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Prestimulus Activity in the Cingulo-Opercular Network Predicts Memory for Naturalistic Episodic Experience

#Noga Cohen[1,2], #Aya Ben-Yakov[1,3], Jochen Weber[2], Micah G. Edelson[4], Rony Paz[1] and Yadin Dudai[1]

[1]Department of Neurobiology, Weizmann Institute of Science, 761000 Rehovot, Israel

[2]Department of Psychology, Columbia University, New York, NY, USA

[3]MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK

[4]Department of Economics, University of Zurich, 8006 Zurich, Switzerland

# equal contribution

Corresponding author:

Noga Cohen, PhD

Department of Psychology

Columbia University

324 Schermerhorn Hall

1190 Amsterdam Avenue

New York, NY 10027

Email: noga.cohen@columbia.edu phone: 646-575-6456

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Abstract

Human memory is strongly influenced by brain states occurring before an event, yet we know little about the underlying mechanisms. We found that activity in the cingulo-opercular network (including bilateral anterior insula and anterior prefrontal cortex) seconds before an event begins can predict whether this event will subsequently be remembered. We then replicated this finding using an independent data-set and tested how activity in the cingulo-opercular network shapes memory performance. Our findings indicate that prestimulus cingulo-opercular activity affects memory performance by opposingly modulating subsequent activity in two sets of regions previously linked to encoding and retrieval of episodic information. Specifically, higher prestimulus cingulo-opercular activity was associated with a subsequent increase in activity in temporal regions previously linked to encoding and with a subsequent reduction in activity within a set of regions thought to play a role in retrieval and self-referential processing. Together, these findings suggest that prestimulus attentional states modulate memory for real-life events by enhancing encoding and by dampening interference from competing memory substrates.

Keywords: cingulo-opercular network, episodic memory, fMRI, prestimulus, subsequent memory

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Successful memory formation is associated with enhanced activity in brain regions linked to encoding such as the fusiform and medial temporal regions (Paller et al., 1987; Paller and Wagner, 2002; Kim, 2011), and with reduced activity in regions associated with retrieval and self-referential processes, such as the precuneus and posterior cingulate cortex (Kim et al., 2010). Thus far, the examination of the neural correlates of memory formation has focused mainly on the brain activity occurring during (e.g., Davachi et al., 2003; Eichenbaum et al., 2007; Kim et al., 2010; Kim, 2011) or following (Tambini et al., 2010; Ben-Yakov et al., 2011; Ben-Yakov et al., 2013; Staresina et al., 2013; Ben Yakov et al., 2014; Tompary et al., 2015) the presentation of the memoranda. Processes occurring before the onset of an event, however, also shape memory formation (Cohen et al., 2015). While some studies probed the prestimulus brain activity that predicts memory performance, it is yet unclear how prestimulus activity and activity during the stimulus interact to modulate encoding.

Prior studies that have examined memory-predictive prestimulus activity found that activity in regions such as the hippocampus, amygdala, and midbrain (Adcock et al., 2006; Mackiewicz et al., 2006; Wittmann et al., 2007; Park and Rugg, 2010; Addante et al., 2015; de Chastelaine & Rugg, 2015) predicted whether an upcoming event will be later remembered or forgotten. Specifically, compared to subsequently-forgotten stimuli, stimuli that were later remembered showed higher activity in these regions several seconds prior to stimulus onset. It was suggested that prestimulus activity in these regions enhance memory formation by preparing the system to encode the upcoming stimulus (e.g., by lowering the threshold for LTP in the medial temporal lobe; Frey et al., 1993; Huang and Kandel, 1995; Otmakhova and Lisman, 1996).

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While the aforementioned studies provide important insights regarding the prestimulus brain correlates of memory formation, their findings may have been affected by specific task characteristics. Specifically, in most of these studies a cue informed the participant of the content of the upcoming to-be-remembered target. For example, memory-predictive prestimulus activity in the amygdala was found following a cue predicting a subsequent appearance of an unpleasant picture (Mackiewicz et al., 2006), while memory-predictive prestimulus activity in the midbrain was found following a cue predicting a rewarding target (Adcock et al., 2006). Furthermore, these studies did not examine the link between prestimulus activity and online stimulus activity and thus only provide indirect evidence as to how prestimulus activity modulates memory performance. The aim of the current study was therefore twofold: 1) identify prestimulus activity that predicts memory outcome in naturalistic settings, and 2) offer a mechanistic account for the role of this activity in shaping memory formation.

We first identified memory-predictive prestimulus activity using a subsequent memory functional magnetic resonance imaging (fMRI) study (Experiment 1). Participants were presented with realistic memoranda (brief narrative movie clips) and their memory for the main episode in each of the clips was tested following the scan using a cued-recall task. In Experiment 2 we analyzed an independent dataset to replicate the findings of Experiment 1 and to test two possible mechanistic accounts for the role of the observed prestimulus activity in shaping memory performance. Following the findings of Experiment 1 showing memory-predictive prestimulus activity in the cingulo-opercular network, which is commonly associated with top-down control of attention, we conducted two multi-level mediation analyses to test the following predictions regarding prestimulus

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cingulo-opercular activity: 1) it enhances memory performance by boosting online encoding activity; 2) it enhances memory by suppressing task-unrelated, self-generated thoughts.

Experiment 1

Experiment 1 included a subsequent memory task in which participants were presented with realistic memoranda (brief narrative movie clips) in an fMRI scanner. Memory for the clips was tested outside the MRI about 20 minutes following the scan. In addition to BOLD signal, we collected eye tracking data (eye-movements, blinks and pupil size). These measures were used to control for participants' engagement and arousal during the task and are reported in the Supplementary Information.

