The Challenge of Forgetting: Neurobiological Mechanisms of Auditory Directed Forgetting

Olga Lucía Gamboa ^{1†*} Kenneth Sung Lai Yuen,^{2†*}
Frederic von Wegner,^{1,3} Marion Behrens,⁴ and Helmuth Steinmetz¹

¹Department of Neurology and Brain Imaging Center, Goethe University, Frankfurt am Main, Germany

²Neuroimaging Center Mainz (NIC), Focus Program Translational Neuroscience, Johannes Gutenberg University Medical Center, Mainz, Germany

³Epilepsy Center Rhein-Main and Brain Imaging Center, Goethe University, Frankfurt am Main, Germany

⁴Department of Neurology, Institute of Microanatomy and Neurobiology, Johannes Gutenberg University Medical Center, Mainz, Germany

Abstract: Directed forgetting (DF) is considered an adaptive mechanism to cope with unwanted memories. Understanding it is crucial to develop treatments for disorders in which thought control is an issue. With an item-method DF paradigm in an auditory form, the underlying neurocognitive processes that support auditory DF were investigated. Subjects were asked to perform multi-modal encoding of word-stimuli before knowing whether to remember or forget each word. Using functional magnetic resonance imaging, we found that DF is subserved by a right frontal-parietal-cingulate network. Both qualitative and quantitative analyses of the activation of this network show converging evidence suggesting that DF is a complex process in which active inhibition, attentional switching, and working memory are needed to manipulate both unwanted and preferred items. These results indicate that DF is a complex inhibitory mechanism which requires the crucial involvement of brain areas outside prefrontal regions to operate over attentional and working memory processes. *Hum Brain Mapp* 39:249–263, 2018. © 2017 Wiley Periodicals, Inc.

Key words: auditory directed forgetting; memory; response inhibition; intentional forgetting; attention

INTRODUCTION

Additional Supporting Information may be found in the online version of this article.

*Correspondence to: Olga Lucía Gamboa, Department of Neurology and Brain Imaging Center, Goethe University, Schleusenweg 2-16, 60528 Frankfurt am Main, Germany. E-mail: olgalucia.gamboa@kgu.de (or) Kenneth Sung Lai Yuen, Neuroimaging Center Mainz (NIC), Focus Program Translational Neuroscience, Johannes Gutenberg University Medical Center, Mainz, 55131, Germany. E-mail: k.yuen@uni-mainz.de

[†]These authors contributed equally to this work.

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Forgetting is often considered as a behavioral deficit resulting from a decaying memory trace or retrieval failure commonly associated with aging or neuropsychological dysfunctions. Nevertheless, forgetting can also be an active, adaptive mechanism that enables an individual to dismiss irrelevant or outdated information that could interfere with correct task performance [Anderson and Hanslmayr, 2014; Bjork, 1989; Hardt et al., 2013]. This view could be traced back to Freud's idea of repressed memories [Freud, 2008], which is systematically studied by investigating the mechanisms behind intentional forgetting through different methods such as retrieval-induced forgetting paradigms [Anderson and Green, 2001; Depue, 2012] and directed forgetting (DF) paradigms [Fawcett and Taylor, 2008; Lee,

2012]. Two competing hypotheses for DF have been proposed: (1) the selective rehearsal/passive decay hypothesis states that individuals rehearse the test materials until an instruction is provided, granting increased encoding to the to-be-remembered items (TBR) while ignoring the to-be-forgotten items (TBF); (2) the attentional inhibition/executive control hypothesis postulates that individuals actively inhibit TBF words by executive control. These hypotheses have been tested primarily in the visual domain (letters, words, stories, or pictures).

