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# Left out: An fMRI study exploring handedness-based exclusion in memory research

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## Abstract

About 11% of the world population is left-handed, a significant minority of the potential research participant pool for functional MRI (fMRI) studies. However, convention in fMRI research dictates these potential participants be excluded due to evidence that left-handed people (LH) may have different lateralization of neural functioning than right-handed people (RH). This difference in lateralization may cause different areas of the brain to be activated by the same task. The current study investigates the lateralization differences between N=26 LH and N=27 RH during encoding and recognition memory tasks for words and faces. Additionally, we measured participants' laterality index by administering a semantic fluency task. We found localized evidence of differential activation between LH and RH groups at both encoding and retrieval. To measure if including LH in fMRI studies would alter results significantly, we calculated memory effects in a priori regions of interest (ROI) for the RH only, and then examined the effect of substituting in progressively more LH for RH. We found that subsequent memory effects at encoding were not reduced by adding in LH. However, at retrieval, significant memory effects diminished in the bilateral precuneus for faces and in the left hippocampus for words when substituting in six and five LH, respectively. These findings suggest that while the blanket exclusion of LH in memory research is not warranted, exclusion for research in specific ROI may be justified.


## Introduction

Traditionally, left-handed (LH) individuals have been excluded from fMRI research based on the idea that brain lateralization differs significantly between LH and right-handed (RH) people to the degree that including them in a sample would significantly interfere with the results. Although LH individuals make up 11.1% of the U.S. population (Gilbert & Wysocki,

1992), they are only represented in 3-4% of neuroimaging research (Bailey, McMillan, & Newman, 2020). Due to the methodology of fMRI analyses (which are comparative by nature), including subjects with differing brain lateralization patterns may skew results by introducing variability in activation beyond that which is caused by the phenomena of interest. However, excluding LH individuals may lead to systematic bias in studies where LH-ness is not significantly related to levels of activation in regions of interest (ROI).

In some areas of fMRI study, the brain lateralization for LH and RH individuals has been shown to be especially divergent, which often leads to LH individuals being excluded from these types of research (e.g., language and motor-skills based research; McManus, 2019; Bailey, McMillan, & Newman, 2020). One area of the literature that lacks substantial research is the brain lateralization of memory in LH and RH people. Exclusion from fMRI studies on the basis of handedness exacerbates the already difficult participant selection process, as it excludes more than one-tenth of the US population (Gilbert & Wysocki, 1992). Moreover, given that LH individuals make up more than 11% of the population (a number larger than many other smaller populations sampled and controlled for), the baseless exclusion of LH individuals from all areas of fMRI research is ethically questionable.

Although certain areas of the brain have been shown to have differences in lateralization between LH and RH individuals—for example, the fusiform face area, intraparietal sulcus, and right-ventral and dorsal premotor cortex—many areas of the brain have not shown this handedness-driven lateralization (Martin, Jacobs & Frey, 2011; Frässle, Krach, Paulus, & Jansen, 2016). In fMRI language research, LH individuals are typically excluded because research has concluded that they are more likely than RH individuals to exhibit atypical brain lateralization (Szaflarski, Binder, Possing, McKiernan, Ward, & Hammeke, 2002; but see Szaflarski,

Rajagopal, Altaye, Byars, Jacola, Schmithorst, Schapiro, Plante, & Holland, 2012). In facial recognition research, creation and comparison of facial representations have shown less activation in the right-hemisphere (Rhodes, 1985), and left-visual field superiority has been shown for facial recognition (Hilliard, 1973). Given recent data indicating that the hippocampus preferentially responds to information in the contralateral visual field (Silson et al., 2021) — consistent with the theory of lateralized functioning in the hippocampus—there is a basis for testing whether handedness would affect the activation in memory research. However, the effects of handedness on the lateralization of memory functions have yet to be thoroughly explored.

Golby et al. (2002), concluded that the most important aspect of memory encoding lateralization related to the verbalizability of the stimuli by observing that verbal encoding resulted in left-lateralized activation of the inferior prefrontal cortex and the medial temporal lobe, whereas pattern encoding activated the right inferior prefrontal cortex and the right medial temporal lobe, and scenes and faces resulted in fairly similar activation in both regions. However, Golby et al. (2002) did not use handedness as a variable in their research and merely looked at lateralization differences of memory functions. While Cuzzocreo et al. (2009) found a difference in activation of lateralization in fMRI memory research on the basis of handedness, their study's generalizability was limited in that they only tested verbal memory by means of an auditory word-pair-associates learning task in participants above the age of 50. Additionally, while Cuzzocreo et al., attribute the difference found in activation to differences in lateralization on the basis of handedness, no laterality indices (LI's) were calculated for participants to rule out other explanations. Because verbal and spatial memory functions have been shown to change in lateralization due to aging (Reuter-lorenz et al., 2000), age could be an important factor in lateralization.

Our study builds on previous research by including a younger population, measures of both verbal and nonverbal memory, and LI's calculated for each participant. Consistent with previous research, we hypothesized that when performing verbal and nonverbal memory tasks, there would be lateralized activation differences in memory-dependent contrasts between LH and RH at both encoding and retrieval. Given the large body of research that shows strong lateralization of language based on handedness, and the lack of research showing lateralization in facial recognition due to handedness, we also hypothesized that at both encoding and retrieval (tested separately) there would be a group by stimulus type interaction such that the lateralized activation differences between groups would be stronger for words than for faces.

Our second research question was if including LH individuals would lessen any activation effects (i.e., does adding LH individuals to an analysis that is significant for RH individuals make the effect fail to reach significance) and if so, how many LH participants can be added into an analysis before the effect was diluted enough to fail to be detected. Given previous research that shows handedness-based lateralization differences, we hypothesized that at both encoding and retrieval we would see the difference in activation for memory effects decrease (become less significant) as more RH participants were replaced by a LH counterpart in the analysis.