Materials and Methods

Participants

Experiment 1 included 28 participants (12 male, mean age = 25.5 $\pm$ 3.2). Two participants were excluded due to excessive head movements, three participants were excluded due to technical problems during the Study session, one participant was excluded due to low memory performance (correctly recalled less than 10% of the movies), hence the resulting sample included 22 participants (9 males, mean age = 25.7 $\pm$ 3.4). The study was approved by the ethics committee of the Weizmann Institute of Science and all subjects gave informed consent prior to the experiment.

Stimuli

Each participant viewed 160 audiovisual clips (Ben-Yakov and Dudai, 2011). Of these clips, 140 were narrative movie clips and were used for the current analysis. Each

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clip lasted 8 s and was preceded by an instruction stimulus (7/9/11 s) that included the Hebrew word for remember (לזכור) or look (לראות).

Experimental protocol

Study session. The Study session took place in an fMRI scanner and was divided into four scanning runs. Each run started and ended with the presentation of a blank screen for 10 s. Each trial (see Figure 1 for an example) started with a fixation cross for 2 s. Then, an instruction word ("remember"/"look") was presented for a jittered length (7/9/11 s with an average of 8.5 s). In order to eliminate temporal anticipation effects, the distribution of instruction lengths was determined using the nonaging foreperiod distribution (Niemi & Näätänen, 1981). Specifically, there was a 50 % probability that the clip will appear in any given foreperiod. This structure was designed specifically to eliminate participants' ability to predict when the clip will appear following the onset of the instruction cue. There were 80 trials in the 7 s foreperiod, 40 trials in the 9 s foreperiod, and 20 trials in the 11s foreperiod. In addition, 20 catch trials were included, in which the clip was a visually scrambled clip accompanied by a non-distinctive background noise. Catch trials were always preceded by the longest foreperiod duration (11 s instruction), thus making it impossible for participants to predict whether the instruction would be followed by a narrative or by a control clip. Following the instruction word, a clip was presented for 8 s. Each trial ended with a fixation cross for 3 s.

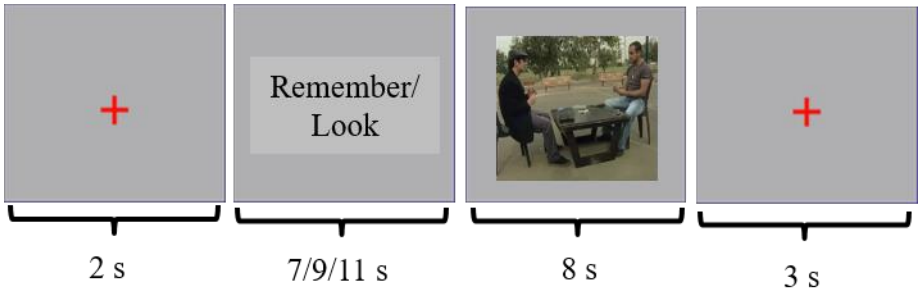

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Figure 1. Example of a trial in the Study session.

Test session. The Test session took place outside the scanner, 20 min after the Study session. Participants were informed beforehand about the format of the Test session. The Test session consisted of questions about the gist of each of the clips (e.g., "What did the parents say to their son?"). Clips that received a correct answer were labeled as "remembered" and clips that received a wrong answer or no answer were labeled as "forgotten". In cases where it was not completely clear whether an answer was correct, the corresponding clip was labeled as "X" and excluded from analysis. The test probed memory for all clips, including those preceded by the "look" instruction.

fMRI acquisition and data analysis

The experiment was carried out on a 3T Trio Magnetom Siemens scanner at the Weizmann Institute of Science, Rehovot, Israel. BOLD contrast was obtained using a gradient-echo EPI sequence (FOV – 216 cm, matrix size – 72 x 72, voxel size – 3 x 3 x 4 mm^3, TR/TE/FA = 2,000 ms / 30 ms / 75 degrees, 32 axial slices). A T1-weighted 3D MPRAGE sequence was used to collect anatomical scans (voxel size – 1 x 1 x 1 mm^3, TR/TE/FA = 2,300 ms / 2.98 ms / 9 degrees).

fMRI data pre-processing

fMRI data were processed and analyzed using Statistical Parametric Mapping software (SPM8; Wellcome Department of Imaging Neuroscience, London, UK) with MATLAB 7.14.0 (the Mathwork, USA). Pre-processing included slice timing correction to the middle slice, motion correction using realignment to the first volume, and co-registration to the individual high-resolution anatomical image. Then, normalization to

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Montreal Neurological Institute (MNI) space (Mazziotta et al., 1995) was performed using the unified segmentation approach (Ashburner and Friston, 2005). Images were then spatially smoothed with a 6-mm full width at half maximum (FWHM) Gaussian kernel. Voxel size following pre-processing was set to be 3 x 3 x 3 mm^3.

