

# Neural Correlates of the Spacing Effect in Explicit Verbal Semantic Encoding Support the Deficient-Processing Theory

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**Abstract:** Spaced presentations of to-be-learned items during encoding leads to superior long-term retention over massed presentations. Despite over a century of research, the psychological and neural basis of this spacing effect however is still under investigation. To test the hypotheses that the spacing effect results either from reduction in encoding-related verbal maintenance rehearsal in massed relative to spaced presentations (deficient processing hypothesis) or from greater encoding-related elaborative rehearsal of relational information in spaced relative to massed presentations (encoding variability hypothesis), we designed a vocabulary learning experiment in which subjects encoded paired-associates, each composed of a known word paired with a novel word, in both spaced and massed conditions during functional magnetic resonance imaging. As expected, recall performance in delayed cued-recall tests was significantly better for spaced over massed conditions. Analysis of brain activity during encoding revealed that the left frontal operculum, known to be involved in encoding via verbal maintenance rehearsal, was associated with greater performance-related increased activity in the spaced relative to massed condition. Consistent with the deficient processing hypothesis, a significant decrease in activity with subsequent episodes of presentation was found in the frontal operculum for the massed but not the spaced condition. Our results suggest that the spacing effect is mediated by activity in the frontal operculum, presumably by encoding-related increased verbal maintenance rehearsal, which facilitates binding of phonological and word level verbal information for transfer into long-term memory. *Hum Brain Mapp* 31:645–659, 2010. © 2009 Wiley-Liss, Inc.

**Key words:** fMRI; encoding; frontal operculum; spacing effect; maintenance rehearsal; elaborative rehearsal; hippocampus; encoding; verbal learning; semantic

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## INTRODUCTION

In the spacing effect, spaced presentations of to-be-learned items lead to superior performance on delayed retention tests compared to massed presentations [Melton,

1967]. Although the spacing effect has been known for over a century [Ebbinghaus, 1964] and is one of the most robust effects in psychology [Dempster, 1990; Janiszewski et al., 2003], its behavioral and neural bases are still unclear. Our aim in this study is to determine the neural

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basis of the spacing effect related to explicit verbal encoding.

A number of psychological theories aimed at accounting for the spacing effect are still being entertained [Cepeda et al., 2006]. Among these theories, the deficient-processing theory and the encoding variability theory have received considerable attention [Cepeda et al., 2006; Hintzman, 1974]. According to the deficient-processing theory, the repeated consecutive presentation of the same item in the massed condition leads to a high feeling of knowing [Zechmeister and Shaughnessy, 1980] resulting in less attentive maintenance rehearsal needed to maintain the item in working memory. Spaced presentations however are not present in the working memory store at the time of later presentations, leading to a low feeling of knowing, and thus these repeated items have increased attentive maintenance rehearsal relative to the massed items leading to more encoding [Cuddy and Jacoby, 1982; Rundus, 1971]. According to the encoding variability theory spaced items are learned better than massed items because their repeated distributed presentation results in a larger number of associations with pre-existing knowledge facilitating their later retrieval [Landauer, 1969; Melton, 1967]. These two theories mirror the two (nonexclusive) views on verbal memory encoding: Encoding results from transfer of short-term memory to long-term memory through maintenance rehearsal [Atkinson and Shiffrin, 1968; Davachi et al., 2001] or from association of new knowledge with pre-existing relational knowledge through elaborative rehearsal [Anderson, 2000; Baddeley, 1997].

To test these two psychological theories of the spacing effect, we use reverse inference [Poldrack and Wagner, 2004]: The degree of activity in particular brain regions involved specifically with maintenance rehearsal or elaborative rehearsal is hypothesized to reflect the relative contribution of these functions in task-related encoding. The two theories posit the involvement of different encoding systems in the brain, which may not be mutually exclusive. Because our study investigates semantic encoding of verbal information, we focus our investigation on regions of the brain related to verbal processing.

According to the deficient processing hypothesis, the enhanced performance for spaced over massed items results from relatively more encoding-related maintenance rehearsal in working memory. Neuroimaging studies suggest the verbal working memory system consists of the lateral inferior prefrontal cortex, the posterior parietal cortex, the supplementary motor area SMA, and the cerebellum [Davachi et al., 2001; Jonides et al., 1998]. Within this broad network, the prefrontal regions have been implicated with processes related to long-term encoding of verbal information [Buckner, 2000; Fiez et al., 1996; Kapur et al., 1996; Wagner et al., 1998]. Specifically, the frontal operculum has been implicated in both performance-related maintenance rehearsal of verbal information [Fiez et al., 1996] and in verbal encoding [Fiez et al., 1996; Wagner et al., 1998]. The frontal operculum is involved in a variety of other verbal

and nonverbal functions, such as acoustic-articulatory processing [Fiez et al., 1995; Paulesu et al., 1993], syllable sequence production [Bohland and Guenther, 2006], implicit priming [Wagner et al., 2000], orthographic/phonological segmentation [Burton et al., 2005], as well as object and face memory [Smith et al., 1995]. However, within the context of the design of this experiment, we evaluate the role of the frontal operculum in explicit verbal encoding, as it relates to the spacing effect.

According to the encoding variability hypothesis, the spacing effect is a result of greater associative encoding of the spaced items due to variability of distributed lags in presentation to pre-existing relational information that is mediated by a process of elaborate rehearsal [Greene, 1992]. Although some prefrontal regions have been identified to be involved in processing of relational information [Davachi et al., 2001], it is primarily the hippocampus and parahippocampus that are implicated in relational encoding for verbal information [Henke et al., 1999; Meltzer and Constable, 2005]. Furthermore, in a task in which subjects were given explicit instructions to elaborately encode words, only activity in the hippocampus was correlated with later memory performance [Davachi et al., 2001; Davachi and Wagner, 2002]. The hippocampus and parahippocampus are also involved in a variety of functions beyond encoding of relational information, such as visual navigation [Epstein and Kanwisher, 1998], processing of facial emotion [Lee et al., 2008], as well as novelty detection [Knight, 1996]. However, given the design and goals of our experimental task, we evaluate the role of the hippocampus in explicit relational encoding, as it relates to the spacing effect.

To explore the neural basis of the spacing effect, we used an explicit declarative semantic verbal encoding task that mimicked second language vocabulary learning. Subjects were instructed to learn paired-associates presented in a spaced manner and other paired-associates presented in a massed manner during fMRI scanning. Each paired-associate was made of a common English word and an unknown word of an artificial language. The use of an artificial language in which phonotactic relations are controlled allows for investigation of neural processes underlying encoding of the binding of phonological and semantic information. We consider the associative pairing of a novel phonological sequence to the lexical aspects of a known word (which by definition contains its meaning) to constitute the binding of phonological and semantic information for transfer into long-term memory. We acknowledged that we dismiss the possibility that the pairing between the novel phonological sequence and the word is accomplished only by means of phonological association. Given that the words we used were highly familiar monosyllabic nouns, however, it is unlikely that the subjects dismissed the words semantic content and learned the word-nonword pairing based solely on phonological association. Subjects were given both a 10-min and a 1-day delayed cued-recall test on the

pairs presented during the learning session (see Materials and Methods for more details).

