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Methamphetamine-related working memory difficulties underpinned by reduced frontoparietal responses

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Abstract

Working memory difficulties are common, debilitating, and may pose barriers to recovery for people who use methamphetamine. Yet, little is known regarding the neural dysfunctions accompanying these difficulties. Here, we acquired cross-sectional, functional magnetic resonance imaging while people with problematic methamphetamine-use experience (MA^+, $n = 65$) and people without methamphetamine-use experience (MA^-, $n = 44$) performed a parametric *n*-back task (0-back through 2-back). Performance on tasks administered outside of the scanner, together with *n*-back performance, afforded to determine a latent dimension of participants' working memory ability. Behavioural results indicated that MA^+ participants exhibited lower scores on this dimension compared to MA^- participants ($d = -1.39$, $p < .001$). Whole-brain imaging results also revealed that MA^+ participants exhibited alterations in load-induced responses predominantly in frontoparietal and default-mode areas. Specifically, while the MA^- group exhibited monotonic activation increases within frontoparietal areas and monotonic decreases within default-mode areas from 0-back to 2-back, MA^+ participants showed a relative attenuation of these load-induced activation patterns ($d = -1.55$, $p < .001$). Moreover, increased activations in frontoparietal areas from 0- to 2-back were related to greater working memory ability among MA^+ participants ($r = .560$, $p = .004$). No such effects were observed for default-mode areas. In sum, reductions in working memory ability were observed alongside load-induced dysfunctions in frontoparietal and default-mode areas for people with problematic methamphetamine-use experience. Among them, load-induced activations within frontoparietal areas were found to have a strong and specific relationship to individual differences in working memory ability, indicating a putative neural signature of the working memory difficulties associated with chronic methamphetamine use.

KEYWORDS
default mode, fMRI, frontoparietal, methamphetamine, working memory

1 | INTRODUCTION

Cognitive difficulties are common and debilitating among people who use methamphetamine. The most severe difficulties typically present on constituent measures of executive control, like working memory.[1] Impairments in working memory, a process supporting the temporary storage and manipulation of goal-relevant information, may pose barriers to daily functioning and recovery for people who use methamphetamine.[2,3] Behavioural therapies oriented toward redressing deficits in working memory and broader executive-control abilities have had preliminary successes in reducing the severity of methamphetamine-dependence symptoms.[4] Noninvasive neurostimulation therapies, which have been shown to mitigate the antecedents to methamphetamine relapse (e.g., cue-induced cravings), also specifically target substrates critical for working memory, such as dorsolateral prefrontal cortex.[5,6] Moreover, basal working memory ability has been shown to relate to the efficacy of these therapies among people with methamphetamine use disorder (MUD) and the therapies themselves have had preliminary successes in improving working memory for people with MUD.[7,8] Despite these mounting implications for working memory and its associated neural substrates in treating MUD, little is known regarding the potential neurofunctional alterations associated with the working memory difficulties facing people who use methamphetamine.

A recent meta-analysis on methamphetamine-related cognitive difficulties demonstrated that people with MUD exhibited reliably worse working memory performance compared to controls.[1] Therein, the detrimental effect of MUD on working memory was greater than its detrimental effect on many other facets of cognition (e.g., attention, verbal fluency, processing speed). Neuroimaging studies have further documented methamphetamine-related alterations to several neural substrates implicated in working memory performance, such as decreases in dorsolateral prefrontal cortex volume, decreases in white-matter integrity (via fractional anisotropy) within superior longitudinal fasciculi, as well as decreased resting-state functional connectivity between frontoparietal and default-mode networks.[9–11] To our knowledge, however, only one study has sought to leverage imaging to characterize methamphetamine-related neurofunctional alterations during a working memory task.[12] In that study, the authors administered a parametric working memory task (i.e., the *n*-back) during functional magnetic resonance imaging (fMRI). There, recently abstinent participants with MUD exhibited globally reduced functional connectivity during the *n*-back task relative to non-methamphetamine-using controls. This work was pioneering in revealing neural network alterations during working memory among people with MUD. However, the lack of association between those functional connectivity findings and performance on the *n*-back leaves the specific neural dysfunctions underlying methamphetamine-related working memory difficulties unclear.

The goal of the current study was to identify neurofunctional signatures of working memory difficulties among people who use methamphetamine. We acquired fMRI while participants with recent problematic methamphetamine-use experience (MA^+; i.e., MUD symptoms within 12 months and/or using at least 20 of the past 30 days) and participants without methamphetamine-use experience (MA^-) completed a parametric *n*-back task. Participants were also administered four working memory tasks outside of the scanner. While it is common to obtain a single working memory measure, it is challenging for performance observed on one measure to be interpreted as reflecting one's ability.[13] Performance on a single measure could be specific to that measure alone due to factors like task instructions or response modality (i.e., measurement error). By collecting multiple measures, the current study sought to recover a latent dimension that accounted for systematic variation in performance across measures to estimate individual and group differences in general working memory ability.[14]

We tested whether the MA^+ group exhibited altered neural activations in response to increasing *n*-back loads compared to the MA^- group. Network activations demonstrate predictable patterns with increasing working memory load. Frontoparietal regions, such as dorsolateral prefrontal and posterior parietal areas, show increases in positive activations as a function of increasing working memory load.[15–17] Conversely, default-mode regions, such as ventromedial prefrontal and posterior cingulate areas, show increasingly negative activations.[18–20] Together, these load-induced activation patterns may indicate an increasing bias of information processing toward external, task-relevant stimuli and away from task-irrelevant streams of thought (e.g., mind wandering)—both of which would be expected to impact working memory performance.[21,22] We hypothesized that these canonical, load-induced frontoparietal and default-mode responses would be attenuated for the MA^+ relative to the MA^- group. Specifically, consistent with prior studies of populations who exhibit working memory difficulties, we hypothesized that the MA^+ group would exhibit lesser *increases* in activations within frontoparietal areas and lesser *decreases* in activations within default-mode areas with increasing working memory loads relative to the MA^- group.[18,20,23,24] To determine whether load-induced dysfunctions in such activations bear relevance to methamphetamine-related working memory difficulties, we tested the extent to which they were associated with individual differences in working memory ability among MA^+ participants.

2 | METHODS

2.1 | Participants and procedure

Data were collected as part of an ongoing, longitudinal project examining relationships between brain function and methamphetamine use. Study procedures were approved by the University of Nebraska-Lincoln Institutional Review Board, informed consent was obtained before study procedures, and participants were compensated for their time. No aspect of this study or its parent project involved a clinical trial.

Participants were English-speaking adults, ages 21–60 years. Prospective cases were identified from a larger cohort of people who use illicit drugs recruited via community sampling (i.e., not recruited from legal, treatment or medical settings).[25] Pre-screening included:

methamphetamine use within 6 months, methamphetamine as their preferred substance, MRI contraindications and willingness to abstain from using alcohol or illicit substances for at least 12 hours before study sessions. Prospective cases were then interviewed by trained staff regarding their recent methamphetamine use and DSM-5 stimulant-use disorder criteria adapted for MUD within the past 12 months. The problematic methamphetamine-use experience group (MA^+) comprised people reporting symptoms that met the DSM-5 clinical threshold for MUD within the past 12 months and/or reporting using methamphetamine at least 20 of the past 30 days via the Risk Behaviour Survey.[26] Only one MA^+ participant did not meet the clinical threshold for MUD but reported using at least 20 of the past 30 days. Community recruitment and the inclusive MA^+ group definition sought to sample a wide range of recent problematic methamphetamine-use behaviours and associated traits, including cognitive abilities. Controls (MA^-) were identified via online advertisements and a local research registry and consisted of participants reporting neither a history of methamphetamine use nor a history of any substance use disorders.