fMRI data analysis

Prestimulus activity during the instruction time-window was modeled using box-car epochs with variable durations (i.e., from instruction onset to clip onset, lasting 7, 9, or 11 seconds), convolved with the canonical hemodynamic response function (HRF). For each participant, a set of eight regressors were constructed, for all possible combinations of instruction type (remember/look) and clip type (remembered/forgotten/control/x). This resulted in the following conditions: remember-remembered, remember-forgotten, remember-control, remember-X, look-remembered, look-forgotten, look-control, look-X. In addition, six motion realignment nuisance regressors, as well as white matter (WM) and cerebrospinal fluid (CSF) regressors, were added to the GLM, and a high-pass filter of 100 s was applied. The single-subject contrasts were then taken to a standard full factorial ANOVA with the relevant task conditions as factors (remember-remembered, look-remembered, remember-forgotten, look-forgotten). We used a second-level contrast to assess the main effect of interest (remembered > forgotten). See Supplementary Information for the main effect of instruction type (remember > look) and for control analyses showing no indication for sequential effects or modulation of the main effect by instruction duration or by prestimulus arousal (indicated by pupil size). The interaction between instruction type and memory performance did not reveal significant activations and therefore we collapsed across the two instruction types in the time course illustration

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(Figure 2b; see Supplementary Information for time courses representing all four conditions).

For the whole-brain analysis, we used a voxel-level threshold of $p < 0.001$ and a cluster-level threshold of pFWE < 0.05, using SPM's built-in Gaussian Random Fields (GRF) correction procedure. The cluster-forming threshold (CFT, $p < 0.001$) was chosen to approximately correctly account for the expected false-positive rate using GRF (Eklund et al., 2016). For illustration purposes, time courses were extracted by Z-scoring the raw BOLD signal for each run of each participant. The time courses were then averaged across all events from the same type (remember-remembered, remember-forgotten, look-remembered, look-forgotten) within each participant and then across participants. Time courses are displayed with error bars indicating the standard error of the mean across participants (random-effects).

Results

Memory performance

Participants remembered 39% $\pm$3.16% of the clips. See Supplementary Information for behavioral effects related to instruction type.

Prestimulus activity in the cingulo-opercular network predicts subsequent memory.

In order to identify regions demonstrating higher prestimulus activity for subsequently remembered vs. forgotten clips, we conducted a whole-brain analysis (cluster-forming threshold $p < 0.001$, cluster-pFWE < 0.05), in the instruction time window (7/9/11 sec). This analysis yielded significant activity in a set of regions usually considered to be part of the cingulo-opercular network (see Figure 2a and Table 1). Illustration of this

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effect can be seen in Figure 2b, which depicts the mean BOLD signal for remembered and forgotten clips, extracted from two selected regions of interest (ROI).

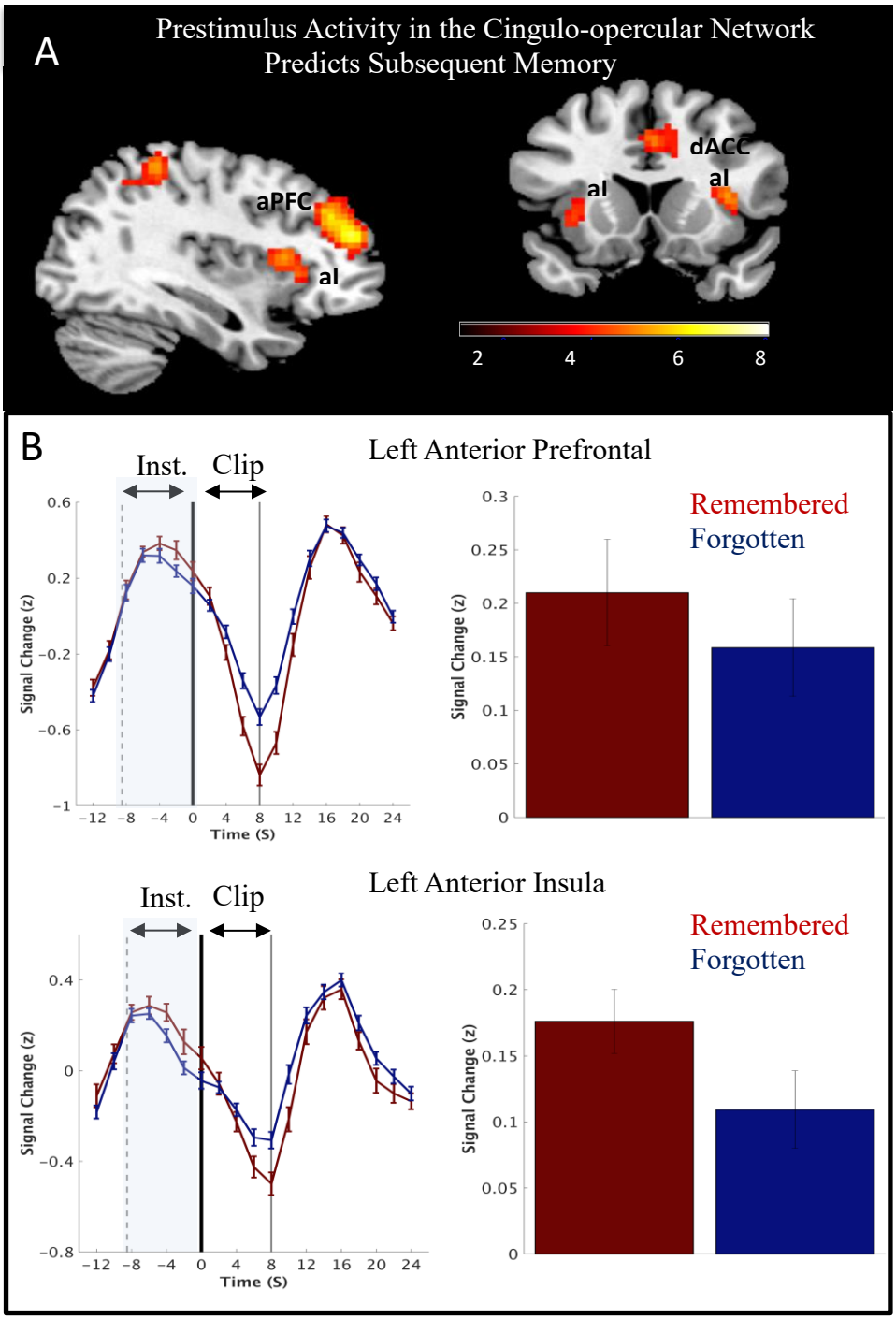

Figure 2. **A)** Regions demonstrating higher prestimulus BOLD activity for remembered vs. forgotten clips ($p < 0.001$, cluster pFWE < .05) in Experiment 1. Data are shown on