Brain regions involved with the spacing effect can be investigated by contrasting the spaced condition (episodes 2–4 relative to its control, see Materials and Methods) with that of the massed condition (episodes 2–4 relative to its control). Additional analyses showing that activity in regions differing between spaced and massed conditions was correlated with behavioral performance were conducted to support the functional relationship of these regions to encoding. In support of the deficient-processing theory, we predict that the spacing effect in verbal learning is a result of the need to use more attentive encoding-related verbal maintenance rehearsal within the frontal operculum upon subsequent presentation of an item in the spaced condition relative to the massed condition. This is because the consecutive presentation of items in the massed condition results in little interference or decay of the working memory store between presentations than in the spaced condition in which the item needs to be attentively rehearsed into working memory again upon subsequent presentation. In support for the encoding variability hypothesis, we predict that the hippocampus, which underlies relational learning between novel and pre-existing knowledge (see above), exhibits stronger activity in the spaced than in the massed condition because of the greater variability of relational information with distributed presentations. Our control condition accounts for differences between spaced and massed conditions related solely to their lag characteristics that are not involved with encoding the binding of a known word with a novel phonological pattern. Additionally, to test the predicted pattern of change across episodes of presentation of a paired-associate for the massed and spaced conditions, linear trend analyses were conducted (see Materials and Methods). The deficient processing hypothesis predicts that the massed (but not spaced) condition will show a significant decrease in activity (in the frontal operculum) with subsequent episodes of presentation indicating less encoding-related rehearsal. The encoding variability hypothesis predicts that the spaced (but not massed) condition will show a significant increase in activity (in the hippocampus) with subsequent episodes of presentation indicating greater encoding of relational information. It is entirely possible that both the deficient processing and elaborative rehearsal accounts of the spacing effect are correct. In this case, we predict that both verbal maintenance rehearsal and elaborative rehearsal processes related to encoding (located in the frontal operculum and hippocampus, respectively) will show greater differential activity for the spaced than the massed condition.

## MATERIALS AND METHODS

### Subjects

Thirteen 27- to 43-year-old (mean 32 years of age, SD 5.0 years; 11 males, 2 females) right-handed subjects partici-

pated in this study. All subjects were proficient English speakers including six non-native speakers. It is important to note that there was no difference in performance on the task between subjects who were native speakers and those who were not (see Results). Subjects gave written informed consent for experimental procedures, approved by the ATR Human Subject Review Committee. Subjects had no history of neurological or psychiatric diseases.

### Procedure and Stimuli

The experiment consisted of an English vocabulary pretest taken outside the fMRI scanner, an encoding phase inside the scanner, a distracter task inside the scanner, and two post-tests outside the scanner (10 min and 1 day after the end of the encoding phase). Several days before the fMRI experiment, the subjects were given a list of 150 words that could potentially be used in the study. The pretest involved rating whether the words were of high or low familiarity. Because some subjects were not native English speakers only those who rated all words as being highly familiar were included in the study.

The encoding phase conducted during fMRI scanning consisted of learning paired-associates between the known English words and novel phonological sequences. Two conditions of learning were employed: Massed and Spaced. The massed condition consisted of presenting the same paired-associates four times in a row (episodes 1–4) within the same scanning run. The spaced condition consisted of presenting the paired-associates once during each of four fMRI scanning runs (the scanning run number is the episode numbers 1–4). A single presentation of a pair was 8 s long followed by a 1-s intertrial interval. In our analysis, each 9-s time between presentations constituted a block for the fMRI analysis. Although 9 s is relatively short for a block design, we use a short block length to maximize the difference between spaced and massed learning. It is known that performance improves as the number of spaced repetitions increases [Ebbinghaus, 1964; Greene, 1992]. We designed the study such that massed learning was four times as long as a single-spaced learning trial without the massed learning becoming excessively long. As shown by our behavioral results, four 9-s presentations for the spaced condition and one 36-s presentation (four sequential presentations of the same pair to be learned) for the massed condition was a reasonable trade off between long enough trials for the spaced condition and not too long trials for the massed condition such that the subject completely loses concentration.

The BOLD response reaches its plateau in  $\sim 6$  s [Bandettini, 1999], but higher signal-to-noise ratio and smaller signal variations occur with a longer build up of the BOLD response with blocks of over 20 s. Thus, the percent signal change in our analysis is likely to be lower than that when longer blocks were used. Our design with 9-s block durations used somewhat resembles an event-related design

without jittering of the stimuli. We did not choose an event-related design however because we were interested in activity during the entire 9 s of encoding rather than the activity related to the onset of the event (corresponding to the visual presentation of the paired-associates). Given the limitations imposed by the goals of the experiment in determining differences between verbal encoding of spaced and massed trials, we selected to use a short-duration block design. Even though our short-duration block design may be less sensitive than longer-duration block designs or typical event-related designs in which the stimuli are jittered, we were nevertheless able to find some robust fMRI results.

Comparison between massed and spaced trials is made possible by using a condition controlling for general processes related to verbal working memory in which subjects were instructed to rehearse mentally an English word paired with itself. This control condition permitted attentive verbal maintenance rehearsal and verbal elaborative rehearsal processes specific to the task of encoding the binding of known words to novel phonological patterns to be investigated beyond processes active during verbal rehearsal of a known word paired with itself. Additionally, the control conditions had the same lag characteristics between presentations of identical pairs as their respective matched massed and spaced conditions in an attempt to account for activity that may be related to the temporal differences in the presentation of these two conditions such as repetition priming effects and attention switching effects related to stimulus predictability. Directly comparing the spaced and massed conditions, without reference to their respective controls, is prohibitive because the results would likely be confounded by these lag effects.

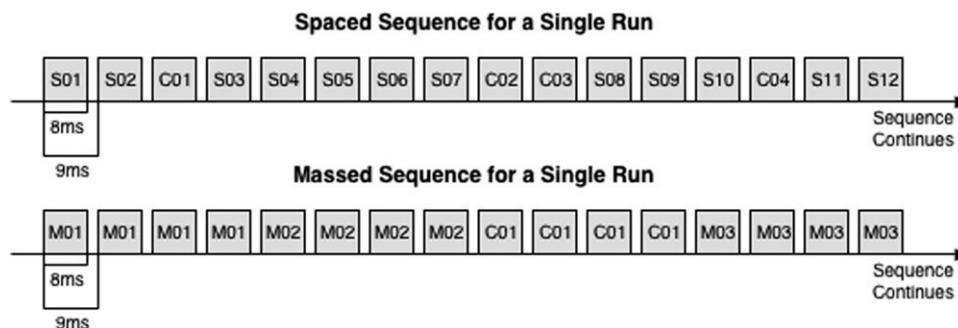
The use of stimuli composed of a pairing of a known word to a novel phonological sequence was to explore the spacing effect as it relates to encoding. The subjects were instructed that they would be given recall tests to determine the extent of encoding of the paired-associates. In contrast the subjects were instructed to only verbally rehearse during the control condition (containing a real word paired with itself) and that there would be no recall test for these words. It is important to note that this study is concerned with the spacing effect as it relates to encoding of a word to a novel phonological sequence and as such the control condition in which there is no pairing to be encoded does not consist of an encoding-related spacing effect.

Both the deficient processing hypothesis and the encoding variability hypothesis posit that the spacing effect is a result of the degree of processing rather than an altogether different type of processing between spaced and massed items. Therefore, the contrast of the spaced and massed conditions to their respective control conditions is predicted to show activity in largely overlapping regions. While the control conditions account for general processes associated with attentive verbal rehearsal and semantic relational information of known words, the task of binding

a known word with a novel phonological pattern in the experimental conditions likely involves additional phonological and orthographic processing demands beyond that of encoding using maintenance rehearsal or elaborative relational processes. However, brain regions specifically involved with encoding of the binding (paired association) of a known word with a novel phonological pattern can be determined by correlating brain activity with behavioral performance.

