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Distinct brain networks for remote episodic memory depending on content and emotional experience

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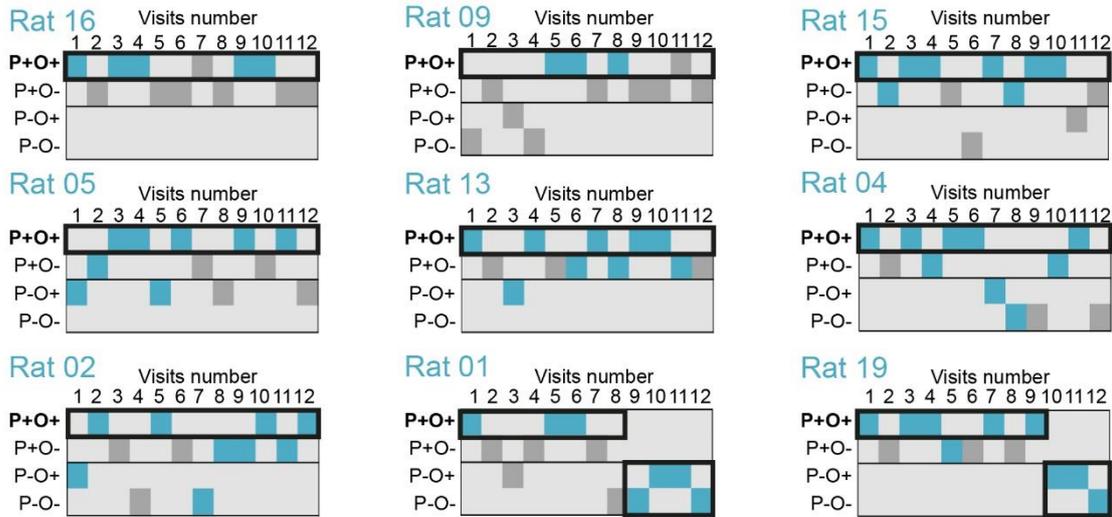
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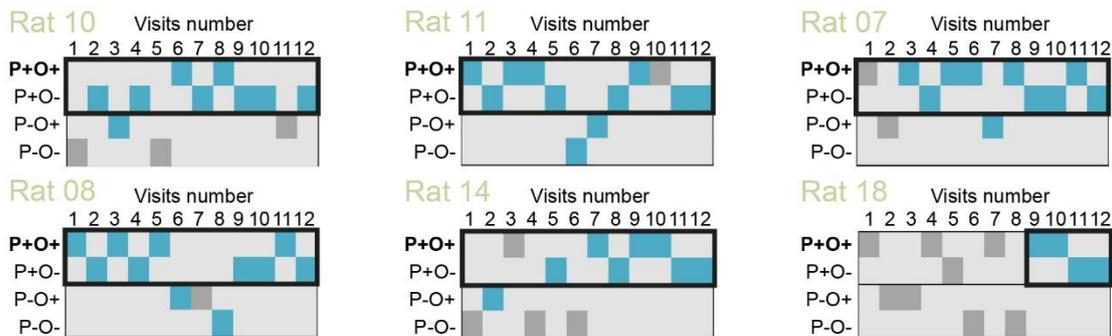
Supplementary figure legends

