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The functional connectome of 3,4-methyldioxymethamphetamine-related declarative memory impairments

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Abstract

The chronic intake of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") bears a strong risk for sustained declarative memory impairments. Although such memory deficits have been repeatedly reported, their neurofunctional origin remains elusive. Therefore, we here investigate the neuronal basis of altered declarative memory in recurrent MDMA users at the level of brain connectivity. We examined a group of 44 chronic MDMA users and 41 demographically matched controls. Declarative memory performance was assessed by the Rey Auditory Verbal Learning Test and a visual associative learning test. To uncover alterations in the whole brain connectome between groups, we employed a data-driven multi-voxel pattern analysis (MVPA) approach on participants' resting-state functional magnetic resonance imaging data. Recent MDMA use was confirmed by hair analyses. MDMA users showed lower performance in delayed recall across tasks compared to well-matched controls with moderate-to-strong effect sizes. MVPA revealed a large cluster located in the left postcentral gyrus of global connectivity differences between groups. Post hoc seed-based connectivity analyses with this cluster unraveled hypoconnectivity to temporal areas belonging to the auditory network and hyperconnectivity to dorsal parietal regions belonging to the dorsal attention network in MDMA users. Seed-based connectivity strength was associated with verbal memory performance in the whole sample as well as with MDMA intake patterns in the user group. Our findings suggest

that functional underpinnings of MDMA-related memory impairments encompass altered patterns of multimodal sensory integration within auditory processing regions to a functional heteromodal connector hub, the left postcentral gyrus. In addition, hyperconnectivity in regions of a cognitive control network might indicate compensation for degraded sensory processing.

KEYWORDS
auditory network, cognitive control network, imaging, MDMA, memory consolidation, MVPA, serotonin, stimulants, verbal memory

1 | INTRODUCTION

3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") acutely acts on the brain by increasing the extracellular levels of 5-HT and norepinephrine, and to a lesser extent of dopamine (Lyles & Cadet, 2003), evoking its unique empathogenic and stimulant-like effects (Gamma et al., 2000). Repeated MDMA consumption in turn results in long-term 5-HTergic hypofunction, which was indicated by decreases in 5-HT reuptake transporter binding in humans (Müller et al., 2019). Furthermore, animal studies demonstrated inhibition of the 5-HT rate-limiting enzyme tryptophan hydroxylase after MDMA administration, resulting in lasting reductions of central 5-HT availability, and reduced 5-HT axon density in the hippocampus and other cortical areas (Green et al., 2003).

The cognitive profile of MDMA users is characterized by deficits in declarative memory (which includes semantic and episodic memory) (Kalechstein et al., 2007; Montgomery & Roberts, 2022). This is consistent with the idea of 5-HT being involved in mnemonic processes (Coray & Quednow, 2022; Meneses, 2017). At the molecular level, memory formation is characterized by functional strengthening of existing synapses and de novo synaptogenesis (Radwanska et al., 2011). Here, 5-HT is involved in protein synthesis and gene transcription for synaptic plasticity (Bailey et al., 2000) as well as in modulating the timing of coincident firing between glutamatergic neurons (Zeng et al., 2023). Consequently, the administration of MDMA in rodents has profound impacts on gene expression patterns and induces lasting synaptic reorganization within brain regions associated with learning and memory (Hemmerle et al., 2012; Petschner et al., 2018).

However, the functional underpinnings of MDMA-induced memory deficits in humans remain rather unexplored to date. One examination found decreased cortical glucose metabolism in recurrent MDMA users, which was correlated to verbal memory performance in bilateral frontal and parietal regions (Bosch et al., 2013). Task-based functional magnetic resonance imaging (fMRI) studies have revealed distinct patterns of brain activity in MDMA users during memory encoding or recall. Working memory was related to reduced activity in the cingulate cortex and temporal lobe, increased activity in the frontal cortex, and altered activity in the parietal lobe (Daumann et al., 2004). Episodic and prospective memory were associated with reduced left hippocampal activity (Daumann et al., 2005) and delayed memory retrieval with increased activity in the medial superior frontal gyrus, the thalamus, and in the hippocampus (Moeller et al., 2004). Semantic encoding was associated with greater activity in somatosensory areas, the supramarginal gyrus, and the angular gyrus (Watkins et al., 2013) (see (Roberts et al., 2018) for recent review). To date, however, resting-state functional connectivity (FC) has not been examined in chronic MDMA users before.

Resting-state FC has been previously related to memory performance and memory impairments (Gamboa et al., 2014). It allows the study of complex networks that are required for cognition in general and memory in particular (Suri et al., 2017). Moreover, intrinsic FC changes have been observed subsequent to the application of pharmacological challenges to the 5-HT system before (Conio et al., 2020; Grandjean et al., 2021). Specifically, the acute effects of MDMA on FC were understood through the distribution of 5-HT_{1A} receptors and serotonin transporters (Dipasquale et al., 2019). Here, we aimed to investigate whether functional networks and network interactions are impaired in MDMA users and how they relate to declarative memory tests. A whole-brain multi-voxel pattern analysis (MVPA) was performed to detect brain areas with different FC patterns in MDMA users compared to MDMA-naïve controls (Whitfield-Gabrieli & Nieto-Castanon, 2012). Resulting clusters were then used as unbiased seed regions to explore memory-associated FC differences between groups in post hoc seed-based analyses.

We expected to detect FC differences in regions that are innervated by 5-HTergic projections, enriched with 5-HTergic binding sites and typically recruited during declarative memory performance. Specifically, we predict FC differences in areas such as the medial temporal lobe, the hippocampus, or in neocortical processing regions, as these together form ensembles for storing newly formed declarative memories (Horner et al., 2015).

2 | MATERIALS AND METHODS

2.1 | Participants'

In total, 49 chronic MDMA users and 47 MDMA-naïve healthy controls (age: 18–45 years) were recruited for this cross-sectional case–control study. Diffusion tensor imaging, quantitative susceptibility mapping, and substance use data from this sample have been

published before (Zimmermann et al., 2022). The groups were matched regarding age, sex, verbal intelligence, years of education, and smoking status. MDMA users had to report a minimum of 25-lifetime occasions and at least one occasion of MDMA consumption within the past 4 months. We verified the subjective reports of consumption within the past 4 months by toxicological analyses of a 4 cm long hair strand (assessment methods are described in detail below). Participants' reporting a current or previous neurological disease or psychiatric Axis I disorder (except for MDMA use disorder in MDMA users), medical illness, head or spinal injury, history of heroin injection, daily cannabis consumption, a family history of schizophrenia, bipolar disorder, or obsessive-compulsive disorder were excluded. Further excluded were control participants' reporting more than 15 lifetime occasions of illegal substance use, except for cannabis. From the total sample ($n = 96$), five MDMA users and six MDMA-naïve controls were excluded. Within the user group, the reasons for exclusion were either no verification of MDMA consumption during the past 4 months ($n = 4$) or the diagnosis of an Axis I DSM-IV psychiatric disorder ($n = 1$). Controls had to be excluded because of the detection of residual MDMA in hairs ($n = 5$) or missing data ($n = 1$).

Participants' had to abstain from illegal substances at least 5 days before testing and from alcohol at least 24 h before testing, respectively. Compliance with these instructions was verified by urine drug testing. The study adhered to the principles of the Declaration of Helsinki and all participants' provided written informed consent prior to their participation. The study protocol was reviewed and approved by the Ethics Committee of the Canton Zurich (BASEC-Nr. 2018-02125).