Spoken language is one of the most important tools used by humans to communicate with each other enabling them to prompt reactions and behaviors from their peers [Schirmer, 2010]. Despite this fact, studies evaluating the influence of auditory information in the forgetting phenomenon are scarce. Recently, the neural basis of intentional auditory forgetting was assessed using the Think/No-Think (TNT) paradigm using EEG [Cano and Knight, 2016]. In this study, the authors used stimuli with neutral emotional valence. It is known that information delivered with emotional content is more persuasive than neutral information [Leitman et al., 2010]; thus assessing the interaction between auditory intentional forgetting processes and emotions is of great interest. To the best of our knowledge emotional auditory DF so far has been evaluated only at the behavioral level [Gamboa et al., 2017; Yang et al., 2013]. Therefore, the goal of our study was first to explore intentional forgetting of auditory material, hoping to gain insight into the mechanistic underpinnings of DF and about the competing hypotheses proposed in the visual domain and second to investigate the effect of emotional material (negative, neutral) on the DF mechanism.

To achieve this, we used the item-method DF paradigm in combination with functional magnetic resonance imaging (fMRI). Different from the TNT paradigm, which relies on testing the strength of prelearned cue-target word associations to indirectly infer the effect of suppression, the item-method requires subjects to forget a word stimulus immediately after active encoding. Additionally, we decided to induce multimodal encoding of emotional words and to test if this memory trace can be instructed to forget. We reasoned that the combination of auditory presentation of the stimuli combined with visual imagery will lead to better encoding that will make the process of successful forgetting more difficult [Craik and Lockhart, 1972; Quak et al., 2015]. However, if forgetting is successful, we expect to get a robust pattern of brain activation that will reflect the true neural signature of DF. We employed a combination of analysis approaches to study the neural mechanisms associated with DF. Patterns of regional Blood Oxygen Level Dependent (BOLD) signal changes associated with forgetting were submitted to a novel tool (Neurosynth, <http://neurosynth.org>) for reverse inference on the possible cognitive mechanisms involved, accompanied by a detailed qualitative analysis on the strategies used by the participants during forgetting. Functional connectivity analysis was performed to further our understanding of

the interregional influence associated with the forgetting instruction.

Based on previous forgetting studies using visual stimuli, we anticipated differences favoring emotional valence and the remembering instruction at the behavioral level. We expected to see such differences reflected in the brain activation maps at the neural level as well as distinctive activation patterns for incidental and intentional forgetting.

MATERIALS AND METHODS

Overall Experimental Design

The overall experimental design is depicted in Figure 1A. Participants attended one experimental session, which consisted of a study phase and a test phase (inside the MRI scanner), separated using a distraction task to prevent rehearsal (10 min), verbatim report on the strategy used (5 min), a free recall test and finally a recognition test inside the scanner.

Subjects

Thirty-six healthy volunteers participated in this study, but finally a total of 31 healthy volunteers (15 females, mean age = 27.5 years, SD = 5.61, range 20–40) were considered in the analyses. Three participants were excluded from the study due to anomalously high false alarm rates on the recognition test (> 45% new words recognized as old) and two participants were removed due to excessive head motion in the MR scanner. To screen for short term memory functioning, participants performed the digit span test prior to the start of the experiment (digit span forward, mean = 8.81, SD = 1.62, digit span backwards, mean = 7.31, SD = 1.92).

All subjects were informed about all aspects of the experiment and written informed consent was obtained from each participant at the beginning of the experimental session. All participants were native German speakers and right-handed according to the Edinburgh handedness inventory [Oldfield, 1971]. We conformed to the Declaration of Helsinki and the experimental protocol was approved by the Ethics Committee of the Goethe-University, Frankfurt.

Procedures

Stimuli

One hundred and sixty-four words were selected from the Berlin Affective Word List - Reloaded (BAWL-R), a German database with more than 2,900 German words containing normative ratings for emotional valence, emotional arousal, and imageability [Vo et al., 2009]. It was composed of 80 negative nouns and 80 neutral nouns. To avoid the effects of primacy and recency [Capitani et al., 1992], 4 additional words, (2 pairs of negative – neutral words) were introduced, both at the beginning and end of the study phase. These words were excluded from the analyses. Negative and neutral words were different as for

Figure 1.