Supplementary FIGURE 1

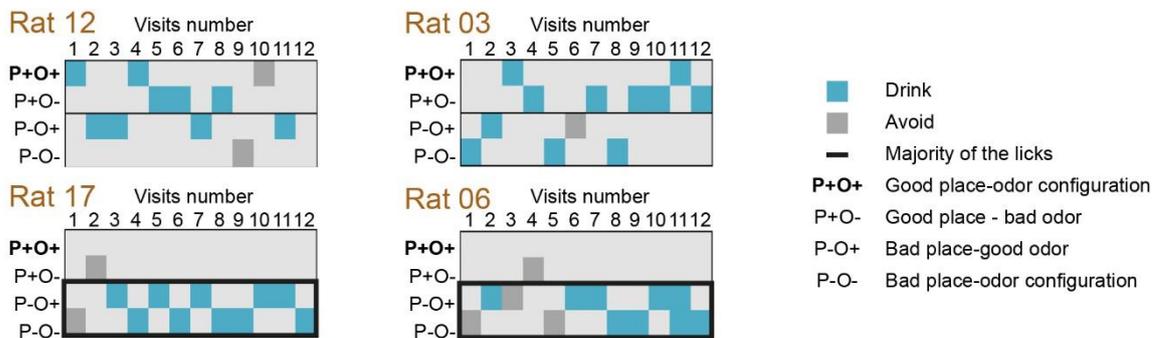
a. WWW Profile



b. Where Profile



c. Indeterminate Profile

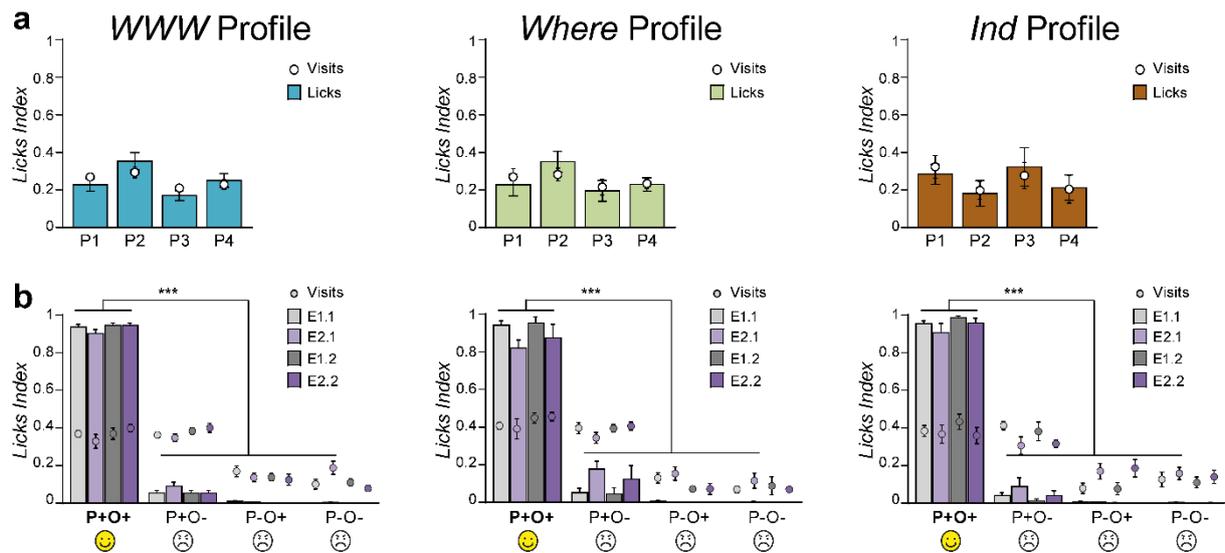


Supplementary Figure 1. Robustness and stability of remote memory profiles during the recall test

Individual and dynamic analyses during the recall test for each memory profile ($n_{WWW} = 9$, $n_{Where} = 6$, $n_{Ind} = 4$). For each rat, all visits (columns numbered from 1 to 12) are presented in front of the configuration encountered by the rat (lines P+O+, P+O-, P-O+, P-O-). A blue square

indicates that a rat drank, and a grey square indicates that a rat did not drink from the given configuration. **(a)** *WWW* profile, with the black frame highlighting that rats predominantly drank from the P+O+ configuration and avoided other configurations during the recall test. **(b)** *Where* rats mainly visited and drank from the good ports (P+O+ and P+O-) during the session. **(c)** *Indeterminate* profile of two rats that drank from all configurations (Rats 12, 03) and two rats that mainly visited and drank from the wrong port (P-O+ and P-O-) during the recall test. P+O+ (good port and good odour); P+O- (good port and bad odour); P-O+ (bad port and good odour); P-O- (bad port and bad odour).