2.2 | Substance use and clinical assessment

To objectively assess substance-use over the past 4 months, a toxicological hair analysis with liquid chromatography–tandem mass spectrometry (Scholz et al., 2021) was carried out by the Institute of Forensic Pharmacology and Toxicology, Zurich. This allowed the validation of MDMA-intake within the past 4 months in the MDMA-user group. Subjective history of current and lifetime substance consumption was inquired with a structured and standardized Interview for Psychotropic Drug Consumption (Quednow et al., 2004). Amounts and frequency of present and past consumption of all known psychotropic substances were quantified on this basis.

The Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) was used to screen for psychiatric disorders. Substance use disorders were assessed by the Structured Clinical Interview for DSM-5 Axis I diagnoses, Module E (First, 2014). For additional assessments of depressive symptoms and sleep disturbances the Center for Epidemiologic Studies Depression Scale (Eaton et al., 2004) was applied. Symptoms of attention deficit/hyperactivity disorder (ADHD) were assessed with the ADHD Self-Rating Scale (Rösler et al., 2004). Verbal IQ was estimated by a German vocabulary test (Mehrfachwahl-Wortschatz-Intelligenztest) (Lehrl et al., 1995).

Self-reported MDMA amounts assessed with the *Psychotropic Drug Consumption Interview* were summarized to four representative scores. Those included (1) *consumption within the past 12 months*, (2) *lifetime consumption*, (3) *maximal intake within a week*, and (4) *days since the last consumption*. Specifically, all scores were z-transformed first, and next, the summarized scores were calculated as follows: (1) *MDMA consumption within the past 12 months* = (MDMA occasions within the last 12 months + gram per occasion)/2, (2) *lifetime consumption* = (years of use + lifetime gram + lifetime occasions)/3, (3) *maximal intake within a short timeframe* = (max gram per week + max occasions per week + max gram per day)/3, and (4) *days since the last consumption constituted another score*. To control for substance co-consumption, a further covariate was calculated (after z-transforming the respective variables) as follows: (∑(lifetime amounts + gram per occasion intaken within the last 12 months) for cannabis, amphetamine, and cocaine)/6 + (∑(lifetime occasions + occasions within the last 12 months) for cannabis, amphetamine, and cocaine)/6.

2.3 | RAVLT

The RAVLT consists of a list of 15 noun words (list A) read aloud to participants' a total of five times in the same order (encoding phase, trials 1–5). This is followed by the presentation of an interference list (15 additional nouns) and three delayed recall timepoints: after the interference (short-term recall, trial 6), after 2 h (delayed recall, trial 7), and on the next day after 24 h (delayed recall, trial 8). Word recognition was measured at both delayed recall timepoints by a list of words containing 35 distractor words and the 15 learned noun words (Bean, 2011).

To define verbal long-term memory for further analyses, sum scores of totally remembered words in the delayed recall phase (*T-recall* = trial7 + trial8), totally forgotten words (*T-forgot* = ((trial5–trial7) + (trial5–trial8)), and for chance corrected totally recognized words (*T-recognition* = (Recognition_ListA/15-(False_Alarm_ListA + False_Alarm_ListB)/20 + 1) × 0.5 + (Recognition_ListB/15-(False_Alarm_ListA + False_Alarm_ListA)/20 + 1) × 0.5) were calculated. To define verbal short-term memory, a score reflecting the loss of words after the interference task (*Interference-loss* = trial6–trial5) was built. In addition, recall consistency over learning trials was defined (*Recall-consistency* = 100/(∑trials 1–4)) × (∑conjoint recalls of words between trials 1, 2; trials 2, 3; trials 3, 4; trials 4, 5) (Quednow et al., 2006).

2.4 | Animal movie task

This task was developed for assessing visual associative learning and memory functions, piloted, and published before (Schneider et al., 2019). A clip featured five animals that were crossing the scene one-by-one from left to right or vice versa. In total, four such clips were presented to each participant. A hiding-place was located within the center of each scene where crossing animals disappeared and were no longer visible to the observer. Animals either passed directly through the hiding-place and left the scene or they could rest there for a certain time. While one animal lingered in the hiding place, other

animals could enter the scene and the hiding place, thus some animals encountered each other in the hiding place and others did not. The encoding task for participants' was to memorize the temporal overlaps of animals inside the hiding-place; this instruction was provided at beginning. After each clip, there was a quiet rest period of 40 s. The short rest period allows for short-term consolidation. The movies were shown twice in a row. After the second rest period of 40 s, the retrieval task followed, where 10 different pairs of animals were presented consecutively, covering each possible combination. Participants' were asked to decide for each pair whether the depicted animals met inside the hiding-place or not in a forced-choice task.

2.5 | MRI acquisition

Imaging data were collected on a 3 T Philips Intera Achieva scanner (Philips Medical Systems, Best, The Netherlands) during a 10 min eyes-closed resting state fMRI scan. Whole-brain multiband echo-planar imaging (EPI) acquisitions were carried out with a 32-element phased-array receive head coil using a gradient-echo EPI sequence with TR = 2 s, TE = 35 ms, FA = 82°. Thirty-two slides were acquired (4 mm; in-plane resolution 2.75 × 2.75 mm) in sequential order, with orientation parallel to AC–PC plane. Anatomical images were acquired using a T1-weighted three-dimensional turbo field-echo sequence (170 sagittal slices of 1-mm thickness; in-plane resolution 1 × 1 mm; TR = 9.9 s; TE = 4.6 ms; and FA = 81°).

2.6 | Study procedure

Participants' were recruited by online advertisement and underwent an examination on two consecutive days at the Psychiatric University Hospital, Zurich. First, participants' were informed about the study and their right to withdraw at any time before they signed the consent form. Next, a comprehensive screening and clinical assessment was carried out, followed by the hair sample collection. Afterward, the first part of the two memory tests was presented (see above). Subsequently, the MRI examination was executed, which lasted approximately 2 h. At the end of the first day, participants' were asked to recall the list of words learned in the RAVLT (delayed recall after 2 h). The second day was continued with several behavioral tasks measuring reward processing, social cognition (which will be published elsewhere) and the delayed memory recalls of both memory tests (delayed recalls after 24 h). The test sessions lasted approximately 4 h per day. Drug abstinence was monitored by urine drug testing at the beginning of both test days. Participants' were compensated after completing all tasks with a monetary reward.

2.7 | MRI preprocessing

Preprocessing of each individual's EPI volumes was performed using the FMRI Expert Analysis Tool, which is a part of FSL (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl, v6.0). Preprocessing steps included motion correction (Jenkinson et al., 2002), realignment, spatial smoothing with a 5 mm Gaussian kernel (full-width-at-half-maximum), and temporal high-pass filtering (100 s). On the high-resolution T1-weighted structural images, the brain extraction tool (Smith, 2002) was applied. EPI volumes were then co-registered to their corresponding high-resolution T1-weighted images using boundary-based registration (FLIRT) (Jenkinson et al., 2002). A multivariate exploratory linear optimized decomposition into independent components (MELODIC) was conducted (with "automatic dimensionality estimation" option) to decompose individual preprocessed 4D data sets into spatial and temporal components. Next, the data sets derived from MELODIC were denoised using FMRIB's Independent Component Analysis-based X-noiseifier (FIX) (Griffanti et al., 2014). The FIX classifier was trained by manually labeled, subject-level independent component analysis data from a random sample of 11 subjects of each group (MDMA users and controls) and then applied to all subjects with a threshold of 20. We have taken the more conservative nonaggressive approach for FIX cleanup, to avoid removing variance of interest from the data (Griffanti et al., 2014).

