REPORT

BRAIN RESEARCH

Causal neural network of metamemory for retrospection in primates

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We know how confidently we know: Metacognitive self-monitoring of memory states, so-called "metamemory," enables strategic and efficient information collection based on past experiences. However, it is unknown how metamemory is implemented in the brain. We explored causal neural mechanism of metamemory in macaque monkeys performing metacognitive confidence judgments on memory. By whole-brain searches via functional magnetic resonance imaging, we discovered a neural correlate of metamemory for temporally remote events in prefrontal area 9 (or 9/46d), along with that for recent events within area 6. Reversible inactivation of each of these identified loci induced doubly dissociated selective impairments in metacognitive judgment performance on remote or recent memory, without impairing recognition performance itself. The findings reveal that parallel metamemory streams supervise recognition networks for remote and recent memory, without contributing to recognition itself.

Introspection on memory states (*1*), or self-monitoring (*2*, *3*) and evaluation (*3*–*5*) of our own memory (*6*), makes us feel retrospective. This self-reflective mental process had been commonly believed to be unique to humans because it requires a higher level of cognition about our own cognition. This meta-level memory process is termed "metamemory" (*1*, *6*–*8*), and is conceptually considered to supervise the process of memory execution itself (i.e., encoding, maintenance, and retrieval). However, the neural mechanism of metamemory, even the cortical distribution of responsible neural activities, is totally unknown, whereas the neural basis of memory execution has been precisely revealed as a multitiered brain-wide network in humans and animals (*1*, *6*, *9*, *10*). Therefore, it remains elusive whether and, if so, how metamemory is implemented in the brain as an independent and integrative neural process that is distinct from the memory execution process itself.

For exploration of unknown neural substrates, it is efficient and fruitful to combine whole-brain searches for neural correlates and subsequent examinations of causal behavioral impacts by finely targeted neural intervention (*11*). The psychological and behavioral framework for experimentation on metacognitive skills has been developed only recently in nonlinguistic animals (*12*, *13*). Studies in rats (*14*) and macaques (*15*–*17*) recorded neuronal activity that was related to the metacognitive judgment on perception rather than on memory. These studies identified the neural correlates of the self-monitoring skills used to make adaptive decisions based on real-time experiences: Single-cell activity carried information that correlated with both perceptual metacognition and perception itself (*14*–*17*). In contrast, metamemory requires the reconstruction of past experiences as present mental representations and, thus, naturally requires more self-reflective and introspective information processing than perceptual metacognition. We developed a nonhuman primate neurobiological model of metamemory using macaque monkeys, because—together with apes and dolphins—they are the only animals besides humans that were recently demonstrated to exhibit metamnemonic skills (*12*, *13*). Both whole-brain searches and finely targeted neuronal interventions can be applied to macaque monkeys (Fig. 1A).

Monkeys were required to perform a yes/no visual memory recognition test (*13*, *18*, *19*) (memory stage; Fig. 1B) and to make self-confidence judgments regarding their own retrieved memory (*20*) using the postdecision wagering paradigm (*17*) (bet stage; Fig. 1B). In the memory stage, recognition performance for the cue item at each position (OLD1 to OLD4) was significant [corrected recognition rate (hit rate − false alarm rate): $t_{31} > 3.42$, $P < 0.008$, corrected for multiple comparisons with Bonferroni's test] [Fig. 2A (left)]. Correct response rates exhibited U-shaped serial position curves (*18*) with both a significant primacy effect [first item (OLD1) versus middle items (OLD2 and OLD3): $t_{31} = 2.38$, $P = 0.023$, Bonferroni's correction, following analysis of variance (ANOVA), $F_{3,90} = 2.93$, $P = 0.037$] and a significant recency effect [last item (OLD4) versus middle items (OLD2 and OLD3): $t_{31} = 2.39$, $P = 0.022$]. These results were confirmed by d' of type I signal detection theory ($t_{31} = 4.71$, $P = 4.9 \times 10^{-10}$) [Fig. 2A (right) and fig. S1A]. Responses for successful retrieval of the last item were faster than those of the other items [OLD4 versus OLD1, OLD2, OLD3: $t_{31} > 2.17$ $P < 0.05$ corrected for multiple comparison with Holm's test; recent OLD (OLD4) versus remote OLD (OLD1, OLD2, and OLD3): $t_{31} = 2.99$, $P = 0.0053$] (fig. S1B) and suggested that recent memory processes for retrieval of the latest items were distinct from remote memory processes for the initial three items. In the bet stage, the monkeys more frequently chose "high bets" when they correctly answered the precedent test than when they failed it ($t_{31} > 4.63$, $P < 1.8 \times 10^{-4}$ for both OLD and NEW conditions) (Fig. 2B). Confidence judgment performances evaluated by the phi coefficient (Φ) (*21*), a contingency table–based statistical index of preference for optimal choice, were significantly positive (Φ^{OLD}: $t_{31} = 5.60$, $P = 3.8 \times 10^{-6}$; Φ^{NEW}: $t_{31} = 5.60$, $P = 3.8 \times 10^{-6}$) (see also fig. S1C). Optimal choices in confidence judgment were also confirmed by significantly positive meta-d' (*22*) ($t_{31} = 9.37$, $P = 4.6 \times 10^{-10}$), an index based on type II signal detection theory, which was highly correlated with Φ across experimental days (sessions) [correlation coefficient (r) = 0.84, $P = 1.0 \times 10^{-9}$] (fig. S1D) (see methods for details). For the relation with the serial position effect, in the OLD1, OLD4, and NEW conditions, recognition performance was better for high-bet trials than for low-bet trials [main effect of confidence: $F_{1,30} = 35.4$, $P = 1.6 \times 10^{-6}$; high bet versus low bet: $t_{31} = 4.21$, $P = 6.0 \times 10^{-4}$ (OLD1); $t_{31} = 2.60$, $P = 0.042$ (OLD4); $t_{31} = 5.97$, $P = 3.9 \times 10^{-6}$ (NEW), Bonferroni's correction] (Fig. 2C). Moreover, high-bet preference was correlated with recognition performance across sessions ($r = 0.46$, $P = 0.0077$) (fig. S1E). Despite the longer response time for incorrect responses (incorrect versus correct: $t_{31} = 2.74$, $P = 0.010$), monkeys did not use response latency of the memory stage as an external behavioral cue for making a bet decision (high bet versus low bet: $t_{31} = 0.81$, $P = 0.42$ for correct trials; $t_{31} = 1.01$, $P = 0.32$ for incorrect trials) (Fig. 2D). Both the confidence judgment and recognition performance were consistent across monkeys (fig. S2).