Exclusion criteria were current pregnancy, chronic or uncontrolled illness, current/active psychosis, uncorrected visual impairments, neurological conditions, neurodevelopmental disorders (excluding ADHD), trauma resulting in extended unconsciousness, and MR contraindications (e.g., ferrous implants). Neither psychiatric conditions nor polysubstance use were exclusionary as these are common among the broader population of people who use methamphetamine[27–29] and their exclusion could risk limiting the generalizability of study findings.[30] Participants were required to abstain from using alcohol and/or illicit substances at least 12 hours prior to participating. This was confirmed at study intake via breathalyser, self-report of recent use, and overt signs of intoxication. No participant was excluded on the basis of these procedures. A 14-panel urine-drug screen was also administered at study intake. One-hundred and nine ($N = 109$) participants completed the *n*-back task and met group criteria ($n_{MA+} = 65$, $n_{MA-} = 44$).

2.2 | In-scanner working memory task

The *n*-back paradigm reliably evokes load-related positive activations in frontoparietal regions and negative activations in default-mode regions.[31,32] Participants were trained on *n*-back instructions and completed a practice task before imaging. During imaging, participants completed two runs of a block-design, *n*-back task (7 min/run). They were instructed to indicate via button press every time a letter on the current screen matched a letter displayed in the one or two screens preceding it (i.e., 1-back, 2-back conditions). For the 0-back condition, participants were instructed to respond every time the letter "W" was displayed. Combined, the three conditions provided a parametric manipulation of the working memory load. Specifically, task demand ranged from sustaining vigilance for cues matching the maintained goal-relevant target (i.e., respond if "W" is displayed) to needing to consistently update the goal-relevant target and the contents of working memory (e.g., respond if the letter displayed matches the letter presented two screens prior). Performance on the *n*-back paradigm used here has been shown to load significantly on latent factors of working memory ability.[14]

Each block began with condition instructions, followed by a brief fixation cross to indicate task onset. For each trial, a white letter was displayed on a black background for 0.5 s, followed by a fixation cross (2.5 s; see Figure 1A). Participants were allotted this 3 s window to respond. Valid probe letters were presented in 30% of trials. Jittered rest periods separated blocks (5, 15, 17 or 19 s). Ten trials were presented per each 30 s block. Each load condition was presented in 6 blocks across 2 runs (60 trials per load condition). Dependent variables were: response time, the total proportion of accurate responses and the proportion of hits for valid probes (i.e., total accuracy and hit accuracy, respectively).

2.3 | Image acquisition and processing

2.3.1 | Acquisition

Images were acquired via a Siemens 3-Tesla MAGNETOM Skyra and a 32-channel head coil. To enhance reproducibility, Human Connectome Project sequences were used. Whole-brain anatomical images (160 sagittal slices) were acquired with volumetric navigators for prospective motion correction to increase image fidelity and limit data loss.[33] These used a multiband, T1w-MPRAGE sequence: TR = 2,530 ms, $TE_{1/2/3/4}$ = 1.55/3.04/4.53/6.02 ms, FoV = 256 mm, Flip Angle = 7.0 °, 1.0mm^3 isometric voxel. Functional images were acquired using Gradient-recalled echo-planar sequences to recover whole-brain (51 axial slices) blood-oxygen-level-dependent (BOLD) signal via the following parameters: TR = 1,000 ms, TE = 29.80 ms, FoV = 210 mm, Flip Angle = 60 °, 2.5mm^3 isometric voxel. Phase encoding was reversed (AP-PA) between *n*-back runs to facilitate spatial normalization.

2.3.2 | Processing

A standardized, *fmriprep* (*v23.1.2*)[34] preprocessing workflow was used, including bias-field corrections, brain extraction, nonlinear spatial normalization to the ICBM-152 Nonlinear Asymmetrical template, compartment segmentation (i.e., grey/white matter, cerebrospinal fluid), as well as motion correction and quantification via affine transformations. Vectors for motion censoring were obtained using an a priori threshold (framewise displacement > 0.7).[14,35,36] Preprocessed functional volumes were spatially smoothed via a 6 mm Gaussian kernel. AFNI's *3dDeconvolve* was used to construct generalized linear models estimating activations during the *n*-back task conditions while (1) controlling for translation and rotation motion parameters, and framewise displacement[37]; (2) preventing volumes deemed motion outliers from influencing task-activation outputs (i.e., censoring) and; (3) employing an automatic polynomial (high-pass) filter to minimize temporal trends (e.g., signal drifts). Within these models, participant-level task activations were obtained by convolving the task-design matrix and AFNI's

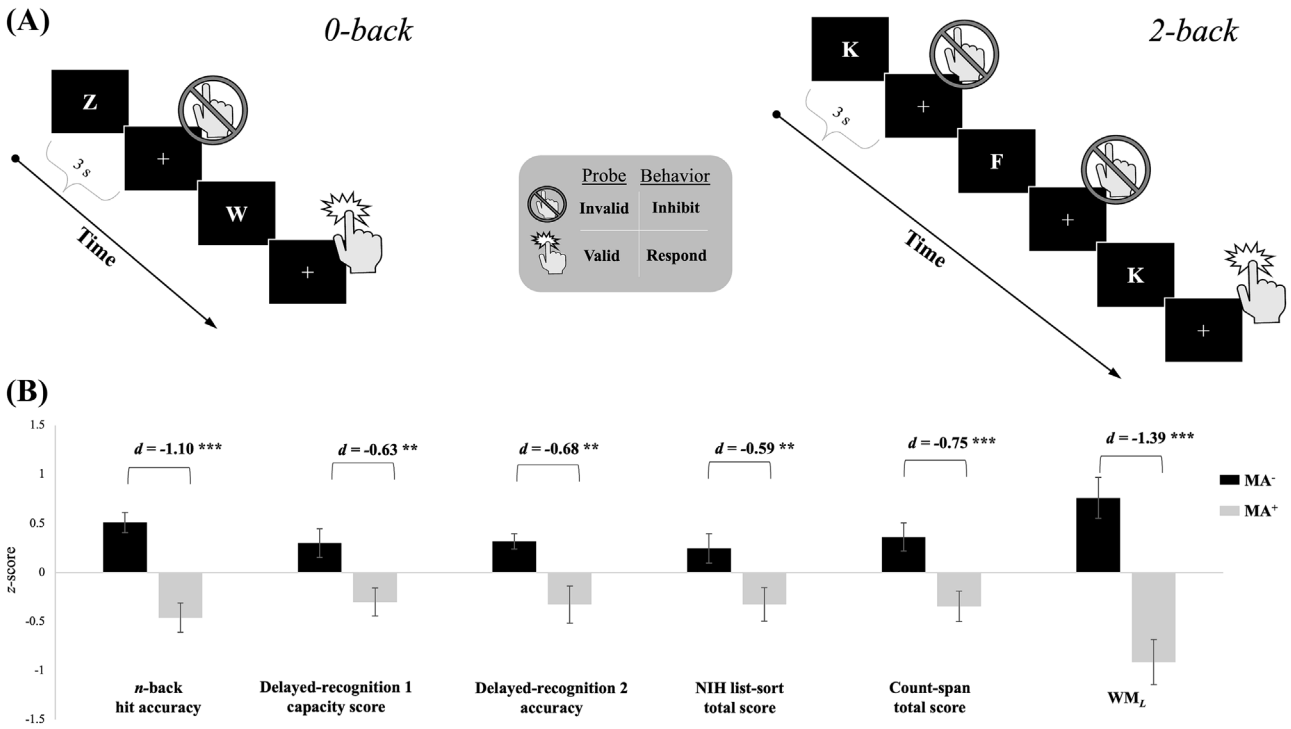

FIGURE 1 *N*-back illustration and working memory group effects. (A) Example of 0-back (left) and 2-back (right) load conditions. For the 0-back condition, the valid probe was fixed stimulus (i.e., the letter "W"). For 1- and 2-back conditions, valid probe-stimuli were varied. In the 2-back condition, a valid probe was any letter that was displayed two screens prior (e.g., "K" in the provided example). (B) Group comparisons on the 5 targeted working memory performance measures and the latent working memory dimension (WM_L). MA^- = people without methamphetamine experience; MA^+ = people with problematic methamphetamine-use experience. *d* = Cohen's *d* group effect size; ** = $p < .01$; *** = $p < .001$.

block impulse-response functions, the product of which was regressed onto participants' BOLD time series' while controlling for the aforementioned nuisance factors. These provided the beta weights for 0-, 1- and 2-back conditions that were used in subsequent analyses.