FIX cleaned individual EPI volumes were then imported into the CONN toolbox (www.nitrc.org/projects/conn) (Whitfield-Gabrieli & Nieto-Castanon, 2012). Functional and anatomical data were normalized into standard Montreal Neurological Institute (MNI) space and segmented into gray matter, white matter, and CSF tissue classes using CONN built in preprocessing steps which rely on the Statistical parametric mapping (SPM12) unified segmentation and normalization procedure (Ashburner & Friston, 2005). In the first-level analysis, nuisance regressors included subject-specific cerebral white matter and CSF parameters derived using the CONN-implemented CompCor method. In addition, 16 motion parameters (Friston et al., 1996) and scrubbing parameters for outlier volumes were estimated (Power et al., 2014). These noise components were removed separately for each voxel and each subject by application of Ordinary Least Squares regression. Finally, EPI volumes were band-pass filtered (0.008–0.1 Hz).

2.8 | Multivariate pattern analysis

To capture differences in the brain-wide resting-state connectome between MDMA users and well-matched controls, we employed a data-driven and unbiased whole-brain MVPA approach. MVPA advantages the capability of detecting even subtle group-differences in connectome-wide FC patterns between each voxel and the rest of the brain (Nieto-Castanon, 2020; Nieto-Castanon, 2022). This whole-brain connectome approach has been well validated (Wang et al., 2019) and demonstrates a reduced potential of false negatives compared to principal component analyses or independent component analyses (Nieto-Castanon, 2022; Whitfield-Gabrieli & Nieto-Castanon, 2012). Clusters revealed by MVPA were then used as seed points of interest to explore the topography and direction of FC differences between groups in association with differences in memory

performance, as well as recent and lifetime amounts of MDMA intake in the user group (Katsumi & Moore, 2022). In contrast to a priori seed regions definition, this method is particularly powerful to characterize anatomically unconstrained and specific aspects of FC differences (Nieto-Castanon, 2022).

At the first-level, MVPA computes the BOLD time-series average of each voxel between every pair of voxels, yielding a concatenated matrix of M (number of participants') × N (number of voxels) for each single voxel (Mateu-Estivill et al., 2021). The dimensions of these multivariate patterns were then reduced with a principal component analysis extracting 64 components separately for each subject. This is a form of subject-level dimensionality reduction typically used in other established whole–brain data-driven approaches as a first step to reduce the complexity of the subsequent analyses (Guell et al., 2020). The six strongest components, explaining the most variance, were retained from the principal component decomposition and taken to the group-level for an omnibus *F* test using the MDMA > controls contrast. In this second-level analysis, age and handedness were included as covariates. The number of components was chosen following conventions from previous investigations (Thompson et al., 2016) and only clusters surviving a height threshold of $p < .001$ and FDR cluster-level threshold of $p < .05$ were taken for post hoc analyses. The MVPA-derived clusters of interest were then used as seed regions of interest (ROIs) to explore seed-based FC differences between groups. The analysis was again controlled for age and handedness. For this, Pearson's cross-correlation coefficients between the averaged time courses of each ROI and all other voxels in the brain were computed and z-transformed by Fisher's transformation (Nieto-Castanon, 2020; Whitfield-Gabrieli & Nieto-Castanon, 2012). Those subject-specific z-maps which differed between groups were then submitted to partial correlation analyses to define memory performance in association with FC, including age and years of education as covariates. The same analysis, with age as covariate, was performed within the user group only to define the association between past and current MDMA consumption and FC strength.

2.9 | Mapping with functional atlases

To map clusters resulting from post hoc seed based connectivity analyses to functional networks, we used the network atlas from Smith (Smith et al., 2009). Clusters were first transformed into the FSL-MNI space using the FLIRT function applyXFM (Jenkinson et al., 2002). Next, the command fslcc included in Fslutils was applied to run cross-correlations between every 4D volume and the atlas volume with a threshold of 0.04. In addition, we mapped peak activity of clusters by eye inspection to the Yeo-Schaefer atlas (Schaefer et al., 2018).

2.10 | Statistical analyses

Linear mixed effect (LME) models were used to analyze repeated recalls in memory tests (*lme4* package, v. 1.1-18-1) (Bates et al., 2014) in R (v. 3.5.2) (Team RC, 2021). LME models were fit by maximum likelihood estimation and *p*-values were obtained by Satterthwaite's approximation to the denominator degrees of freedom (lmerTest package, v.3.0–1) (Kuznetsova et al., 2017). ANCOVAS were calculated using the car package (v. 3.0.12) (Fox et al., 2012) and type three sums of squares. Box-Cox transformations were carried out using the MASS package (v. 7.3.54) (Venables & Ripley, 2013) and partial Spearman correlations with the ppcor package (v. 1.1) (Kim, 2015). Graphics were produced with the ggplot2 package (v. 3.3.5) (Wickham, 2016).

3 | RESULTS

The final sample for the resting-state fMRI analyses consisted of 44 MDMA users and 41 MDMA-naïve controls. The demographic comparisons revealed close matching between the groups regarding age, years of school, verbal IQ, and current nicotine use (except lifetime cigarettes). The groups were relatively similar in the extent of alcohol consumption, except that MDMA users drank more per occasion and had a higher lifetime amount. However, the groups differed in the amounts of cannabis, cocaine, and amphetamine use (Table 1). Groups did not differ regarding ADHD and depressive symptoms, as well as sleep quality measurements (Supplementary Table 1).

3.1 | RAVLT

Regarding the RAVLT delayed recall, data of one user and one control was missing. For the RAVLT recognition tests, data of two users was missing.

In the first analysis, two separate linear mixed models were conducted, one for the learning trials (trials 1–5) and one for the free recall trials (trials 6–8). Trials were used as a within-subject variable and the between-subject variable was group. Total years of education and age were included as covariates into the model, to account for age-related memory decline and preexisting differences in learning abilities.

For the first model (trials 1–5), there was a strong main effect of trial ($F_{[1,\ 81]} = 253.95$, $p < .001$, $\eta^2p = 0.75$), reflecting the improvement in performance over learning trials for both groups. The MDMA users' learning performance was slightly but not significantly worse ($F_{[1,\ 81]} = 3.21$, $p = .077$, $\eta^2p = 0.04$). The interaction trial × group was not significant. In addition, there was an effect of total years of education ($F_{[1,\ 81]} = 6.06$, $p = .016$, $\eta^2p = .07$) but no effect of age.

The second model (trials 6–8) examined differences between groups after the interference list and the delayed recalls. The strong effect of trial ($F_{[2163]} = 14.49$, $p < .001$, $\eta^2p = 0.96$) reflects the decrease in memory performance with time. There was a strong main effect of group ($F_{[1,\ 81]} = 16.49$, $p < .001$, $\eta^2p = 0.17$) but no effect of the interaction trial × group, suggesting a worse delayed recall performance for MDMA users in general. In addition, the analysis yielded a significant effect for total years of education ($F_{[1,\ 81]} = 9.80$, $p = .002$, $\eta^2p = 0.89$), whereas no effect was obtained for age.

TABLE 1 Sociodemographic characteristics and substance use.