Using whole-brain functional mapping, we identified cortical areas involved in metamemory processing by comparing brain activity between high-bet and low-bet trials in memory retrieval [Fig. 3, A and B, (left)] (see discussion for exclusion of possible components of reward or memory strength). The majority of the metamemory processing areas activated in OLD (hit) condition were localized within the dorsal prefrontal cortex, around the posterior supraprincipal dimple [$P < 0.05$, family-wise error correction (FWE) across the whole-brain volume] [Fig. 3A (right) and table S1A, see also fig. S3A], whereas those in NEW (correct rejection) condition were distributed within the posterior parietal cortex ($P < 0.05$, whole-brain corrected) [Fig. 3B (right) and table S1B; see also

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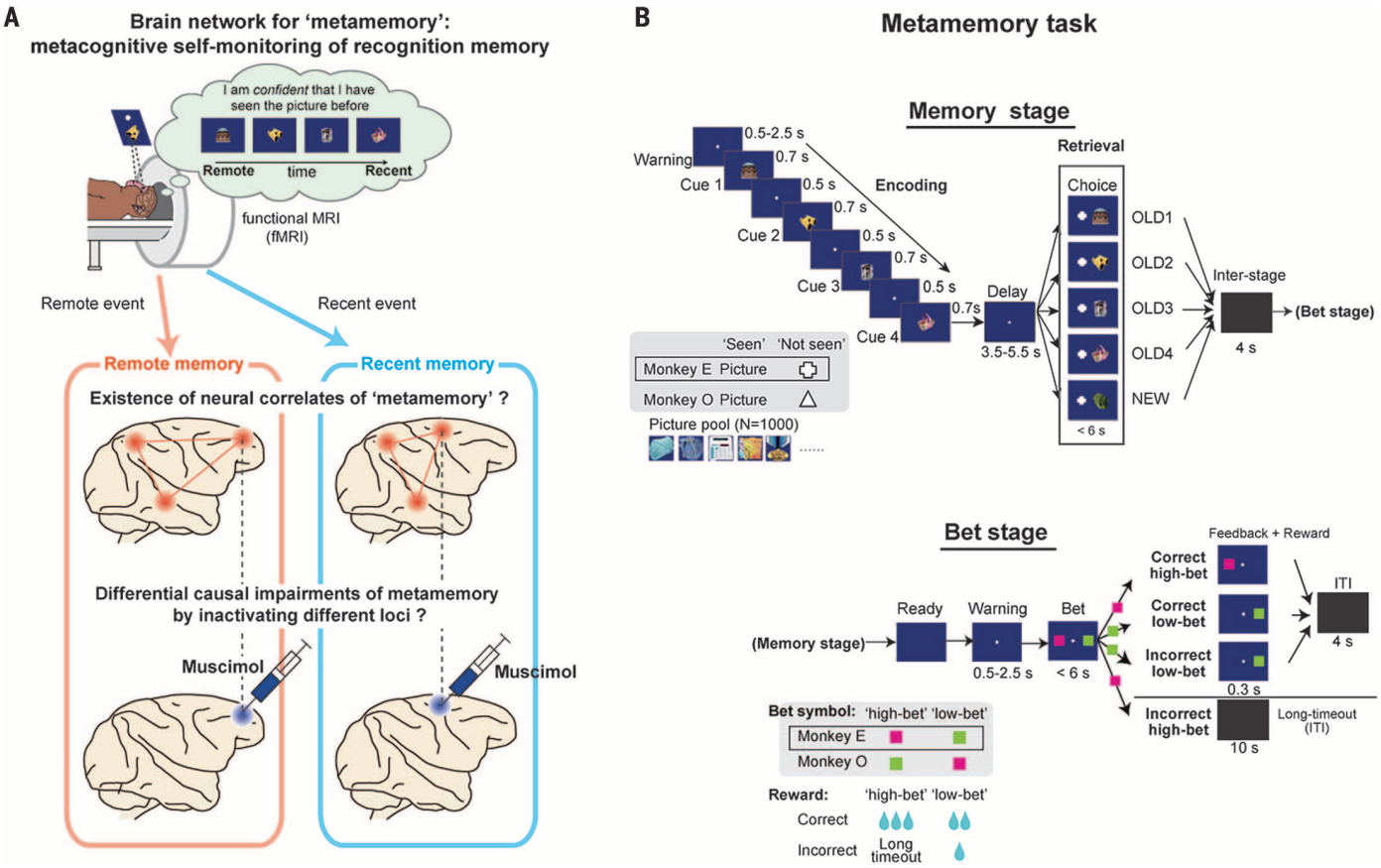