2.3.3 | Quality assurance

Characteristics of retained participants are found in Table 1. Quality-assurance procedures excluded participants if their images had irreconcilable artefacts or if ≥ 30% of their functional volumes were deemed motion outliers in accordance with an a priori-determined threshold. Participants failing to achieve at least 50% hit accuracy on the *n*-back were also excluded. This criterion ensured findings were based solely on participants who provided sustained, above-chance performance (hit chance = 30%). In total, quality assurance excluded 18 MA^+ and 0 MA^- participants ($N = 91$). Comparisons between excluded and retained MA^+ samples are provided in the Supplemental Methods and Results.

2.4 | Latent working memory dimension

Four working memory tasks were administered outside of the scanner. These included a count-span task,[40] the NIH-toolbox list-sorting working memory test,[41] and two delayed-recognition tasks.[14,17] Among them, these tasks featured unique load manipulations, response modalities, memoranda (i.e., visual arrays, images/spoken words, letter lists), as well as required different operations to be performed within working memory (i.e., enumerate targets and ignore distractors vs. sort and sequence memoranda vs. maintain lists over delay; see the Supplemental Methods). Thus, along with *n*-back performance, these were used to assess working memory across varied contexts to estimate participants' general working memory ability.[13,40] This was achieved via principal component analysis (PCA) applied to performance metrics from all five tasks.[14] Parametric bootstrapping determined components that accounted for significant variance across the working memory measures and the extent to which each measure contributed significantly to each component.

2.5 | Analytic approach

2.5.1 | Whole-brain analyses

Whole-brain Group, Load and Group × Load effects were first determined using AFNI's mixed-effect modelling program, *3dMVM*.[38] This 2 × 3 repeated measure ANOVA was confined to a sample-wide, grey matter mask. Voxel-wise, family-wise error rate was controlled using a cluster-extent threshold provided via nonparametric permutation of

TABLE 1 Characteristics of retained sample by group.

		MA^+	MA^-	Statistic
N		47	44	-
Age (Mean/Range)		41.36 (21–56)	38.64 (21–56)	$t = 1.33$ NS
Gender (M:F:NBT)		24:21:02	26:18:00	$\chi^2 = 0.30$ NS a
Education (% endorsing)				$\chi^2 = 43.03$ ***
	No degree	12.77	00.00	
	High school/GED	38.30	09.09	
	Some college/Associates	46.81	27.27	
	Four-year degree	02.13	36.36	
	Graduate degree	00.00	27.27	
Race (% endorsing)				$\chi^2 = 0.04$ NS b
	Asian/Pacific Islander	00.00	11.36	
	Amer. Indian/Alaska Native	06.38	02.27	
	Black/African Amer.	06.38	00.00	
	Caucasian	74.47	79.55	
	Multiple	08.51	06.82	
	Unknown	04.26	00.00	
Ethnicity (% endorsing)				$\chi^2 = 1.11$ NS c
	Hispanic/Latine	04.26	11.36	
	Not Hispanic/Latine	78.72	86.36	
	Unknown	17.02	02.27	
Mental Status/Neuropsych. (Mean/SEM)				
	MoCA	23.91 (0.38)	26.40 (0.39)	$t = -4.54$ ***
	Full-scale IQ-2	87.48 (1.84)	102.3 (1.84)	$t = -5.71$ ***
Psych. Rx Status (% endorsing)				
	Any	25.53	22.73	$\chi^2 = 0.10$ NS
	Antidepressant	17.02	15.91	$\chi^2 = 0.02$ NS
	Stimulant	08.51	06.82	$\chi^2 = 0.09$ NS
Psych. Symptoms (Mean/SEM)				
	Anhedonia (SHAPS)	43.20 (0.91)	48.28 (0.68)	$t = -4.43$ ***
	Major Dep. (PHQ-9)	11.45 (1.14)	04.00 (0.64)	$t = 5.67$ ***
	Gen Anxiety (GAD-7)	10.40 (1.00)	04.86 (0.67)	$t = 4.55$ ***
	PTSD (PCL-5)	31.09 (3.11)	11.36 (1.56)	$t = 5.63$ ***
Cigarette pack/day (Mean/SEM)		01.14 (0.19)	00.13 (0.20)	$t = 3.63$ ***
Alcohol drink/day (Mean/SEM)		01.20 (0.32)	00.42 (0.32)	$t = 1.75$ NS
Methamphetamine				
Lifetime Use (% endorsing)		100.0	-	-
Any 30-day Use (% endorsing)		87.23	-	-
Use-days in past 30 (Mean/SEM)		17.05 (1.61)	-	-
Urine Drug Screen (% positive)		69.57	-	-

Abbreviations: MA^+ = problematic methamphetamine-use experience; MA^- = no methamphetamine experience. M = male; F = female; NBT = nonbinary/third gender. SEM = pooled standard error. MoCA = Montreal Cognitive Assessment. Full-scale IQ-2 = WASI-II full-scale IQ-2. GAD-7 = Generalized Anxiety Disorder Scale. PHQ-9 = Patient Health Questionnaire. PCL-5 = PTSD Checklist for DSM-5. SHAPS = Snaith-Hamilton Pleasure Index. *NS* = $p > .05$;
*= $p < .05$; ***= $p < .001$.
[a, b, c]Tests performed on reduced groupings due to limited class samples:
[a]Male vs. Female;
[b]Caucasian vs. Not Caucasian/Multiple;
[c]Hispanic/Latine vs. Not Hispanic/Latine.
Measures and additional characteristics are detailed in Supplemental Materials.

residuals from Group tests among the different Load conditions,[39] and selecting the most stringent cluster size provided by *3dClustSim* ($k > 62$ faces-touching voxels) that yielded an estimated family-wise error rate < .05, given a $p \leq .001$.

2.5.2 | Effects by network label

We next sought to investigate the Group × Load interaction effects specifically in frontoparietal and default-mode regions. Here, voxel clusters that exhibited significant Group × Load interactions in the whole-brain analyses were investigated. To examine potential network effects, beta weights were averaged among those clusters that featured voxels within frontoparietal or default-mode anatomical boundaries defined by the Yeo 7-network atlas.[42] Thus, beta weights were averaged among the four significant clusters that had voxels within frontoparietal network boundaries. Similarly, beta weights were averaged among the four significant clusters that had voxels within default-mode network boundaries. An omnibus Group × Load × Network (2 × 3 × 2) repeated-measures ANOVA was then computed to determine whether these frontoparietal and default-mode voxel clusters demonstrated distinct activation patterns to increasing *n*-back loads (i.e., Load × Network interaction). Importantly, this model was used to test whether groups differed in these network activations by load (i.e., Group × Load × Network interaction).

To specifically test our directional hypothesis that the MA^+ group would exhibit lesser increases in frontoparietal areas and lesser decreases in activations within default-mode areas with increasing working memory loads, a maximum network difference was calculated. This determined combined activation changes in these network areas from the lowest- to the highest-Load conditions (i.e., 0-back and 2-back). Therein, beta-weights averaged among the default-mode clusters were subtracted from those averaged among the frontoparietal clusters for both 0- and 2-back conditions. The maximum network difference was then calculated by subtracting the network difference obtained during the 2-back condition from those obtained during the 0-back condition. Thus, participants with *greater* maximum network difference coefficients exhibited larger combined increases in frontoparietal positive activations and decreases in default-mode cluster activations from 0- to 2-back conditions.

2.5.3 | Potential confounding factors

Covariates were used to determine whether potential confounds influenced primary between- and within-group effects. Confounding effects were evaluated by individually entering covariates into the statistical models.[35] Covariate measurements are detailed in the Supplemental Methods. The influence of 15 covariates was evaluated on the primary between-groups working memory effects including demographic characteristics (e.g., age, education), neuropsychological baselines (i.e., full-scale IQ, current cognitive status), other substance use (i.e., alcohol, tobacco), current psychiatric symptoms (e.g., anhedonia, anxiety, PTSD) and medications. The influence of these and four additional covariates which accounted for *n*-back performance and in-scanner head motion was evaluated on the primary between-groups brain imaging effects. The influence of 30 covariates was evaluated for the primary within-MA^+ group effects. These analyses tested whether covariates influenced the significance of relationships between network cluster activations and working memory ability among the MA^+ participants. There, 14 additional covariates were evaluated, encompassing recent substance use (e.g., past 30-day substance use, urine drug-screen status), as well as past methamphetamine-induced and organic psychosis symptoms.