In total, there were eight fMRI scanning runs, four massed runs were interleaved with four spaced runs, with the order counterbalanced across subjects. In total for all scanning runs, subjects had to learn 24 paired-associates in the massed and 24 paired-associates in the spaced conditions and had eight control pairs matched for lag presentation characteristics of the respective conditions. For each of the four runs of the massed condition, there were six paired-associates and two control pairs (the same pair presented four times in a row) for a total of 32 trials per run. For each of the four runs of the spaced condition, there were 24 paired-associates and 8 control pairs (each presented once for each of the four runs) for a total of 32 trials per run. The position of the experimental as well as the control trials within a run for both the massed and spaced conditions was randomly determined. For each trial the English word was presented above a fixation cross (always present on the screen—used to avoid excess eye movement) with the paired phonological sequence presented below the fixation cross (for control trials the same English word appeared above and below the fixation cross). Each presentation lasted 8 s, with 1 s between presentations (only the fixation cross remained on the screen during the 1 s between presentations); thus, each paired-associate was presented for 32 s (36 s if you count the 1-s interval between presentations) in both conditions. Because the positions in each run were randomized, successive presentations of the same pair in the random condition were separated by intervals ranging from 5 to 10 min. See Figure 1 for a pictorial presentation of the sequencing pattern of the massed and spaced conditions.

The stimuli consisted of English words and novel phonological sequences. The English words were common [Word Frequency > 5; Kuchera and Francis, 1967] monosyllabic nouns composed of four to five letters with a regular orthographic to phonological pattern. The novel phonological sequences were generated to control for phonotactic structure and word length. The same consonant-vowel pattern was used for all novel words (CVCVC). Five possible consonants (p,t,k,b,d) and five possible vowels (a,i,e,o,u) were randomly assigned to each of the corresponding positions. Randomly generated words that happened to be real English words were eliminated. The assignment of the word pairs to the massed and spaced experimental and control conditions was randomly determined for each subject to ensure that overall the conditions were composed of stimuli that were equally



**Figure 1.**

Example sequence patterns for spaced and massed fMRI runs. Only part of the run is shown. For the spaced sequence, there are twelve more spaced stimuli and four more control stimuli that are not shown that finish off the run. For the massed sequence, there are three more massed stimuli and one more control stimuli to finish off the run. The order and position of the experimental and control stimuli are random for both massed and spaced conditions. M denotes a massed trial; S denotes a spaced trial; C denotes a control trial.

difficult. The following is an example of an experimental pair (bench kodad) and a control pair (shirt shirt).

After the encoding phase of the experiment, subjects took part in a perceptual speech-in-noise experiment within the fMRI scanner, serving as a distracter task. The attentional demands of the experiment were such that they precluded continued rehearsal of the learned paired-associates. Following the end of the speech-in-noise experiment (~ 10 min after the end of the paired-associate encoding phase), subjects took a computerized delayed cued-recall test in which the 48 English words to be learned from the massed and spaced conditions were randomly presented and the corresponding novel phonological sequence words had to be typed. Subjects were instructed to recall as many letters as possible. One day later, subjects took the cued-recall test once more. At each presentation, subjects were instructed to recall as many letters of the paired word as possible. Performance was indexed by percent correct recall of three or more letters in the correct position of the paired word. Both the 10-min and the 1-day cued recall tests were conducted outside the MRI. Subjects were instructed not to attempt to encode word pairs except when presented on the screen and not to discuss or continue practicing/rehearsing the pairs for the day following the experiment when the second recall test was given.

### fMRI Data Collection and Preprocessing

A Shimadzu-Marconi's Magnex Eclipse 1.5 T PD250 scanner, located at the ATR Brain Activity Imaging Center, was used in this experiment. Functional T2\*-weighted images were acquired using a gradient echo-planar imaging sequence (echo time 48 ms; repetition time 3,000 ms; flip angle 90°). Thirty sequential contiguous axial slices were acquired with a 3.5 × 3.5 × 5 mm<sup>3</sup> (4 mm with 1

mm gap) voxel resolution covering the entire brain including the cerebellum. For a single run, 111 scans were taken. In total, for the entire 8 runs, there were 888 scans. The first five scans were discarded from each run. At the beginning of the experiment, the fixation cross was shown for 18 s; brain activity during this period was used as an implicit baseline for each run in the analysis. Images were preprocessed using programs within SPM2 (Wellcome Department of Cognitive Neurology, University College London). Images were realigned, unwarped, and spatially normalized to a standard space (default) using a template EPI image (3 × 3 × 4 mm<sup>3</sup> voxels) and were smoothed using a 7 × 7 × 10 mm<sup>3</sup> FWHM Gaussian kernel. The onset of trial presentation was synchronized with the beginning of the scan using the Neurobehavioral System's Presentation software. The data was assessed (SPM2) using a general linear model employing a boxcar function convolved with a hemodynamic response function. High pass filtering (cutoff period 128 s) was carried out to reduce the effects of extraneous variables (scanner drift, low frequency noise, etc.). Autoregression was used to correct for serial correlations. Each 9-s trial presentation (8-s trial + 1-s inter-trial interval) signified the duration of the individual blocks used in the analysis. Experimental blocks and control blocks for episodes 1–4 were modeled for each run. Episode 1 is the initial learning episode of the paired-associates and theoretically should not differ from spaced or massed learning. Therefore, episodes 2–4 were combined for direct comparison between spaced and massed conditions as well as for correlation analyses with behavioral performance. To assess the pattern of change in activity across the episodes of presentation, a linear trend analysis was conducted such that episodes 1–4 were weighted, respectively, with the following contrast: –3 –1 1 3. All analyses were conducted using SPM2.

All voxel coordinates reported in this study use the Montreal Neurological Institute MNI convention. Voxels reported to be active for the random-effects paired *t*-tests and the regression analyses (see below) are additionally significant with respect to the experimental condition of interest (spaced or massed episodes 2–4) relative to its respective control condition (Threshold criteria:  $T = 3.05$ ;  $P < 0.005$  uncorrected; spatial extent threshold = 20 voxels).

## RESULTS

### Behavioral Performance: Replication of the Spacing Effect

As expected, compared to the massed condition, the spaced condition led to superior performance both on the 10-min delayed cued-recall test (median performance: massed 20.83%; spaced 54.17%;  $P = 0.0005$ ;  $n = 13$ ; Wilcoxon signed rank test for matched samples) and on the 1-day cued-recall test (median performance: massed 25.0%; spaced 41.67%;  $P = 0.0171$ ;  $n = 13$ ; Wilcoxon signed rank test for matched samples; see Fig. 2) (No significant difference was present between 10-min and 1-day cued-recall tests,  $P > 0.05$ .) Subjects reported using both verbal rehearsal and elaborative rehearsal strategies for encoding in both conditions. No significant differences in encoding performance were found between native and non-native speakers for the 10-min delayed cued-recall test nor for the 1-day cued-recall test (ranksum  $P > 0.05$ ). Neither was there a significant interaction between native/non-native and spaced/mass conditions [ANOVA;  $F(1,11) = 0.002$  (10-min),  $F(1,11) = 0.422$  (1-day);  $P > 0.05$ ].