Task and behavioral results. **A:** Experimental procedure: The upper part denotes the trial structure during fMRI scanning. **B:** Mean percentage of words recalled as a function of the instruction and emotional valence. **C:** Mean percentage of words correctly recognized as old for the remembering and forgetting conditions and new for the foil group in function of the

emotional valence ($F(1, 162) = 2659.45$, $P < 0.0001$), emotional arousal ($F(1, 162) = 5880.46$, $P < 0.0001$), but similar in terms of imageability ($F(1, 162) = 0.38$, $P = 0.536$). Additionally, words to be studied were kept similar in length for each condition, ($F(3, 76) = 0.97$, $P = 0.414$). Two sets of 80 words (40 items/emotion) equally distributed were created. One set was presented during the study phase, whereas the others were used as “foil” items (new words) during recognition. In the study phase, half of the items of each emotion (20 items) were randomly selected and assigned to an instruction, either remember (R) or forget (F).

Words were created by a human voice generator program (AT&T Labs Natural Voices Text-to-Speech Demo and Free Natural Readers –<http://www.naturalreaders.com/index.html>). Male and female voices were produced in neutral tone at 16 kHz linear PCM (pulse-code modulation), with the amplitude normalized by the root-mean-square value. In order to make sure words were recognizable, a group of 3 people were invited to hear the full set of words inside the scanner and evaluate them as either understood or not

emotional valence. **D:** Reaction times of words correctly recognized as old or new. Significant differences between groups have been indicated with “*” ($P < 0.05$, ** $P < 0.001$). Bars represent standard errors of the mean (SEM). [Color figure can be viewed at wileyonlinelibrary.com]

understood. Unclear words were either recorded with a new voice or replaced (first trial understood words: mean = 158.67, SD = 2.309).

DF task

The item-method DF paradigm consists of a study and a test phase. The study phase was performed inside the MR scanner. The participants were instructed to lie still with their eyes closed. To ensure participants were paying attention, they were required to classify each word as negative or neutral by button press. Auditory stimuli were presented and responses (negative/neutral classification) were recorded using the Presentation software (Neurobehavioral Systems, <https://www.neurobs.com>) via an MR-compatible response box. The sound volume for stimulus presentation was adjusted individually to a level at which participants confirmed they could reliably hear the stimuli. Moreover, participants performed a training session of 10 trials with 5 negative and 5 neutral words to guarantee full understanding of the task instructions. Words

used during this part were different from the items used during the “Experimental” section.

Study phase (encoding)

Words were delivered individually (1 s duration). Participants were asked to rapidly evaluate the valence of the word (negative or neutral) by pressing a button and instructed to think about a meaningful image related to the word (3.5 s). After that, either the “forget” or “remember” instruction was given (0.5 s), the post – cue length varied randomly from trial to trial and ranged from 6 to 7 s (Fig. 1A). The item order was randomized for each trial, with the constraint of a maximum of three consecutive trials of the same kind [Emotion (negative – neutral) $\times$ Instruction (Remember – Forget)]. The study phase was followed by a resting session (~15 min) in which they performed a distraction task (duration: 10 min) and reported their forgetting and remembering strategies (~5 min).

Distraction task

As a means to avoid rehearsal of the items presented during the study phase and to facilitate forgetting, a distraction task was presented during the resting period. This task consisted in finding 12 differences in two apparently identical pictures. The task was not cognitively demanding and up to three sets of images were solved by the participants in a period of 10 min.

Test phase (recalling – recognition)

During this section, two tasks were executed by the participants:

- a. Recalling (outside the MR scanner): the participants were asked to write down all the words remembered from the study phase regardless of the given instruction.
- b. Recognition (with fMRI scanning): to rule out that participants withheld recalls in order to meet the experimenter’s expectation, they had to classify a list of words (including previously presented words and foil words) as either old or new in a subsequent recognition task. Old words (TBR and TBF) with an equal number of foils were presented pseudorandomly in an event – related fMRI design. Using two buttons, participants categorized the word either as “old” if recognized from the study phase (special emphasis was placed on the fact that classification should be done regardless of the instruction given during the study phase) or as “new” if not recognized. There are four possible outcomes concerning the TBR and TBF words:

1. Successful forgetting or intended forgetting: TBF items forgotten during recognition.

2. Successful remembering or intended remembering: TBR items remembered during recognition.
3. Unsuccessful forgetting or incidental remembering: TBF items remembered during recognition.
4. Unsuccessful remembering or incidental forgetting: TBR items forgotten during recognition.