Fig. 1. Experimental design and metamemory task. (**A**) Whole-brain functional localization of metamemory networks for "remote" and "recent" events via functional magnetic resonance imaging (fMRI) and behavioral reversible inactivation with a $GABA_A$ receptor agonist (muscimol) in macaque monkeys performing a metamemory task. (**B**) Metamemory task sequence. In the memory stage, if the picture in the choice period was included in the encoded item list, monkeys were required to choose the picture (OLD condition); if not, they were to choose the "not seen" symbol (NEW condition). In the bet stage, monkeys were required to place either high or low bets on the basis of confidence about memory in a postdecision wagering paradigm.

fig. S3, A and B]. Overlap between the distributions of the OLD and NEW metamemory processing areas was marginal (fig. S3C). Because the behavioral results indicated that distinct memory processes operate for retrieval of the latest items (fig. S1B), metamemory processing areas were then examined for successful retrieval of remote memory (remote OLD) and recent memory (recent OLD) separately. For remote OLD condition, metamemory processing areas were localized bilaterally around the lateral area 9 and area 8B ($P < 0.05$, whole-brain corrected) (Fig. 3C and table S2A), especially on the region anteriorly from the posterior supraprincipal dimple (aPSPD) within area 9 and 9/46d. For recent OLD condition, metamemory-related activations were localized at anterior part of the supplementary eye field (SEFa) within area 6 (Fig. 3C and table S2B) ($P < 0.05$, whole-brain corrected). aPSPD was consistently activated for each of three remote items (OLD1, 2, and 3) ($P < 0.001$, Bonferroni's correction) [Fig. 3D (top)], but not for the last recent item, whereas SEFa was especially activated during retrieval of the last recent item ($P < 0.001$, Bonferroni's correction) [Fig. 3D (bottom)], but not for either of three remote items. Metacognitive roles for area 9, especially at aPSPD, have never been discovered before, although the contribution of supplementary eye field to perceptual metacognition has been suggested (*17*) (for roles of SEF, see supplementary text). We then examined how activity within each metamemory processing area contributed to behavioral performance in confidence judgment by calculating the session-by-session correlation between task-evoked functional magnetic resonance imaging (fMRI) activity and Φ index (Fig. 3E). We identified aPSPD as the locus for the remote items ($r = 0.48$, $P = 0.0047$, Bonferroni's correction), but not for the recent or new items. In contrast, the SEFa was identified as the locus for the recent item ($r = 0.38$, $P = 0.045$, Bonferroni's correction), but not for the remote or new items (for direct comparisons of these correlations see fig. S6A). fMRI activity in the other metamemory processing areas localized for remote OLD and recent OLD conditions could not predict performance for any items (Fig. 3F). Metamemory-related activities in aPSPD and SEFa (fig. S4), and their contribution to confidence judgment performance (fig. S6B), were consistent across monkeys (see also table S4 and fig. S5 for the whole-brain activities in each monkey).

Next, we examined how these metamnemonic loci interact with other areas during the metamemory task by psychophysiological interaction (PPI). Activity in aPSPD was dominantly coupled with area PG in the inferior parietal lobule for metamnemonic judgment on remote items (Fig. 3G and table S3) ($P < 0.05$, false discovery rate corrected at cluster level across the whole brain), whereas activity in SEFa was dominantly coupled with area PEa in the superior parietal lobule for metamnemonic judgment on recent items (Fig. 3G and table S3) ($P < 0.05$, cluster-level corrected). Area PG and area PEa were also active during retrieval of remote or recent items, respectively, in an identical recognition memory test without wagering (*18*).