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sagittal and axial slices of an MNI template. aI - anterior insula; aPFC - anterior prefrontal; dACC - dorsal anterior cingulate cortex. **B)** For illustration purposes, mean group BOLD signal (after z scoring each time course) for remembered and forgotten clips in Experiment 1 were extracted from two regions of the cingulo-opercular network using a functional ROI. The black lines indicate the onset of clip presentation, the gray lines indicate the offset of the current clips, and the dashed lines represent the mean onset of the instruction cue. The bar figures represent the mean activity during the instruction time-window for each of the conditions.

Side	Region	MNI Coordinates (x, y, z)			t-value	Voxels
L	Anterior Prefrontal	-27	38	7	6.36	375
R	Anterior Prefrontal + Insula	33	47	22	6.12	234
R	Superior Frontal	15	62	1	4.99	232
L	Anterior Insula	-33	14	4	4.65	53
R	Postcentral	36	-40	58	4.59	85
L	Precuneus	12	-70	43	4.41	126
R	Dorsal anterior Cingulate	3	20	37	4.36	175
L	Inferior Parietal	-36	-52	40	4.28	62

Table 1. Brain activity for the whole-brain analysis of the remembered > forgotten contrast ($p < .001$, cluster pFWE < .05). Note that the right anterior prefrontal cluster extended to the right anterior insula.

Experiment 2

Data from a second experiment were used to replicate the findings of Experiment 1 and to explore the role of the cingulo-opercular network in modulating memory performance. The cingulo-opercular network is usually associated with adaptive control of attention (Dosenbach et al., 2008) and therefore we predicted that this network may set the

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stage for encoding by modulating online clip-related activity. In order to test this prediction we probed for possible mediators linking prestimulus cingulo-opercular activity and memory performance using a parametric analysis. Then, we conducted two multi-level logistic Bayesian mediation models to examine the role of these potential mediators in the association between cingulo-opercular activity and memory performance.

Materials and methods

A data-set from an independent study previously conducted in our lab (Experiment 3 in Ben-Yakov and Dudai, 2011) was used in the current experiment.

Participants

Experiment 2 included 21 participants. Three participants were excluded due to low memory performance (correctly recalled less than 10% of the movies), hence the resultant sample included 18 participants (11 males, mean age = 26.7 $\pm$ 2.8). The study was approved by the ethics committee of the Weizmann Institute of Science and all subjects gave informed consent prior to the experiment.

Stimuli

Each participant viewed 128 clips. Of these clips, 112 were narrative movie clips and were used in the current analysis. The clips were of varied lengths (32 clips of 8 s, 64 clips of 12 s, and 16 clips of 16 s). The task included also control clips and 4 brief blocks of a go/no-go task (Ben-Yakov et al., 2011).

Experimental protocol

Study session. The Study session took place in an fMRI scanner and was divided into two scanning runs. The clips were presented in random order; each clip was preceded by a fixation screen of jittered length (8/10/12/14/16 s with average of 10.75 s).

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Test session. The Test session was similar to the one used in Experiments 1, but was administered one day following the Study session.

fMRI acquisition and data analysis

The experiment was carried out on a 3T Trio Magnetom Siemens scanner at the Weizmann Institute of Science, Rehovot, Israel. BOLD contrast was obtained using a gradient-echo EPI sequence (FOV – 24 cm, matrix size – 80 x 80, voxel size – 3 x 3 x 4 mm^3, TR/TE/FA = 2,000 ms / 30 ms / 75 degrees, 36 axial slices). A T1-weighted 3D MPRAGE sequence was used to collect anatomical scans (voxel size – 1 x 1 x 1 mm^3, TR/TE/FA = 2,300 ms / 2.98 ms / 9 degrees).

Data pre-processing

See Experiment 1. In the current experiment, we omitted the first 15 volumes (during this time there was an audiovisual clip for accommodation to fMRI).

Network definition

In order to replicate the findings of Experiment 1, we created an ROI of the cingulo-opercular network based on a study by Dosenbach et al (2007), using WFUpickatlas toolbox (Maldjian et al., 2003; http://fmri.wfubmc.edu/software/PickAtlas). As in Dosenbach et al's paper, this ROI included 12mm spheres around peak coordinates (see Table 2) of the right and left anterior insula (aI), right and left anterior prefrontal (aPFC), and dorsal anterior cingulate cortex (dACC).

Side	Region	MNI Coordinates (x, y, z)		
L	Anterior Prefrontal	-28	51	15
R	Anterior Prefrontal	27	50	23
L	Anterior Insula	-35	14	5

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R	Anterior Insula	36	16	4
	Dorsal Anterior Cingulate	-1	10	46

Table 2. Coordinates of the cingulo-opercular network based on Dosenbach et al (2007).