fMRI data acquisition

Functional MR images were obtained with a 3-T Siemens Allegra scanner with a 4-channel transmit/receive head coil. During the tasks (study and recognition phases) an echoplanar imaging (EPI) sequence was acquired (310 volumes, 39 axial slices, repetition time/echo time = 3,000/30 ms; flip angle = 90°; FOV = 192 mm²; matrix size = 64 $\times$ 64; voxel size = 3 $\times$ 3 $\times$ 3 mm³; distance factor = 33%; slice thickness = 3 mm). The first 9 s (3 volumes) were discarded to allow for T1 equilibrium magnetization. All MR-imaging was performed at the Brain Imaging Center in Frankfurt, Germany.

Behavioral Data Analyses

Recalling task

A 2 $\times$ 2 repeated measures ANOVA (rmANOVA) with factors Instruction (Remember – Forget) and Emotion (negative – neutral) was used to assess changes in recalling accuracy. Recalling accuracy was defined as the percentage of words correctly recalled by the participants.

Recognition task

A 3 $\times$ 2 rmANOVA with factors Type (TBR – TBF – foil) and Emotion (negative – neutral) was used to assess changes in accuracy and reaction time. Recognition accuracy was defined as the percentage of words correctly classified as old (previously presented words) or new (foil words) by the participants.

Sphericity was assessed with Mauchly’s test, and Greenhouse-Geisser correction was used when sphericity was violated. Statistical tests were performed using SPSS version 20.0 (SPSS, Chicago) and P -values ≤ 0.05 were considered statistically significant.

Analysis of self-reported forgetting strategies

The forgetting strategies used by the participants were evaluated by two panels of independent expert psychologists who were blinded to the purpose of this study in two separate stages. In the first stage, two psychologists were asked to examine the verbatim responses and to provide a list of cognitive mechanisms they deemed fit to describe the subjects’ forgetting strategies. They were asked to provide operational definitions of the cognitive mechanisms they proposed. Using the operational definitions from these two raters, another four expert psychologists were asked to

judge the involvement of the proposed cognitive mechanisms in each individual verbatim script. We tabulated the total vote count and considered a cognitive mechanism plays a role in the verbatim script when at least 3 out of 4 raters classified it to be relevant. At the end, the raters were also asked to freely group the list of cognitive mechanisms based on conceptual similarities to reveal how the cognitive mechanisms were related to each other.

Functional Imaging Analyses

The event – related general linear model (GLM) designs were analyzed using the Statistical Parametric Mapping software (SPM12, <http://www.fil.ion.ucl.ac.uk/spm>). All EPI images were realigned, normalized to MNI space and spatially smoothed (Gaussian kernel, 6 mm full width at half maximum). The motion parameters estimated during realignment were modeled as confounds by including them as regressors in the design matrix of the GLM [Laufs et al., 2007].

In the study phase, the regressors of interest were the four different experimental conditions: negative remember, negative forget, neutral remember, and neutral forget (See Supporting Information Figure S1 for an exemplar design matrix). Each word was considered an event and modeled separately (event duration = 0). The onset of each event was set at 0.5 s after the onset of the instruction (Forget/Remember) to avoid interference of the processes taking place during the delivery of the instruction.

After the within-subject analysis, a second level random effects group analysis was carried out to identify regions of activation during DF performance. We used the full factorial design and modeled factors of Instruction (Remember – Forget) and Emotion (negative – neutral). Different levels of the factor Instruction were assumed to be dependent and equal variance was expected. The main effects of Instruction and Emotion, and their interactions were examined with appropriate t-contrasts. A whole brain cluster threshold of $P < 0.05$, FWE corrected for multiple comparisons with an underlying uncorrected threshold of $P < 0.001$ was used for all analyses (including all subgroup and PPI analyses). The Talairach daemon was used to label the anatomical landmarks of the activation peaks [Lancaster et al., 1997, 2000].