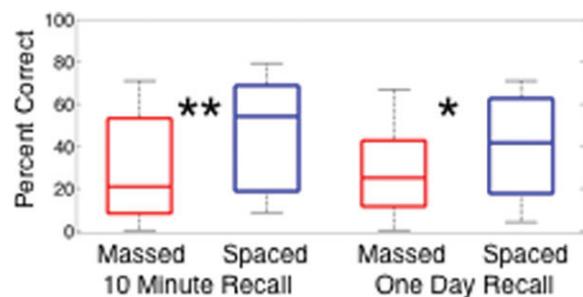
### Spaced and Massed Presentations Activate Largely Overlapping Networks

We first determined the brain regions underlying spaced and massed encoding relative to their respective control verbal working memory conditions for episodes 1–4 individually and combined episodes 2–4 (see Fig. 3). Both spaced and massed conditions activated the left and right inferior frontal gyrus IFG the left premotor cortex PMC, supplementary motor area SMA, the left inferior IPL and superior parietal cortices SPL, and the left basal ganglia (random-effects analysis;  $n = 13$ ; threshold criteria:  $T = 3.05$ ;  $P < 0.005$  uncorrected; spatial extent threshold = 20 voxels) (see Fig. 3, Table I). Thus, for the most part, the spaced and massed conditions were associated with brain activity in similar brain regions. Figure 3A,B shows that activity was fairly similar for episodes 1 and 2 for both massed and spaced conditions but that there was a marked decrease in activity in episodes 3 and 4 for the massed but not for the spaced condition. In particular, frontal operculum activity was present for both massed and spaced conditions on episodes 1 and 2 but was only

present for the spaced in episodes 3 and 4 (Fig. 3A,B). The analysis over the combined episodes 2–4 shows significant activity in the frontal operculum for the spaced but not the massed condition (Fig. 3C,D, Table I). No significant differential activity was found in our regions of interest (the frontal operculum, inferior frontal gyrus, or hippocampus) in the control conditions relative to their respective massed and spaced experimental conditions (random-effects analysis threshold criteria:  $T = 3.05$ ;  $P < 0.005$  uncorrected;  $n = 13$ ). These results ensure that there was no excessive masking by the control condition.

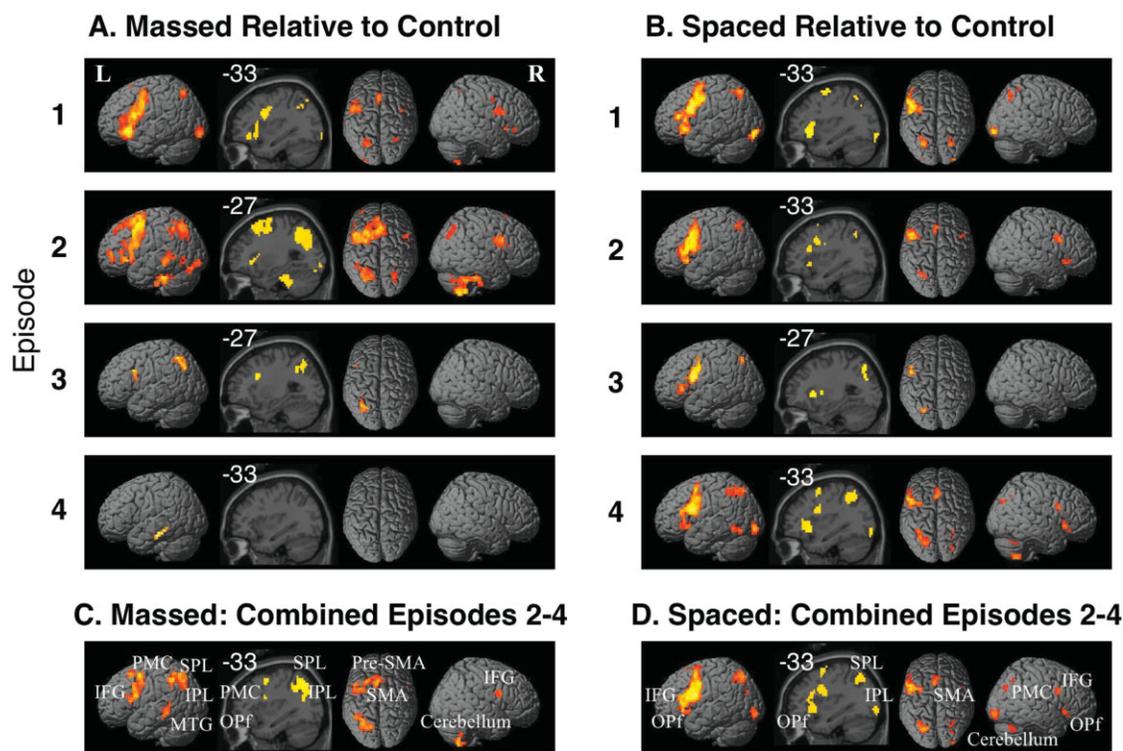
### Relationship Between Learning Performance With Spaced and Massed Brain Activity

We conducted a random-effects correlation analysis to determine the relationship between subject recall performance and corresponding brain activity for the spaced and the massed conditions relative to their respective control conditions (combined episodes 2–4) ( $t = 3.11$ ;  $P < 0.005$  uncorrected;  $n = 13$ ) (Table II). For both the massed and spaced conditions, brain activity was significantly correlated with recall performance (10-min and 1-day recall) in a large number of brain regions. The massed condition showed brain activity correlated with performance in the left frontal operculum, left IFG, left STG, left IPL, and left SPL (Table II). The spaced condition showed brain activity correlated with performance in the left frontal operculum, left and right IFG, left and right PMC, pre-SMA, left dorsolateral prefrontal cortex DLPFC, left IPL and left basal ganglia (Table II). Only the left frontal operculum and the left IFG commonly showed correlated activity with recall performance (10-min and 1-day) for massed and spaced conditions (Table II).



**Figure 2.**

Performance on the 10-min and 1-day delayed cued-recall test for the massed and spaced conditions. The lines of the boxes show the lower quartile, median, and upper quartile values; the whiskers represent the range of the data. A Wilcoxon signed rank test for matched samples revealed that performance for the spaced condition was significantly greater than the massed condition for both 10-min and 1-day cued-recall tests. \* $P < 0.05$ , \*\* $P < 0.0005$ .



**Figure 3.**

Random-effects *t*-test rendered on the brain showing significantly greater activity for the (A) massed and (B) spaced conditions relative to their respective control conditions ( $T = 3.05$ ;  $P < 0.005$  uncorrected, spatial extent = 20 voxels) for each episode (1–4) of presentation of a paired-associate. (C) Combined episodes 2–4 relative to its respective control for the massed condition. (D) Combined episodes 2–4 relative to its respective

control for the spaced condition. Sagittal slice selected to show frontal operculum activity. L = left; R = right; OPf = frontal operculum; PMC = premotor cortex; IFG = inferior frontal gyrus; SMA = supplementary motor area; MTG = middle temporal gyrus; IPL = inferior parietal lobule; SPL = superior parietal lobule.