2.5.4 | Image mappings and significance thresholds

Surface-based projections were used in main text figures to provide efficient visualization of primary imaging findings. Those projections are equivalent to their volume-based counterparts detailed in the Supplemental Materials. For network-label analyses, Bonferroni procedures were used to adjust for the number of follow-up comparisons across the three Load conditions, yielding a corrected critical threshold of $\alpha < .0167$ ($p_{Bonferroni} < .05$). All other *p*-values were uncorrected.

3 | RESULTS

3.1 | Working memory behavioural effects

The MA^+ group was slower and less accurate (i.e., overall accuracy and hit accuracy) in responding to *n*-back probes compared to MA^- participants (*p*s < .001; see the Supplemental Results). The MA^+ group also exhibited reduced performance on all five of the targeted working memory performance measures compared to the MA^- group (*p*s <.05; see Figure 1B). The PCA recovered a single component that accounted for significantly greater-than-chance variance in performance across the five targeted measures ($\lambda_1 = 1.95$ [Bootstrap 95% CL: 1.54–2.32]). Positive and significant loadings on this component, along with significant contributions to it by each of the five working memory performance measures supported the use of its factor scores as a latent dimension of working memory ability (hereafter, WM_L; see Tables S3–S4).[14] The MA^+ group demonstrated lower WM_L scores relative to MA^- participants ($p < .001$; see Figure 1B), supporting that the former had reduced working memory ability. None of the 15 between-groups covariates altered the significance of this finding (ANCOVA retained effects range: $\eta_p^2 = .127–.334$, *p*s < .001).

3.2 | Whole-brain effects

The whole-brain Group × Load (2 × 3) repeated-measures ANOVA yielded a significant main effect of Group within one cluster in the

primary visual cortex (MNI isocenter: 02, 93, 04; see the Supplemental Results). Significant main effects of Load were also observed (see the Supplemental Results). Significant Group × Load interaction effects were observed predominantly within regions associated with frontoparietal and default-mode networks (see Figure 2A, Table 2).

3.3 | Effects by network label

3.3.1 | Omnibus model

The Group × Load × Network (2 × 3 × 2) repeated-measures ANOVA, Greenhouse–Geisser corrected for sphericity, indicated

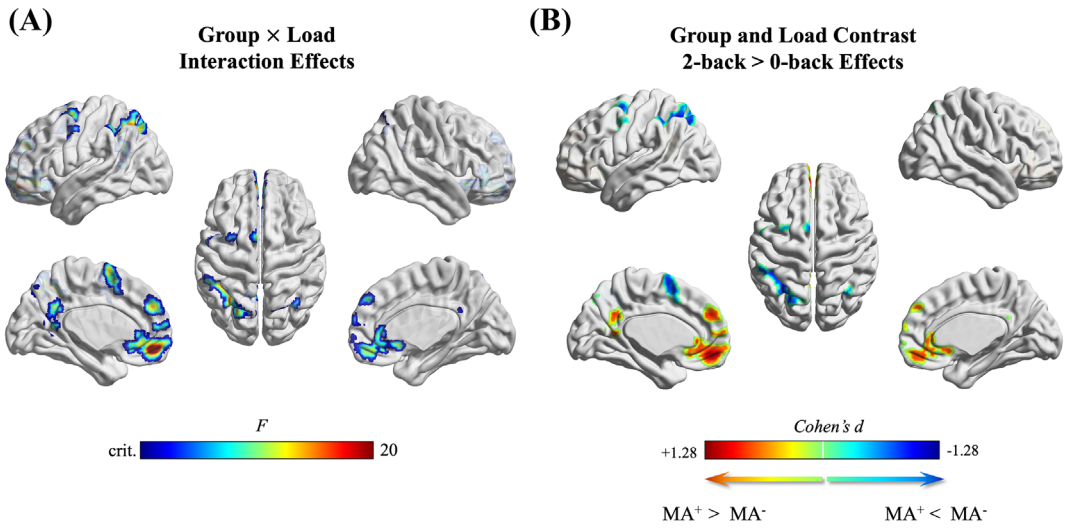

FIGURE 2 Whole-brain group × Load interaction effects. (A) Cortical surface projections of significant group × load interactions. Nine significant voxel clusters were observed (see Table 2, Figure 3). Significance was determined via $p \leq .001$ and $k > 62$ faces-touching voxel thresholds, yielding an estimated family-wise error rate < .05. (B) Example of group × load directional effects. Group effects from 2-back > 0-back load contrast shown within significant clusters from the group × load interaction. Warmer colours indicate MA^+ exhibited a more positive (i.e., less negative) load-induced activation effect compared to MA^-. Cooler colours indicate MA^+ exhibited less positive load-induced activation effect compared to MA^-. Whole-brain volume-based maps of group and load main effects, group × load interaction effects, are provided in the Supplemental Materials along with load effects separated by group.

TABLE 2 Whole-brain group × load significant voxel clusters.

Atlas label (BAs)	X	Y	Z	Voxels	Area	Network
Medial Orbitofrontal (24,32)	02	−45	−09	697	vmPFC	DMN
L Superior Parietal Lobule (7,40)	32	58	47	614	L PL	FPN
Superior Frontal (6)	07	−05	59	141	dACC	-
Precuneus (23,31)	09	55	22	140	pCC	DMN
Superior Frontal (8,9)	04	−50	32	131	dmPFC	DMN
L Caudal Middle Frontal/ Precentral (6,8,9)	47	−03	42	114	L dlPFC	FPN
R Superior Parietal Lobule (7)	−26	70	57	094	R PL	FPN
Superior Frontal (9)	−01	−58	14	089	mPFC	DMN
L Caudal Middle/ Superior Frontal (6)	27	00	62	074	L dPFC	FPN

Note: Coordinates reflect isocenter of voxel cluster in MNI space. Labels adapted from Desikan–Killiany atlas reflect those with greatest overlap with voxel clusters. Brodmann Area's (BA) within 5 mm of isocenter of voxel cluster, listed in order of proximity. Lateral distinctions are not made within 10 mm of midline. Areas reflect functional neuroanatomic conventions. Network labels were ascribed to clusters with voxels within the default mode or frontoparietal network boundaries from the Yeo 7-network atlas. Significance threshold evaluated at $p < .001$, k-faces-touching voxels > 62; family-wise error rate corrected $p < .05$.

Abbreviations: DMN = default-mode network; FPN = frontoparietal network. dACC = dorsal anterior cingulate cortex; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; mPFC = medial prefrontal cortex; pCC = posterior cingulate cortex; PL = parietal lobule; vmPFC = ventromedial prefrontal cortex.

significant main effects of Load, $F(1.96,145.79) = 24.21$, $\eta_p^2 = .214$, $p < .001$ and Network, $F(1,887.813) = 625.81$, $\eta_p^2 = .875$, $p < .001$. Expectedly, a significant Load × Network interaction, $F(1.64,145.79) = 257.52$, $\eta_p^2 = .743$, $p < .001$, indicated large and opposite changes from baseline were observed between frontoparietal and default-mode areas with increasing Load (see Figure S6). Importantly, the model indicated a significant Group × Load × Network interaction, $F(1.64,145.79) = 43.07$, $\eta_p^2 = .326$, $p < .001$ (see Figure 3B). None of the 19 between-groups covariates altered the significance of this interaction (retained effects range: $\eta_p^2 = .114–.324$, $ps < .001$). Post-hoc, *t*-tests confirmed that group differences emerged with increased Load. Specifically, the MA$^+$ group exhibited significantly less positive frontoparietal activations ($t[89] = 5.23$, $d = -1.10$, $p_{Bonferroni} < .001$) and significantly less negative default-mode activations ($t[89] = 5.23$, $d = 0.97$, $p_{Bonferroni} < .001$) compared to MA$^-$ participants during the 2-back condition (see Figure 3). No other significant, post-hoc effects were observed ($p_{Bonferroni} > .05$). No other significant main or interaction effects were observed in the omnibus model ($ps > .05$).

