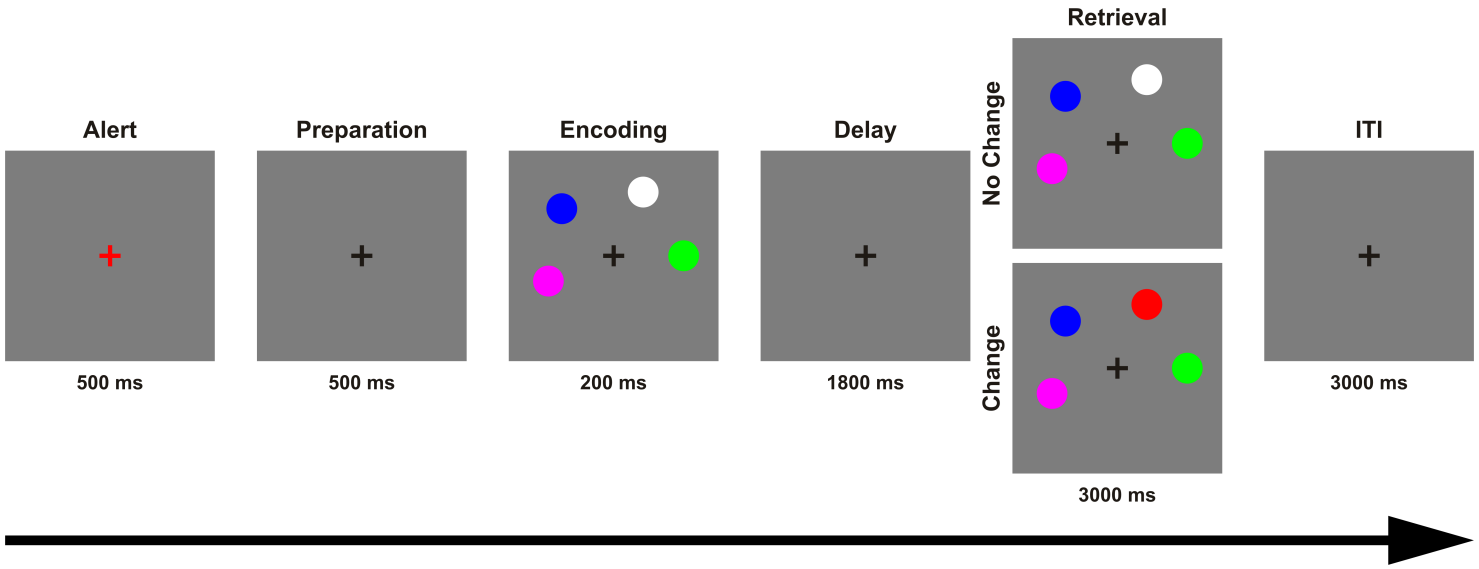


Figure 2

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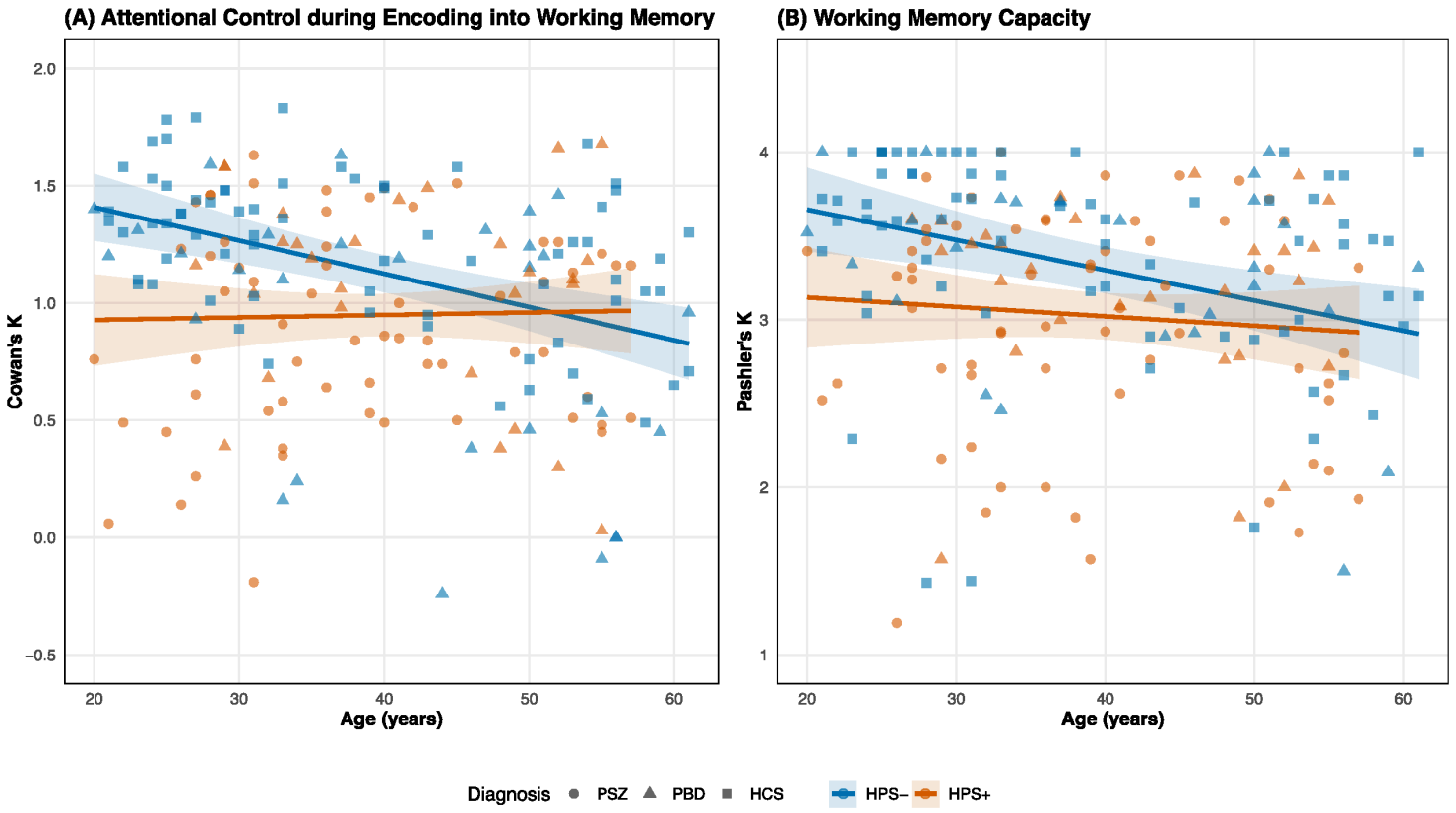


Figure 3

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