### Differential Activity Between Spaced and Massed Encoding

Differences between spaced and massed conditions (combined episodes 2–4) were compared using a random-effects paired *t*-test. The paired contrast of the spaced relative to control in relation to the massed relative to control was evaluated (threshold criteria:  $t = 3.43$ ;  $P < 0.005$  two-tailed uncorrected;  $n = 13$ ; spatial extent threshold = 20 voxels). Greater activity associated with the spaced condition over the massed condition was only present in a single cluster in the region of the frontal operculum (Fig. 4A) (peak voxel  $-27,18,0$ ;  $T = 5.83$ ;  $P < 0.00005$  two-tailed uncorrected). To test the hypothesis on the role of the frontal operculum in encoding via verbal maintenance rehearsal, we conducted a region of interest analysis in the frontal operculum, at coordinates  $(-29,15,7)$  given in Fiez et al. [1996] as a site reflecting performance-related maintenance of verbal information. Significant differential activity was found for the spaced over massed condition relative to their respective control conditions [random-effects

paired *t*-test;  $T = 5.83$ ; false discovery rate (FDR)  $P < 0.05$  two-tailed small volume corrected (SVC) for multiple comparisons; search radius 12 mm; peak voxel  $-27,18,0$ ]. This differential activity overlaps with the cluster given in Fiez et al. [1996].

For both the massed and spaced conditions (combined episodes 2–4), the correlation of activity of the voxels composing the frontal operculum cluster (given in Fig. 3A) with behavioral performance was assessed using a region of interest analysis. Within this region, a significant correlation of spaced relative to control activity with behavioral performance was present for both 10-min (peak voxel  $-30,18,0$ ;  $T = 2.92$ ; SVC FDR  $P < 0.05$ ) and 1-day (peak voxel  $-27,21,4$ ;  $T = 3.13$ ; SVC FDR  $P < 0.05$ ) delayed cued-recall test. Although the activity in this region is significantly greater for the spaced over the massed condition, a significant correlation of massed relative to control activity to behavioral performance was also present for both 10-min (peak voxel  $-33,21,-4$ ;  $T = 4.21$ ; SVC FDR  $P < 0.05$ ) and 1-day (peak voxel  $-30,18,0$ ;  $T = 4.59$ ; SVC FDR  $P < 0.05$ ) delayed cued-recall test. Figure 4B indicates

**TABLE I. Random-effects analysis of the spaced and massed conditions relative to their respective control verbal working memory conditions**

Brain region	Combined episodes 2–4			
	Massed		Spaced	
	<i>t</i>	MNI ( <i>x,y,z</i> )	<i>t</i>	MNI ( <i>x,y,z</i> )
IFG BA44	3.87	–48,9,20	9.07*	–51,6,20
	4.39	45,3,24	3.41	48,9,24
IFG BA45	4.05	–45,18,12	6.19*	–54,18,16
Frontal operculum BA13,47			6.09*	–27,21,0
			4.51	30,24,0
Premotor cortex BA6	4.03	–42,0,48	5.76*	–39,6,56
	5.02	36,–6,28	4.82	–54,0,44
SMA BA6	5.69	–9,15,52	5.11*	–3,15,60
Pre-SMA BA8	5.85	–3,21,52		
Cingulate BA32			4.7	–6,21,48
Anterior cingulate BA33			4.25	–3,9,24
MTG BA22	5.41	–48,–42,–4		
Inferior parietal BA7,40	4.42	–48,–48,44	4.61	–33,–57,44
Superior parietal BA7	5.46	–33,–60,52	5.45*	–24,–69,48
			4.43	30,–63,44
Inferior occipital BA18			4.48	–30,–90,–8
			4.55	30,–96,–8
Basal ganglia	4.31	–18,–3,16	6.78*	–24,–6,12
	4.47	27,–33,12		
Brain stem	4.74	–6,–27,–20		
Cerebellum	4.41	39,–57,–44		

Threshold criteria:  $t = 3.05$ ;  $P < 0.005$  uncorrected;  $n = 13$ .

The location of active peak voxels was determined by reference to the Talairach atlas (Talairach and Tournoux, 1988) after transforming from the MNI to the Talairach coordinate system (<http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>).

MNI, Montreal Neurological Institute; IFG, inferior frontal gyrus; SMA, supplementary motor area; MTG, middle temporal gyrus.

\* $t$  values of peak voxels that are significant at FDR  $P < 0.05$  corrected for multiple comparisons across entire volume.

that subjects who performed well on the massed test had high levels of frontal operculum activity, similar to that of high performance on the spaced test, but that overall subjects performed lower on the massed test reflecting lower activity than that of the spaced test. This figure depicts how the spaced condition can show significantly greater activity than the massed condition and yet both the massed and spaced conditions are correlated with performance. It is important to note that the results of the correlation analysis were not just driven by the non-native English-speaking subjects. The results of a SPM analyses between non-native and native speakers in the cluster defining the frontal operculum (as shown in Fig. 3A) did not reveal any significant statistical differences for the spaced and massed relative to control conditions ( $P > 0.05$ ), whereas the SPM regression analysis over the native as well as the non-native subjects showed significant correlation with activity in the frontal operculum for both the 10-min and 1-day cued recall test ( $P < 0.05$ ) suggesting that the results were not driven solely by the non-native speakers but were present also for native speakers as well.

No significant differential activity was present for the massed over the spaced conditions (threshold criteria:  $T = 3.43$ ;  $P < 0.005$  two-tailed uncorrected;  $n = 13$ ; spatial extent threshold = 20 voxels). Furthermore, significant differential activity between the spaced and massed conditions in the frontal operculum and the lack of a finding in the hippocampus was not a result of activity in the control relative to the experimental conditions. Analyses over episodes 1–4 individually as well as the combined episodes 2–4 for the control relative to massed and spaced experimental conditions did not reveal any significant differential activity (threshold criteria:  $T = 3.05$ ;  $P < 0.005$  uncorrected;  $n = 13$ ; spatial extent threshold = 20 voxels) in the frontal operculum and hippocampus as well as in regions found to be active in any region given in Figure 3. Additionally, it should be noted that there was no significant differential activity (threshold criteria:  $T = 3.43$ ;  $P < 0.005$  two-tailed uncorrected;  $n = 13$ ; spatial extent threshold = 20 voxels) in the frontal operculum between spaced and massed conditions for episode 1.

**TABLE II. Random-effects correlation analysis of the spaced and massed conditions with behavioral recall performance**

Brain region	Combined episodes 2–4 correlated with behavioral performance							
	Massed				Spaced			
	10-min recall		1-day recall		10-min recall		1-day recall	
	<i>t</i>	MNI ( <i>x,y,z</i> )	<i>t</i>	MNI ( <i>x,y,z</i> )	<i>t</i>	MNI ( <i>x,y,z</i> )	<i>t</i>	MNI ( <i>x,y,z</i> )
IFG BA44	3.57	–45,9,20	7.23	–45,9,28	3.25	48,7,22	3.14	48,7,20
	5.86	–42,9,28			3.12	–54,3,28	3.76	–57,6,28
IFG BA45	3.55	–57,18,24	3.46	–45,18,20				
Frontal operculum BA13,47	4.21	–33,21,–4	4.59	–30,18,0	3.97	–27,18,8	3.68	–27,18,8
Premotor cortex BA6					4.81	–57,3,32	3.31	–39,9,48
							4.39	51,3,36
Pre-SMA BA8					4.50	0,36,56	4.19	0,36,56
DLPFC BA46					4.79	–45,42,4	4.62	–45,45,–4
STG BA22	4.97	–63,–54,8	4.50	–63,–54,8				
Inferior parietal BA7,40			4.02	–45,–45,44	3.30	–36,–51,40		
Superior parietal BA7	4.21	–21,–66,56	6.22	–30,–72,44				
Basal ganglia					3.34	–27,–3,4	4.64	–30,–3,0

Threshold criteria:  $t = 3.11$ ;  $P < 0.005$  uncorrected;  $n = 13$ .