3.3.2 | Directional hypothesis test

The maximum network difference coefficient was used to formally test the hypothesized direction of the Group × Load × Network interaction. Consistent with our hypothesis, the MA$^+$ group exhibited reduced maximum network difference coefficients relative to the MA$^-$ group ($p < .001$; see Figure 4). Specifically, compared to MA$^-$ participants, the MA$^+$ group exhibited a combined pattern of lesser increases in activations within frontoparietal clusters and lesser decreases in activations within default-mode clusters with increasing working-memory loads. None of the 19 between-groups covariates altered the significance of this finding (ANCOVA retained effects range: $\eta_p^2 = .138–.378$, $ps < .001$).

3.4 | Within-MA$^+$ group relationships with working memory ability

Linear regressions tested the extent to which activations within the frontoparietal and default-mode clusters had significant relationships with MA$^+$ participants' WM_L scores. Participants in the MA$^+$ group exhibiting greater increases frontoparietal cluster activations from 0- to 2-back conditions had significantly greater WM_L scores compared to MA$^+$ participants exhibiting lesser increases in these activations (see Figure 5A). None of the 30 within-subjects covariates altered the significance of this relationship (partial effects range: $r_{X.Y|Z} = .461–.611$, $p = .033–.002$). No significant relationship was observed between load-induced activations in the default-mode clusters and WM_L scores for the MA$^+$ group (see Figure 5B). Even after controlling for these activations in the default-mode clusters, the

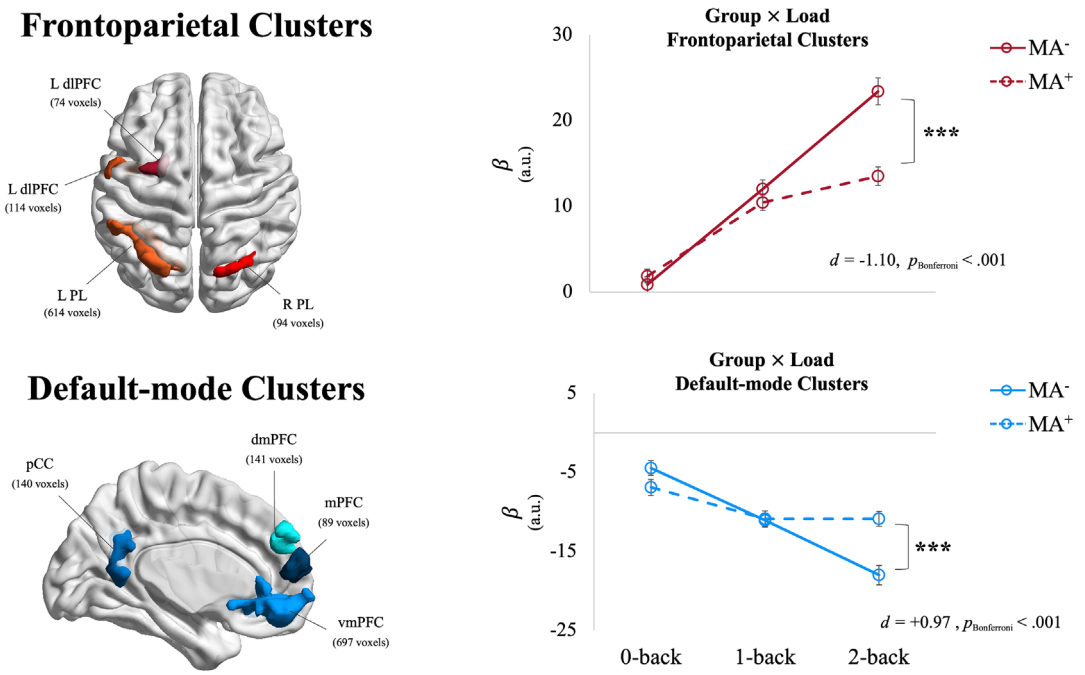

FIGURE 3 Effects by network label. Cortical surface projections of significant voxel clusters separated by frontoparietal and default-mode network labels (smoothed for display). (Top/warm colours) Dorsal view of the four frontoparietal voxel clusters and group effects on cluster activations by load. (Bottom/cool colours) Medial view of the four default-mode voxel clusters and group effects on cluster activations by load. Post-hoc tests indicated significant group differences emerged for clusters in both networks during the 2-back condition. *d* = Cohen's *d* group effect size; $p_{Bonferroni}$ indicates *p*-value corrected for the number of post-hoc tests. Voxels = voxels within each cluster. See Table 2 for description of area labels and expanded cluster details.

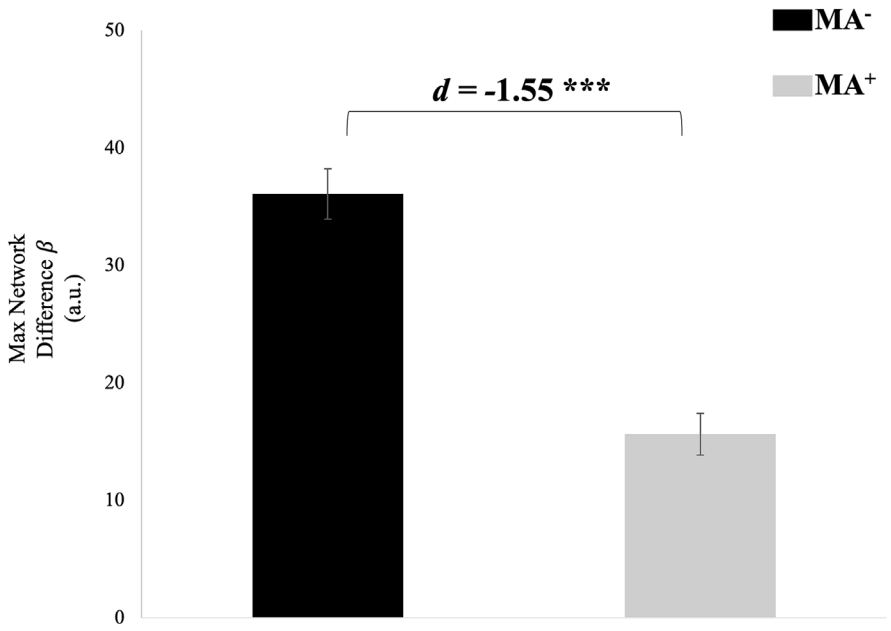

FIGURE 4 Test of maximum network difference effects. Y-axis reflects combined changes in frontoparietal and default-mode cluster activations from 0- to 2-back. Greater maximum network difference coefficients indicate larger combined load-induced increases in frontoparietal activations and load-induced decreases in default-mode cluster activations. d = Cohen's d effect size. *** = $p < .001$.

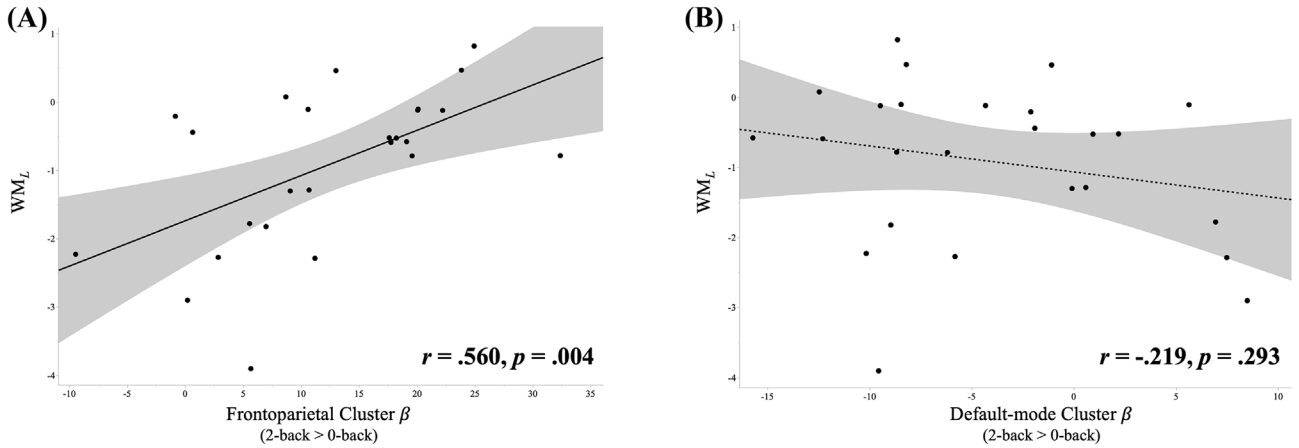

FIGURE 5 Activations within network clusters and MA^+ Participants' working memory ability. (A) Greater increases in activation within frontoparietal clusters from 0-back to 2-back was correlated with greater working memory ability (i.e., WM_L) among MA^+ participants. (B) No significant effect was observed for activations in default-mode clusters on MA^+ participants' working memory ability. Shaded areas reflect 95% confidence bands. Removal of potential leverage point on Y-axes (lowest WM_L score; −1.62 SD) did not impact the significance of results: (A) $r = .570$, $p = .003$; (B) $r = -.374$, $p = .072$.