## Methods

### Participants

Sixty participants (31 LH and 29 RH individuals) were recruited through a university campus and the surrounding community. All participants were between the ages of 19-48 (mean =22.7, SD=4.5). Inclusion criteria required participants to be in good overall health and have no history of physiological or neurological disorders. Participants were prescreened for handedness

using the Edinburgh Handedness Inventory (EHI). Eligibility for inclusion as a LH participant required an EHI score of ≤-40, and RH participants were eligible for inclusion with EHI scores ≥40 to ensure a clear handedness orientation (Oldfield, 1971; Edlin et al., 2015). Safety screening was also conducted to ensure participants were eligible for MRI scanning. Participants received either $20 or a ¼-scale 3D-printed model of their brain as remuneration for their participation. The BYU Institutional Review Board approved all study protocols and procedures, and participants gave informed consent before participating. Six participants were excluded from the analyses: five due to excessive movement and one due to a high number of nonresponses (defined as greater than 2 *SD*s above the mean). Accordingly, final analyses of fMRI data were conducted on 54 participants (26 LH).

**Procedure**

Participants completed, in order, a faces encoding task, a words encoding task, a semantic fluency task (Brumer et al., 2020), a faces retrieval task, and a words retrieval task while undergoing fMRI scanning. In the encoding tasks, participants were shown 100 face stimuli and then 100 words and were asked to determine whether they considered each item presented to be pleasant or unpleasant (by pressing one of two buttons on an MR-compatible response device) in order to promote deeper stimulus encoding (Guerin & Miller, 2009). Each stimulus was presented for 2.5 seconds and the delay between stimuli was jittered 0.5-1.5 seconds, to allow deconvolution of overlapping BOLD signal responses to stimuli (Amaro & Barker, 2006). In between stimuli, participants were shown a blank screen with a black crosshair (+) in the middle of the screen. The order of the individual faces and words were randomized at both encoding and retrieval. Responses made after a stimulus was no longer displayed on the screen were not recorded. Faces were selected from a database (Minear & Park, 2004) made to be equally

representative of various adult ages, genders, and races. Fifty facial stimuli were selected from each age range (18-29, 30-49, 50-69, 70-93), and within each age range an equal number of male and female pictures were selected. Words were selected from the MRC database (Coltheart, 1981) with high concreteness (ratings ≥600) and familiarity (ratings ≥400).

We administered a semantic decision task (a type of semantic fluency task that has been shown to demonstrate greater activation in temporoparietal ROI (Bradshaw et al., 2017) to calculate a LI for each participant using an fMRI protocol consisting of six 30-second cycles alternating between activation and baseline conditions (Harrington et al., 2006; Brumer et al., 2020). For the activation cycles, participants were shown randomized abstract and concrete words and were asked to identify whether each word was abstract or concrete by pressing one of two buttons. Concrete and abstract words were selected from the MRC database (Coltheart, 1981) with a familiarity rating of ≥400 and with abstract words having ratings of ≤400 and concrete words having ratings of ≥600 in concreteness score.

For the baseline cycles, participants were shown randomized strings of upper and lowercase letters using Random (https://www.random.org/strings) and were asked to identify whether the words were upper or lowercase by pressing one of two buttons. For the retrieval tasks, participants were shown the same 100 words and faces they had seen during encoding in addition to 100 novel words and faces (200 words shown first, 200 faces shown second). Stimuli were shown in randomized order for each participant. Participants were asked to identify between the previously seen (“old”) and novel (“new”) stimuli by pressing one of two buttons. Similar to the encoding portion of the study, each stimulus was presented for 2.5 seconds, the delay between stimuli was jittered 0.5-1.5 seconds during which time participants were shown a blank screen with a single black crosshair in the middle of the screen. The retrieval tasks were

each broken up into two scan runs with 100 trials (two sets of 100 stimuli for both the words retrieval task and the faces retrieval task). Prior to being positioned in the MRI scanner, participants were given instructions regarding the behavioral task they would be performing, in addition to information concerning MRI safety measures. Participants used a four-button response cylinder (Current Designs Inc.; Philadelphia, PA) and were instructed to press the first button with their pointer finger to indicate "lowercase/old/concrete/pleasant" stimuli, and to press the second button with their middle finger to indicate "uppercase/new/abstract/unpleasant" stimuli. An MRI compatible LCD monitor (BOLDscreen; Cambridge Research Systems; Rochester, UK) was used to display stimuli. This monitor was located at the head-end of the MRI scanner and viewed by means of an adjustable mirror that was attached to the head coil. Prior to the initial functional scan, participants were given the definition and examples of "abstract" vs "concrete" words. Instructions regarding which button corresponded with which stimulus type were listed on each slide throughout each phase of the study (see Figure 1).