The location of active peak voxels was determined by reference to the Talairach atlas (Talairach and Tournoux, 1988) after transforming from the MNI to the Talairach coordinate system (<http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>).

MNI, Montreal Neurological Institute; IFG, inferior frontal gyrus; SMA, supplementary motor area; STG, superior temporal gyrus; DLPFC, dorsal lateral prefrontal cortex; BA, Brodmann area.

### Decreasing and Increasing Linear Trend in Activity for Spaced and Massed Encoding

Decreasing and increasing linear trend in activity from episodes 1 to 4 was assessed for both massed and spaced conditions (Fig. 5A,B). The massed condition shows a significant decreasing linear trend in activity relative to control in the left and right frontal operculum, IFG, and PMC, inferior occipital cortex, as well as the SMA and right cerebellum ( $T = 3.43$ ;  $P < 0.005$  two-tailed uncorrected; FDR  $P < 0.05$  corrected; spatial extent 20 voxels) (Fig. 3A). The inferior parietal cortex showed a significant increasing linear trend in activity for the massed condition ( $T = 3.43$ ;  $P < 0.005$  two-tailed uncorrected) (Fig. 3A). The spaced condition did not show a significant decreasing or increasing linear trend in activity from episodes 1 to 4. The massed condition over the spaced condition relative to their respective control conditions showed a significantly greater decreasing linear trend in activity in the left and right frontal operculum, left IFG, left PMC, and SMA (paired  $t$ -test  $T = 3.43$ ;  $P < 0.005$  two-tailed uncorrected;  $n = 13$ ; spatial extent threshold = 20 voxels) (Fig. 5C, Table III). Figure 5D clearly depicts the linear decrease in frontal operculum activity (contrast estimate) from episodes 1 to 4 for the massed but not for the spaced condition. No significant increasing linear trend in activity was found for the massed over the spaced condition. Finally, the linear trend in activity for the massed over the spaced condition does not reflect decreasing or increasing trends resulting from the control condition (see Supporting Information Fig. 1).

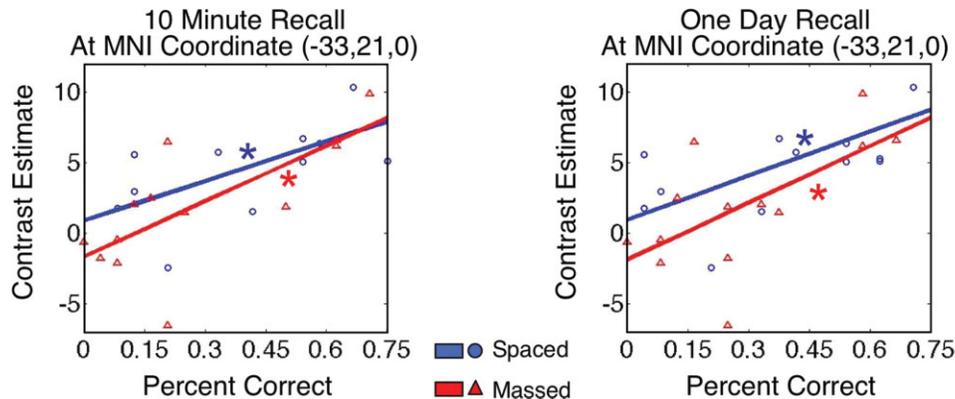
### DISCUSSION

The explicit phonological-to-semantic learning task employed in our study exhibited a significant spacing effect; items presented in a spaced manner show better recall performance than items presented in a massed manner (see Fig. 2). We found behaviorally related increased activity in the spaced relative to the massed condition in only one region, the left frontal operculum (see Fig. 4A,B), which is known to be involved with verbal maintenance rehearsal and encoding [Davachi et al., 2001; Fiez et al., 1996; Wagner et al., 1998]. Furthermore, this region was also found to decrease in activity with subsequent episodes of presentation for the massed condition relative to that of the spaced condition (Fig. 5A–D, Table III). Our results are consistent with predictions of the deficient processing hypothesis suggesting that the spacing effect in verbal learning is a result of the greater need to re-encode items in the spaced condition, thus greater verbal maintenance rehearsal, than in the massed condition. This deficient processing is made evident in Figures 3 and 5D in which it can be clearly seen that there is a decrease in activity in the frontal operculum with subsequent episodes of presentation for the massed but not for the spaced condition. Our results are inconsistent however with the predictions of the encoding variability theory: No significant difference or increase in hippocampal [a region known to be involved in relational encoding between novel and pre-existing knowledge (Davachi and Wagner, 2002; Hannula and Ranganath, 2008)] activity with subsequent episodes

**A. Spaced Vs Massed: Combined Episodes 2-4**



**B. Correlation of Frontal Operculum Activity with Behavioral Performance**



**Figure 4.**

(A) Paired t-test rendered on the brain showing significantly greater activity for spaced over massed (relative to controls) in the left frontal operculum ( $T = 3.43$ ;  $P < 0.005$  two-tailed uncorrected; spatial extent threshold = 20 voxels). (B) The correlation of spaced and massed brain activity located in the frontal operculum at  $-33,21,0$  with behavioral 1-day cued recall performance. Both spaced and massed trials show significant correlation with performance for the 10-min and 1-day recall

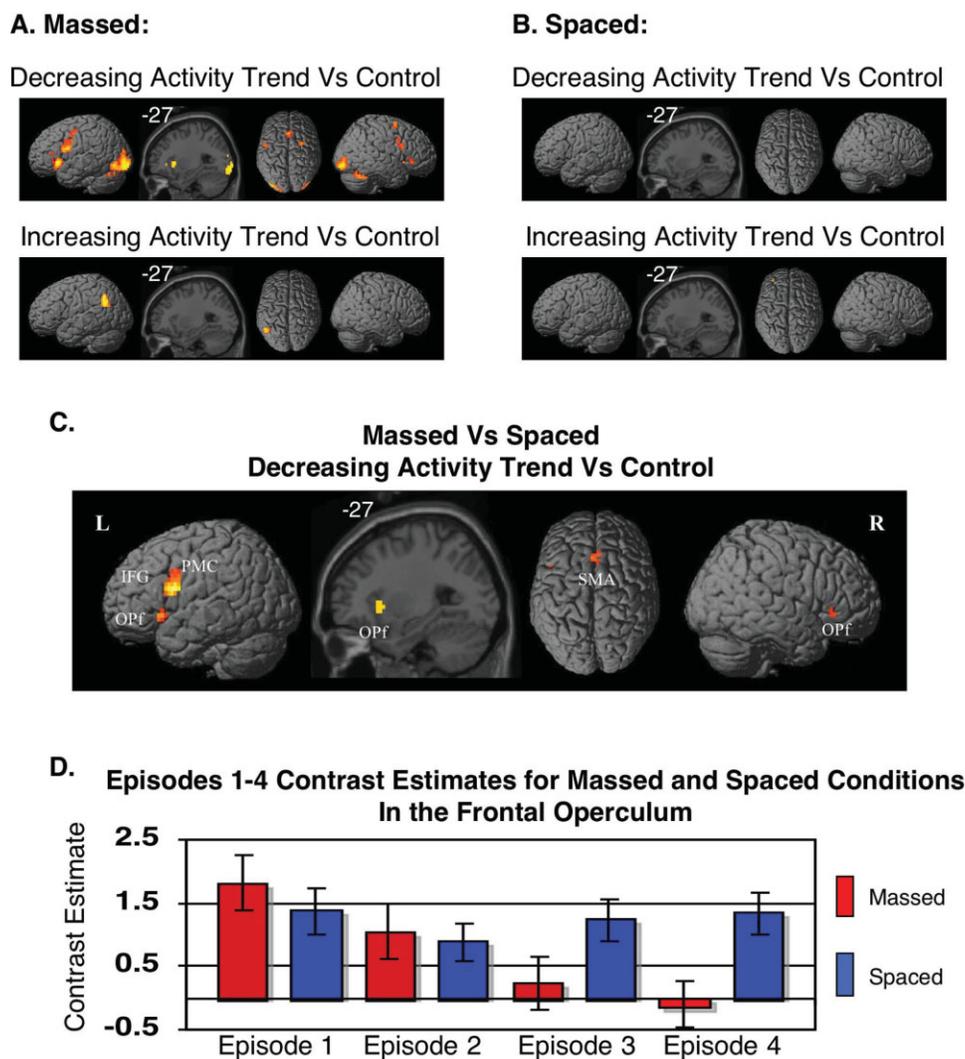
tests (brain activity at MNI coordinate  $-33,21,0$  correlated with performance: 10-min recall spaced:  $T = 2.67$ ;  $P < 0.05$ ; 1-day recall spaced:  $T = 2.95$ ;  $P < 0.05$ ; 10-min recall massed:  $T = 3.49$ ;  $P < 0.05$ ; 1-day recall massed:  $T = 2.74$ ;  $P < 0.05$ ). However, spaced trials have higher overall activity than massed trials (at MNI coordinate  $-33,21,0$ :  $T = 5.21$ ;  $P < 0.0001$ ); L = left; R = right; OPf = frontal operculum.