Finally, to examine the direct causal impact of neuronal activity in aPSPD or SEFa on metamnemonic performance, we bilaterally microinjected a γ-aminobutyric acid receptor type A ($GABA_A$ receptor) agonist (muscimol) separately into each of these loci (Fig. 4A) and evaluated the severity of impairment in confidence judgment by comparing Φ after injection and Φ before injection [$\Delta\Phi = \Phi(\text{POST injection}) - \Phi(\text{PRE injection})$] for remote OLD ($\Delta\Phi^{Remote}$), recent OLD ($\Delta\Phi^{Recent}$), and NEW ($\Delta\Phi^{New}$) conditions, separately. The results demonstrated doubly dissociated behavioral impairments in confidence judgment between the loci: Comparisons of ΔΦ

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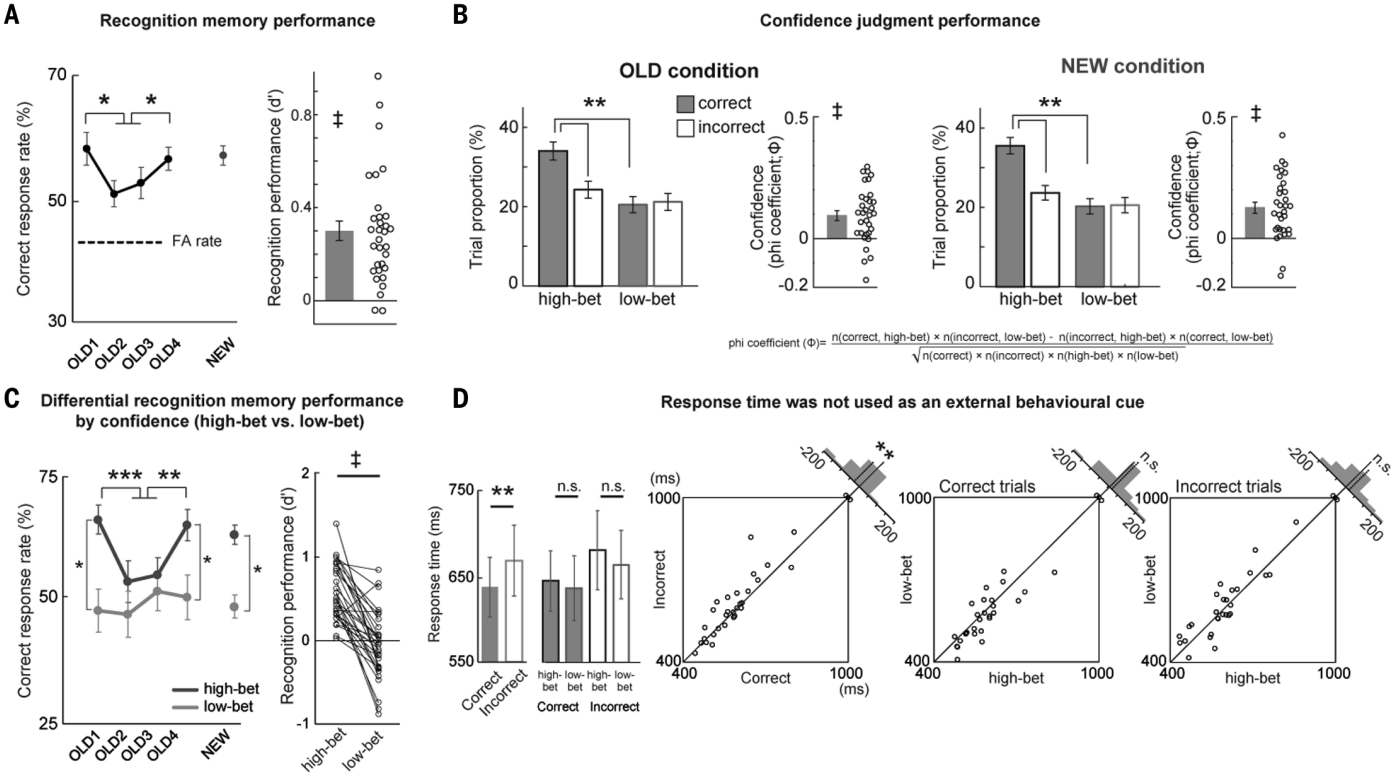

Fig. 2. Behavioral performance of metamemory task. (**A**) Recognition memory performance. (Left) Serial position curve of correct response rate with significant primacy and recency effects. *P < 0.05, paired t test (Bonferroni's correction). (Right) The d' of signal detection theory. ‡P < 0.001, t test against zero. (**B**) Confidence judgment performance evaluated by trial proportion and phi coefficient (Φ). **P < 0.01, paired t test (Bonferroni's correction). ‡P < 0.001, t test against zero. (**C**) Recognition performance in high- and low-bet trials. (Left) Correct response rates for high-bet (dark gray) and low-bet (light gray) trials. *P < 0.05, **P < 0.01, ***P < 0.001, paired t test (Bonferroni's correction). (Right) Differences in d' of signal-detection theory between high- and low-bet trials. ‡P < 0.001, paired t test. (**D**) Differences in response time according to recognition performance (correct or incorrect) and confidence judgment (high bet or low bet). (Left bar graphs) Response time. **P = 0.01, paired t test. No significant interaction (correct or incorrect × high bet or low bet) was found in either of the animals (monkey E: $F_{1,15}$ = 0.17, P = 0.67; monkey O: $F_{1,15}$ = 1.51, P = 0.23). (Right scatter plots) Relation of session-by-session response times for labeled conditions. Each open circle in this figure represents a single session (N = 32). Histograms show distribution of session-by-session difference. Dotted line denotes mean. Error bars denote SEM.

