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Building Memories: Remembering and Forgetting of Verbal Experiences as Predicted by Brain Activity

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A fundamental question about human memory is why some experiences are remembered whereas others are forgotten. Brain activation during word encoding was measured using blocked and event-related functional magnetic resonance imaging to examine how neural activation differs for subsequently remembered and subsequently forgotten experiences. Results revealed that the ability to later remember a verbal experience is predicted by the magnitude of activation in left prefrontal and temporal cortices during that experience. These findings provide direct evidence that left prefrontal and temporal regions jointly promote memory formation for verbalizable events.

Memory encoding refers to the processes by which an experience is transformed into an enduring memory trace. Psychological studies have shown that the memorability of an experience is influenced greatly by the cognitive operations engaged during initial encoding of that experience, with semantic processing leading to superior memorability relative to nonsemantic processing (1). Functional neuroimaging studies have implicated left prefrontal cortex in verbal encoding: left prefrontal activation is greater during semantic relative to nonsemantic encoding (2), and left prefrontal participation decreases and memorization is impaired when semantic encoding operations are disrupted (3). These studies have all relied on blocked experimental designs, where trials from each encoding condition are presented sequentially, inseparable from each other during the functional scan. While blocked designs allow comparison between encoding conditions that yield, on average, higher or lower levels of subsequent recoll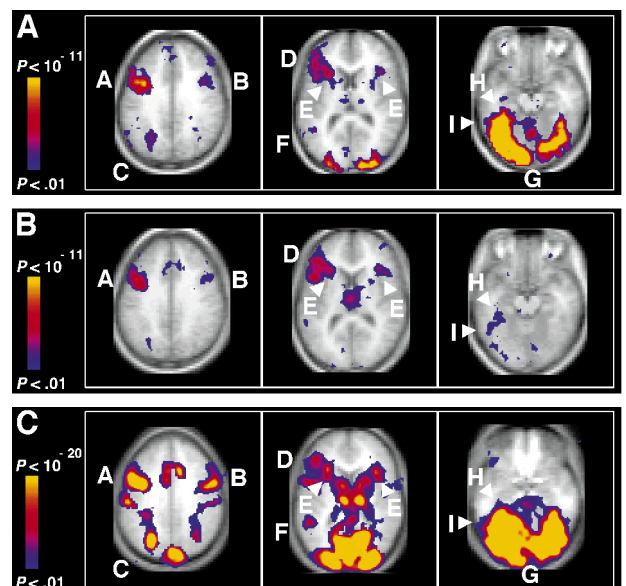ection, they do not allow a direct trial-by-trial comparison between specific encoding trials that lead to subsequent remembering and those that lead to subsequent forgetting. Results from event-related potential (ERP) studies, which allow for trial-by-trial analysis, suggest that the neural signature during verbal encoding differs for subsequently remembered and subsequently forgotten experiences, with remembered experiences being associated with a greater positive-going response over frontal and parietal regions (4). However, ERP studies are characterized by limited spatial resolution. Thus, the precise functional neuroanatomic encoding differences that predict whether a particular verbal experience will be remembered or forgotten are currently unknown.

A second unanswered question concerns the exact roles of medial temporal structures in memory encoding. Lesion studies in humans and other species indicate that medial temporal regions are essential for the processing of experiences such that they can be remembered at a later time (5). However, modulated medial temporal activation has been notably absent in neuroimaging studies that systematically varied the nature of cognitive operations engaged during encoding (2). Rather, parahippocampal gyrus, a subcomponent of the medial temporal memory system, has been indirectly implicated in memory encoding because parahippocampal activation is greater during the processing of novel stimuli relative to familiar stimuli (6). These results raise the possibility that parahippocampal contributions to encoding may be restricted to novelty detection processes.