of presentation was present between spaced and massed conditions. It should be noted that the reverse inference paradigm in neuroimaging [Poldrack and Wagner, 2004] is limited in that it operates on the assumption that no additional brain regions than those ascribed to carry out a certain psychological function also carry out that same function. In our study, the frontal operculum, a region known to be involved with verbal maintenance rehearsal, was the only region showing a significant difference between spaced and massed trials even using a somewhat lenient threshold (Fig. 4A).

Because we found a positive correlation between behavioral performance and activity in the frontal operculum for both conditions (Fig. 4B, Table II), our results suggest that the subjects also used encoding-related verbal maintenance rehearsal mechanisms in the massed condition, but to a lesser extent. Furthermore, correlations between behavioral performance and brain activity within the frontal operculum (Fig. 4B) were similar for the 10-min and for the 1-day cued recall tests, suggesting that

the encoding was long-lasting and was not due to additional learning of the pairs after the encoding phase of the experiment.

Results from previous studies suggest that the region of the frontal operculum that we found differentially active for spaced over massed conditions is involved with binding and encoding of verbal information via subvocal maintenance rehearsal. This region of the frontal operculum (see Fig. 5A) has notably been proposed to be involved in mapping of auditory-to-articulatory information [Fiez et al., 1996; Paulesu et al., 1993], which likely underlies its contribution to tasks involving subvocal rehearsal [Fiez et al., 1996] and encoding of verbal information [Kapur et al., 1996; Wagner et al., 1998]. In our study, the peak differential activity between spaced and massed conditions found in the left frontal operculum ( $-27,18,0$ ) is near coordinates reported in verbal maintenance rehearsal ( $-36,24,-3$ ;  $-33,24,12$  [Davachi et al., 2001];  $-29,15,7$  [Fiez et al., 1996]) and verbal encoding ( $-31,22,6$  [Wagner et al., 1998]). It is, however, more posterior, superior, and less



**Figure 5.**

Test of decreasing and increasing linear trends in activity from episodes 1 to 4 rendered on the surface of the brain. **(A)** Decreasing and increasing linear trend in activity for the massed relative to its respective control condition ( $T = 3.43$ ;  $P < 0.005$  two-tailed uncorrected; spatial extent threshold = 20 voxels). **(B)** No Significant decreasing and increasing linear trend in activity for the spaced relative to its respective control condition was present ( $T = 3.43$ ;  $P < 0.005$  two-tailed uncorrected; spatial

extent threshold = 20 voxels). **(C)** Activity showing a greater decreasing linear trend for the massed versus the spaced condition relative to their respective controls (paired  $t$ -test  $T = 3.43$ ;  $P < 0.005$  two-tailed uncorrected; spatial extent threshold = 20 voxels). **(D)** The contrast estimates at MNI coordinate  $-27, 21, 0$  for episodes 1–4 of massed and spaced conditions. L = left; R = right; OPf = frontal operculum; PMC = premotor cortex; IFG = inferior frontal gyrus.

lateral than the area of the anterior lateral prefrontal gyrus ( $-45, 30, -9$ ) involved with elaborative rehearsal [Davachi et al., 2001]. These results are consistent with the role of the frontal operculum in binding phonological and word level semantic information, which has been previously conjectured [Hagoort, 2005]. It should be noted that our results are not solely due to greater verbal maintenance rehearsal, but are also related to encoding as activity in this

region is correlated with behavioral recall performance (Fig. 4B).

The relationship between brain activity and performance in both spaced and massed conditions can be understood with reference to cognitive processes thought to be carried out in relevant brain regions. The pattern of brain activity for the spaced and massed conditions relative to their respective controls (Fig. 3, Table I) shows that both

**TABLE III. Random-effects analysis of the decreasing linear trend in activity from episodes 1 to 4 for the massed versus the spaced condition relative to their respective control verbal working memory conditions**

Brain region	Massed versus Spaced Decreasing activity trend relative to control	
	<i>t</i>	MNI ( <i>x,y,z</i> )
IFG BA44	7.30*	-48,9,20
Frontal operculum BA13,47	5.66*	-33,18,4
	5.54*	30,30,0
Premotor cortex BA6	6.86*	-36,3,28
SMA BA6	3.98	-3,21,56
Cingulate BA32	5.03*	6,24,44

Threshold criteria:  $t = 3.43$ ;  $P < 0.005$  uncorrected two-tailed;  $n = 13$ . The location of active peak voxels was determined by reference to the Talairach atlas (Talairach and Tournoux, 1988) after transforming from the MNI to the Talairach coordinate system (<http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html>). MNI, Montreal Neurological Institute; IFG, inferior frontal gyrus; SMA, supplementary motor area; BA, Brodmann area. \**t* values of peak voxels that are significant at FDR  $P < 0.05$  corrected for multiple comparisons across entire volume.

conditions engage the verbal working memory network consisting of left prefrontal cortex, the left parietal cortex, and the right cerebellum. The results of several studies suggest that maintenance rehearsal in verbal working memory is carried out by this network of brain regions and that the prefrontal cortex in particular is related to more long-term encoding of verbal information [Buckner, 2000; Fiez et al., 1996; Jonides et al., 1998; Kapur et al., 1996; Wagner et al., 1998]. Consistent with these studies, the results of our correlation analysis for the spaced and massed conditions (Table II) revealed prefrontal activity at the time of encoding in the frontal operculum and the inferior frontal gyrus to be predictive of later recall performance. Consistent with the findings of Davachi et al. [2001], activity in the parietal cortex was additionally found to be predictive of later recall performance (Table II).