showed a significant interaction between injected loci and memory task conditions [(aPSPD and SEFa) × (remote OLD, recent OLD, NEW); $F_{2,28}$ = 5.95, P = 0.007] (Fig. 4B), with no difference in impairment between monkeys (interaction for injected loci × memory conditions × monkeys; $F_{2,28}$ = 0.32, P = 0.72). This double-dissociation was confirmed by the signal-detection theory-based metacognitive efficiency index [Δ(meta-d' – d')] (*22*) (interaction for injected loci × memory task conditions: $F_{1,7}$ = 6.41; P = 0.039) (fig. S7B). aPSPD injections evoked a significantly greater metamnemonic impairment for remote OLD condition than for the other conditions ($\Delta\Phi^{Remote}$ versus $\Delta\Phi^{Recent}$ and $\Delta\Phi^{Remote}$ versus $\Delta\Phi^{New}$: P < 0.05, corrected with post hoc Ryan's test; $\Delta\Phi^{Recent}$ versus $\Delta\Phi^{New}$: P > 0.05), whereas SEFa injections evoked a significantly greater impairment for recent OLD condition than for the others ($\Delta\Phi^{Recent}$ versus $\Delta\Phi^{Remote}$ and $\Delta\Phi^{Recent}$ versus $\Delta\Phi^{New}$: P < 0.05, Ryan's correction; $\Delta\Phi^{Remote}$ versus $\Delta\Phi^{New}$: P > 0.05). Significant metamnemonic impairment was observed only in remote OLD condition of aPSPD injection ($\Delta\Phi^{Remote}$ < 0; t_8 = –6.29, P = 0.0014, Bonferroni's correction) (Fig. 4B) and in recent OLD condition of SEFa injection ($\Delta\Phi^{Recent}$ < 0; t_8 = –3.52, P = 0.046, Bonferroni's correction) [see also fig. S7A and C for session-by-session data and impairment evaluation by Φ(POST injection)]. In contrast, saline injection at aPSPD and SEFa did not result in any impairments in confidence judgments (t_7 < 0.48, P > 0.9; interaction for injected loci × memory task conditions: $F_{2,22}$ = 0.42, P = 0.66) (Fig. 4C). Notably, muscimol injection did not impair the recognition memory process itself: The difference between d' after injection and d' before injection (Δd') was not significant under any condition (t_8 < 0.77, P > 0.9) (Fig. 4D) and showed no significant interaction between injected loci and recognition memory task conditions ($F_{1,14}$ = 0.002, P = 0.96). Additionally, a serial position curve with significant primacy and recency effects was retained even after muscimol injection (OLD1 versus OLD3, OLD4 versus OLD3: P < 0.05) [Fig. 4E (top)], and recognition memory performance remained statistically significant in all conditions (P < 0.05) [Fig. 4E (bottom)]. Both the results from whole-brain functional MRI mapping and causal behavioral tests reveal that the whole-brain metamemory process is composed not of a unitary stream but of parallel streams with multiple readout cores directing one-on-one remote and recent memory networks (Fig. 4F).

The following three lines of behavioral evidence demonstrate that monkeys performed this postdecision wagering metacognitive judgment task (Fig. 1B) on the basis of their confidence about memory. First, monkeys more frequently placed high bets after a successful performance on the preceding memory tasks (Fig. 2B and fig. S1, C and E), as confirmed by both the contingency table–based Φ (*17*) and signal detection theory–based meta-d' indices (*22*) (fig. S1D). Second, a serial position curve with significant primacy and recency effects was observed for high-bet, but not for low-bet, conditions (Fig. 2C); this corresponds with predictions from signal detection theory (*13*). Third, monkeys did not use response latency as a behavioral cue for making bet decisions (*20*) (Fig. 2D); this observation satisfies the established criterion required for demonstrations of animal metacognition in laboratory environment when using the postdecision wagering paradigm (*12*).