To address these issues, the neural correlates of incidental word encoding were examined in two whole-brain functional magnetic resonance imaging (fMRI) studies. One ex-

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Fig. 1. Statistical activation maps are shown for the blocked-design and event-related data. Images are transverse sections for the data averaged across subjects. The left hemisphere of the brain corresponds to the left side of the image. (**A**) In the blocked-design experiment, greater activation during word processing relative to fixation was noted in the posterior and dorsal extent of left inferior frontal gyrus (A: −34, 6, 34 and −43, 6, 31; BA 44/6), right inferior frontal gyrus (B: 37, 6, 34; BA 44/6), left lateral parietal cortex (C: −28, −68, 43; BA 7), anterior and ventral left inferior frontal gyrus (D: −46, 34, 15 and −43, 28, 12; BA 45/47), bilateral frontal operculum (E: left −31, 19, 12, and −40, 25, 3; right 34, 19, 6; BA 47), left middle temporal gyrus (F: −59, −43, 3; BA 21), bilateral visual cortex (G: BA 17/18/19), parahippocampal gyrus near fusiform gyrus (H: −31, −43, −18; BA 36/37/35), and fusiform gyrus (I: −37, −58, −15; BA 37). Other regions included the hippocampus (−37, −15, −15), supplementary motor area (0, 6, 62; BA 6), medial superior frontal gyrus (−3, 6, 50; BA 6), and right lateral cerebellum. (**B**) Regions demonstrating greater activation during semantic relative to nonsemantic processing included left frontal (A: −43, 9, 34 and −43, 13, 28; D: −40, 22, 21 and −40, 31, 12; E: −28, 22, 6), parahippocampal (H: −34, −40, −12), and fusiform (I: −43, −58, −9) cortices. (**C**) In the event-related study, comparison of word processing trials to fixation trials revealed many of the same regions noted in the blocked-design experiment. Complete listings of stereotaxic coordinates are available from the author upon request.

periment used blocked-design procedures to investigate how systematic manipulation of the encoding task affects prefrontal and medial temporal activation, whereas the other used newly developed event-related procedures (7) that allow direct comparison between specific encoding trials that result in subsequent remembering and forgetting. In the blocked-design experiment, activation during performance of a semantic processing task (deciding if a word is abstract or concrete) was compared to that during a nonsemantic processing task (deciding if a word is printed in upper- or lowercase letters). Twelve normal, right-handed subjects were scanned while performing alternating task-blocks consisting of semantic processing, nonsemantic processing, and visual fixation (8, 9). The novelty of the words in the semantic and nonsemantic blocks was equivalent. Behaviorally, reaction times (RTs) were longer for semantic (873 ms) relative to nonsemantic (539 ms) decisions. Subsequent memory was superior following semantic (85% recognized) than following nonsemantic (47% recognized) processing (10).
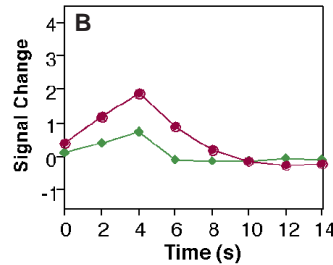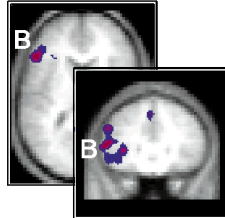
Many brain regions demonstrated significantly greater activation during word processing relative to visual fixation (Fig. 1) (11). These activations likely reflect processes associated with memory encoding and also more general processes associated with stimulus perception and response generation. To identify regions that demonstrate differential activation during encoding conditions that yield higher relative to lower subsequent memory, we directly compared the semantic and nonsemantic processing conditions. Regions demonstrating greater activation during semantic processing included several areas in left prefrontal cortex, as well as left parahippocampal and fusiform gyri (Fig. 1). Although these results indicate that temporal and prefrontal processes influence the encoding of verbal experiences, they do not directly specify the encoding differences that predict whether a specific experience will be later remembered or forgotten.