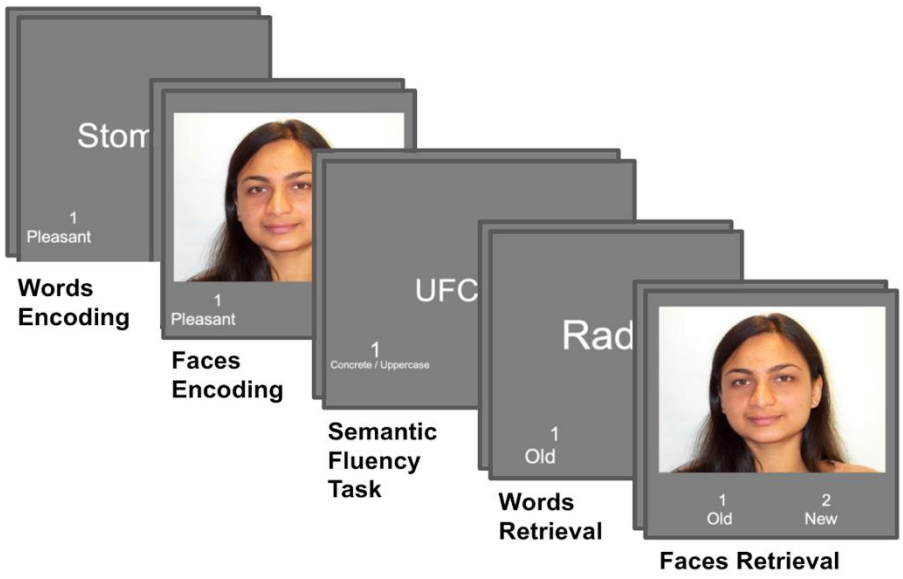


**Figure 1**
The encoding, semantic fluency task, and retrieval tasks were presented to participants during functional (fMRI) scans. Each stimulus appeared for 2,500ms with an interstimulus interval jitter of 500-1,500ms (represented as blank screens with a single crosshair in the center between stimuli).

All MRI imaging was performed on a Siemens 3 Tesla TIM Trio scanner (Erlangen, Germany), using a 32-channel head coil. Each participant contributed a T1-weighted structural scan and echo-planar imaging (EPI) scans for each of the tasks. The T1-weighted MP-RAGE used the following parameters: 176 slices; TR = 1900 ms; TE = 4.92 ms; flip angle = 9°; field of view = 256 mm; slice thickness = 1 mm; voxel resolution = .97 × .97 × 1.0 mm; 1 average. EPI scans used a T2*-weighted pulse sequence utilizing a multiband (MB) technique (Xu et al., 2013) with the following parameters: 72 interleaved slices; TR = 1800 ms; TE = 42 ms; flip angle 90°; field of view = 180mm; slice thickness = 1.8 mm; voxel resolution = 1.8 × 1.8 × 1.8 mm; MB factor = 4. Each functional run had 195 acquisitions except for the semantic fluency task, which had 200. The first four TRs of each run were discarded to allow for T1 equilibration.

**Data Analysis**

Data were preprocessed in several steps: First, structural and functional scans were converted from DICOM to NIfTI format using program *dcm2niix* (Li et al., 2016) and structural scans were de-faced for anonymity using in-house scripts. Second, the functional and structural scans were uploaded to BrainLife (brainlife.io; Avesani et al., 2019) for preprocessing using the FreeSurfer and FMRIprep pipelines found there. The following text is auto-generated by the FMRIprep pipeline and is included here for reproducibility:

> Results included in this manuscript come from preprocessing performed using *fMRIPrep* 20.2.1 (@fmriprep1; @fmriprep2; RRID:SCR_016216), which is based on *Nipype* 1.5.1 (@nipype1; @nipype2; RRID:SCR_002502).
>
> **Anatomical data preprocessing**
>
> A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with

`N4BiasFieldCorrection` [@n4], distributed with ANTs 2.3.3 [@ants, RRID:SCR_004757], and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using NKI as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` [FSL 5.0.9, RRID:SCR_002823, @fsl_fast]. Brain surfaces were reconstructed using `recon-all` [FreeSurfer 6.0.1, RRID:SCR_001847, @fs_reconall], and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle [RRID:SCR_002438, @mindboggle]. Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* [@mni152nlin2009casym, RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym], *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* [@mni152nlin6asym, RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym],

**Functional data preprocessing**

For each of the 1 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. A deformation field to

correct for susceptibility distortions was estimated based on *fMRIPrep*'s *fieldmap-less* approach. The deformation field is that resulting from co-registering the BOLD reference to the same-subject T1w-reference with its intensity inverted [@fieldmapless1; @fieldmapless2]. Registration is performed with `antsRegistration` (ANTs 2.3.3), and the process regularized by constraining deformation to be nonzero only along the phase-encoding direction, and modulated with an average fieldmap template [@fieldmapless3]. Based on the estimated susceptibility distortion, a corrected EPI (echo-planar imaging) reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration [@bbr]. Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using `mcflirt` [FSL 5.0.9, @mcflirt]. BOLD runs were slice-time corrected using `3dTshift` from AFNI 20160207 [@afni, RRID:SCR_005927]. The BOLD time-series were resampled onto the following surfaces (FreeSurfer reconstruction nomenclature): *fsaverage*. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*.

*Grayordinates* files [@hcppipelines] containing 91k samples were also generated using the highest-resolution `fsaverage` as intermediate standardized surface space. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, @power_fd_dvars) and Jenkinson (relative root mean square displacement between affines, @mcflirt). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* [following the definitions by @power_fd_dvars]. The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction [*CompCor*, @compcor]. Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted from a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each

CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each [@confounds_satterthwaite_2013]. Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using `antsApplyTransforms` (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels [@lanczos]. Non-gridded (surface) resamplings were performed using `mri_vol2surf` (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.6.2 [@nilearn, RRID:SCR_001362], mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation.

**Copyright Waiver**

Following pre-processing using BrainLife, functional data were blurred with a 4mm FWHM Gaussian blur and scaled by the mean of the overall signal for each run. Functional volumes with large motion events, defined as TRs with a Euclidean norm (ENORM) of the temporal derivative of motion estimates (rotations and translations) greater than 0.3, along with TRs immediately before a motion-contaminated TR, were excluded from single-participant regression analyses (see below for details on regression models).

Separate single-subject regression models were created for the face encoding, word encoding, face retrieval, word retrieval, and semantic fluency tasks. For both encoding tasks, behavioral regressors coded for subsequent hits, subsequent misses, and trials of no interest (e.g., non-responses at either encoding or retrieval). For both retrieval tasks, behavioral regressors coded for hits, misses, correct rejections (CRs), false alarms (FAs), and trials of no interest. For all encoding and behavioral tasks, events were modeled as a canonical hemodynamic response function convolved with a boxcar function of 2.5-second duration. The semantic fluency task was modeled as a block-design, with a 30-second boxcar for the active task condition convolved with the canonical hemodynamic response function. All single-subject regression models included six regressors for motion (3 translation, 3 rotation) and polynomial regressors coding for run (in the case of the retrieval tasks that had two scan runs each) and scanner drift. The resulting statistical maps of fit coefficients (β-coefficients) were then entered into group analyses as described below.