Metamemory signals derived from comparisons between high-bet and low-bet conditions in whole-brain imaging are at risk of confounding with reward-related signals (reward proper,

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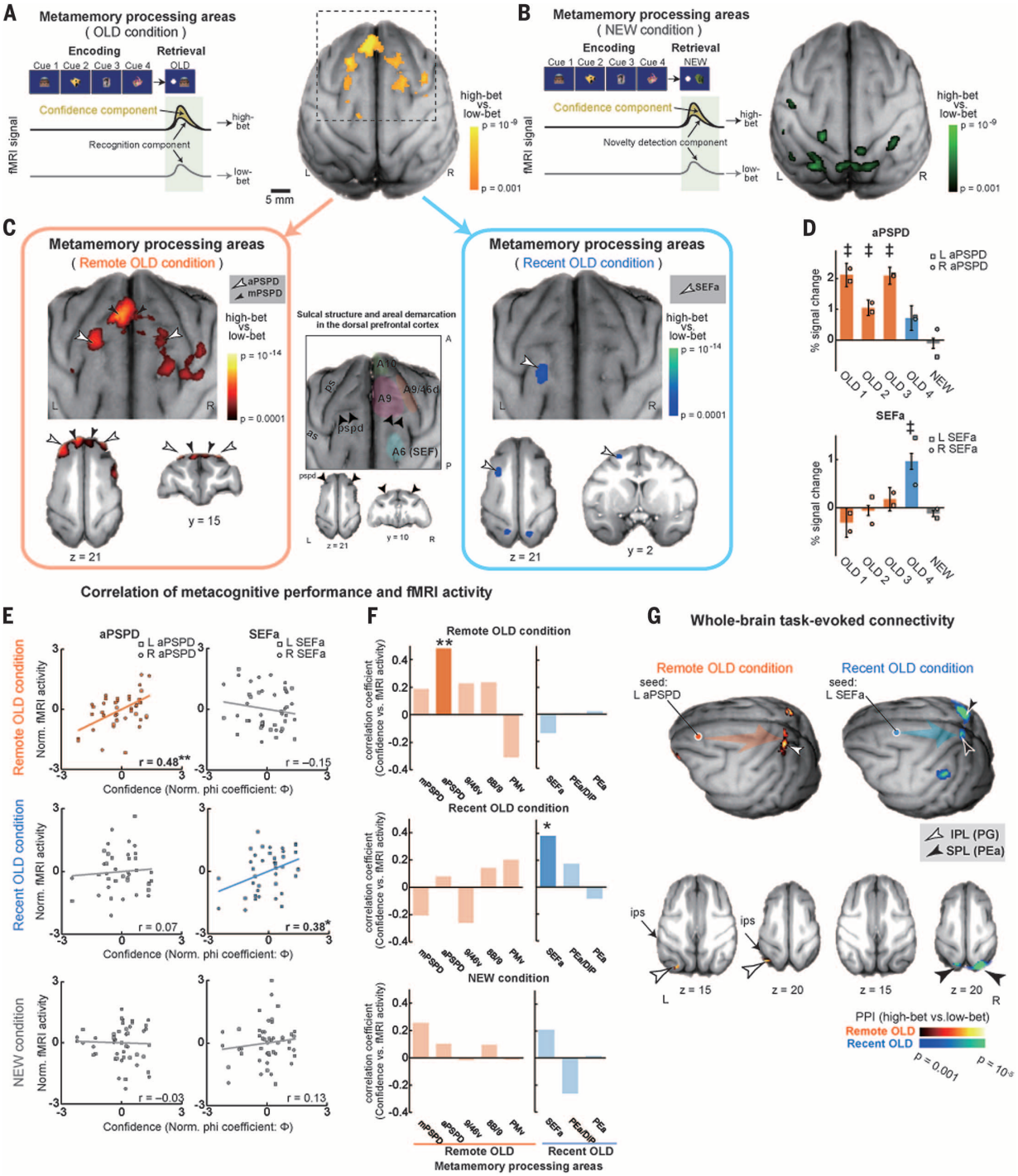

Fig. 3. Whole-brain functional mapping of metamemory network. (**A**) (Left) fMRI subtraction schema for metamemory-related signals (confidence components). (Right) metamemory processing areas for OLD conditions identified by the subtraction (high bet versus low bet; $z > 3.1$, $P < 0.001$, uncorrected for display purpose). Dashed line frames magnified brain region in (C). (**B**) Metamemory processing areas for NEW conditions. (**C**) (Left) Metamemory processing areas for remote OLD condition (OLD1–3) ($z > 3.7$, $P < 0.0001$, uncorrected for display purpose). (Right) Metamemory processing areas for recent OLD condition (OLD4). pspd, posterior supraprincipal dimple; ps, principal sulcus; as, arcuate sulcus; aPSPD, metamemory area anteriorly from pspd; mPSPD, metamemory area medially from pspd; SEFa, metamemory area in anterior part of supplementary eye field (SEF). (**D**) Percent signal changes in each cue position of OLD conditions (OLD1–4) and in NEW conditions at bilateral aPSPD and SEFa (square, left; circle, right). ‡$P < 0.001$, t test against zero, Bonferroni's correction. Error bar, SEM. (**E**) Intersession correlation between confidence judgment performance [phi coefficient (Φ), z-transformed] and fMRI activity (high bet versus low bet, z-transformed). *$P < 0.05$, **$P < 0.01$, Bonferroni's correction. Each symbol represents data from each session (square, left; circle, right). (**F**) Correlation coefficients between Φ and fMRI activity [as calculated in (E)] for all metamemory processing areas. *$P < 0.05$, **$P < 0.01$, Bonferroni's correction. PMv, ventral premotor area; PEa/DIP, area PEa/depth of intraparietal area. (**G**) Task-evoked connectivity maps [psychophysiological interaction (PPI) for high bet > low bet] for the seed at left aPSPD in remote OLD condition and for the seed at left SEFa in recent OLD condition ($z > 3.1$, $P < 0.001$, uncorrected for display purpose). IPL, inferior parietal lobule; SPL, superior parietal lobule; ips, intraparietal sulcus.