Contrary to the predictions of the encoding variability theory, we did not find significant differential hippocampal activity in the spaced condition relative to its respective control condition (see Fig. 3), nor was a significantly increasing trend in hippocampal activity found in the hippocampus for the spaced condition with subsequent episodes of presentation (see Fig. 5). It should also be noted that no significant hippocampal activity was found for the massed condition relative to its respective control or for the control respective to massed or spaced conditions. The lack of hippocampal activity in the experimental conditions (spaced and massed) relative to control conditions is somewhat puzzling given its involvement in processing novelty [Hunkin et al., 2002]. Novelty processing is known to enhance encoding of verbal paired-associates [Hunkin

et al., 2002]. While the control conditions account for many confounds, they do not control for novelty-related activation that would be expected to occur in response to the novel phonological sequences to be associated in the experimental conditions. Therefore, one would expect both spaced and massed conditions to show hippocampal activity. Additionally, it is unclear why hippocampal activity was not present, as previous studies involved with second-language vocabulary learning have shown that hippocampal activity is related to successful encoding [Callan and Schweighofer, 2008]. Because hippocampal encoding is modulated by anxiety [Callan and Schweighofer, 2008], it is possible that we did not find performance-related activity because of elevated stress for the difficult task used in this experiment of binding known words to novel phonological patterns. While the results of our experiment are certainly contrary to the encoding variability account of the spacing effect, its contribution cannot be definitively ruled out. It is possible that future experiments using different experimental designs may reveal hippocampal activity consistent with the encoding variability account of the spacing effect.

Besides the hippocampus, a number of other brain regions, including large parts of the prefrontal cortex, are also implicated in novelty processing [Ranganath and Rainer, 2003]. Furthermore, novelty processing in prefrontal and medial temporal cortices has been associated with increased encoding via increased attention [Ranganath and Rainer, 2003]. Our results of decreased activity in the left frontal operculum for subsequent episodes of presentations in the massed condition (Figs. 3 and 5) are not contradictory with novelty-enhanced encoding. Each paired-associate in our experiment comprises a novel word, and subjects must encode a relatively large number of pairs. While repetition of pair in a massed condition would lower novelty in the massed condition, resulting in lower attention, the spaced presentations, because they are placed far apart and surrounded by many other pairs, may lead to novelty effect even in later presentation, which may increase activity in the frontal operculum on subsequent presentations and lead to increased encoding. In summary, deficient processing in the massed presentations would be due to an “inattention effect” that would decrease encoding.

The design of our experiment allows us to rule out many potential confounds that could account for frontal operculum activity differences between the spaced and massed conditions apart from explicit encoding-related verbal maintenance rehearsal. Two primary confounds of concern are attentional switching and implicit priming. Because of the successive presentation of stimuli in the massed condition, one might expect less attentional switching than when items are spaced in a distributed manner such that each successive presentation is a different item. The degree of attentional switching resulting from successive or distributed presentation of items in the massed and spaced conditions, respectively, is accounted

for because the control condition contains these same presentation lag characteristics. Another potential confound is that of implicit priming. Implicit priming is characterized by a reduction in brain activity upon subsequent presentations of the same stimulus, also referred to as a repetition suppression effect [Wagner et al., 2000]. Successive presentation of identical stimuli in the massed condition has greater implicit priming than repeated presentations of the same stimuli with longer distributed lags in the spaced condition. It is unlikely that the differential activity we found between spaced and massed conditions result from implicit priming, because the control conditions had the same lag characteristics as their respective experimental counterparts and thus have the same potential for implicit priming.

Because in the spaced condition a new pair is presented at each trial and compared to the massed condition in which a new pair is presented only every four trial, one may expect greater activity in brain regions involved with switching of orthographic/phonological processing. Although the frontal operculum is known to be involved in orthographic/phonological segmentation processes [Burton et al., 2005], the results of our regression analysis show that the greater activity in the frontal operculum for spaced over massed trials was not related merely to switching of orthographic/phonological segmentation processes independent of verbal encoding processes. In such case, there would be no correlation between brain activity in this region and delayed cued-recall performance for both spaced and massed conditions as we found (Fig. 4B, Table II).

Although our subjects consisted of both native and non-native English speakers, there were no statistically significant differences in delayed cued-recall performance between native and non-native English speakers or for delayed cued-recall performance between native/non-native and spaced/massed conditions. Furthermore, although the frontal operculum is known to predict second language proficiency [Callan et al., 2004; Tatsuno and Sakai, 2005], we found here no difference in brain activity within the frontal operculum between native and non-native English speakers. Rather, for both groups, activity in the frontal operculum was correlated with delayed cued-recall performance. These findings suggest that the results of our experiment are not driven solely by the non-native speakers but were present also for native speakers as well.

Our experiment suggests that the decrease in performance in the massed condition is a result of the decrease in processing in the frontal operculum especially on episodes 3 and 4. It should be noted that our study tests a specific aspect of the spacing effect of paired-associates that are spaced versus those that are strictly massed (there is probably little, if any, interference or forgetting effects to occur in our study during the 1-s interval between subsequent presentations in the massed condition). Future research could assess the generalizability of these results by

addressing whether varying degrees of spacing (spaced and more spaced) will also reflect differences in frontal operculum activity that are related to behavioral performance. Additionally, in this study, because the spaced and massed trials were blocked separately in different runs, it is possible that subjects deliberately choose different encoding strategies. Future studies could also investigate whether the results found in this study are maintained when spaced and massed trials are mixed within the same run.

While our study focuses on the neural processes related to immediate encoding, there are likely other neural processes including those related to forgetting that may also be important for fully explaining the spacing effect but are beyond the scope of our study. Indeed, forgetting is known to be faster after massed practice [Bahrick et al., 1993; Pavlik and Anderson, 2005]. Despite this concession, the results of our experiment strongly suggest that frontal operculum activity during immediate encoding is predictive of later recall performance and is greater for spaced over massed presentations (Figs. 4 and 5; Tables II and III).

Considerable behavioral research has compared the advantages of maintenance versus elaborative rehearsal in vocabulary learning; while elaborative rehearsal has a large number of proponents, not all studies have clearly shown an advantage of one method over the other [Nation, 1982]. Although we do not explicitly address this question in this experiment, the results of the spaced as well as the massed conditions strongly suggest that our subjects preferably used a verbal maintenance rehearsal encoding strategy (see Figs. 4 and 5). Thus, our results are consistent with the seminal Atkinson and Shiffrin model [Atkinson and Shiffrin, 1968] and a recent imaging study [Davachi et al., 2001] supporting that verbal encoding results from transfer of short-term memory to long-term memory through maintenance rehearsal. In our study, we did not specify to subjects to use maintenance or elaborative rehearsal but allowed them to use whatever strategy they desired as to not influence possible causes of the spacing effect. In future studies, it may be possible to manipulate the degree of encoding-related maintenance and elaborative rehearsal and its influence on the spacing effect; however, this is likely to be challenging given that it requires controlling an individual's subjective effort.

The results of our experiment suggest that the spacing effect in verbal learning is due to enhanced maintenance rehearsal in spaced relative to massed presentations. More specifically, encoding-related maintenance rehearsal appears to be deficient upon subsequent episodes of presentation in the massed condition. Such rehearsal, which occurs in the left frontal operculum, facilitates binding of phonological and word level verbal information for transfer into long-term memory. These results have practical implications as they suggest that verbal learning can be improved by maintenance rehearsal of items presented in a spaced manner.

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