To define the LI, we conducted a meta-analysis of fMRI papers in the PubMed database using NeuroSynth (https://neurosynth.org) for the term “language”. The uniformity test z-map, which identifies regions that are consistently active in studies that load heavily on the term “language” (see Yarkoni et al., 2011), was resampled to match our functional resolution,

thresholded, and then left-right mirrored to be symmetrical across the midline. Consistent with previous studies (Bradshaw et al., 2017a; Brumer et al., 2020; Harrington et al., 2006; Jensen-Kondering et al., 2012), we focused on the cluster of voxels identified in the left and right temporal lobes (primarily superior temporal gyrus) to calculate the LI. The LI was calculated for each subject by z-transforming the single-subject regression results for the semantic fluency task and then thresholding the output at $p<.05$ (Bradshaw et al., 2017b). We then extracted the mean activation for all voxels within the left and right temporal lobe language clusters that were more active for the task than the baseline in the semantic fluency task. The LI was calculated as (L-R)/(L+R), where L is the mean activation in the left temporal lobe and R is the mean activation in the right temporal lobe.

Whole-brain analyses were performed on the encoding and retrieval data using repeated-measures ANOVAs as indicated below. All analyses were confined to voxels identified as within both the gray matter of the MNI template used for spatial normalization and the signal coverage for each individual subject. To correct for multiple comparisons, we estimated the smoothness of the residuals of the individual regression analyses, which were then used to perform Monte Carlo simulations using noise with similar smoothness characteristics. Using this process, we set a family-wise error (FWE) rate of $p<.05$ with a voxel-wise $p<.001$ and spatial extent threshold $k\geq24$ contiguous voxels.

To independently identify brain regions involved in encoding and retrieval while avoiding a circular analysis, we again conducted meta-analyses using NeuroSynth for the terms “subsequent memory” and “memory retrieval”. Again, NeuroSynth masks were resampled to match our functional resolution and then thresholded but were not mirrored across the midline.

## Results

### Behavioral Results

Mean (and SD) proportions of responses in the words recognition task and faces recognition task are reported in Table 1. There was no significant difference between the proportion of responses for the LH or RH groups for either words or faces. To examine memory discriminability, we calculated d' as z(hits)-z(false alarms) for words and faces. There was no difference in memory discrimination (d') between LH and RH groups for either words or faces.

**Table 1.** Mean (and SD) proportions of responses, t-test and d' scores

| | Words hits | Correct Rejections for words | d' words | Face hits | Correct Rejections for faces | d' faces |
|---|---|---|---|---|---|---|
| Right-handed | 84.39 (11.87) | 84.46 (12.20) | 2.71 | 63.75 (14.60) | 80.36 (10.51) | 1.47 |
| Left-handed | 86.92 (10.25) | 85.64 (8.33) | 2.60 | 62.04 (12.79) | 80.24 (10.85) | 1.42 |
| t-test (df=53) | 0.45 | 0.74 | 0.28 | 0.77 | 0.45 | 0.41 |
| p-value | 0.65 | 0.46 | 0.78 | 0.45 | 0.65 | 0.66 |

### Laterality Indices

After performing a t-test, we found that there was not a significant difference between LH and RH participants in laterality (see Table 2). All the RH participants were left-lateralized, and the majority of the LH (19 out of 26) were also left-lateralized (see Figure 2).

**Table 2.** Mean (and SD), ranges, t-test, and p-value of LIs

| | Mean (SD) | Range (Min-Max) | t-test (df=53) | p-value |
|---|---|---|---|---|
| Right-handed | 0.261 (0.149) | 0.015-0.568 | 0.21 | .834 |
| Left-handed | 0.184 (0.276) | -0.406-0.626 | | |