load-induced frontoparietal activations still retained a significant relationship with MA^+ participants' WM_L scores, $r_{X,Y|Z} = .542$, $p = .007$. Finally, we evaluated a voxel cluster that showed significant Group × Load interaction effects in the whole-brain analyses but, was not ascribed either a frontoparietal or default-mode network label (i.e., dorsal anterior cingulate [dACC]). Activations from 0- to 2-back in this dACC cluster showed a significant relationship with MA^+ participants' WM_L scores ($r = .395$, $p = .051$). Yet, this relationship did not retain significance when controlling for activations in frontoparietal clusters (dACC: $r_{X,Y|Z} = .137$, $p = .512$); whereas the load-induced frontoparietal activations retained significance in this model (frontoparietal: $r_{X,Y|Z} = .488$, $p = .027$).

4 | DISCUSSION

This study investigated working memory ability and neural responses to increasing working memory load among people with and without problematic methamphetamine-use experience. Reduced performance was observed for the MA^+ group on a battery of working memory measures. Examining performance across this battery via a latent dimension indicated that, compared to MA^- participants, the MA^+ group exhibited significantly reduced working memory ability. Whole-brain findings demonstrated load-induced activation differences between groups primarily emerged in voxel clusters within frontoparietal and default-mode areas. These areas were strongly influenced by

working memory load (see the Supplemental Materials), but not group status alone. Thus, the group activation differences arose within frontoparietal and default-mode clusters specifically when the demands placed upon working memory increased. The hypothesized directional pattern of load-induced dysfunctions was supported via the maximum network difference analyses. Specifically, these findings indicated that the MA^+ group exhibited lesser load-induced increases in activations in frontoparietal clusters and lesser load-induced decreases in activations in default-mode clusters compared to the MA^- group.

Frontoparietal functions support working memory by biasing information processing toward task-relevant stimuli.[43,44] This is typically antagonistic with default-mode functioning, which is posited to be involved in more unconstrained or task-irrelevant streams of thought.[24] Thus, when the demands placed upon working memory increase, both networks are expected to respond, albeit oppositely. These canonical activation patterns were exemplified by the MA^- group, who exhibited monotonic increases in activations within frontoparietal clusters and monotonic decreases in activations within default-mode clusters as a function of *n*-back load. The MA^+ group, however, exhibited attenuated load-induced responses in these areas—with their activations failing to reach the levels of those demonstrated by the MA^- group at the highest load. These effects emerged specifically at the highest *n*-back load, which intimates methamphetamine-related dysfunctions in working memory maintenance and updating processes, as opposed to purely attentional/encoding processes—which were presumably involved across *n*-back loads.[15] One potential mechanism to support this conclusion involves dopaminergic functioning, which is downregulated with chronic methamphetamine use.[45,46] Specifically, dopaminergic signals communicated through striatocortical circuits are theorized to facilitate working memory maintenance and updating processes.[14,47,48] Moreover, enhancing dopamine availability has been shown to increase positive activations in some frontoparietal areas and decrease activations in some default-mode areas as a function of *n*-back load.[49] Thus, it is plausible to speculate that the attenuations of frontoparietal positive activations and default-mode negative activations observed specifically during the highest *n*-back load indicated methamphetamine-related dysfunction in working memory maintenance and updating processes, driven by downregulation of dopaminergic functioning.

The current findings demonstrated that, compared to never-using people, people who use methamphetamine exhibit load-induced neurofunctional alterations during working memory. To our knowledge, only one prior study has investigated similar effects.[12] Although that study observed functional connectivity differences between its MUD and control groups during the *n*-back task, it did not observe significant group effects on neural activations. This discrepancy may relate to methodological or power differences between that prior study and the present one. Importantly, however, *n*-back effects found within other substance-use groups are broadly consistent with those observed here.[49–51] For instance, one study demonstrated that people with cocaine use disorder exhibited lesser increases in activations within frontoparietal areas with increasing load compared to people without the disorder.[49] Another study showed that people with problematic alcohol-use experience exhibited lesser decreases in activations within a core default-mode area (i.e., ventromedial prefrontal cortex) with increasing load compared to those without such experience.[51] Moreover, evidence has accumulated across studies of multiple populations with working memory difficulties showing that these populations tend to exhibit lesser increases in frontoparietal activations and/or lesser decreases in default-mode activations in response to increased working memory load.[18,20,23,24]

Compared to MA^- participants, MA^+ participants exhibited attenuated load-induced responses in frontoparietal and default-mode clusters. However, only load-induced responses in frontoparietal clusters demonstrated significant relationships with MA^+ participants' working memory ability. Specifically, MA^+ participants exhibiting greater increases frontoparietal cluster activations from 0- to 2-back conditions had greater WM_L scores. Conversely, those MA^+ participants exhibiting lesser increases in these activations had lower WM_L scores. Supporting the specificity of this brain–behaviour relationship,[14,36] even when controlling for activations in default mode or other relevant areas (i.e., dACC), load-induced frontoparietal activations still retained a significant relationship with the latent working memory dimension. Critically, this relationship was also retained when controlling for demographics, neuropsychological ability, recent methamphetamine or other substance use, psychiatric symptoms and other potential confounds. This suggests that the extent to which frontoparietal regions respond to increasing working memory demands could serve as a strong and unbiased neural signature of the working memory difficulties facing people who use methamphetamine.

4.1 | Limitations and future directions

The present findings should be considered in the context of several limitations. First, this study recruited a community cohort and did not exclude participants for polysubstance use or psychiatric comorbidities. This was intentional in seeking to discover brain–behaviour relationships characteristic of the broader population of people using methamphetamine[30]—who do not often obtain residential treatment and are likely to struggle with polysubstance and psychiatric issues.[27–29] Yet, our approach was distinct from most imaging research on methamphetamine use, which typically studies treatment-seeking people within residential facilities and also utilizes more restrictive inclusion criteria to limit variability arising from the recency of use as well as the influence of other substances or disorders. Although our findings were not impacted by related factors (i.e., positive drug screens, 30-day use patterns, current psychiatric symptoms), replication in controlled environments and within samples without polysubstance use or psychiatric disorders is needed to definitively rule out those confounds. Second, and relatedly, between-group differences were observed in neuropsychological baseline measures (i.e., IQ, mental status) and educational attainment. While neither was found to impact our findings, case–control matching on these factors could be utilized in future work to definitively rule out

any conceivable impact. Third, MA+ participants excluded via quality-assurance procedures were more likely to provide a positive urine screen for methamphetamine and showed worse performance on one working memory task compared to those who were retained (see the Supplemental Results). This could indicate that those excluded were struggling with more severe methamphetamine use and/or greater working memory difficulties relative to those retained. Thus, it is possible that the quality-assurance procedures led to an underestimation of our between-group effects. Fourth, we did not collect peripheral physiological measures during imaging and, thus, it is also possible that peripheral noise may have diminished our effects. Finally, our design was cross-sectional and associational. Therefore, we cannot distinguish whether the observed working memory reductions and load-induced neural alterations were the consequences of methamphetamine use or whether these existed prior to ever using.