	Controls	MDMA users		
	N = 41	*N* = 44	Statistic	*p*-Value
Sex			$X^2 = 0$	1
Male	44%	43%		
Female	56%	57%		
Age	30 (±7)	30 (±7)	$t = 0.074$	.941
Years of school	10 (±1)	10 (±1)	$U = 767$	.188
Verbal IQ	105 (±10)	102 (±10)	$U = 1084$	.110
Alcohol				
Used in the past 12 months	*N* = 35	*N* = 44	$X^2 = 4.88$	**.027**
Amount (g) per occasion	37 (±62)	66 (±44)	$U = 429$	**<.001**
Occasions/12 months.	108 (±90)	113 (±90)	$U = 893$	.940
Used during lft.	*N* = 38	*N* = 44	$X^2 = 1.53$	.216
Amount lft. (kg)	94 (±138)	154 (±206)	$U = 679$	**.050**
Occasion lft.	1742 (±1951)	1710 (±1750)	$U = 873$	.802
Years of use	12 (±8)	14 (±7)	$t = 1.01$	.315
Nicotine				
Used in the past 12 months	*N* = 23	*N* = 30	$X^2 = 0.86$	.355
Daily cigarettes/12 months.	3 (±5)	4.4 (±6.2)	$U = 742$	.149
Cigarettes/12 months.	1084 (±1954)	1609 (±2295)	$U = 742$	.149
Used during lft.	*N* = 28	*N* = 35	$X^2 = 0.88$	.349
Cigarettes lft.	20,174 (±36,400)	41,920 (±69,400)	$U = 671$	**.040**
Years of use	7 (±8)	10 (±9)	$U = 730$	.127
MDMA				
Amount (g) per occasion	0.00 (±0.00)	0.28 (±0.19)		
Occasions/12 months.	0.12 (±0.64)	21.1 (±21.6)		
Amount lft. (g)	0.02 (±0.09)	91 (±148)		
Occasion lft.	0.1 (±0.6)	261 (±296)		
Years of use	0.00 (±0.00)	9 (±6)		
Max amount per week (g) lft.	0.00 (±0.00)	0.34 (±0.37)		
Days since last intake	135 (±610)	22 (±18)		
Hair conc. (pg/mg)	0.5 (±2.3)	4828 (±13,185)		
Cannabis				
Used in the past 12 months	*N* = 12	*N* = 28	$X^2 = 8.73$	**.003**
Amount (g) per occasion	0.06 (±0.13)	0.18 (±0.25)	$U = 571$	**.002**
Occasions/12 months.	15 (±42)	32 (±69)	$U = 594$	**.003**
Used during lft.	*N* = 27	*N* = 39	$X^2 = 5.10$	**.023**
Amount lft. (g)	223 (±606)	734 (±1125)	$U = 527$	**<.001**
Occasion lft.	679 (±1949)	1099 (±1342)	$U = 533$	**.001**
Years of use	5 (±7)	9 (±8)	$U = 560$	**.002**
THC hair conc. (pg/mg)	1 (±5)	10.7 (±25.6)	$U = 693$	**.007**
Cocaine				
Used in the past 12 months	*N* = 3	*N* = 30	$X^2 = 30.6$	**<.001**
Amount (g) per occasion	0.01 (±0.02)	0.37 (±0.42)	$U = 313$	**<.001**
Occasions/12 months.	0.12 (±0.51)	8.83 (±18.7)	$U = 330$	**<.001**
Used during lft.	*N* = 7	*N* = 34	$X^2 = 28.4$	**<.001**
Amount lft. (g)	0.03 (±0.09)	37.4 (±85.2)	$U = 262$	**<.001**

TABLE 1 (Continued)

	Controls	MDMA users		
	N = 41	*N* = 44	Statistic	*p*-Value
Occasion lft.	0.37 (±1.04)	92.7 (±250.5)	$U = 264$	**<.001**
Years of use	0.00 (±0.00)	4 (±6)	$U = 472$	**<.001**
Hair conc. (pg/mg)	6.66 (±31.2)	4766 (±25,999)	$U = 334$	**<.001**
Amphetamine				
Used in the past 12 months	$N = 0$	$N = 25$	$X^2 = 30.3$	**<.001**
Amount (g) per occasion	0 (±0.0)	0.17 (±0.25)	$U = 390$	**<.001**
Occasions/12 months.	0 (±0.0)	6 (±14)	$U = 390$	**<.001**
Used during lft.	$N = 2$	$N = 36$	$X^2 = 47.8$	**<.001**
Amount lft. (g)	0.01 (±0.03)	103 (±342)	$U = 180$	**<.0010**
Occasion lft.	0.07 (±0.35)	109 (±274)	$U = 182$	**<.001**
Years of use	0 (±0.0)	5 (±7)	$U = 492$	**<.001**
Hair conc. (pg/mg)	3.73 (±19.1)	171 (±418)	$U = 455$	**<.001**

Note: *N* = number of participants'. Mean for *t* test, median for Mann–Whitney *U* test is shown. Standard deviation is shown in parentheses. Percentage of participants' sex is shown, chi-quadrat test for difference of proportions. Lft = lifetime. Amount = average gram per occasion within the last 12 months. Occasions = number of occasions within the last 12 months. Used during lft. = number of participants reporting having used the substance. Amount lft. amount = cumulative lifetime use in gram or kilograms. Occasion lft. = cumulative occasions in lifetime. *p*-Value is based on Mann–Whitney *U* tests, *t* test, or chi-quadrat test. Bold values indicate statistically significant result (< .05).
Abbreviation: THC, tetrahydrocannabinol.

For each summarized score, an ANCOVA was conducted to examine differences between groups after controlling for age and years of education (Figure 1). If necessary, dependent variables were Box-Cox transformed to achieve a normal distribution of the residuals. This was done for *T-recall* and *T-recognition*. For *Recall-consistency* and *Interference-loss*, we could not achieve a normal distribution of the model residuals despite trying out various approaches (Box-Cox-, log-, and square root transformations). Therefore, a Wilcox test (without control variables) is additionally reported for each. To test, whether memory performance is different between woman and men, the same ANCOVAS were conducted with the additional factor *Sex* (Supplementary Table 2).

ANCOVAS yielded robust group differences for *Interference-loss* ($F_{[1,\ 80]} = 11.01$, $p = .003$, $\eta^2p = 0.10$), *Recall-consistency* ($F_{[1,\ 81]} = 10.98$, $p = .001$, $\eta^2p = 0.11$), *T-recall* ($F_{[1,\ 79]} = 19.44$, $p < .001$, $\eta^2p = 0.17$), *T-forgot* ($F_{[1,\ 79]} = 15.33$, $p < .001$, $\eta^2p = 0.14$) and *T-recognition* ($F_{[1,\ 79]} = 13.48$, $p = .001$, $\eta^2p = 0.12$). Results of the Wilcox tests confirmed group differences for the non-normally distributed variables *Recall-consistency* ($W = 1303$, $p < .001$, $r = .38$) and *Interference-loss* ($W = 609$, $p = .009$, $r = .29$). Memory performance in the RAVLT did not significantly differ between women and men (Supplementary Table 2).

3.2 | Animal movies task

Data of two users was missing from the animal movies task.

The ANCOVA for delayed recall revealed group differences when controlling for age and years of education ($F_{[1,\ 79]} = 5.75$, $p = .019$, $\eta^2p = 0.05$), whereas no differences were found for immediate retrieval. To account for the 50% chance of getting a correct answer by guessing, we created the *Twice-known* score. This score included the number of the pairs of animals that had been remembered correctly twice, at immediate retrieval and delayed recall. We considered the pairs that had been known twice as truly learned animal pairs (correctly encoded and correctly remembered). The ANCOVA with *Twice-known* animal pairs as dependent variable yielded a significant group difference ($F_{[1,\ 79]} = 6.72$, $p = .011$, $\eta^2p = 0.07$) after controlling for age and total years of education (Figure 1). Also, memory performance in the animals movie task was not significantly different between sexes (Supplementary Table 2).