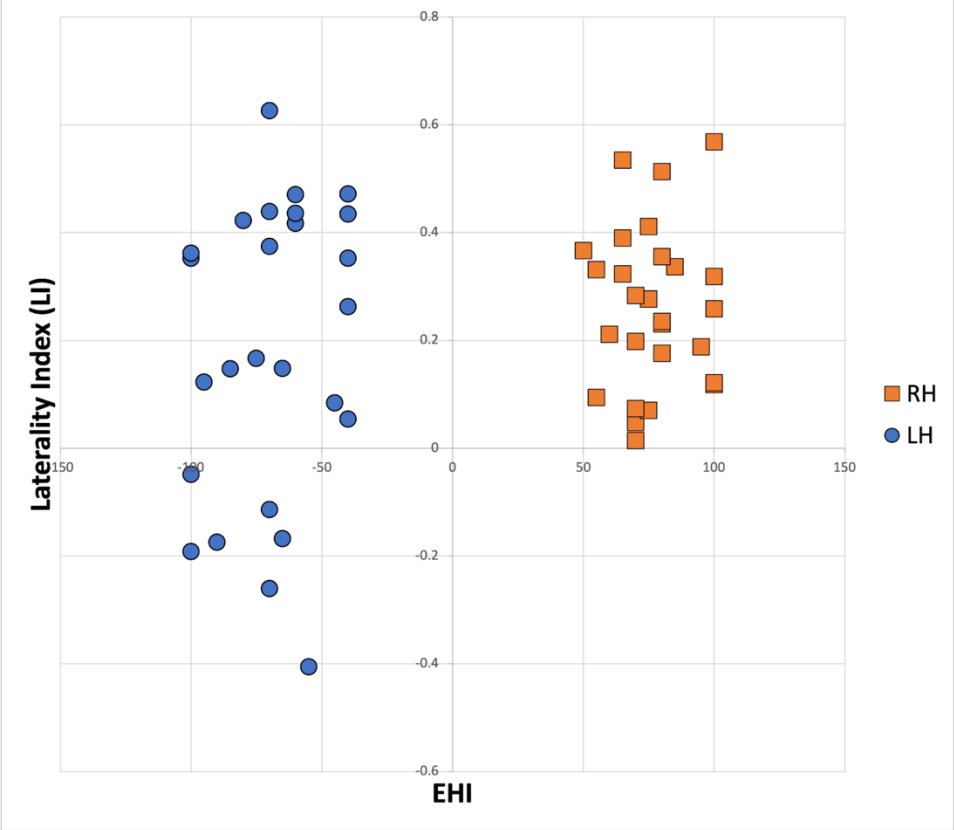


**Figure 2**
Laterality indices (LI) and Edinburgh Handedness Inventory (EHI) scores for left- and right-handed participants.

## Neuroimaging Results

Our first research question was whether LH and RH participants' brains would activate differently in a memory test. We hypothesized that there would be lateralized activation differences in memory-dependent contrasts between LH and RH groups at both encoding and

retrieval. To test this we conducted whole-brain analyses using repeated-measures ANOVAs for the encoding and retrieval data separately. The encoding ANOVA had stimulus type (words, faces) and trial outcome (subsequent hit, subsequent miss) as within-subjects factors and EHI as a between-subjects factor. This approach identifies any brain region where there is a significant difference in activation between two levels of these factors. As our first question regarded differential activation for subsequent hits vs. subsequent misses between LH and RH groups, we examined the EHI by trial outcome interaction (collapsing across words and faces), which identified one significant cluster in the right posterior cingulate cortex. Figure 3 depicts the cluster of activation that was significantly different for LH and RH individuals at encoding. Figure 4 shows that the lateralization of activation in the contrast of subsequent hits and subsequent misses were different for LH and RH. We also conducted a similar repeated-measures ANOVA for the retrieval data with stimulus type (words, faces) and trial outcome (hits, correct rejections or CRs) as within-subjects factors and EHI as a between-subjects factor. There were no significant differences in activation at retrieval between the LH and RH groups.

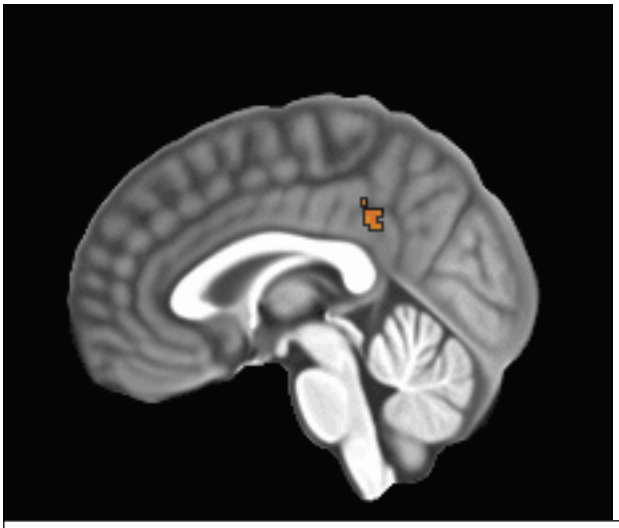

**Figure 3**
Significant cluster (at encoding) in whole-brain repeated-measures ANOVA. Highlighted region is the right posterior cingulate cortex.