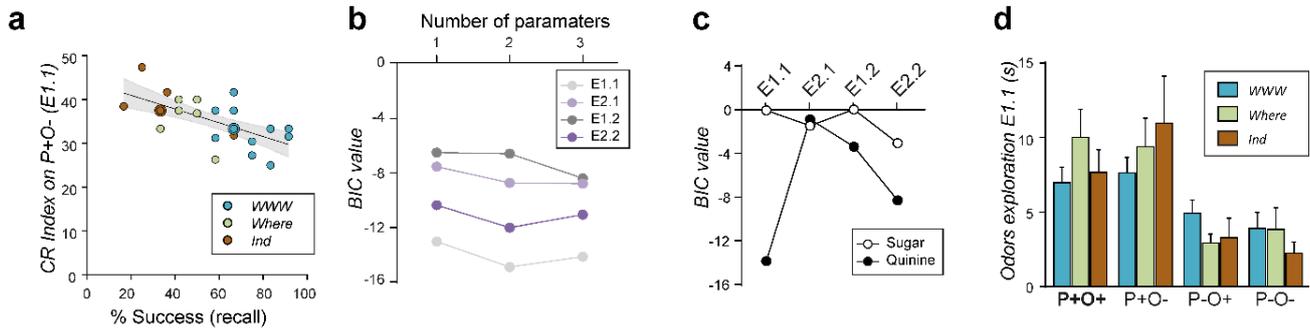
Supplementary FIGURE 2



Supplementary Figure 2. Remote memory profiles are not related to biased experiences during routine sessions or episode encoding

Indices of licks and visits during routine sessions (**a**) and episode encoding (**b**) for each memory profile. During routine sessions before episode encoding, rats of all memory profiles visited the 4 ports and drank equally from them. During episodes, regardless of the profile, the rats visited and drank from the P+O+ configuration, which was associated with a pleasant experience of sugar solution, significantly more than the other configurations. Group data are expressed as the mean \pm SEM ($n_{WWW} = 9$; $n_{Where} = 6$; $n_{Ind} = 4$). *** $p < 0.005$, Friedman tests followed by Wilcoxon tests for statistical comparisons between configurations. P1 (Port 1); P2 (Port 2); P3 (Port 3); P4 (port 4). E1.1 (first episode E1); E2.1 (first episode E2); E1.2 (second episode E1); E2.2 (second episode E2). P+O+ (good port and good odour); P+O- (good port and bad odour); P-O+ (bad port and good odour); P-O- (bad port and bad odour).

Supplementary FIGURE 3

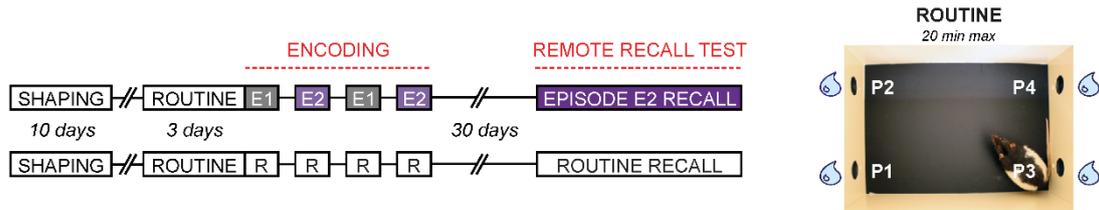


Supplementary Figure 4. Accuracy of remote episodic memory depends on negative experience during the first episode