3.3 | MVPA results

After the PCA decomposition of six factors, an *F*-test was performed on the extracted components. The MVPA revealed two clusters of connectivity differences between groups. The larger cluster was located in the left postcentral gyrus (LPCG; cluster A [−48 −24 +46]; $p < .0001$ FDR, $k = 109$). The smaller cluster was located in the right precentral gyrus (cluster B [+46 −06 +38]; $p = .046$ FDR, $k = 20$). Details of clusters are reported in Table 2 and are depicted in Figure 2. For post hoc seed-based connectivity analyses, only the cluster located in the LPCG was used, since the second cluster was rather small and statistically less robust. Nevertheless, for the interested reader, the results of a seed-based analysis with the cluster located in the right precentral gyrus are reported in the supplementary material (Supplementary Table 3 and Supplementary Figure 1).

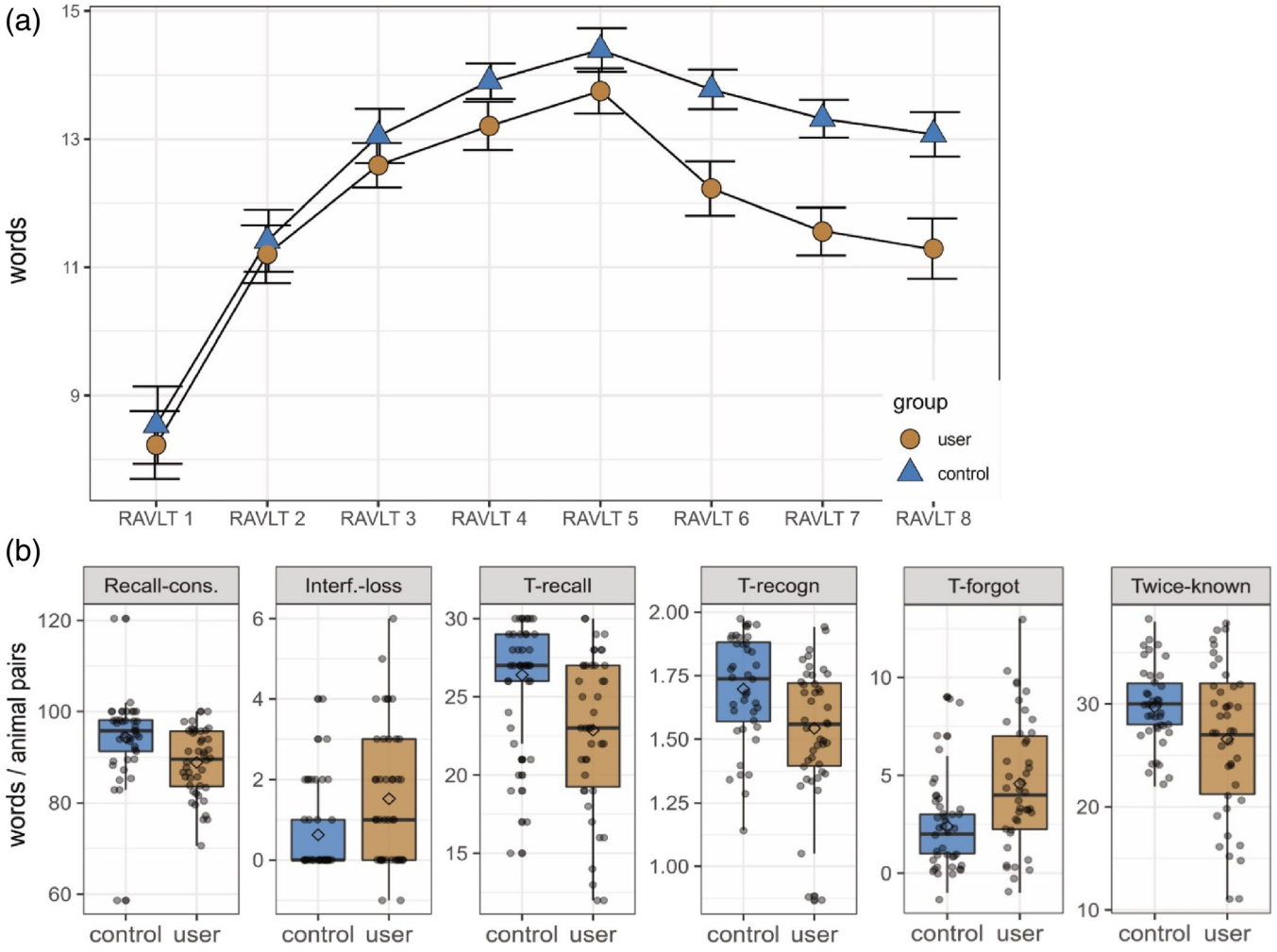

FIGURE 1 (a) Learning curve (RAVLT 1 – RAVLT 5), recall after interference (RAVLT 6), and delayed recalls (2 h: RAVLT 7, 24 h: RAVLT 8). Error bars represent within-subject standard errors. (b) Boxplots of calculated sum scores. From left to right: recall-consistency, recalled words after the interference list, total words at delayed recalls, chance corrected totally recognized words, totally forgotten words, and twice-known animal pairs. Octahedron represents group mean.

TABLE 2 MVPA derived clusters.

Cluster	Cluster coordinates			BA	Location (AAL)	Network	*k*	Size *p*-uncorrected	Size *p*-FDR corrected
A	−48	−24	+46	3	LPCG/L inferior parietal lobule	Dorsal attention, boarder to somatomotor	109	<.0001	<.0001
B	+46	−06	+38	4	R precentral gyrus	No network label	20	0.001	.046

Note: Cluster coordinates are in MNI space. Networks derived from Schaefer-Yeo atlas (400 parcels).
Abbreviations: AAL, automated anatomical labeling atlas; BA, Brodmann area; K, cluster size; L, left; LPCG, left postcentral gyrus; MNI, Montreal Neurological Institute; MVPA, multi-voxel pattern analysis; R, right.

3.4 | Post hoc seed-to-voxel analysis of MVPA-derived clusters

Post hoc seed-to-voxel analysis using the MVPA-derived cluster ($k = 109$) as a seed revealed several cortical bilateral symmetric clusters of hypo- and hyperconnectivity in MDMA users when compared to MDMA-naïve controls. Age and handedness were included as second-level covariates. Details are shown in Figure 3 and tabulated in Table 3. Clusters that exhibited higher FC to LPCG in MDMA users corresponded to the dorsal attentional network (or the visual network for occipital regions) according to the Schaefer-Yeo atlas (400 plots (Schaefer et al., 2018)) or correlated most strongly with the dorsal attention and somatomotor networks according to the Smith atlas (Smith et al., 2009). Clusters that showed lower FC to the LPCG in MDMA users corresponded to the auditory network according to both atlases (also named temporoparietal network).

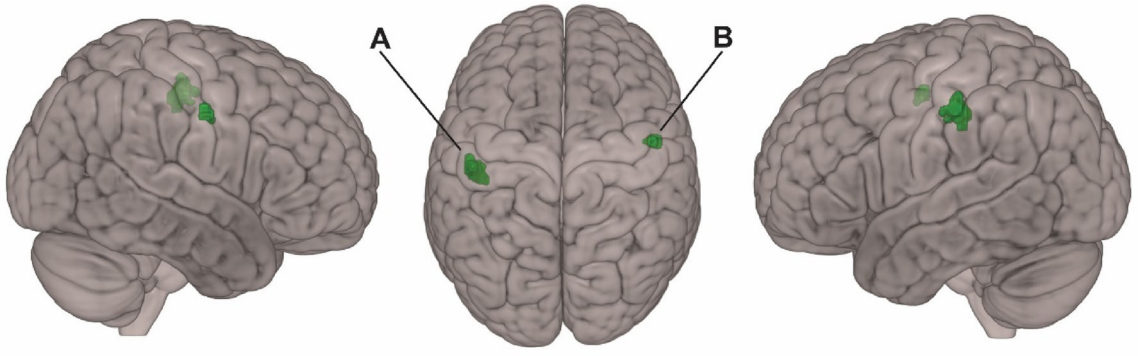

FIGURE 2 Whole-brain multi-voxel pattern analysis (MVPA) derived clusters (3,4-methylenedioxymethamphetamine [MDMA] users > controls). Clusters are FDR corrected ($p < .0001$ and $p = .046$, respectively).