Data analysis

As in Experiment 1, prestimulus activity was modeled using box-car epochs convolved with the canonical hemodynamic response function (HRF) on the prestimulus time-window (8-16 sec preceding clip onset). For each participant, a set of five regressors were constructed, coding for the different prestimulus events (remembered/forgotten/control/x/go-nogo). In addition, six motion realignment nuisance regressors, as well as WM and CSF regressors, were added to the GLM, and a high-pass filter of 100 s was applied. As in Experiment 1, we computed the statistics for two additional control models (see Supplementary Information). The single-subject contrasts were then taken to a repeated-measures ANOVA with all task conditions as factors. A specific contrast assessed the main effect of interest (remembered > forgotten). A small volume correction (SVC) analysis using a threshold of pFWE < .05 (Friston et al., 1996) was performed on the cingulo-opercular ROI.

Identifying mediators

A parametric analysis was conducted to explore the role of prestimulus activity in shaping online stimulus activity. This analysis searched for regions in which activity during clip presentation correlated with prestimulus cingulo-opercular activity. A new first-level model was created, in which we collapsed across remembered and forgotten trials (to increase power and to avoid a dependency between the parametric modulator and the main effect of memory performance). Therefore, the model included three regressors (narrative

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clips [both remembered and forgotten], control clips, and go/no-go events), and their parametric modulation regressors. Since the cingulo-opercular regions were highly correlated, the parametric modulation regressors included ROI-averaged activity from all significant voxels within the cingulo-opercular mask (taken as a single ROI), as indicated by the SVC analysis described above for the remembered > forgotten contrast. A second-level analysis (one sample t-test, voxel-level threshold of $p < 0.001$ and a cluster-level threshold of $pFWE < 0.05$) was conducted only on the parametric regressor of the narrative clip events. We computed both the positive (1 coded) and negative (-1 coded) contrasts for the parametric regressor.

Multi-level logistic mediation

Multi-level logistic mediation analyses were conducted to examine whether the link between the observed prestimulus cingulo-opercular activity and subsequent memory is mediated by clip-related activity in candidate regions found in the parametric analysis. For this purpose, two additional regression models were estimated, in each of which we constructed separate regressors for each trial (e.g., Rissman et al., 2004). In the first of these single-trial models, we modeled the prestimulus phase of each event (total of 128 regressors), convolved with the canonical HRF. The second model was constructed analogously, but the actual clip stimulus period was modeled (into an equal number of 128 regressors). For each of the prestimulus and clip stimulus periods, we then extracted the ROI-averaged beta (amplitude) estimates for the cingulo-opercular network ROI for the prestimulus period, and for two sets of regions that were identified using the parametric model described above. The extracted and averaged betas were then, together with the memory performance (coded as 0 for forgotten and 1 for remembers), subjected to two

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Bayesian multi-level logistical mediation analyses, which were conducted using the bmlm R package (Vuorre, 2017; Vuorre and Bolger, 2017). Bmlm uses the RStan interface to conduct the Bayesian inference (Stan Development Team, 2016). For each path (a, b, c, c', ab) we present the fixed-effect parameter, and its associated credible intervals (95% mass of the marginal posterior distribution).

Results

Memory performance

Participants remembered 27.6±3.9% of the clips.

Prestimulus activity in the cingulo-opercular network predicts subsequent memory.

In order to assess the robustness of the findings in Experiment 1, an ROI of the cingulo-opercular network was used in a small volume correction (SVC) analysis. This analysis revealed significant activations in all regions of the network (see Table 3 and Figure 3; results of a whole-brain analysis are presented in the Supplementary Information).

Side	Region	MNI Coordinates (x, y, z)			t-value	Voxels
L	Anterior Prefrontal	-33	41	13	6.56	58
	Dorsal Anterior Cingulate	0	11	43	6.33	86
R	Anterior Prefrontal	36	50	22	5.82	44
L	Anterior Insula	-36	11	-2	4.78	25
R	Anterior Insula	39	14	-2	4.32	14

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Table 3. Brain activity for the SVC analysis testing for cingulo-opercular activity in the remembered > forgotten contrast during the prestimulus time-window ($p < .001$, cluster pFWE < .05).