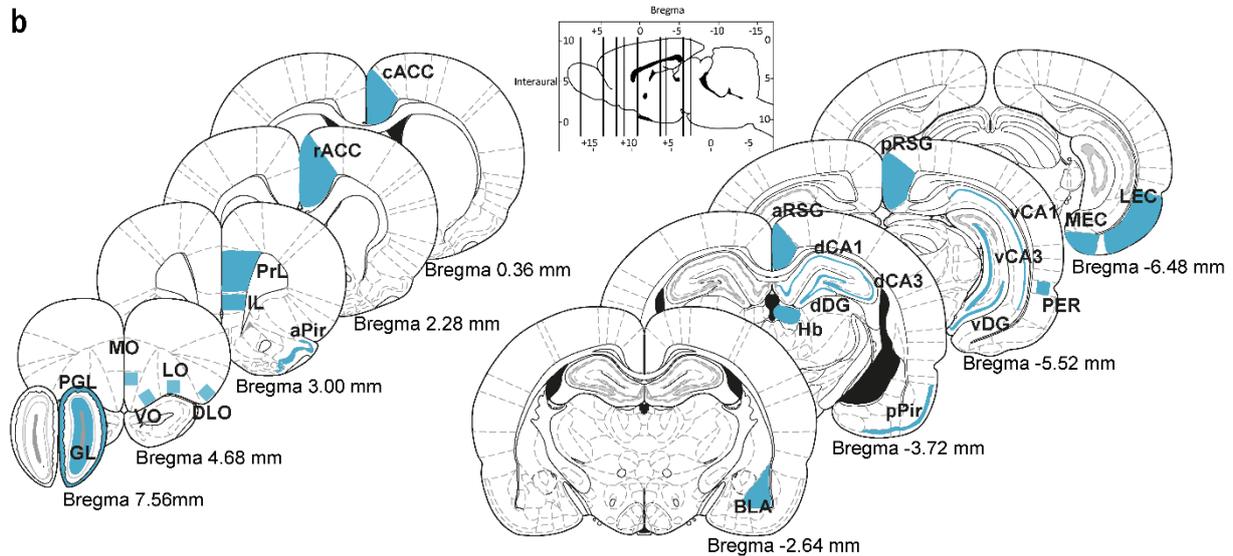
(a) Remote episodic memory performance (success rate during the recall test) was negatively correlated with the correct rejection index on P+O- during E1.1 ($n = 24$; $p_{\text{Spearman}}=0.0024$; $Rho=-0.63$). (b) BIC value of each regression model (for all episode sessions), showing the critical role of the initial episode E1 (E1.1) in the remote memory performance, with lower BIC values regardless of the number of parameters used in the model. (c) BIC value of each regression model for sugar *versus* quinine experience during each episode session, showing that an unpleasant experience during the first episode E1 (E1.1) was a strong predictor of remote episodic memory precision. (d) The duration of odour exploration for each configuration during the first episode E1 was similar for all memory profiles. Group data are represented as the mean \pm SEM ($n_{WWW} = 12$, $n_{Where} = 7$, $n_{Ind} = 5$). Kruskal–Wallis tests for statistical comparisons between memory profiles. E1.1 (first episode E1); E2.1 (first episode E2); E1.2 (second episode E1); E2.2 (second episode E2); P+O+ (good port and good odour); P+O- (good port and bad odour); P-O+ (bad port and good odour); P-O- (bad port and bad odour).

Supplementary FIGURE 4

a



b



Supplementary Figure 4. Protocol for analysing brain networks of remote episodic memories according to IEG expression

(a) Timeline of the behavioural protocol for rats that experienced the episodes ($n = 15$) and control rats ($n = 6$) that experienced only routine sessions (no odour, neutral context and only water). **(b)** Rat brain coronal sections showing regions of interest selected for counting c-Fos⁺ and Zif268⁺ cells. The distance from the bregma is indicated for each coronal section. The densities of IEG⁺ cells were analysed in 23 different brain areas in 2 sections spaced by 168 μm . For the olfactory bulb (OB), counts were performed on 3 slices spaced 504 μm apart. Squares (500 μm *500 μm) were cut for the MO, VO, LO, and DLO. GL (granular layer of the olfactory bulb); PGL (periglomerular layer of the olfactory bulb); aPir/pPir (anterior and posterior piriform cortices); MO-VO (medio-ventral), LO-DLO (dorso-lateral) part of the orbitofrontal cortex; PrL (prelimbic) and IL (infralimbic) cortices; rACC, cACC (rostral and

caudal anterior cingulate cortices); aRSG, pRSG (anterior and posterior retrosplenial cortices); BLA (basolateral amygdala); Hb (habenula); dDG, vDG (dorsal and ventral dentate gyrus); dCA1, dCA3 (dorsal) and vCA1, vCA3 (ventral) hippocampus; PER (perirhinal cortex); LEC, MEC (lateral and medial entorhinal cortices).