In a second experiment, event-related fMRI was used while participants performed a single incidental encoding task. The objective was to determine whether trial-by-trial differences in encoding activation predict subsequent memory for experiences even when the processing task was held constant. Thirteen normal, right-handed subjects underwent six fMRI scans, each consisting of word and fixation events presented in a continuous series of 120 rapidly intermixed trials (12). During word trials, subjects made a semantic decision ("abstract or concrete?"). Following the encoding scans, memory for the words was assessed by a recognition test. Subjects indicated whether they recognized each test word as studied, reporting their confidence (high or low) when they recognized
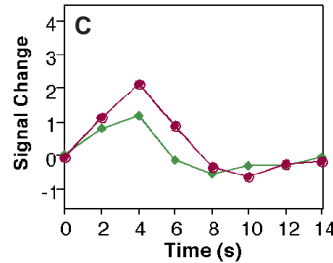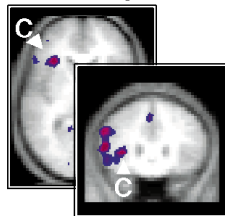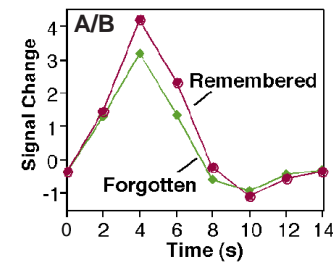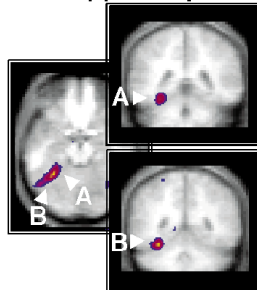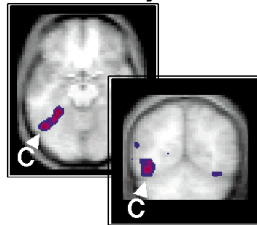

Posterior LIFG
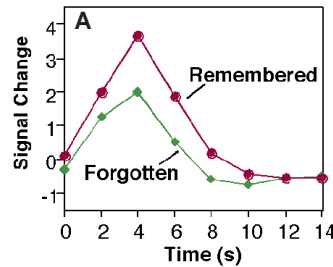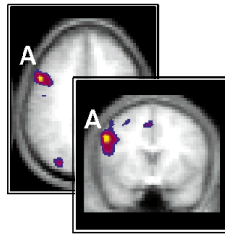
Anterior LIFG

Frontal Operculum

Fig. 2. Statistical activation maps encompassing frontal regions that demonstrate a greater response during the encoding of words later remembered (high confidence hit trials) relative to words later forgotten (miss trials). Displayed at the left are transverse and coronal sections through the activation foci for the event-related data averaged across subjects. Greater activation was noted in the posterior and dorsal extent of left inferior frontal gyrus (LIFG) bordering precentral gyrus (A: −50, 9, 34; BA 44/6), the anterior and ventral extent of LIFG (B: −50, 25, 12; BA 45/47), and the left frontal operculum (C: −31, 22, 6; BA 47). Time courses were derived for each condition within a three-dimensional region surrounding the peak voxel and reflect raw mean signal changes. Regions were defined, using an automated algorithm that identified all contiguous voxels within 12 mm of the peak that reached the significance level.

Parahippocampal / Fusiform Gyri

Fusiform Gyrus

Fig. 3. Activation maps and the corresponding time courses from temporal regions are shown for the trial comparison of remembered (greater response) to forgotten (lesser response) words. Temporal foci included a region (−31, −46, −12) that encompassed parahippocampal gyrus (A: BA 36/37/35) and the more medial extent of fusiform gyrus (B: BA 37), and a region that encompassed the lateral extent of fusiform gyrus and portions of inferior temporal gyrus (C: −43, −55, −9; BA 37). Other regions, including visual (L., left) and motor (R., right) cortices, did not show modulated activation across remembered and forgotten trials.

L. Visual Cortex   **R. Motor Cortex**

the word (*13*). Behavioral results indicated that subjects discriminated between previously studied and unstudied words when responding with high confidence, but not when responding with low confidence (*14, 15*).

The fMRI data were analyzed by categorizing encoding trials based on whether the word was subsequently remembered or forgotten on the postscan memory test. There were four trial types: high confidence hits, low confidence hits, misses, and fixation. Word processing relative to fixation resulted in greater activation in many brain regions, replicating most of the regions noted in the blocked-design study (Fig. 1). Importantly, the event-related design also permitted identification of regions that demonstrate differential activation during the encoding of words subsequently remembered and those subsequently forgotten. When comparing high confidence hits to misses, greater activation was noted in multiple left prefrontal regions (Fig. 2) and left parahippocampal and fusiform gyri (Fig. 3) (*16, 17*). This pattern was independently present and significant for these regions when comparing high confidence hits to misses within each of the word types (abstract or concrete). The subsequent memory effect was rather specific: other regions active during word processing relative to fixation failed to demonstrate greater activation during high confidence hits relative to misses (Fig. 3).