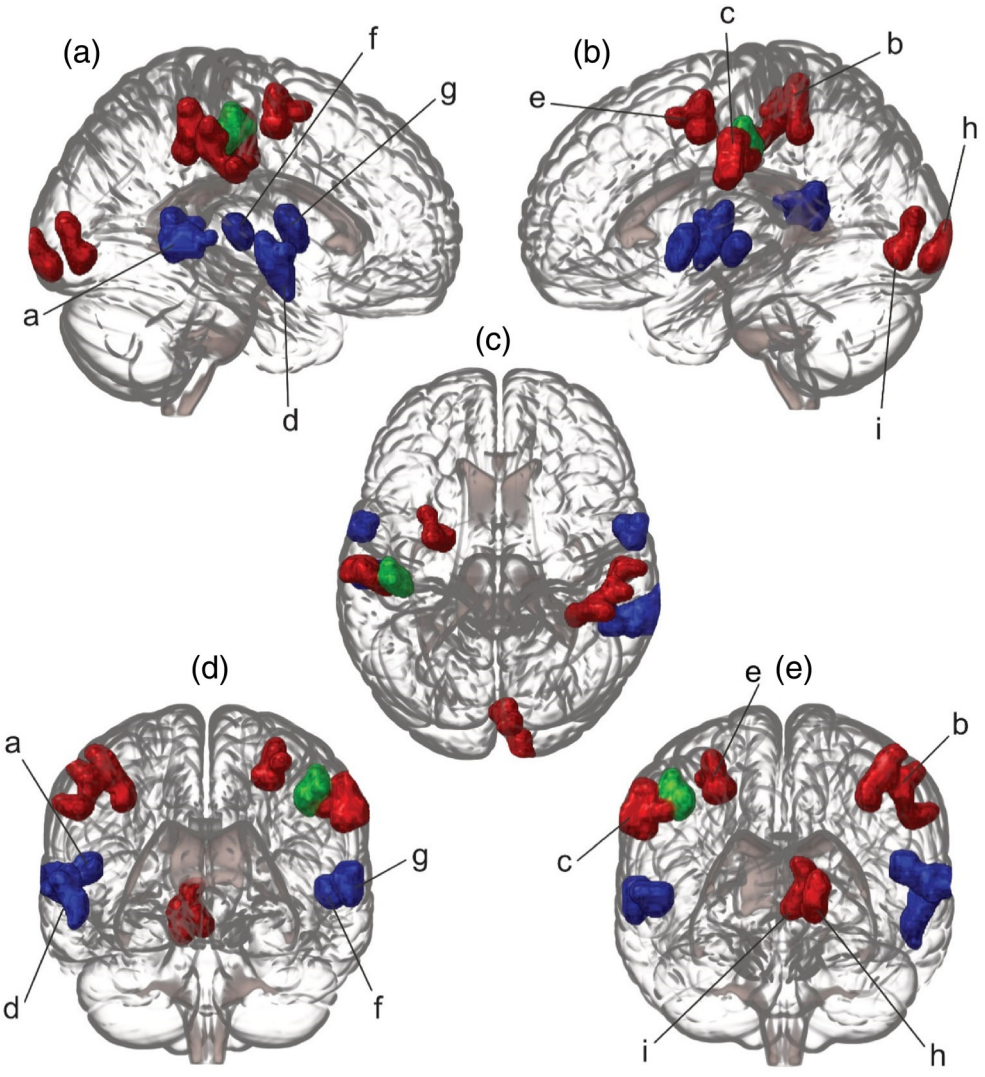

FIGURE 3 Post hoc seed-based functional connectivity (FC) using the multi-voxel pattern analysis (MVPA)-derived cluster (3,4-methylenedioxymethamphetamine [MDMA] users > controls) located in the left postcentral gyrus (LPCG) (−48, −24, 46; $k = 109$) as seed. *Green*: seed region. *Blue*: clusters showing less correlation with seed region in MDMA users compared to controls. *Red*: clusters showing more correlation with seed region. *A*: right side view. *B*: left side view. *C*: superior view. *D*: anterior view. *E*: posterior view.

3.5 | Memory-associated FC

In order to assess the relations between FC and memory performance, partial Spearman correlations between the z-scores obtained by the seed-based connectivity analysis (Table 3) and the memory scores were calculated. Age and years of education were controlled for in the partial correlation analysis (Figure 4, Supplementary Table 4 and Supplementary Figure 2). Z-scores represent the level of FC between

TABLE 3 Results post hoc seed-based analysis.

Cluster	Cluster coordinates (MNI)			BA	Location (AAL)	Network Schaefer/Smith	*k*	*p*-uncorr.	*p*-FDR corr.
a	+64	−38	+10	22	R mid temporal G, temporo-occipital part/ inf post supramarginal G	Auditory or temporal parietal	258	<.0001	<.0001
b	+44	−38	+54	2, (40)	R sup postcentral G/supramarginal G/S intraparietalis	Dorsal attention (somatomotor)	253	<.0001	<.0001
c	−60	−22	+44	3, (2, 43, 48)	L sup supramarginal G/S postcentralis	Dorsal attention (somatomotor)	218	<.0001	<.0001
d	+60	−04	+02	48, (21, 22, 38)	R ant sup temporal G/planum polare	Auditory or temporal parietal	156	<.0001	0.001
e	−28	−04	+46	6	L mid frontal G/L precentral G/S superior frontalis	Dorsal attention (somatomotor)	75	0.002	0.032
f	−52	−22	00	22, (21, 48)	L planum temporale	Auditory or temporal parietal	69	0.003	0.032
g	−62	−02	+06	48, (21)	L sup temporal G/L rolandic operculum	Auditory or temporal parietal	69	0.003	0.032
h	14	−102	−4	17	R occipital pole	Visual/dorsal attention/ somatomotor	63	0.004	0.040
i	4	−86	6	17	R lingual G/R occipital pole	Visual/dorsal attention/ somatomotor	58	0.005	0.050

Note: Cluster coordinates are in MNI space.
Abbreviations: AAL, automated anatomical labeling atlas; ant, anterior; BA, Brodmann area; G, gyrus; inf, inferior; L, left.; Mid, middle; post, posterior; R, right; S, sulcus; sup, superior.