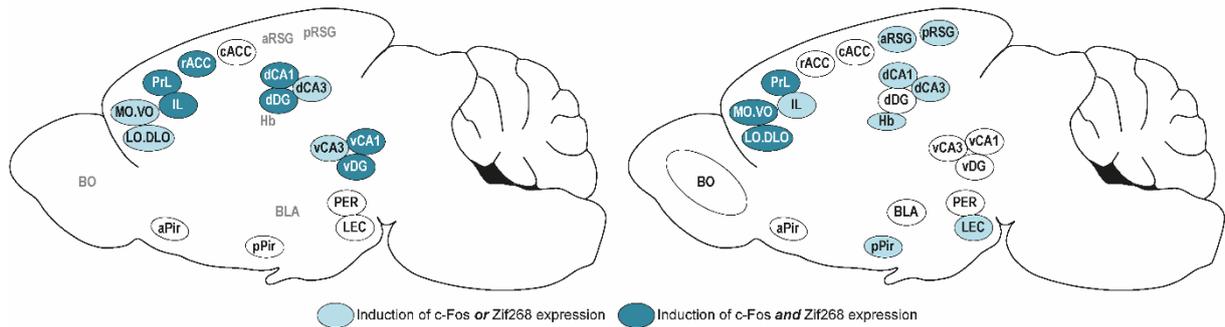
Supplementary FIGURE 5

a WWW network - 24 hours

Veyrac *et al.*, 2015

b WWW network - 30 days

Present study: Fig 6c



Supplementary Figure 5. How brain networks associated with complete episodic memory evolve over time

(a) Summary diagram representing brain areas recruited for WWW rats during recall 1 day³⁰ or (b) 30 days after episode encoding. While recent episodic memories recruited the entire hippocampus³⁰, only the dorsal part was recruited after a long delay. The cortical memory trace reorganized over time since the rACC was no longer in the remote memory network, whereas the OFC remained critical. The pPir and LEC, which are implicated in odour processing, were recruited only after 30 days of retention, suggesting the key role of odours in remote episodic memories. OB (olfactory bulb); aPir/pPir (anterior and posterior piriform cortices); MO. VO (medio-ventral), LO. DLO (dorso-lateral) part of the orbitofrontal cortex; PrL (prelimbic) and IL (infralimbic) cortices; rACC, cACC (rostral and caudal anterior cingulate cortices); aRSG, pRSG (anterior and posterior retrosplenial cortices); BLA (basolateral amygdala); Hb (habenula); dDG, vDG (dorsal and ventral dentate gyrus; dCA1, dCA3 (dorsal) and vCA1, vCA3 (ventral) hippocampus; PER (perirhinal cortex); LEC, MEC (lateral and medial entorhinal cortices).

Supplementary TABLE 1

		Clustering Coefficient		Global Efficiency	
		Data	Bootstrap p value	Data	Bootstrap p value
<i>c-Fos</i>	<i>WWW</i>	0.02	0.008	0.36	0.050
	<i>Where</i>	0.04	0.010	0.41	0.723
<i>Zif268</i>	<i>WWW</i>	0.38	0.010	0.38	0.010
	<i>Where</i>	0.02	0.020	0.24	0.307

Supplementary Table 1. Statistical properties of remote episodic memory brain networks.

Clustering coefficient and *global efficiency* for each memory profile (*Where* and *WWW*) for *c-Fos* and *Zif268* functional networks ($n_{WWW} = 9$; $n_{Where} = 6$). *P* values from bootstrap analyses show that *clustering coefficients* were significantly different from those of a random network for all graphs. Recall of incomplete episodic memories (*Where* profile) was related to less efficient functional networks since the *global efficiency* of *c-Fos* and *Zif268* functional networks did not differ from that of a random network.

Supplementary TABLE 2

a

	<i>Where c-Fos network</i>			<i>WWW c-Fos network</i>		
	Degree	Strength	Betweenness	Degree	Strength	Betweenness
CG	-	-	-	4	6170*	29
PGL	-	-	-	5**	7530**	129
aPir	5	5541	7	3	4465	162*
pPir	5	5542	7	2	2799	34
MO.VO	4	7198	45	3	4931	34
LO.DLO	4	7113	57	1	1333	0
PrL	1	-1885	0	2	2965	130
IL	3	1885	52	2	2899	160*
rACC	3	5313	31	2	2923	0
cACC	1	1885	0	2	266	112
aRSG	3	1800	28	3	4570	8
pRSG	2	3428	0	4	6674*	48
BLA	1	-2000	0	1	-1466*	0
Hb	-	-	-	3	1832	34
dDG	5	-9198**	7	1	-1433*	0
dCA1	1	1885	0	1	1633	0
dCA3	6*	6970	75	-	-	-
vDG	-	-	-	-	-	-
vCA1	5	5198	7	-	-	-
vCA3	2	-3656**	28	-	-	-
PER	-	-	-	2	2932	64
LEC	5	5542	7	2	133	90
MEC	4	7085*	27	3	1366	166**
Mean	3.3	2758.1	21.0	2.4	2764.3	63.2