We further analyzed our fMRI data by classifying the presented TBF words as successfully or unsuccessfully forgotten (UF) using the recognition test results. Using the clusters identified by the contrast examining the main effect of Instruction as regions-of-interest (ROIs), the average beta value estimate of successfully forgotten (SF) words as well as UF words (regardless of the emotion) was extracted for the encoding phase and the recognition phase. Students' paired sample *t*-tests were used to test for significant differences between forgetting successfully and unsuccessfully. Since not all participants exhibited forgetting in all conditions, results presented in this analysis

consist of a subgroup of $n = 28$ (For details regarding the number of trials used in each condition, see Table S1 of the Supporting Information).

Intentional versus incidental forgetting

To assess the differences between intentional and incidental forgetting, the fMRI data obtained during the study phase was reanalyzed using as regressors of interest the eight possible outcomes of the recognition task (negative intentional remembering, negative incidental remembering, negative intentional forgetting, negative incidental forgetting, neutral intentional remembering, neutral incidental remembering, neutral intentional forgetting, and neutral incidental forgetting). For the second level analysis we used the full factorial design and modeled factors of Outcome (intentional – incidental), Instruction (Remember – Forget) and Emotion (negative – neutral). The main effects of Outcome, Instruction and Emotion, as well as their interactions were examined with appropriate t-contrasts. Since incidental forgetting is caused by memory failure [Nowicka et al., 2011; Wylie et al., 2008] there is a possibility that forgotten TBF words in “good” incidental forgetters occurred for the same reason and not as a result of a strategy to forget. Therefore, searching for specific DF mechanisms we limited this analysis to only those subjects ($n = 16$) whose number of intentionally forgotten words (forgotten words instructed to forget) was higher than incidentally forgotten words (forgotten words instructed to remember).

Functional Connectivity Analyses– Psychophysiological Interaction (PPI)

PPI analysis helps to explain modulatory interactions between regionally specific neuronal responses during a particular psychological process [Friston et al., 1997]. To see how the instruction to forget is modulating the connectivity between brain regions, PPI analyses were executed over the brain areas specific for DF obtained from the univariate analyses revealed by the $F > R$ contrast. ROIs used as seeds include middle frontal gyrus (MFG), posterior cingulate gyrus (PCG), and inferior parietal lobule (IPL), all on the right hemisphere. The variable describing the psychological process of interest (Forgetting vs. Remembering) was a task vector that coded negative/neutral forgetting trials as 1 and negative/neutral remembering as $[-1 \ 1 \ -1 \ 1]$. The subject-specific time course for each ROI was extracted with 8-mm-radius spheres centered at the voxel showing the maximum significance for the $F > R$ contrast. Consequently the interaction term was calculated by multiplying the physiological factor by the psychological factor. PPI analyses were then performed for each subject and parameter estimates of the interaction term were then entered into the second level where separate group-level, random effects analyses were performed for each seed. To further examine the change of connectivity between the seed region and the

brain areas that showed significance in the PPI, we extracted the beta values estimates of the seed and peak voxels from the original GLM and plotted their correlations.

Reverse Inference–Neurosynth

To aid interpretation of the activation patterns obtained from above, we used the Bayesian reverse inference software Neurosynth to identify the possible cognitive processes involved in a particular activation network [Yarkoni et al., 2011]. Neurosynth uses an automatic parsing algorithm to extract the most frequent keywords from the abstracts of over 11,000 published neuroimaging studies. Using the database of reported brain activation loci, it calculates a Bayesian estimate of the probability for a given function mentioned in the literature when brain activation in a particular region is observed. This provides an empirical interpretation of specific patterns of brain activations. When entering the coordinates of an activation peak into the system, the posterior probability of terms found in the database given an observation of activation in that region is supplied. Correspondingly, a Z-value testing the significance of the term is also obtained. Recruiting both metrics (posterior probability estimation, Z-statistics) allows the interpretation of neurocognitive processes associated with a particular activation at a certain spatial location.

Another prominent feature of Neurosynth is cognitive decoding. When an unthresholded T-statistics map is submitted to the Neurosynth decoder, the spatial correlation with the metaanalytic activation maps available in Neurosynth yields a list of functional terms. This kind of correlation can be used to interpret the involved neurocognitive processes when whole brain pattern of activities are considered. Thus, we submitted our main contrast-of-interest and PPI results to the Neurosynth decoder to assist our interpretation of the respective activation pattern.