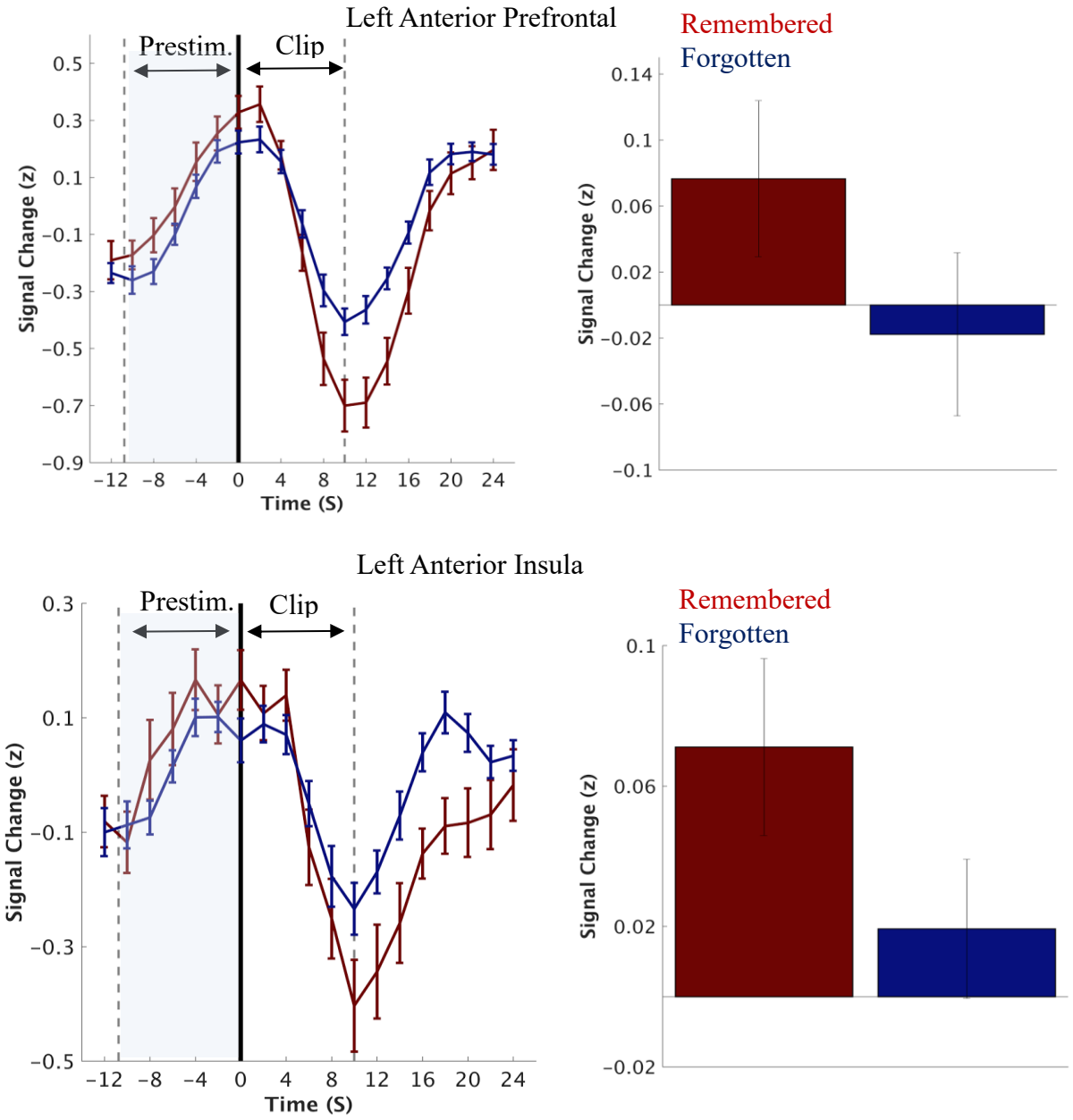

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Figure 3. For illustration purposes, we present the mean group BOLD signal (after z scoring each time course) for remembered and forgotten clips in Experiment 2. BOLD activity was extracted from two example regions of the cingulo-opercular network using a functional ROI. The black lines indicate the onset of clip presentation, the gray lines indicate the offset of the current clips, and the dashed lines represent the mean onset of the instruction cue. The bar figures represent the mean activity during the instruction time-window for each of the conditions.

Parametric analysis probing possible mediators for the cingulo-opercular – memory link.

A parametric analysis was conducted in order to explore whether prestimulus activity in the cingulo-opercular network modulated activity during clip presentation. A whole-brain analysis was used to detect brain regions that, during the clip time-window, were positively or negatively associated with cingulo-opercular prestimulus activity. Regions that were positively associated with prestimulus activity were regions showing an increase in their activity during clip presentation following a higher prestimulus cingulo-opercular activity. Regions that were negatively associated with prestimulus activity were regions showing a *reduction* in their activity during clip presentation following a higher cingulo-opercular activity in the prestimulus phase.

The whole-brain analysis (see Table 3) for positive modulation by cingulo-opercular activity revealed significant activations in the fusiform gyrus and middle temporal regions. The whole-brain analysis for the negative parametric modulation showed

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significant activations in a set of regions that included the cingulate, precuneus, and striatum.

Side	Region	MNI Coordinates (x, y, z)			t-value	Voxels
	Positive Parametric Contrast (+1)					
R	Fusiform & Middle Temporal Gyrus	30	-67	-8	9.06	1572
L	Fusiform & Middle Temporal Gyrus	-30	-61	-5	7.92	901
R	Precuneus	15	-46	46	6.48	138
R	Inferior Frontal	57	32	1	5.88	189
L	Cerebellum	-12	-70	-38	5.87	97
	Rectus	0	56	-17	5.24	53
	Negative Parametric Contrast (-1)					
L	Middle Cingulate	-3	-23	31	13.73	1009
R	Middle Frontal	30	50	19	10.85	360
L	Middle Frontal	-36	47	16	10.05	769
L	Precuneus	-9	-67	46	8.33	370
L	Middle Cingulate	-3	-22	31	7.90	176
L	Insula	-36	17	4	7.36	475
R	Striatum (Caudate, Putamen)	18	20	-5	6.81	145
R	Insula	33	23	7	6.73	222
L	Inferior Parietal	-39	-49	43	6.72	283
L	Striatum (Caudate, Putamen)	-15	17	-5	6.23	47
R	Inferior Parietal	54	-43	40	5.67	107
R	Middle Cingulate	6	-28	46	5.57	44

Table 4. Brain activity for the whole-brain parametric analysis of the positive (+1) and negative (-1) contrasts. Prestimulus cingulo-opercular activity served as a parameter to predict correlated clip-related activity ($p < .001$, cluster pFWE $< .05$).