b

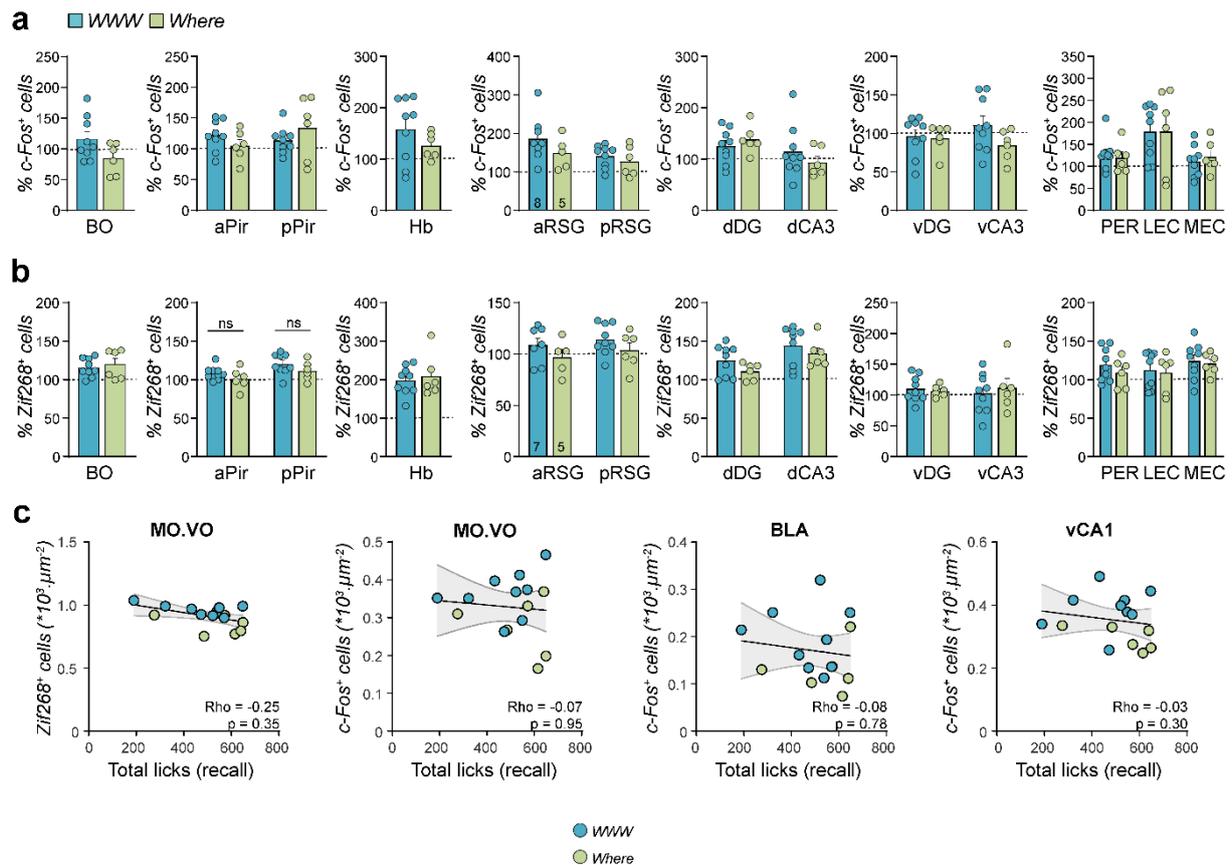
	<i>Where Zif268 network</i>			<i>WWW Zif268 network</i>		
	Degree	Strength	Betweenness	Degree	Strength	Betweenness
CG	1	1771	0	-	-	-
PGL	-	-	-	1	1523	0
aPir	4*	7198*	10	1	1500	0
pPir	3	5313	3	5	7621	10
MO.VO	2	3656	10	1	1366	0
LO.DLO	-	-	-	2	3252	0
PrL	-	-	-	1	1366	0
IL	2	3542	0	1	1500	0
rACC	-	-	-	5	7993	20
cACC	1	1885	0	-	-	-
aRSG	-	-	-	7*	11235*	55*
pRSG	-	-	-	8*	12406*	73**
BLA	-	-	-	1	-1466*	0
Hb	-	-	-	1	-1466*	0

dDG	1	1657	0	2	3032	0
dCA1	2	3428	2	5	8012	21
dCA3	3	5085	16	1	1523	0
vDG	-	-	-	4	6574	1
vCA1	-	-	-	6*	9159*	31
vCA3	2	3542	2	4	6303	0
PER	3	5427	1	6	9351*	14
LEC	1	1885	0	-	-	-
MEC	1	1657	0	6*	9330*	39
Mean	2	3542	3.4	3.4	5005.7	13.2