Our results specify how the neural signature during encoding differs for events subsequently remembered and events subsequently forgotten. When task demands were held constant across trials, similar regions were engaged during the encoding of both remembered and forgotten words. However, the magnitude of activation differed across remembered and forgotten experiences in anatomically specific brain regions. These effects cannot be attributed to differences in performance accuracy during encoding because accuracy was comparable for high confidence hits and misses. One possible interpretation is that the present modulations reflect time-on-task or duty-cycle effects (*18*), such that subsequently remembered experiences are those that merely happened to be processed for a longer duration during learning. To examine the possible contribution of time-on-task, the event-related data were reanalyzed after matching the encoding RTs for high confidence hit and miss trials. Even when RTs were matched, left prefrontal and temporal regions still demonstrated significantly greater activation during the encoding of items subsequently remembered than during the encoding of items forgotten (*19*).

Our studies, together with previous results (*2*), suggest that what makes a verbal experience memorable partially depends on the extent to which left prefrontal and medial

temporal regions are engaged during the experience. Although modulated parahippocampal activation has not been noted in many studies, our experiments demonstrate that left parahippocampal gyrus is more active during the encoding of verbal experiences that are later remembered relative to those later forgotten, even though these two classes of experiences were equally novel within the context of the experiment [see also (*20*)]. These results indicate that, although medial temporal regions are sensitive to stimulus novelty (*21*), the role of parahippocampal gyrus in memory encoding extends beyond novelty detection and encompasses more general encoding mechanisms. Parahippocampal gyrus is the principal neocortical input pathway to the hippocampal region (*22*), and thus it is suitably situated to play an important role in memory formation.

Parahippocampal and prefrontal regions may act interdependently to promote the encoding of event attributes important for conscious remembrance. Verbal experiences may be more memorable when semantic and phonological attributes of the experience are extensively processed via participation of left prefrontal regions (*2, 23*). Left prefrontal regions may serve to organize these attributes in working memory, with this information serving as input to parahippocampal gyrus and the medial temporal memory system (*24*). A specific experience may elicit the recruitment of these processes to a greater or lesser extent because of variable task demands, shifts in subjects' strategies, characteristics of target items, or attentional modulations. Regardless of the source of this variability, greater recruitment of left prefrontal and temporal processes will tend to produce more memorable verbal experiences.