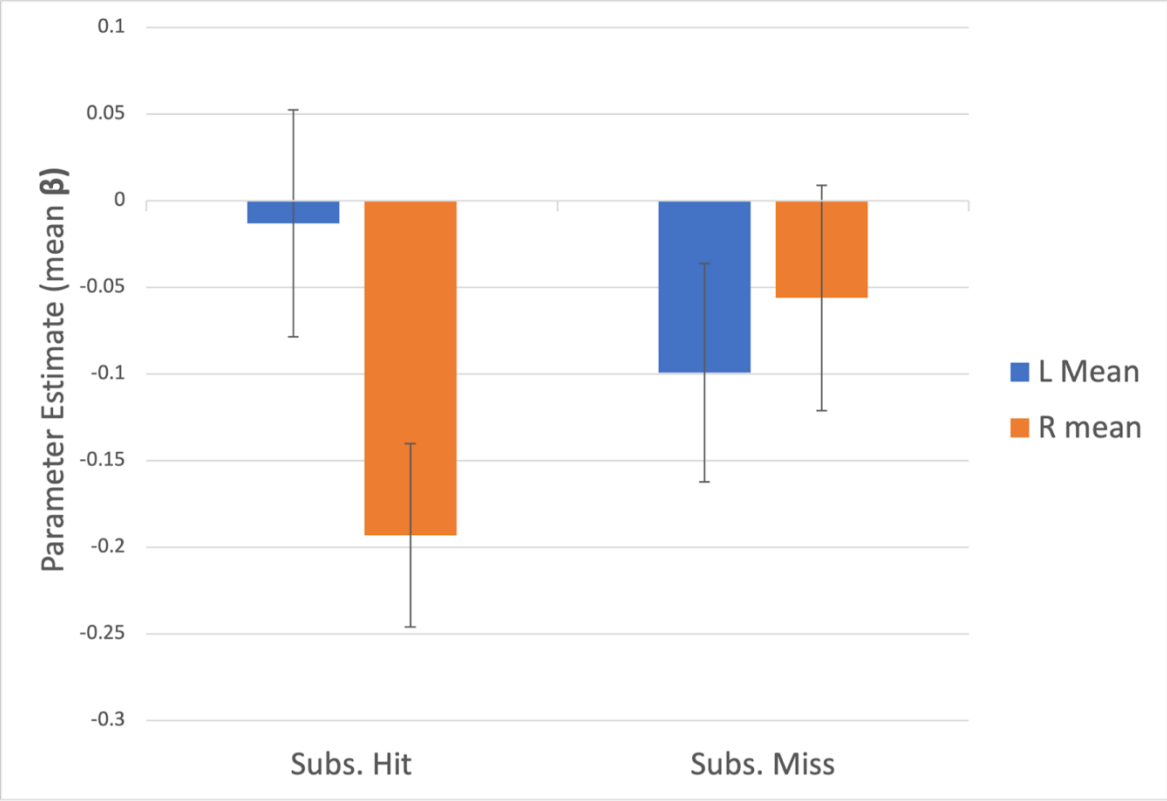


**Figure 4**
Mean beta values of the subsequent hits vs misses for left- and right-handed participants, showing that the lateralization of activation in the contrast of subsequent hits and subsequent misses were different for left- and right-handers.

We further hypothesized that there would be a group by stimulus type interaction such that the lateralized activation differences between groups would be stronger for words than for faces at both encoding and retrieval. There were no significant activations identified by the EHI by trial outcome by stimulus type interaction at encoding. At retrieval, however, we identified four significant clusters of activation in the left inferior frontal gyrus, left angular gyrus, right angular gyrus, and left superior medial gyrus. Figure 5 depicts the activation clusters where activity was significantly different between LH and RH participants during retrieval. In these clusters, LH had significantly more activation for words than for faces, whereas in the left inferior frontal gyrus and left superior medial gyrus RH had the opposite pattern with more activation in faces than for words. In the angular gyrus clusters, the pattern is similar for RH and

LH (activation is greater for words), but the relationship is not as strong for LH compared to the other clusters and not significant for the RH (see Figure 6).

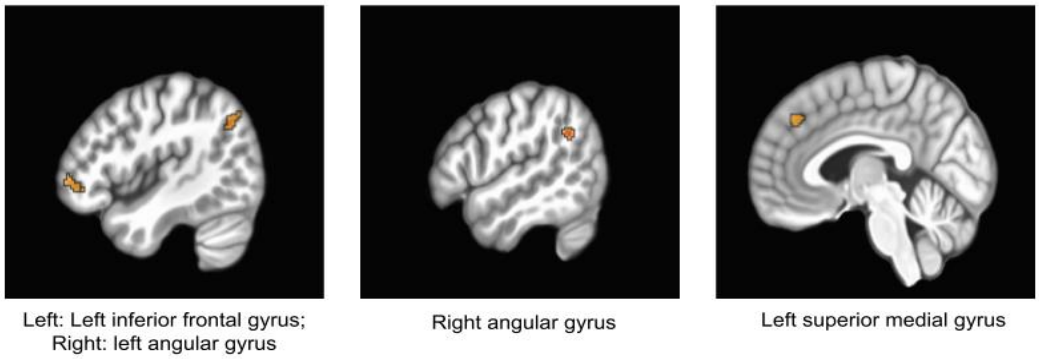


**Figure 5**
Significant clusters and corresponding labeled regions of interest for whole-brain repeated-measures ANOVA where brain activation by stimulus type differed between left- and right-handed participants in a memory retrieval task.

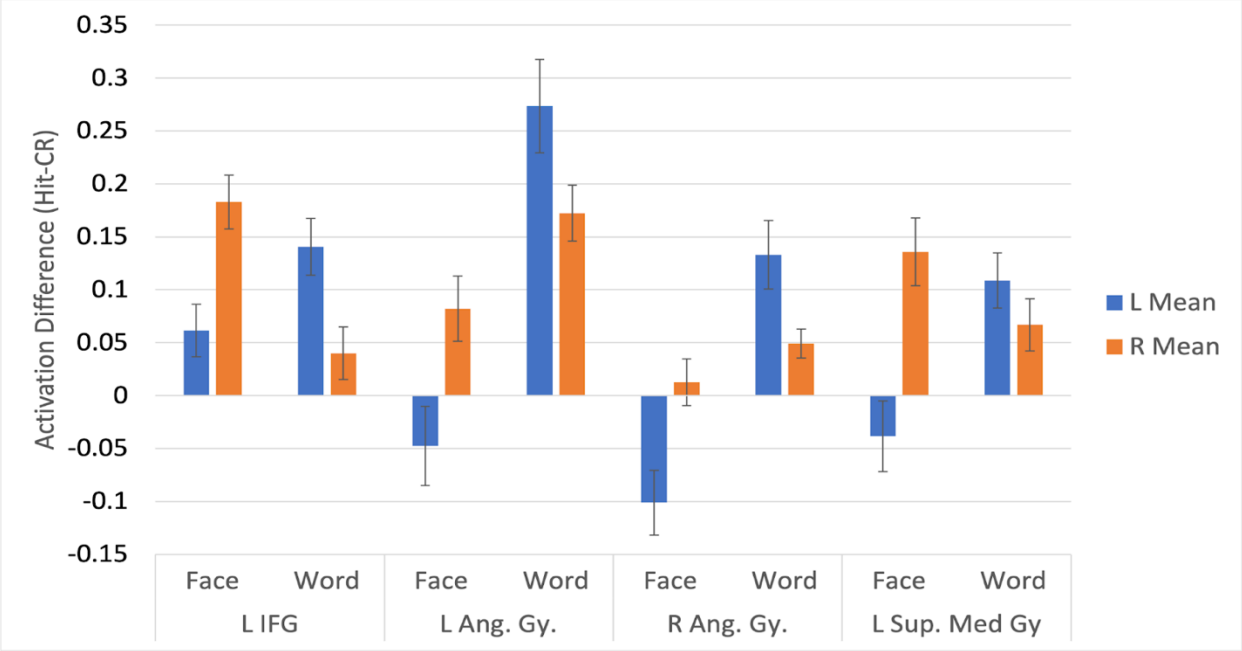


**Figure 6**
Mean activation difference (Hit-Correct Rejection) of left-handed (LH) and right-handed (RH) participants during retrieval. LH participants had significantly more activation for words than for faces. In the left inferior frontal gyrus and left superior medial gyrus RH participants had the opposite pattern with more activation in faces than for words. In the angular gyrus clusters, the activation is similar in both groups, but with weaker activation in LH participants (compared to other regions of interest) and is non-significant for the RH participants.