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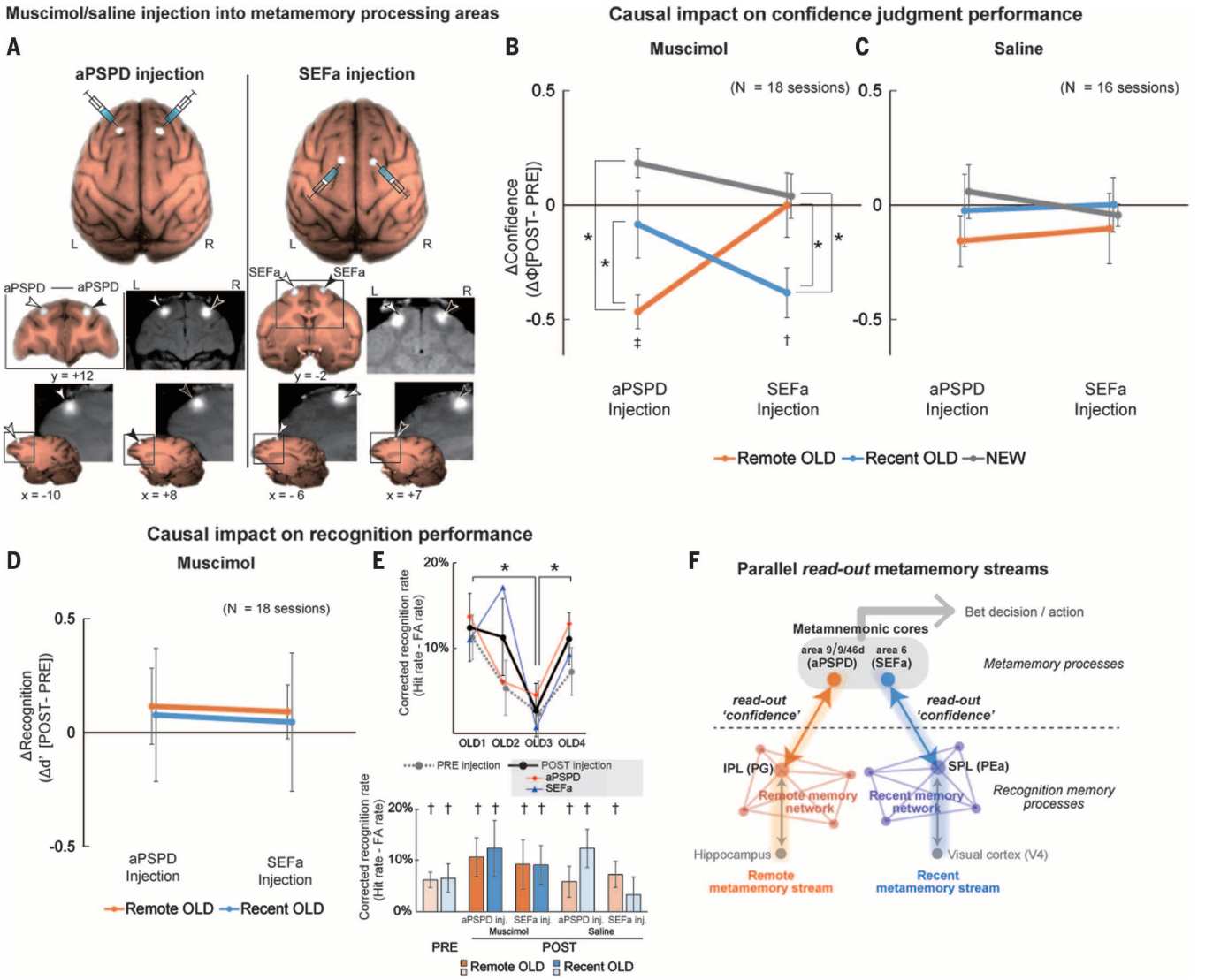