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8. Informed consent was obtained from all subjects (seven men, five women, aged 18 to 29 years). Echo planar and conventional imaging was performed on a 1.5-T GE Signa scanner with an ANMR upgrade. Imaging procedures [see R. L. Buckner, W. Koutstaal, D. L. Schacter, A. D. Wagner, B. R. Rosen, *Neuroimage* **7**, 151 (1998)] included collection of structural images [radio frequency–spoiled GRASS (gradient-recalled acquisition in the steady state) sequence, 60-slice sagittal, 2.8-mm thickness] and echo planar functional images sensitive to blood-oxygen level–dependent contrast (118 sequential whole-brain acquisitions, 16 slices each, 3.125-mm in-plane resolution, 7-mm thickness, skip 1 mm; T_2*-weighted asymmetric spin-echo sequence: TR = 2 s, TE = 50 ms, 180° offset = –25 ms).
9. During each of four scans, blocks were ordered: nonsemantic (40 s), fixation (24 s), semantic (40 s), fixation, nonsemantic, fixation, semantic. A brief (8 s) fixation block began each scan. During semantic and nonsemantic blocks, 20 words were visually presented: 10 abstract and 10 concrete nouns; half in uppercase and half in lowercase letters. Each word was presented for 1 s followed by 1 s of fixation between words. Subjects responded by left-handed key press. During fixation blocks, a cross-hair ("+") was presented for the entire duration.
10. Alpha was set to $P < 0.05$ for all behavioral analyses. Response latencies differed across tasks [$F(1,11)$ = 89.97]. Memory was assessed in the scanner 20 to 40 m later, using a yes-no recognition procedure (*8*). Subsequent memory differed across tasks [$F(1,11)$ = 69.50].
11. Functional runs were averaged within each subject, transformed into stereotaxic atlas space, and averaged across subjects (*8*). Activation maps were constructed using a nonparametric Kolmogorov-Smirnov statistic to compare (i) word processing (semantic and nonsemantic) to fixation and (ii) semantic to nonsemantic processing. Peak activations were identified by selecting local statistical activation maxima that were $P < 0.001$ within clusters of five contiguous significant voxels. These criteria minimize false positives, as verified using the logic of control functional runs [E. Zarahn, G. K. Aguirre, M. D'Esposito, *Neuroimage* **5**, 179 (1997)].
12. Subjects were six men and seven women (aged 18 to 35 years). Three additional subjects were excluded because of excessively poor performance. Imaging procedures were similar to experiment one with the exception that imaging was performed using an echo planar T_2*-weighted gradient echo sequence (3.0-T, 128 images, TR = 2 s, TE = 30 ms, flip angle = 90°). During each scan, 40 abstract word trials, 40 concrete word trials, and 40 fixation trials were rapidly intermixed, with each trial lasting 2 s. For fixation trials, the fixation point remained on the screen for the entire 2 s. For word trials, the word was presented for 750 ms followed by 1250 ms of fixation. Abstract, concrete, and fixation trials were pseudo-randomly intermixed with counterbalancing (each trial type followed every other trial type equally often).
13. Approximately 20 min later, subjects were administered a memory test consisting of 480 studied and 480 unstudied words. Words were presented individually with self-paced timing. Subjects responded "high confidence studied," "low confidence studied," or "new."
14. An Item Type × Response interaction [$F(1,12)$ = 22.97] revealed that studied items were endorsed as "high confidence studied" more frequently than were unstudied items [52% and 7%, respectively; $F(1,12)$ = 57.04], whereas studied and unstudied items were similarly endorsed as "low confidence studied" [24% and 20%; ($F < 1.0$)]. The low confidence response class likely reflects subject guessing and does not differentiate between encountered and novel stimuli.
15. Encoding task performance was analyzed based on whether the words were subsequently remembered with high confidence ("high confidence hits"), low confidence ("low confidence hits"), or were forgotten ("misses"). Accuracy during encoding was comparable for high confidence hits (88% correct), low confidence

hits (88% correct), and misses (89% correct) ($F < 1.0$). Semantic decision RTs declined across trial types [$F(2,24) = 9.26$]: RTs were longer for high confidence hits (1000 ms) compared to low confidence hits (966 ms) [$F(1,12) = 5.40$], which were in turn longer compared to misses (936 ms) [$F(1,12) = 3.91, P < 0.06$].

16. The procedures for selective averaging and statistical map generation for rapidly intermixed trials are described elsewhere (7). Statistical activation maps were constructed based on the differences between trial types using a t-statistic (7). Fixation trial events were subtracted from the word trial events (collapsing across subsequent memory). Miss trial events and high confidence hit events were subtracted from each other, as were those for miss trial events and low confidence hit events. Clusters of five or more voxels exceeding a statistical threshold of $P < 0.001$ were considered significant foci of activation (7).

17. In addition, modest but significantly greater activation for high confidence hits relative to misses was noted in a more ventral extent of left inferior frontal gyrus [Brodmann's area (BA) 47: $-34, 31, -3$], left precentral gyrus (BA 6: $-31, 0, 56$), medial superior frontal gyrus (BA 8: $-3, 28, 43$), and left superior occipital gyrus (BA

19: $-31, -77, 34$). The superior occipital and medial superior frontal activations can be seen in Fig. 2. Two regions demonstrated less activation for high confidence hits relative to misses: precuneus (BA 31: 3, -43, 40) and left middle frontal gyrus (BA 9: $-12, 31, 34$). No regions demonstrated greater activation for low confidence hits relative to misses, which is in accord with the behavioral data indicating that these two trial types likely did not mnemonically differ.