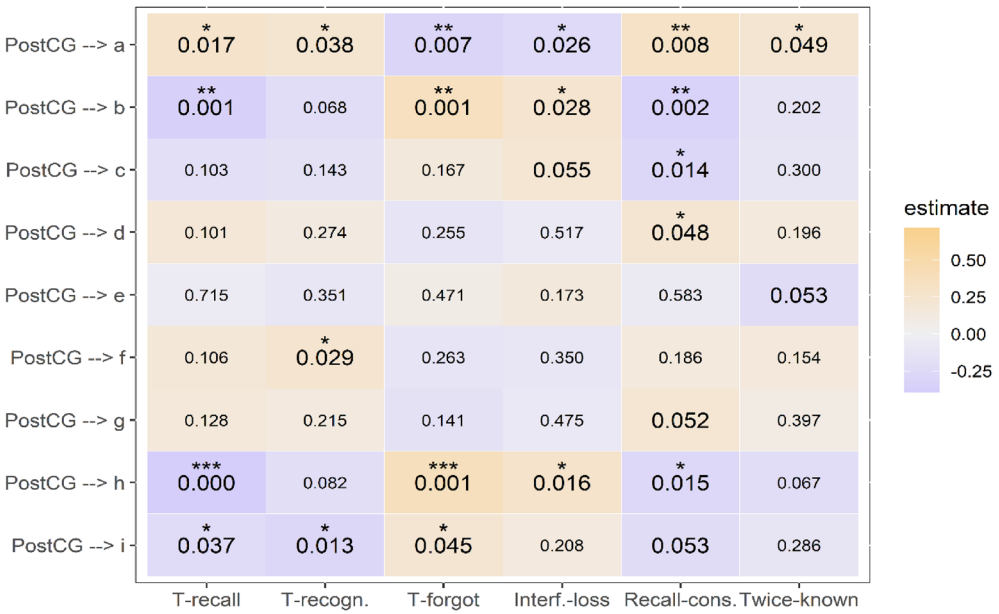

FIGURE 4 *p*-Values of Spearman partial correlations between z-scores of seed-based connectivity and memory scores. *Seed*: left postcentral gyrus (LPCG). Age and years of education are controlled for. *Blue*: positive correlation with memory performance. *Red*: negative correlation with memory performance. *Cluster a* = right middle temporal gyrus, temporo-occipital part. *Cluster b* = right superior postcentral gyrus and supramarginal gyrus. *Cluster c* = left supramarginal gyrus. *Cluster d* = right anterior superior temporal gyrus and planum polare. *Cluster e* = left middle frontal gyrus and precentral gyrus. *Cluster f* = left planum temporale. *Cluster g* = left superior temporal gyrus and rolandic operculum. *Cluster h* = right occipital pole. *Cluster i* = right lingual gyrus and occipital pole. Results are not corrected for multiple comparisons. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

the seed ROI and a certain cluster in the brain. Those were derived by Fisher-transformations of the bivariate correlation coefficients between the seed ROI timeseries and the voxel BOLD timeseries of the specific cluster (Nieto-Castanon, 2020).

All memory scores were correlated to the z-score of the LPCG and *cluster a*. This indicates that stronger FC between those two regions was associated with better memory performance. Moreover, *recall-consistency* was positively associated with *cluster d* and *T-recognition* was positively associated with *cluster f*. Significant negative correlations between z-scores and verbal memory performance were found for several clusters located within the dorsal attention network or the visual network, respectively. Specifically, all RAVLT scores (except *T-recognition*) were negatively correlated to the z-score reflecting the FC between the LPCG and *cluster b*, indicating worse short- and long-term memory performance with stronger FC. In addition, stronger FC with *cluster c* resulted in deteriorated *recall-consistency*, suggesting worse memory organization. Interestingly, we observed strong associations between several RAVLT scores and both visual areas (*cluster h* and *cluster i*), indicating worse short- and long-term verbal memory and memory organization with stronger FC.

3.6 | MDMA-associated FC

We used partial Spearman rank correlations within the MDMA user group only to assess the relationship between FC scores and the four calculated scores, since variables were not normally distributed (Supplementary Figure 3). All correlations were controlled for age and substance co-consumption. *Cluster f* was related to *MDMA consumption within the last 12 months* and the *maximal intake within a week* (12 months: $r_s = -.34$, $p = .001$; max. consumed: $r_s = -.30$, $p = .004$). *Cluster a* was associated with *lifetime consumption* ($r_s = -.23$, $p = .035$). *Clusters d*, *e*, and *g* were correlated with the time since the last consumption (*cluster d*: $r_s = -.31$, $p = .003$; *cluster e*: $r_s = .45$, $p < .001$; *cluster g*: $r_s = -.47$, $p < .001$). Except for *cluster e*, all FC scores were negatively correlated, indicating greater anticorrelation between the LPCG and the target cluster with more MDMA intake and vice versa for *cluster e*. No further significant correlations with other FC scores were found.

4 | DISCUSSION

The aim of the current study was to investigate the neuronal correlates of memory impairments in MDMA users. More broadly, our results may provide insights into the involvement of 5-HT in mnemonic processes in the face of MDMA-associated long-term hypofunction of the 5-HT system.

Most pronounced memory attenuations in MDMA users were found in the verbal domain including recall consistency, recognition, and short- and long-term verbal memory whereas deficits in *visual associative* learning were less pronounced. Of note, memory performance was not different between woman and men in our study and also no sex × group interaction occurred. So far, most studies investigating cognitive functions in recurrent MDMA users reported the deficits in verbal memory with medium-strong effect sizes, whereas attention and spatial learning were not—or only a little—affected (Kalechstein et al., 2007; Laws & Kokkalis, 2007; Quednow et al., 2006; Wunderli et al., 2017). Thus, our results are consistent with a large body of existing evidence.

To decipher the functional underpinnings of memory impairments, we employed an unbiased, connectome-wide MVPA approach and found whole-brain FC differences between MDMA users and MDMA-naïve controls. A large cluster showing FC differences was located in the LPCG extending to the ipsilateral inferior parietal lobule (BA 40). In a second step, the MVPA-derived cluster was used as seed to examine the intrinsic FC patterns between the LPCG and the rest of the brain. The seed-based analyses uncovered nine areas of hypo- or hyperconnectivity in MDMA users compared to controls. Memory performance of participants' was associated with the FC strength between seven areas and the LPCG. Recent or lifetime MDMA consumption in the MDMA-user group was associated with the FC strength between five areas and the seed.

Our results are in line with previous fMRI studies describing the pre- and postcentral gyrus (PCG) as sensitive to serotonergic modulations (Beliveau et al., 2015; Biskup et al., 2016; Klaassens et al., 2018). Moreover, a previous pharmacological fMRI study examining FC alterations during acute MDMA administration found MDMA-associated FC changes in brain regions enriched with 5-HT_{1A} receptors, including the PCG, left lateralized temporal areas, Heschl's gyrus, and superior parietal areas (Dipasquale et al., 2019). Here, we observed similar regions showing hyper- or hypoconnectivity with the PCG in MDMA-users, which were belonging to the dorsal attention network, or to the auditory network, respectively.

On a network level, the PCG was identified as a heteromodal connector hub, linking control and processing networks. On one hand, the PCG regulated dorsal attention network activity (Bagarinao et al., 2020; Gordon et al., 2018). The PCG showed also a high degree of integration (overlap and activity coupling) to the somatomotor and auditory networks and modulated neuronal activity in sensory and motor processing systems (Tomasi & Volkow, 2011). The peak of our MVPA-derived cluster in the LPCG was located at the border of the dorsal attention/somatomotor network according to the Schaefer atlas (Schaefer et al., 2018). The cluster extended into both networks, suggesting that in MDMA users, the PCG might differently modulate information integration and between-network communication of domain-specific sensory processing and the dorsal attention network.

4.1 | FC differences of the sensory-auditory system in MDMA users and relation to memory

We found several clusters of reduced FC to the LPCG in MDMA users. Hypoconnected clusters were located in the bilateral temporal lobe and to a small extent, in the inferior part of the posterior supramarginal gyrus. All clusters combined correlated mostly with the

auditory network (Smith et al., 2009), a network largely overlapping with regions involved in language processes (Hickok, 2012). The PCG is not part of any core memory network (Rottschy et al., 2012; Skinner & Fernandes, 2007). Instead, its most eminent role is the sensory representation of the face and body, and the in integration of somatosensory stimuli. Nevertheless, evidence found the PCG to participate in language and verbal working memory (Emch et al., 2019; Price, 2010). Accordingly, phonological rehearsal occurs in feed-forward and feedback loops within pathways of the auditory and sensory-motor systems (Mainy et al., 2007), and PCG recruitment increased verbal working memory capacity and vivid access to long-term memory representations (Roger et al., 2022; Schwering & MacDonald, 2020).