Mediation analysis for the cingulo-opercular – memory link.

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Two mediation analyses were conducted to measure whether the link between prestimulus cingulo-opercular activity and memory was mediated by activity in the set of brain regions found in the parametric analysis. Specifically, we tested whether activity in regions found in the positive parametric contrast and activity in regions found in the negative parametric contrast mediate the cingulo-opercular - memory link. Both analyses indicated partial mediation, suggesting that around 45% of the link between prestimulus cingulo-opercular activity and successful memory performance was mediated by an increase in clip-related activity in a set of temporal regions (Figure 4a) and by decrease in clip-related activity in a set of regions that included the precuneus, striatum, and cingulate cortex (Figure 4b). Specifically, measuring the path coefficients for a standard three-variable path model that used activity from regions revealed in the positive parametric contrast (+1) as mediator demonstrated credible relationships between prestimulus cingulo-opercular activity and memory performance (path c: b = 0.98, [0.67, 1.3]), prestimulus cingulo-opercular activity and activity in regions found in the positive parametric contrast (path a: b = 0.16 [0.14, 0.19]), and between activity in regions found in the positive parametric contrast and memory performance (path b: b = 2.67 [1.94, 3.43]). Furthermore, the relationship between cingulo-opercular prestimulus activity and memory was reduced when activity in regions found in the positive parametric contrast was included in the model (path ab: b = 0.44 [0.31, 0.58]), although the relationship between the prestimulus cingulo-opercular activity and memory was still present (path c': b = 0.54 [0.26, 0.84]).

Measuring the path coefficients for the model that used activity from regions revealed in the negative parametric contrast (-1) as mediator revealed credible relationships

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between prestimulus cingulo-opercular activity and memory performance (path c: b = 0.93, [0.63, 1.25]), prestimulus cingulo-opercular activity and activity revealed in the negative parametric contrast (path a: b = -0.26 [-0.28 -0.23]), and between activity revealed in the negative parametric contrast and memory performance (path b: b = -1.58 [-2.26, -0.93]). As in the aforementioned model, the relationship between prestimulus cingulo-opercular activity and memory was reduced when the mediator (activity in regions found in the negative parametric contrast) was included in the model (path ab: b = 0.4 [0.23, 0.59]), although the relationship between the prestimulus cingulo-opercular activity and memory was still present (path c': b = 0.53 [0.23, 0.84]).

Thus, the statistical criteria for partial mediation were met in both models, indicating that for the average participant, the enhanced memory performance linked to increased prestimulus activity in the cingulo-opercular network was partially accounted for by the increased activity in a network including temporal regions and decreased activity in a network including the precuneus, cingulate and striatum.

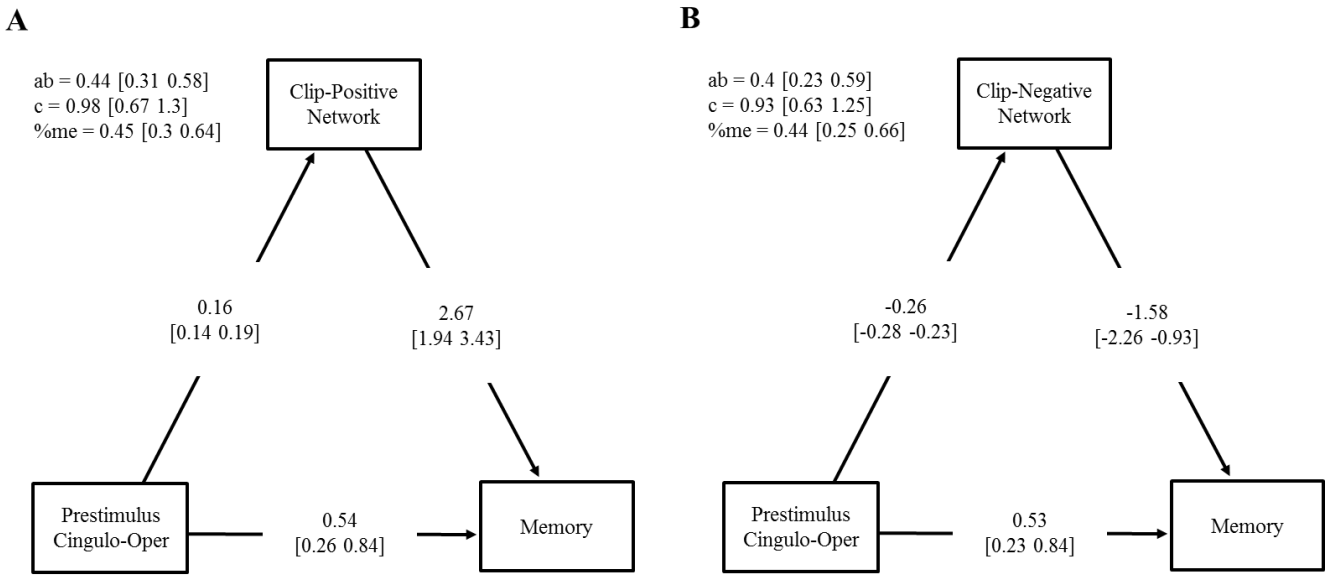

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Figure 4. Multi-level mediation analyses assessing the contribution of regions implicated in the parametric analysis. A) A model including activity from the set of regions found in the positive contrast of the parametric analysis (Clip-Positive Network) as a mediator. B) A model including activity from the set of regions found in the negative contrast of the parametric analysis (Clip-Negative Network) as a mediator.