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19. RTs were matched as follows. First, the median RT across all trial types was determined for each subject. Trials with response latencies that fell below the median RT were selected and sorted based on subsequent memory. Selection of trials in this manner resulted in matched RTs for the high confidence hit (852 ms) and miss (839 ms) trial types [$F(1,12) = 2.32, P > 0.15$].

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Prevention of Allogeneic Fetal Rejection by Tryptophan Catabolism

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In 1953 Medawar pointed out that survival of the genetically disparate (allogeneic) mammalian conceptus contradicts the laws of tissue transplantation. Rapid T cell–induced rejection of all allogeneic concepti occurred when pregnant mice were treated with a pharmacologic inhibitor of indoleamine 2,3-dioxygenase (IDO), a tryptophan-catabolizing enzyme expressed by trophoblasts and macrophages. Thus, by catabolizing tryptophan, the mammalian conceptus suppresses T cell activity and defends itself against rejection.

Medawar (1) considered three mechanisms that might explain the immunological paradox of fetal survival: (i) anatomic separation of mother and fetus, (ii) antigenic immaturity of the fetus, and (iii) immunologic "inertness" (tolerance) of the mother. In view of evidence that the entire repertoire of maternal T cells specific for paternally inherited major histocompatibility complex (MHC) class I alloantigens is transiently affected and tolerized during pregnancy (2, 3), the first two mechanisms cannot explain fetal allograft survival, and attention has focused on the third mechanism. Certain macrophages, induced to express IDO in

response to interferon-γ and other signals from activating T cells, inhibit T cell proliferation in vitro by rapidly consuming tryptophan (4, 5); some tissue macrophages may use this immunosuppressive mechanism in vivo. Because IDO is also expressed by human syncytiotrophoblast cells (6) and systemic tryptophan concentration falls during normal pregnancy (7), we formulated the hypothesis that IDO expression at the maternal-fetal interface is necessary to prevent immunological rejection of fetal allografts. To test this hypothesis, we exposed pregnant mice (carrying syngeneic or allogeneic fetuses) to 1-methyl-tryptophan, a pharmacologic agent that inhibits IDO enzyme activity (8).

First, IDO transcription during pregnancy (9) was assessed in females mated with CBA (syngeneic) or C57BL/6 (B6, allogeneic) males (Fig. 1). IDO transcripts were detected from 7.5 to 9.5 days post coitus (dpc) in all concepti but were not detected at 6.5 dpc. At later gestation times (10.5 and 13.5 dpc), IDO transcripts were detected in placenta but not

in maternal uterus or embryonic tissues. These findings are consistent with the known expression of IDO in human syncytiotrophoblast (6).

Pregnant mice ($n = 8$ to 32) carrying syngeneic or allogeneic concepti were treated with 1-methyl-tryptophan or with placebo, beginning at 4.5 dpc (10). Concepti were examined macroscopically and histologically at various times during gestation (11). At 6.5 dpc, mice from all treatment groups carried normal numbers of concepti and embryonic development was normal (Table 1). At 7.5 to 8.5 dpc, the mean number of allogeneic concepti in females treated with IDO inhibitor was reduced significantly ($P < 0.01$) and extensive hemorrhaging surrounded most of those that remained (Fig. 2A). However, at 7.5 dpc, most remaining allogeneic concepti were developmentally normal (Fig. 2C), with rare embryos showing signs of degeneration. By 8.5 (Fig. 2F) to 9.5 dpc, all allogeneic embryos showed signs of inflammation and progressive deterioration (12). After 9.5 dpc, no allogeneic concepti remained in any mice treated with IDO inhibitor. In contrast, the mean number of syngeneic concepti and the developmental status of embryos were not af-
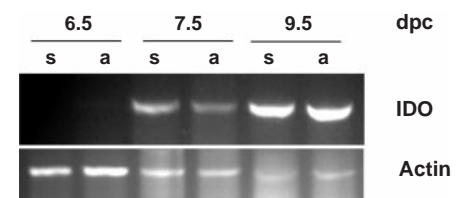
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Fig. 1. Analysis of IDO transcription during murine gestation. PCR products were generated by RT-PCR amplification from RNA samples prepared from pooled syngeneic (s) or allogeneic (a) concepti, at the gestation times indicated (9). Results are representative of three separate experiments.