RESULTS

Behavioral Outcome of DF

Recall test

Under free recall, negative words were better recalled than neutral words ($F(1, 30) = 50.718$, $P < 0.001$) and regardless of the emotion, subjects recalled significantly more TBR words than TBF words ($F(1, 30) = 39.121$, $P < 0.001$, Fig. 1B). However, no significant interaction between Instruction $\times$ Emotion ($F(1,30) = 0.053$, $P > 0.8$) was observed.

Recognition test

Significant main effects of word type (TBR – TBF – foil) and Emotion (negative – neutral) in both, classification accuracy ($F(2, 50.33) = 4.98$ and $F(1, 30) = 4.43$, $ps < 0.05$) and reaction time ($F(2, 48.41) = 45.47$ and $F(1, 30) = 18.35$, $ps < 0.001$, Fig. 1C,D) were detected. Significant interactions

between Emotion $\times$ Type for recognition accuracy and reaction time during the recognition phase were also found ($F(2, 60) = 14.30$ and 24.85 , respectively, $ps < 0.001$).

The interaction Emotion $\times$ Type was also significant ($F(2, 60) = 14.305$, $P < 0.001$). Negative TBF words were better recognized than neutral TBF words ($P = 0.001$), while the opposite occurred in the foil words ($P < 0.001$). No statistically significant differences were found when evaluating the TBR words ($P = 0.058$).

Furthermore, neutral words showed significant differences across word type. Significantly more errors were done classifying correctly neutral TBF words as old than neutral TBR words ($P = 0.001$) and foil words ($P < 0.001$). However, no differences were found regarding the correct classification of neutral words between the TBR and foil words ($P = 0.147$). Negative foil words were significantly worse recognized than negative TBR words ($P = 0.008$) but not when compared with TBF words ($P = 0.120$). No differences were observed between negative TBF and TBR words ($P = 0.136$).

Regarding reaction times, independent of the emotional valence TBR words were recognized faster than TBF words ($P < 0.001$). Meanwhile negative and neutral foil words were recognized significantly slower than their equals TBR and TBF words ($ps \leq 0.05$). However, negative foil words were recognized significantly slower than neutral foil words ($P < 0.001$).

Analysis of forgetting strategies

After evaluating the whole set of forgetting strategies, a total of six cognitive mechanisms (three each) were proposed by the first panel of two independent expert raters. Respectively, they are: (1) Concentrate on a task, (2) Interference, (3) Suppression, (4) Active forgetting, (5) Strategies related to mnemonics, and (6) Focusing attention on a stimuli. Analysis on the subjects' forgetting strategies derived from the ratings performed by the second panel of four independent raters who classified each individual verbatim script in terms of the underlying cognitive mechanisms, revealed that: 1 out of 31 subjects "concentrated on a task," 22 out of 31 subjects used "interference" as a strategy to forget, 9 out of 31 subjects used "suppression" as a forgetting strategy, 10 out of 31 subjects used "active forgetting," 2 out of 31 subjects used "strategies relating to mnemonics" and 6 out of 31 subjects "focused their attention on a stimuli". Results derived from the verbatim analysis suggested that Active forgetting and Suppression are perceived as conceptually equivalent (For a detailed description of the verbatim analysis and the strategies used by the participants, see Supporting Information "Strategy and its operational definition" section).

Neural Correlates of Auditory DF

Aiming to assess the process of intentional forgetting, we identified brain regions exhibiting significant BOLD

Figure 2.

fMRI activations during DF. Main effect of memory instruction: instruction to forget contrasted with instruction to remember ($F > R$) activates the right MFG, right IPL, and right PCG. Beta values estimates for each condition (negative remembering, negative forgetting, neutral remembering, and neutral forgetting) are

plotted in each brain region, showing a general activation during the instruction to forget, irrespective of word valence. Images are $P < 0.05$, FWE corrected for multiple comparisons at the cluster level with an underlying uncorrected threshold of $P < 0.001$. [Color figure can be viewed at wileyonlinelibrary.com]

activations during the instruction phase. Notably, when examining the DF ($F > R$) contrast, we observed significant right lateralized BOLD activations in the MFG, the PCG, and the IPL (Fig. 2, Table I). The parameter estimates of BOLD signal change of these brain regions during the different conditions (remembering negative/remembering neutral, forgetting negative/forgetting neutral) showed significant activities in response to the instruction to forget, but not to remember (Fig. 2, bar plots).