General Discussion

The current study is the first to explore naturally occurring prestimulus brain activity that predicts encoding of novel, real life events. Furthermore, the current study is the first to provide a mechanistic account linking the observed prestimulus activity to memory formation via modulation of online stimulus activity. In two independent data sets, we found that prestimulus activity in the cingulo-opercular network correlates with subsequent memory performance. Mediation analyses revealed that prestimulus cingulo-opercular activity gates memory performance by enhancing clip-related activity in temporal regions and by dampening clip-related activity in a set of regions that include the precuneus, cingulate and striatum.

According to the dual model network of attentional control (Dosenbach et al., 2008), the cingulo-opercular network is associated with adaptive control of attention and the maintenance of task goals. Thus, our findings may indicate that attentional states preceding an event play a crucial role in shaping long-term memory. This idea raises a question regarding the nature of the observed memory-predictive attentional state, and specifically whether memory-predictive activity in the cingulo-opercular network results from a

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deliberate preparatory process or from an incidental attentional state. The fact that we did not observe a main effect for instruction type (remember > look) in the cingulo- opercular network in Experiment 1 (see SI), and that we replicated this effect in Experiment 2 (in which there was no instruction cue prior to the memoranda), suggests that memory-predictive activation in this network was less related to intentional preparation (see also Turk-Browne et al., 2006; Addante et al., 2015). Therefore, we postulate that incidental brain fluctuations in the cingulo-opercular network modulate encoding. Specifically, events starting during incidental high activity in this network may be remembered better than events starting during incidental low activity. In support of this notion are imaging (Yoo et al., 2012), electrophysiological (Burke et al., 2014) and intracranial brain stimulation (Ezzyat et al., 2017) findings showing that prestimulus brain oscillations can influence memory-related processes.

While the current work focused on cingulo-opercular activity in the prestimulus phase, an examination of the time course reveals that this network plays an opposite role during stimulus presentation. Specifically, during the clips, the cingulo-opercular network was deactivated more strongly for subsequently-remembered clips compared to subsequently forgotten ones. This is in line with previous findings (e.g., Daselaar et al., 2004), and may suggest that processes needed for the preparation of efficient encoding during the prestimulus phase are no longer needed (and should even be suppressed) during the event. This finding may also help reconcile the mixed findings regarding the memory-predictive effect of cingulo-opercular activity during stimulus presentation (e.g., Vaden et al., 2017).

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Our findings suggest both direct and indirect influence of prestimulus cingulo-opercular activity on memory performance. Specifically, using a multi-level logistic mediation analyses we showed that the link between prestimulus cingulo-opercular activity and memory is partially mediated by clip-related activity in two distinct networks. Namely, elevated activity in the cingulo-opercular network was associated with enhanced activity in regions such as the fusiform and middle temporal gyrus, which are thought to play a role in encoding (for a meta-analyses see Sapniol et al., 2009; Murty et al., 2010; Kim et al., 2011), and with reduced activity in a set of regions usually observed during retrieval and self-referential processing (for meta-analysis and review papers see: Wagner et al., 2005; Northoff et al., 2006; Kim et al., 2010; Sapniol et al., 2009). These results support previous findings showing a competitive relationship between networks involved in encoding and retrieval (Kuhl et al., 2010; Kim et al., 2010) and suggest a gating role for attention in determining which of these processes will take precedence. Specifically, as attention plays a prominent role in shifting between external and internal focus (Chun et al., 2011; Kucyi et al., 2017), it is possible that prestimulus attentional state enhances encoding by promoting external focus as well as by suppressing interference by internally-generated thoughts (e.g., retrieval of past memories).

Most previous fMRI studies that explored the association between prestimulus activity and memory performance presented a cue that predicted the content of the to-be-remembered event (Adcock et al., 2006; Mackiewicz et al., 2006; Wittmann et al., 2007; Park and Rugg, 2010; Addante et al., 2015), making it possible that the anticipation for specific content modulated the observed effects. Indeed, several of the regions found in these studies seem to be content related since they were not found in other studies (e.g.,

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amygdala predicted memory when participants anticipated an aversive stimulus; Mackiewicz et al., 2006; midbrain predicted memory when participants anticipated a rewarding stimulus; Adcock et al., 2006). In the few studies that did not present a cue prior to the memoranda, temporal anticipation was still present (Fernández et al., 1999; Turk-Browne et al., 2006; Yoo et al., 2012). In the current study, the results cannot be explained by anticipation because no relevant cue was given prior to the movie clips and the effects of degree of temporal anticipation were accounted for in the design (Experiment 1) and analysis (Experiments 1 & 2; see SI).

Additional control analyses (reported in the SI) ruled out sequential effects (i.e., effects related to memory performance in the previous clip), as well as arousal influences (as indicated by a parametric analysis that included pupil dilation). Furthermore, we demonstrated that findings of the current work cannot be explained by temporal anticipation or by overlap between prestimulus and stimulus-related activity. Therefore, the findings of the current work lead to several predictions that may be tested in further studies. Specifically, real-time fMRI and TMS/tDCS/intracranial stimulation studies can provide direct evidence for the role of spontaneous cingulo-opercular fluctuations in memory success. Furthermore, studies manipulating attention and task-goals can provide evidence for the role on intentional attentional states in enhancing encoding and in reducing interference by internal focus.

In conclusion, we propose that prestimulus attentional states as reflected in cingulo-opercular activity may enhance memory encoding by shifting the balance between encoding and retrieval – increasing focus on the external environment while reducing interference from task-unrelated, internally generated, memories.

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