Supplementary Table 2. Statistical properties of functional networks of remote episodic memories

The *degree*, *strength* and *betweenness centrality* of each node for c-Fos (a) and Zif268 (b) functional networks obtained through graph-theoretical analyses. Data are expressed as the mean values for each parameter for *Where* and *WWW* rats ($n_{WWW} = 9$; $n_{Where} = 6$). A bootstrap analysis determined the major hubs in each network by testing whether the node properties differed from chance (highlighted in bold red font). * $p_{bootstrap} < 0.05$; ** $p_{bootstrap} < 0.01$. GL (granular layer of the olfactory bulb); PGL (periglomerular layer of the olfactory bulb); aPir/pPir (anterior and posterior piriform cortices); MO. VO (medio-ventral), LO. DLO (dorso-lateral) part of the orbitofrontal cortex; PrL (prelimbic) and IL (infralimbic) cortices; rACC, cACC (rostral and caudal anterior cingulate cortices); aRSG, pRSG (anterior and posterior retrosplenial cortices); BLA (basolateral amygdala); Hb (habenula); dDG, vDG (dorsal and ventral dentate gyrus); dCA1, dCA3 (dorsal) and vCA1, vCA3 (ventral) hippocampus; PER (perirhinal cortex); LEC, MEC (lateral and medial entorhinal cortices).