No significant Instruction $\times$ Emotion interaction effect was observed. The contrasts $R > F$ (main effect of remembering) and $Neg > Neu$ (main effect of negative emotion) revealed typical memory (Hippocampus, MFG, IFG, IPL) and emotion (medial PFC) areas, serving as a data quality check (See Table I and Supporting Information Figure S2).

To further confirm our qualitative interpretations of the observed BOLD activation patterns, we employed the Neurosynth toolkit [Yarkoni et al., 2011] for Bayesian reverse inference. Correlating the unthresholded whole

brain pattern of the $F > R$ contrast with metaanalytic brain activation maps in the Neurosynth database (i.e., cognitive decoding) suggested that DF-related activations are associated with the term “response inhibition” (Fig. 3A). There is a high degree of overlap between the reverse inference map on the term “response inhibition” and the statistical map of the $F > R$ contrast (Fig. 3B). Since the $F > R$ contrast revealed only brain activation patterns after cognitive subtraction, we further submitted the group beta maps of the forgetting and remembering instructions separately to Neurosynth for cognitive decoding to understand the neurocognitive processes specific to the forgetting instruction. Decoding results suggested that “working memory” is the functional term that gives the highest spatial correlation ($r = 0.218$) with activity patterns during instructions to remember, whereas “response inhibition,” “stop signal,” and “working memory” are functional terms that show the largest correlations with BOLD activations during forgetting ($r = 0.169, 0.157$, and 0.128 respectively).

TABLE I. Activated brain regions during DF

Contrast	Words	Brain region	Side	x, y, z	T	K
F > R	All	IPL	R	58 -38 38	7.50	1,400
		MFG	R	42 26 46	5.47	280
		PCG extending to Paracentral Lobule	R	2 -20 36	4.82	251
	Negative	IPL	R	56 -42 38	6.21	908
	Neutral	IPL	R	58 -38 38	5.75	829
R > F	All	MFG	R	44 28 46	4.76	229
		MFG extending to Inferior Frontal Gyrus	L	-44 16 28	9.76	11,789
		MTG extending to Precuneus	L	-54 -50 -10	7.72	5,203
		Posterior Cingulate extending to Parahippocampal Gyrus & Precuneus	L	-8 -56 18	6.14	595
	Negative	MTG extending to Superior Temporal Gyrus & Superior Occipital Gyrus	R	44 -70 26	5.22	591
		MTG	L	-56 -14 -14	5.17	331
		IPL extending to Postcentral Gyrus	L	-46 -38 38	4.94	189
		Culmen extending to Parahippocampal Gyrus	R	24 -32 -24	4.64	244
		Uvula extending to Culmen & Declive	R	34 -68 -34	7.03	2,621
		Cerebellar Tonsil	R	10 -50 -44	5.08	186
		MFG	L	-42 12 28	7.41	6,496
		Precuneus	L	-26 -76 50	5.68	1,609
		MTG extending to Fusiform Gyrus	L	-54 -50 -10	5.57	680
		MTG extending to Superior Temporal Gyrus	R	46 -70 26	4.19	180
		Posterior Cingulate	L	-6 -54 20	4.78	255
		Thalamus	L	-10 -14 2	4.32	186
		Uvula extending to Culmen & Declive	R	32 -66 -34	4.90	1,200
	Neutral	MFG extending to Inferior Frontal Gyrus & Paracentral Gyrus	L	-44 16 26	8.10	7,959
		MTG extending to Precuneus	L	-54 -52 -8	6.87	3,492
		Hippocampus extending to Claustrum & Medial Globus Pallidus	L	-30 -12 -12	5.37	277
		Posterior Cingulate extending to Parahippocampal gyrus	L	-8 -56 18	5.36	385
		Posterior Cingulate	R	12 -48 10	4.62	237
		Superior Occipital Gyrus extending to MTG & Precuneus	R	42 -80 26	4.37	296
		Declive extending to Culmen	R	34 -72 -30	7.04	2,150
		Fusiform Gyrus extending to Culmen	L	-34 -34 -24	4.48	286
		Medial Frontal Gyrus extending to Superior Frontal Gyrus	L	-6 52 46	5.25	1,459
		Declive extending to Tuber and Pyramis	R	30 -86 -32	5.83	366