Our final hypothesis was that at both encoding and retrieval we would see that the difference in activation of the difference between the hits and misses on the memory tasks would decrease linearly as more RH participants were substituted for LH counterparts in the analyses. These analyses were performed by using LH and RH participants' LIs and matching the most left-lateralized RH participant with the most right-lateralized LH participant, the second most left-lateralized RH participant with the second most right-lateralized LH participant, and so on, until all participants were matched with a participant in the opposite group. This was done to see if, in the worst-case scenario, LI would affect the significance of activation for each memory task. The mean difference in activation in each area of the brain in the subsequent hits and misses for each participant was taken to get a mean of means for all the RH participants. Next, we started our substitution process by taking the mean of all the RH participants minus the most left-lateralized RH participant and substituting them in the analysis for the least left-lateralized LH participant. We continued this substitution until only one RH participant remained in the analysis (the other 26 being LH). We did this for each ROI, recording the means and if the significance level dropped below $p < 0.05$.

For both the word encoding tasks and the face encoding task, the ROIs we measured were the left and right medial temporal lobe and the left ventrolateral prefrontal cortex. For both the words retrieval task and the faces retrieval task, the ROIs we measured were the left dorsolateral prefrontal cortex, the bilateral precuneus, the bilateral superior medial gyrus, the left and right hippocampus, the left anterior insular cortex, and the left and right parietal lobe.

At encoding, we found no significant decrease in activation in any of the ROI for both words and faces—even when all 26 LH participants were substituted in for all but one RH participant. At retrieval as well, most ROIs for both words and faces were not affected even after

substituting in all the LH data. However, for word retrieval, the activation in the left hippocampal ROI became weaker with each LH substitution and eventually failed to reach significance ($p < 0.05$) at the 4th LH substitute and decreased linearly with each LH substitution (see Table 3). For face retrieval, the activation in the bilateral precuneus also became less significant with each LH substitution and failed to reach significance from the 5th LH substitution and on.

**Table 3.** Substitution of right-handed participants for left-handed participants in the bilateral precuneus and left hippocampus.

| Number of left-handed participants substituted for right-handed participants | Mean of Bilateral Precuneus scores for right-handed participants ($p<0.05$*) | Mean of Left Hippocampus scores for right-handed participants ($p<0.05$*) |
|---|---|---|
| 0 | *0.005 | *0.0126 |
| 1 | *0.015 | *0.029 |
| 2 | *0.024 | *0.0261 |
| 3 | *0.034 | *0.049 |
| 4 | *0.027 | 0.082 |
| 5 | 0.068 | 0.214 |
| 6 | 0.222 | 0.246 |
| 7 | 0.374 | 0.327 |
| 8 | 0.293 | 0.268 |
| 9 | 0.391 | 0.447 |
| 10 | 0.418 | 0.853 |

We plotted the data points for both the left hippocampus and the bilateral precuneus and found that the more left-lateralized a participant was, the stronger the memory effect (see Figures 7 and 8). We performed a regression analysis and found a moderate correlation between LI and

subsequent memory effects for the left hippocampus (r=.42) and a small correlation for the bilateral precuneus (r=.21).

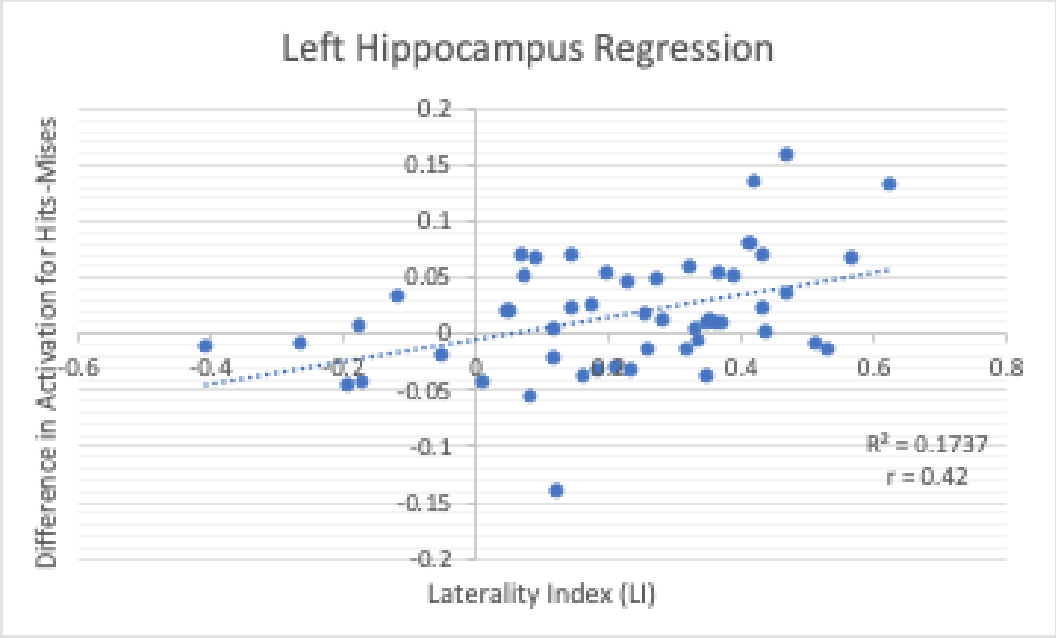


**Figure 7**
Correlation between difference in participants' mean activation of hits-misses and laterality index in the left hippocampus.