Supplementary FIGURE 6

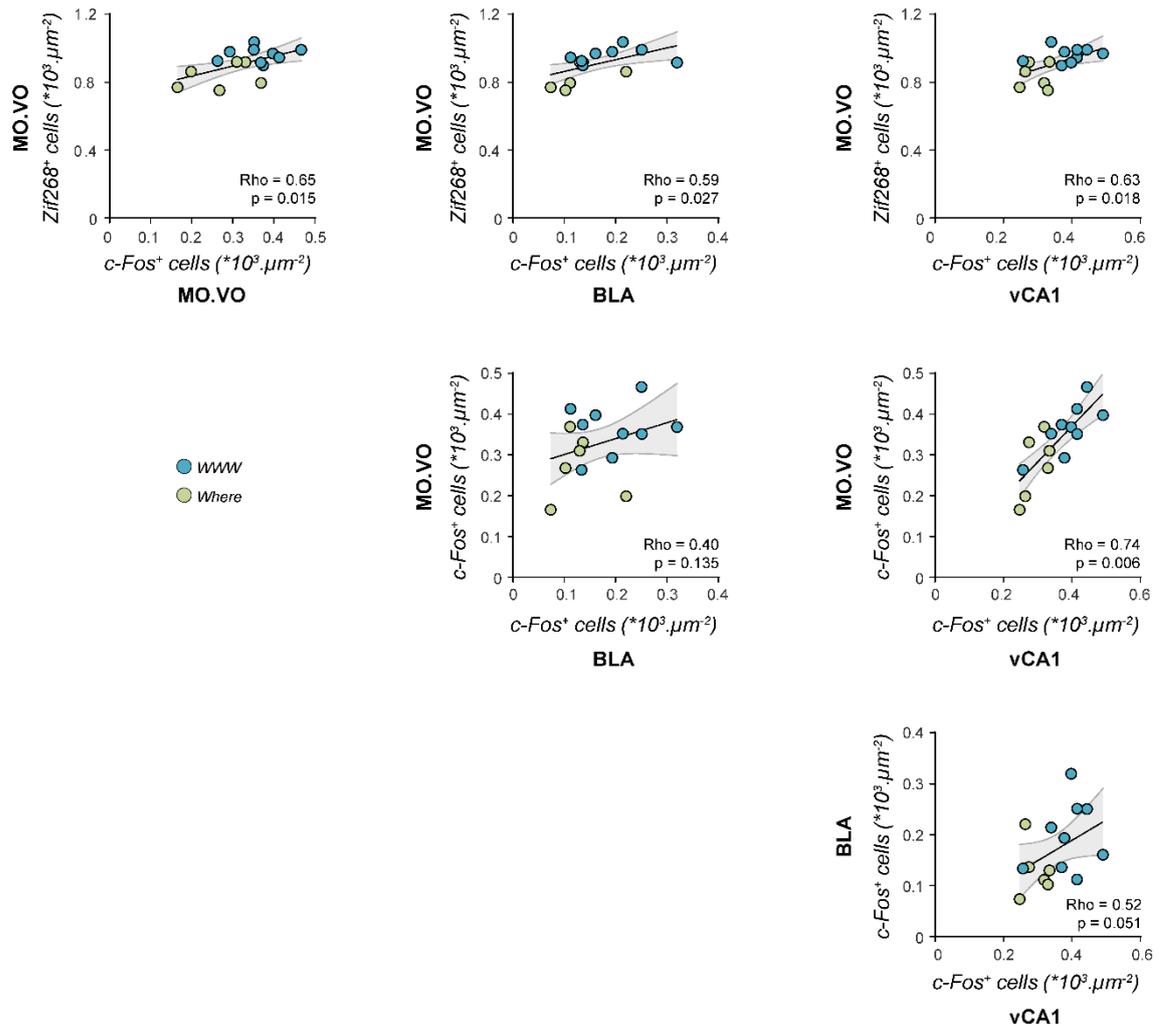


Supplementary Figure 6. Brain areas not involved in complete remote episodic memory and the emotional network on complete remote episodic memory is not related to the reinforcement level during the recall test

Density of c-Fos⁺ (a) or Zif268⁺ (b) cells in brain areas not significantly recruited in WWW versus Where rats ($n_{WWW} = 9$; $n_{Where} = 6$). Data were normalized to the control group (value of 100%). Mann–Whitney U tests were performed for statistical comparisons between profiles that were not significant. (c) Nonsignificant Spearman correlations between IEG (Zif268 or c-Fos) expression in emotional brain areas associated with remote memory precision in WWW and Where rats ($n_{WWW} = 9$; $n_{Where} = 6$) and the total amount of drinking during the recall test (Total licks). OB (olfactory bulb); aPir/pPir (anterior and posterior piriform cortices); Hb (habenula); aRSG, pRSG (anterior and posterior retrosplenial cortices); dDG, vDG (dorsal and

ventral dentate gyrus); dCA3 (dorsal) and vCA3 (ventral) hippocampus; PER (perirhinal cortex); LEC, MEC (lateral and medial entorhinal cortices). MO. VO (medio-ventral) of the orbitofrontal cortex; BLA (basolateral amygdala); vCA1 (ventral hippocampus).

Supplementary FIGURE 7



Supplementary Figure 7. Brain areas in the emotional network involved in accurate episodic recollection are coactivated during the recall test

Spearman correlations between c-Fos and Zif268 expression in emotional brain areas associated with remote memory precision in *WWW* and *Where* rats ($n_{WWW} = 9$; $n_{Where} = 6$). The coexpression of c-Fos and Zif268 was positively correlated between MO. VO, vCA1 and BLA, except for c-Fos expression in the MO. VO and BLA. MO. VO (medio-ventral) of the orbitofrontal cortex; BLA (basolateral amygdala); vCA1 (ventral hippocampus).

Supplementary TABLE 3

Mediation of...	through...	Mediate effect		Direct effect	
		% of mediation	p value	% of direct effect	p value
...for predicting memory precision					
Zif268 MO.VO	c-Fos BLA	30	0.08	70	0.02
Zif268 MO.VO	c-Fos vCA1	9	0.58	91	0.01
Zif268 MO.VO	c-Fos MO.VO	1	0.95	99	0.01
c-Fos BLA	Zif268 MO.VO	43	0.02	57	0.09
c-Fos vCA1	Zif268 MO.VO	76	0.02	24	0.58
c-Fos MO.VO	Zif268 MO.VO	100	0.01	0	0.99

Supplementary Table 3. Statistical properties of mediation analyses on the emotional network involved in accurate episodic recollection

Values and statistical data of mediation analyses that determined relationships between brain areas recruited and remote episodic memory accuracy (n = 15). MO. VO (medio-ventral) of the orbitofrontal cortex; BLA (basolateral amygdala); vCA1 (ventral hippocampus).