Fig. 4. Double dissociation of causal behavioral impact by reversible inactivation of metamnemonic loci. (**A**) Muscimol or saline was bilaterally injected at aPSPD (left) or SEFa (right). (Top) Gadolinium contrast agent visualized by MRI (white) overlaid on the surface of template brain (copper color). (Bottom) Enlarged view of gadolinium injection sites on coronal and sagittal slices of T1-weighted images. Frame, positions of the enlarged views. (**B**) Performance changes in confidence judgment after muscimol injection in aPSPD (nine sessions) and SEFa (nine sessions). Behavioral effects were evaluated using ΔΦ coefficient [ΔΦ: Φ(POST injection) − Φ(PRE injection)]. *$P < 0.05$, paired t test, Ryan's correction. †$P < 0.05$, ‡$P < 0.001$, t test against zero, Bonferroni's correction. (**C**) Performance change in confidence judgment after saline injection in aPSPD (eight sessions) and SEFa (eight sessions). (**D**) Performance changes in recognition memory after muscimol injection. Behavioral effects were evaluated by Δd' [d'(POST injection) − d'(PRE injection)]. (**E**) (Top) Recognition memory performance before (PRE; dotted light gray) and after (POST; black) injection. Red, aPSPD (POST); blue, SEFa (POST). *$P < 0.05$ paired t test, in POST injection. (Bottom) Corrected recognition rates (hit rate − false alarm rate) for all conditions in PRE and POST injections. †$P < 0.05$, t test against zero. No significant difference was found between each POST-injection condition and PRE-injection (t test, $P > 0.05$, Bonferroni's correction). Error bars in (B) to (E), SEM. (**F**) Proposed parallel metamemory streams. aPSPD is the read-out site of confidence for the remote metamemory stream, whereas SEFa is for the recent metamemory stream. These two streams interact with recognition memory networks for remote and recent memories, respectively.

reward expectation, and reward prediction error) (*5*). However, it is unlikely in the present study for two reasons. First, the memory retrieval period in which we extracted metamemory-related signals is sufficiently separate from the reward delivery period to avoid reward-related effects. We confirmed absence of signal enhancement during memory retrieval period in reward-related areas (ventral tegmental area and amygdala), which were active when wagering (fig. S8, C and D). Second, the almost nonoverlapping distribution of metamemory processing areas between OLD and NEW conditions (Fig. 3, A and B) cannot be explained by reward-related signals, because these signals should be carried equally in both conditions. We also note that the metamemory signals derived from these comparisons could potentially reflect attention during memory retrieval. However, monkeys performed the task without behavioral biases for either "seen" or "not-seen" trial (fig. S2B), and the confidence is measured regardless of trial types (see supplementary text). Moreover, even the fMRI signals in area 9/46v, a central region for covert attention to visual stimuli (*23*, *24*), were differentially modulated by remote and recent memories (fig. S8, A and B), as well as those in aPSPD and SEFa (fig. S4B), all of which suggested that the metamnemonic activities we reported do not covary with the previously reported neuronal activity for attention to visual stimuli (*23*).

Contributions of the mid-dorsolateral prefrontal cortex for both self-ordering task and serial order memory task were reported previously (*25*, *26*).

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Breakthroughs for psychological and behavioral experimental framework on metacognition in animals (*12*, *13*), as well as for whole-brain functional imaging, enabled us to extract neural correlates of metamemory in monkeys, one of which locates at aPSPD around the boundary of anatomically defined area 9 and 9/46d (*3*). Further characterization of aPSPD by both its cognitive functional roles and connections with other brain areas (*27*) would extend our knowledge on this almost uninvestigated area in the dorsal prefrontal cortex (see supplementary text).

It was demonstrated that lateral intraparietal cortex (LIP) neurons in the posterior parietal cortex, which contribute to both visual processing and perceptual decision, also carry information on confidence (*15*). In the present study, inactivation of aPSPD and SEFa caused impairments in metamnemonic judgment without impairing recognition itself; this suggests a role for read-out of confidence on memory in the prefrontal cortex (see supplementary text). A human neuroimaging study based on voxel-based morphometry (*28*) identified a frontopolar cortical area (BA 10) as being a neural correlate of introspection on perceptual decisions. We also found that area 10 in the macaque frontopolar cortex possibly engages in metamnemonic processes for NEW items (see fig. S3B). Despite issues with methodological differences (*29*) and interspecies homology in functioning and cortical structures (*30*), these observations provide a new picture of the frontopolar and/or dorsal prefrontal cortical network as having an integrative role for introspective monitoring in primates.

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SUPPLEMENTARY MATERIALS

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Causal neural network of metamemory for retrospection in primates

Kentaro Miyamoto, Takahiro Osada, Rieko Setsuie, Masaki Takeda, Keita Tamura, Yusuke Adachi and Yasushi Miyashita (January 12, 2017)

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Editor's Summary

Are you aware how well you remember?

Self-monitoring and evaluation of our own memory is a mental process called metamemory. For metamemory, we need access to information about the strength of our own memory traces. The brain structures and neural mechanisms involved in metamemory are completely unknown. Miyamoto *et al.* devised a test paradigm for metamemory in macaques, in which the monkeys judged their own confidence in remembering past experiences. The authors combined this approach with functional brain imaging to reveal the neural substrates of metamemory for retrospection. A specific region in the prefrontal brain was essential for meta mnemonic decision-making. Inactivation of this region caused selective impairment of metamemory, but not of memory itself.

Science, this issue p. 188

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