Despite these limitations, our findings are an essential step for determining neurofunctional foundations of the working memory difficulties often facing people who use methamphetamine. Yet, clinical research is still needed to determine whether such findings can provide translational impact. One focus for future research could be to determine the extent to which frontoparietal signatures of working memory ability can predict or improve methamphetamine treatment outcomes. Evidence is available to support relationships between working memory performance and methamphetamine treatment outcomes.[3,4,7] Findings from other substance-use populations also indicate support for leveraging parametric *n*-back responses from frontoparietal areas to predict substance-use-treatment outcomes.[50] However, it is not yet known whether such frontoparietal responses are similarly or more effective in predicting treatment outcomes among people who use methamphetamine. Additionally, it is not known whether fMRI-based neural signatures, like those determined here, could be used to improve neurostimulation treatments for MUD. Leveraging fMRI to target specific neurostimulation sites, dosages and/or prospectively determine a patient's responsiveness has improved outcomes for other clinical disorders.[52] There is growing recognition of the need for related, precision-neurostimulation approaches in treating MUD, as well as evidence to suggest that individual differences in working memory ability may play a role in the efficacy of these treatments for MUD.[7,53] Capitalizing upon frontoparietal signatures of working memory ability to calibrate neurostimulation dosages or prospectively predict a patient's responsiveness may afford future trials the means to improve these treatments for people with MUD.

4.2 | Conclusions

People with recent problematic methamphetamine-use experience had reduced working memory ability compared to those who never used methamphetamine. Those reductions co-occurred with attenuated responses in frontoparietal and default-mode areas to increasing working memory load. Load-induced frontoparietal responses were uniquely related to individual differences in working ability among people with problematic methamphetamine-use experience. Specifically, those exhibiting greater increases in activations in these areas from the lowest- to the highest-load conditions also had greater working memory ability. Thus, those exhibiting lesser activations across these conditions also had lower working memory ability. With current treatments seeking to target working memory and its fundamental neural substrates,[4–6] the link provided here between working memory difficulties and frontoparietal dysfunctions could prove fruitful for optimizing these or related treatments for methamphetamine use disorder.

AUTHOR CONTRIBUTIONS

RJR: analysis, data collection, writing, revisions. MAP: writing, revisions. KTW: writing, revisions. RJRB: conceptualization, analysis, methodology, writing, revisions. NAH: funding, conceptualization, supervision, analysis, methodology, project administration, writing.

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CONFLICT OF INTEREST STATEMENT

The authors do not declare any known conflicts of interest related to this work.

DATA AVAILABILITY STATEMENT

Data supporting study findings are available upon reasonable request to the corresponding author.

ETHICS APPROVAL & CONSENT STATEMENT

Study procedures were approved by the University of Nebraska-Lincoln Institutional Review Board, and informed consent was obtained before study procedures.

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REFERENCES

1. Potvin S, Pelletier J, Grot S, Hébert C, Barr A, Lecomte T. Cognitive deficits in individuals with methamphetamine use disorder— a meta-

analysis. *Addict Behav*. 2018;80:154-160. doi:10.1016/j.addbeh.2018.01.021
2. Weber E, Blackstone K, Iudicello JE, et al. Neurocognitive deficits are associated with unemployment in chronic methamphetamine users. *Drug Alcohol Depend*. 2012;125(1–2):146-153. doi:10.1016/j.drugalcdep.2012.04.002
3. Rubenis AJ, Fitzpatrick RE, Lubman DI, Verdejo-Garcia A. Working memory predicts methamphetamine hair concentration over the course of treatment: moderating effect of impulsivity and implications for dual-systems model. *Addict Biol*. 2017;24(1):145-153. doi:10.1111/adb.12575
4. Anderson AC, Robinson AH, Giddens E, et al. Proof-of-concept trial of goal management training+ to improve executive functions and treatment outcomes in methamphetamine use disorder. *Drug Alcohol Depend*. 2023;246:109846. doi:10.1016/j.drugalcdep.2023.109846
5. Alizadehgoradel J, Nejati V, Sadeghi Movahed F, et al. Repeated stimulation of the dorsolateral-prefrontal cortex improves executive dysfunctions and craving in drug addiction: a randomized, double-blind, parallel-group study. *Brain Stimul*. 2020;13(3):582-593. doi:10.1016/j.brs.2019.12.028
6. Liang Y, Wang L, Yuan T-F. Targeting withdrawal symptoms in men addicted to methamphetamine with transcranial magnetic stimulation. *JAMA Psychiatry*. 2018;75(11):1199-1201. doi:10.1001/jamapsychiatry.2018.2383
7. Wang L-J, Mu L-L, Ren Z-X, et al. Predictive role of executive function in the efficacy of intermittent theta burst transcranial magnetic stimulation modalities for treating methamphetamine use disorder—a randomized clinical trial. *Front Psychiatry*. 2021;12:774192. doi:10.3389/fpsyt.2021.774192
8. Sun Y, Wang H, Ku Y. Intermittent theta-burst stimulation increases the working memory capacity of methamphetamine addicts. *Brain Sci*. 2022;12(9):1212. doi:10.3390/brainsci12091212
9. Nakama H, Chang L, Fein G, Shimotsu R, Jiang CS, Ernst T. Methamphetamine users show greater than normal age-related cortical gray matter loss. *Addiction*. 2011;106(8):1474-1483. doi:10.1111/j.1360-0443.2011.03433.x
10. Ottino-González J, Uhlmann A, Hahn S, et al. White matter microstructure differences in individuals with dependence on cocaine, methamphetamine, and nicotine: findings from the Enigma-Addiction Working Group. *Drug Alcohol Depend*. 2022;230:109185. doi:10.1016/j.drugalcdep.2021.109185
11. Gong M, Shen Y, Liang W, et al. Impairments in the default mode and executive networks in methamphetamine users during short-term abstinence. *Int J Gen Med*. 2022;15:6073-6084. doi:10.2147/ijgm.s369571
12. Nestor LJ, Ghahremani DG, London ED. Reduced neural functional connectivity during working memory performance in methamphetamine use disorder. *Drug Alcohol Depend*. 2023;243:109764. doi:10.1016/j.drugalcdep.2023.109764
13. Kane MJ, Hambrick DZ, Tuholski SW, Wilhelm O, Payne TW, Engle RW. The generality of working memory capacity: a latent-variable approach to verbal and visuospatial memory span and reasoning. *J Exp Psychol Gen*. 2004;133(2):189-217. doi:10.1037/0096-3445.133.2.189
14. Hubbard NA, Romeo RR, Grotzinger H, et al. Reward-sensitive basal ganglia stabilize the maintenance of goal-relevant neural patterns in adolescents. *J Cogn Neurosci*. 2020;32(8):1508-1524. doi:10.1162/jocn_a_01572
15. Rypma B, Prabhakaran V, Desmond JE, Glover GH, Gabrieli JDE. Load-dependent roles of frontal brain regions in the maintenance of working memory. *Neuroimage*. 1999;9(2):216-226. doi:10.1006/nimg.1998.0404
16. Davis SW, Crowell CA, Beynel L, et al. Complementary topology of maintenance and manipulation brain networks in working memory. *Sci Rep*. 2018;8(1):17827. doi:10.1038/s41598-018-35887-2
17. Shah AM, Grotzinger H, Kaczmarzyk JR, et al. Fixed and flexible: dynamic prefrontal activations and working memory capacity relationships vary with memory demand. *Cogn Neurosci*. 2019;11(4):175-180. doi:10.1080/17588928.2019.1694500
18. Fryer SL, Woods SW, Kiehl KA, et al. Deficient suppression of default mode regions during working memory in individuals with early psychosis and at clinical high-risk for psychosis. *Front Psychiatry*. 2013;4:92. doi:10.3389/fpsyt.2013.00092
19. Whitfield-Gabrieli S, Thermenos HW, Milanovic S, et al. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc Natl Acad Sci*. 2009;106(4):1279-1284. doi:10.1073/pnas.0809141106
20. Haatveit B, Jensen J, Alnæs D, et al. Reduced load-dependent default mode network deactivation across executive tasks in schizophrenia spectrum disorders. *NeuroImage: Clin*. 2016;12:389-396. doi:10.1016/j.nicl.2016.08.012
21. Anticevic A, Cole MW, Murray JD, Corlett PR, Wang X-J, Krystal JH. The role of default network deactivation in cognition and disease. *Trends Cogn Sci*. 2012;16(12):584-592. doi:10.1016/j.tics.2012.10.008
22. Murphy AC, Bertolero MA, Papadopoulos L, Lydon-Staley DM, Bassett DS. Multimodal network dynamics underpinning working memory. *Nat Commun*. 2020;11(1):3035. doi:10.1038/s41467-020-15541-0
23. Simioni AC, Dagher A, Fellows LK. Effects of levodopa on corticostriatal circuits supporting working memory in Parkinson's disease. *Cortex*. 2017;93:193-205. doi:10.1016/j.cortex.2017.05.021
24. Whitfield-Gabrieli S, Ford JM. Default mode network activity and connectivity in psychopathology. *Annu Rev Clin Psychol*. 2012;8(1):49-76. doi:10.1146/annurev-clinpsy-032511-143049
25. Gauthier GR, Markowski K, Smith JA, Harcey S, Johnston B. Co-use among confidants: an examination of polysubstance use and personal relationships in southeastern Nebraska. *Addict Behav*. 2022;124:107116. doi:10.1016/j.addbeh.2021.107116
26. Napper LE, Fisher DG, Johnson ME, Wood MM. The reliability and validity of drug users' self reports of amphetamine use among primarily heroin and cocaine users. *Addict Behav*. 2010;35(4):350-354. doi:10.1016/j.addbeh.2009.12.006
27. Han B, Compton WM, Jones CM, Einstein EB, Volkow ND. Methamphetamine use, methamphetamine use disorder, and associated overdose deaths among us adults. *JAMA Psychiatry*. 2021;78(12):1329-1342. doi:10.1001/jamapsychiatry.2021.2588
28. Herbeck DM, Brecht M-L, Lovinger K. Mortality, causes of death, and health status among methamphetamine users. *J Addict Dis*. 2014;34(1):88-100. doi:10.1080/10550887.2014.975610
29. Marshall BD, Werb D. Health outcomes associated with methamphetamine use among young people: a systematic review. *Addiction*. 2010;105(6):991-1002. doi:10.1111/j.1360-0443.2010.02932.x
30. Greene AS, Shen X, Noble S, et al. Brain–phenotype models fail for individuals who defy sample stereotypes. *Nature*. 2022;609(7925):109-118. doi:10.1038/s41586-022-05118-w
31. Caceres A, Hall DL, Zelaya FO, Williams SCR, Mehta MA. Measuring fmri reliability with the intra-class correlation coefficient. *Neuroimage*. 2009;45(3):758-768. doi:10.1016/j.neuroimage.2008.12.035
32. Barch DM, Burgess GC, Harms MP, et al. Function in the human connectome: task-fMRI and individual differences in behavior. *Neuroimage*. 2013;80:169-189. doi:10.1016/j.neuroimage.2013.05.033
33. Tisdall MD, Hess AT, Reuter M, Meintjes EM, Fischl B, van der Kouwe AJ. Volumetric navigators for prospective motion correction and selective reacquisition in neuroanatomical MRI. *Magn Reson Med*. 2011;68(2):389-399. doi:10.1002/mrm.23228
34. Esteban O, Markiewicz CJ, Blair RW, et al. FMRIPrep: a robust preprocessing pipeline for functional MRI. *Nat Methods*. 2018;16(1):111-116. doi:10.1038/s41592-018-0235-4