The differences in memory between groups were primarily linked to the extent of FC differences between the LPCG and the right temporo-occipital region of the medial temporal gyrus and portions of the posterior supramarginal gyrus. These regions have previously been identified as an auditory-somatosensory convergence zone (Foxe et al., 2002; Lohse et al., 2021) and shown to be involved in the maintenance of information over a short decay time (Leff et al., 2009; Sakai & Passingham, 2003). FC differences between the LPCG and regions located in the left superior temporal gyrus and the rolandic operculum, which are involved in speech and language processing (Bhaya-Grossman & Chang, 2022) and the retention of verbal information (Hickok, 2012), were not found to be correlated with any memory score. Recognition was related to the extent of FC differences between the LPCG and the left planum temporale (Wernicke's area), which plays a role in the temporal integration of auditory events (Mustovic et al., 2003), the temporary storage of verbal information (Buchsbaum & D'Esposito, 2008), and the sensorimotor integration of speech processing (Hickok, 2012).

Language and verbal memory are closely related entities (MacDonald, 2016; Roger et al., 2022). Accordingly, memory storage occurs within a network of specialized cortical processing modules, and the same areas are also recruited during perception, encoding and retrieval of the relevant information (Weinberger, 2004). Since Kandel's research in 1980 (Brunelli et al., 1976), the role of 5-HT in modulating synaptic plasticity is established (Mayford et al., 2012). On a network level, 5-HT signaling has been suggested to fine-tune multimodal sensory integration in specific processing areas (Homberg et al., 2016; Hurley & Hall, 2011), and to exert homeostatic control of excitatory and inhibitory inputs in circuitries involved in learning (Lesch & Waider, 2012). Resting-state FC is not a direct measure of brain plasticity but reflects the history of co-activation during task performance—and hence plasticity—between putative brain regions (Guerra-Carrillo et al., 2014; Zhou et al., 2014). Therefore, the reduced FC between somatosensory and verbal processing regions, and negative correlations to verbal memory as found in MDMA users, may reflect altered synaptic plasticity and/or sensory information integration. Since deficits included early performance indices, such as recall consistency, early processes during the formation of a memory trace may already be affected (Wamsley, 2019).

4.2 | FC differences of dorsal-attention system in MDMA users and relation to memory

Seed-based FC analyses from the LPCG revealed several hyperconnected areas in MDMA users. Those were located in the parietal and occipital cortex and belong to the visual/dorsal attention network (Schaefer et al., 2018) and correlated also with the sensorimotor network (Smith et al., 2009). Short- and long-term verbal memory were negatively associated with increased FC between the LPCG and parts of the contralateral superior posterior supramarginal gyrus, the intraparietal sulcus, and the PCG. These areas are known to play a role in visuomotor tasks, object manipulation, and visuospatial attention (Grefkes & Fink, 2005; Perry & Zeki, 2000). Notably, delayed recall of the RAVLT was previously associated with altered glucose metabolism in this same region (Bosch et al., 2013).

Recall consistency was negatively related with increased FC between the LPCG and regions in the ipsilateral superior parietal lobe. These areas have been linked to top-down, volitional allocation of attention to visual aspects of, and coordinated motor actions to, specific regions in extrapersonal space (Hutchinson et al., 2009). Further, the increased FC between the LPCG and ipsilateral parts of the middle frontal gyrus and the precentral gyrus were correlated with lifetime MDMA intake, yet not with any memory performance score. Previous investigations in recurrent MDMA users found reduced activation during a semantic task in these regions (Raj et al., 2010), for which a role in attentional control, planning, and coordination of voluntary movements was suggested (Cieslik et al., 2016). Moreover, acute MDMA administration was demonstrated to affect middle frontal gyrus processes resulting in impoverished memory encoding (Kuypers et al., 2011).

The dorsal attention network serves the top-down guided direction of attention to specific locations in the visual space and to relevant sensory information (Vossel et al., 2014). Alterations in central 5-HTergic signaling pathways were demonstrated to alter FC in the dorsal attention network before (Graf et al., 2013; Madsen et al., 2021). Moreover, decreased attentional functions (Coray & Quednow, 2022; Knorr et al., 2019) have been found after acute administration of selective serotonin reuptake inhibitors. Increased FC within networks for domain-general processes (networks that contribute to a variety of cognitive functions, such as the dorsal attention network) may compensate for the disruption of specialized cognitive functions in case of brain lesion or disease. As such, hyperconnectivity within the dorsal attention network might reflect a compensatory effort in MDMA users to maintain performance (Hartwigsen, 2018). In line with this, increased parietal activation was observed during working-memory in MDMA users but N-back task performance was unimpaired (Daumann et al., 2004). Parietal hyperactivation has also been suggested as a marker of cognitive deficits in cases of substance use (Lees et al., 2021), ADHD (Fassbender & Schweitzer, 2006), and age (Corriveau-Lecavalier et al., 2019; Hoffman & Morcom, 2018).

The present study has some limitations that should be acknowledged. First, in a cross-sectional design, it is not possible to establish

cause-and-effect relationships between substance use and other variables. Second, hair analyses only allowed for objective detection of substances consumed in the past months. Substances consumed prior to 4 months (given 4 cm hair samples) relay on subjective self-reports and especially the estimations of lifetime amounts are rather of heuristic values. Third, the proportion of relatively pure MDMA users was high, but co-consumption was also present. So we cannot exclude that other substance use may have biased our results. Fourth, MVPA is a data-driven approach and replication of the results in independent datasets is crucial to establish the reliability and generalizability of our findings. Fifth, according to our power analysis, with a classical independent *t* test ($p > .05$; power 75%), only moderate effect sizes of 0.50 can be detected with our sample. Finally, this study mainly consisted of white Mid-European participants', future studies are needed that extend to other ethnical and cultural groups. Future studies also might incorporate a task-based approach in addition to the MVPA resting-state analyses, which would offer a more comprehensive understanding of the memory deficits in MDMA users.

5 | CONCLUSION

Altered FC from the LPCG to regions of the dorsal attention network and the auditory network in MDMA users found in the current study suggest functional underpinnings of MDMA induced verbal-declarative memory impairments. Considering previous research on the role of 5-HT in learning and plasticity, our finding revealing primary FC changes in regions of lower- and higher-level language and verbal memory processing is conclusive. Cortical synaptic plasticity in sensory areas participating in mnemonic circuits might be diminished in recurrent MDMA users as consequence of MDMA-associated central 5-HT hypofunction.

AUTHOR CONTRIBUTIONS

Rebecca C. Coray: Conceptualization, methodology, formal analysis, investigation, data curation, writing – original draft, visualization. Josua Zimmermann: Conceptualization, investigation, writing – review and editing. Amelie Haugg: Methodology, formal analysis, writing – review and editing. Markus R. Baumgartner: Toxicological hair analysis. Andrea E. Steuer: Toxicological hair analysis. Erich Seifritz: Funding acquisition. Ann-Kathrin Stock: Writing – review and editing. Christian Beste: Funding acquisition, Writing – review and editing. David M. Cole: Conceptualization, investigation, writing – review and editing. Boris B. Quednow: Conceptualization, methodology, writing – original draft, funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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