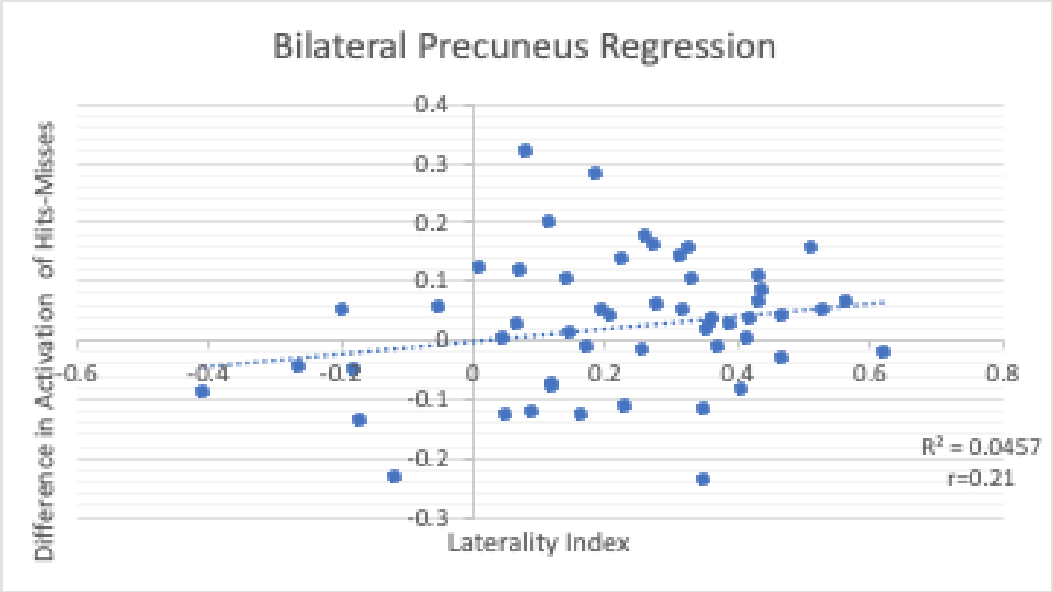


**Figure 8**
Correlation between difference in participants' mean activation of hits-misses and laterality index and in the bilateral precuneus.

## Discussion

The overarching aim of this study was to learn whether there was a basis for exclusion of LH participants from fMRI memory research by determining whether there was a significant difference in brain activation when performing memory tasks between LH and RH participants. In agreement with previous literature, we observed that LH and RH participants had a difference in activation in the lateralization of activation while performing memory tasks (Cuzzocreo et al., 2009). Specifically, we saw these activation differences during encoding in the right posterior cingulate cortex. This finding stands out against previous research, which has not focused on the differences in activation in the posterior cingulate cortex due to handedness but has found some lateralization differences due to neural medical conditions (Rombouts et al., 2007; Il et al., 2008), and research that has shown the posterior cingulate cortex to have negative subsequent memory effects (Daselaar et al. 2004; Turk-Browne et al. 2006; Shrager et al. 2008). We also found that there was a group by stimulus interaction at retrieval in the left inferior frontal gyrus, left angular gyrus, right angular gyrus, and left superior medial gyrus, suggesting that the lateralization differences between LH and RH participants was stronger for words than for faces. This effect has not been thoroughly examined in previous research. Further research should be performed to further investigate the role of these ROIs in the lateralization of memory.

We also found that there was no significant difference between LH and RH participants' LIs, despite screening all participants for a clear handedness-orientation via the EHI. This result suggests that screening LH participants on the basis of EHI score is not effective in determining LIs and further suggests that instead of excluding participants on the basis of EHI score, a more effective means of determining handedness orientation outside of the EHI should be developed to determine whether to exclude LH participants in fMRI memory research. Alternatively, time

and effort should be expended towards including calculation of LIs in future research in order to determine whether participants can be included in memory research.

To test our second research question, we examined the effect of substituting in progressively more LH participants for their RH counterparts. We found that subsequent memory effects at encoding were not reduced by substituting in LH participants. However, at retrieval, significant memory effects diminished in the bilateral precuneus for faces and in the left hippocampus for words when substituting in six and five LH participants, respectively. However, when mapping out the data points, it can be noted that the factor diminishing the memory effects was not adding in LH participants themselves, but rather the substitution of the most left-lateralized RH participants who were driving the effect. A binomial probability distribution calculation can be used to calculate the probability of sampling 5 or more LH individuals in a sample of 27 when the proportion of LH individuals in the general population is 0.11. This probability works out to be 0.169. It is important to note that while this probability is not small, the likelihood of randomly sampling 5 extremely right-lateralized LH participants and no very left-lateralized RH participants is much smaller. If the amount of LH participants in a given sample size was controlled for (to match the occurrence in the population—1.1 LH participants for every 10 RH participants), handedness effects in our analyses were never seen (we didn't see any significant effects "diluted" at 2 or even 3 lefties).

Overall, these results suggest that exclusion of LH participants in fMRI memory research may be warranted in certain circumstances (such as if the main ROI looked at in words is the left hippocampus or the bilateral precuneus for faces or if LIs cannot be calculated), but complete exclusion of all LH participants (at levels below their natural occurrence in the population) is likely unwarranted. One barrier to including LH individuals in studies is the time and expense of

calculating each participant's LI, so further should focus on finding an alternative method that can be used to calculate laterality pre-fMRI scan. Further research should also be performed to determine whether brain activity is lateralized differently enough to warrant exclusion of LH participants in other areas of memory research such as object, abstract, and olfactory memory.

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