35. Hubbard NA, Miller KB, Aloi J, Bajaj S, Wakabayashi KT, Blair RJ. Evaluating instrumental learning and striatal–cortical functional connectivity in adolescent alcohol and cannabis use. *Addict Biol*. 2022;28(1):e13258. doi:10.1111/adb.13258
36. Hubbard NA, Auerbach RP, Siless V, et al. Connectivity patterns evoked by fearful faces demonstrate reduced flexibility across a shared dimension of adolescent anxiety and depression. *Clin Psychol Sci*. 2022;11(1):3-22. doi:10.1177/21677026221079628
37. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*. 2012;59(3):2142-2154. doi:10.1016/j.neuroimage.2011.10.018
38. Chen G, Adleman NE, Saad ZS, Leibenluft E, Cox RW. Applications of multivariate modeling to neuroimaging group analysis: a comprehensive alternative to univariate general linear model. *Neuroimage*. 2014;99:571-588. doi:10.1016/j.neuroimage.2014.06.027
39. Cox RW, Chen G, Glen DR, Reynolds RC, Taylor PA. FMRI clustering and false-positive rates. *Proc Natl Acad Sci*. 2017;114(17):E3370-E3371. doi:10.1073/pnas.1614961114
40. Cowan N, Elliott EM, Scott Saults J, et al. On the capacity of attention: its estimation and its role in working memory and cognitive aptitudes. *Cogn Psychol*. 2005;51(1):42-100. doi:10.1016/j.cogpsych.2004.12.001
41. Tulsky DS, Carlozzi N, Chiaravalloti ND, et al. NIH toolbox cognition battery (NIHTB-CB): list sorting test to measure working memory. *J Int Neuropsychol Soc*. 2014;20(6):599-610. doi:10.1017/s135561771400040x
42. Yeo BT, Krienen FM, Sepulcre J, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106(3):1125-1165. doi:10.1152/jn.00338.2011
43. D'Esposito M, Postle BR. The cognitive neuroscience of working memory. *Annu Rev Psychol*. 2015;66(1):115-142. doi:10.1146/annurev-psych-010814-015031
44. Miller EK, Buschman TJ. Cortical circuits for the control of attention. *Curr Opin Neurobiol*. 2013;23(2):216-222. doi:10.1016/j.conb.2012.11.011
45. Volkow ND, Chang L, Wang G-J, et al. Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry*. 2001;158(3):377-382. doi:10.1176/appi.ajp.158.3.377
46. Kohno M, Okita K, Morales AM, et al. Midbrain functional connectivity and ventral striatal dopamine D2-type receptors: link to impulsivity in methamphetamine users. *Mol Psychiatry*. 2016;21(11):1554-1560. doi:10.1038/mp.2015.223
47. O'Reilly RC. Biologically based computational models of high-level cognition. *Science*. 2006;314(5796):91-94. doi:10.1126/science.1127242
48. Gruber AJ, Dayan P, Gutkin BS, Solla SA. Dopamine modulation in the basal ganglia locks the gate to working memory. *J Comput Neurosci*. 2006;20(2):153-166. doi:10.1007/s10827-005-5705-x
49. Tomasi D, Goldstein RZ, Telang F, et al. Widespread disruption in brain activation patterns to a working memory task during cocaine abstinence. *Brain Res*. 2007;1171:83-92. doi:10.1016/j.brainres.2007.06.102
50. Charlet K, Beck A, Jorde A, et al. Increased neural activity during high working memory load predicts low relapse risk in alcohol dependence. *Addict Biol*. 2013;19(3):402-414. doi:10.1111/adb.12103
51. Wesley MJ, Lile JA, Fillmore MT, Porrino LJ. Neurophysiological capacity in a working memory task differentiates dependent from nondependent heavy drinkers and controls. *Drug Alcohol Depend*. 2017;175:24-35. doi:10.1016/j.drugalcdep.2017.01.029
52. Klooster DCW, Ferguson MA, Boon PAJM, Baeken C. Personalizing repetitive transcranial magnetic stimulation parameters for depression treatment using multimodal neuroimaging. *Biol Psychiatry: Cog Neurosci Neuroimag*. 2022;7(6):536-545. doi:10.1016/j.bpsc.2021.11.004
53. Soleimani G, Kupliki R, Bodurka J, Paulus MP, Ekhtiari H. How structural and functional MRI can inform dual-site TACS parameters: a case study in a clinical population and its pragmatic implications. *Brain Stimul*. 2022;15(2):337-351. doi:10.1016/j.brs.2022.01.008

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