Activations for the main effect of memory instruction F > R and R > F according to their emotional valence and for the effect of Emotion (negative/neutral) in the whole set of words. One-sample t-test, $P < 0.001$, FWE corrected for multiple comparisons at the cluster level $P < 0.05$.

Intentional versus incidental forgetting

To test the specificity of DF-associated activation patterns, we assessed differences between intentional and incidental forgetting. Contrasting SF TBF words versus incidentally forgotten TBR words, we observed a strong recruitment of the right IPL. Additionally, when an exploratory threshold ($P = 0.001$ uncorrected) was used, the observed activations (Fig. 3C) are highly similar to those obtained in the main DF contrast (F > R).

Role of the DF Network during Encoding and Recognition

We performed a ROI-based analysis on BOLD activity during the encoding and recognition phases, with trials regrouped according to the recognition test results. As such, TBF words could be separated into SF or UF words. Using the MFG, IPL, and PCG clusters as ROIs, we extracted the beta value estimates of SF and UF words and performed group comparison using paired t -tests. This

Figure 3.

Reverse inference maps and specific fMRI activations of DF. **A:** Spatial correlation between the unthresholded $F > R$ contrast map with metaanalytic maps of various topics obtained in Neurosynth; **B:** Left: Metaanalytic reverse inference map of the term “response inhibition” available in Neurosynth; Right: Activation map of $F > R$ contrast overlapped with Neurosynth reverse inference map of the term “Response inhibition.” This provides a Bayesian quantitative interpretation of the $F > R$ contrast,

suggesting the role of response inhibition played in DF. **C:** Activation map contrasting intentional forgetting vs. incidental forgetting (Left), and its large overlap with the $F > R$ contrast (Right), showing that the latter contrast is specific to active, intended forgetting processes. All images are $P < 0.05$, FWE corrected for multiple comparisons at the cluster level with an underlying uncorrected threshold of $P < 0.001$. [Color figure can be viewed at wileyonlinelibrary.com]

analysis revealed that during the encoding phase, significantly higher activations in MFG ($t(27) = -2.22$, $P = 0.034$) and IPL ($t(27) = -2.93$, $P = 0.016$) occurred in SF words as compared with the UF words (Fig. 4). However, a significant suppression of BOLD activity was observed in all three regions MFG ($t(27) = 2.09$, $P = 0.045$), IPL ($t(27) = 4.64$, $P \leq 0.0001$) and PCG ($t(27) = 5.48$, $P \leq 0.0001$) in SF words as compared with UF words during the recognition phase. Furthermore, to aid better interpretation of the functional role of the ROIs we also examined the BOLD activity of TBR words when they were successfully versus unsuccessfully remembered as well as foils when they were successfully versus unsuccessfully classified as new in the recognition phase. Specifically PCG showed decreased BOLD signal when comparing unsuccessfully

versus successfully foil words ($t(27) = 5.42$, $P \leq 0.0001$). No differences were observed in the other two ROIs, or in any of the ROIs for the TBR words.

Modulation of Brain Networks during DF-PPI Analysis

To gain a mechanistic understanding of the neurocognitive operation performed by the DF network, we further analyzed DF-related functional connectivity changes. Using the activation peaks from the $F > R$ contrast as ROI, we extracted their respective time courses and searched the whole brain for regions that significantly changed their connectivity with the seed ROIs, while being manipulated by memory instructions (PPI, Fig. 5, Table II). For the right

Figure 4.

ROI-based investigations on the functional role of the DF network. The ROI are being depicted in the panels on the left. The middle and right panels plot the average beta values estimates across each specific ROI, for unsuccessful versus successful TBF items, during the encoding and recognition phase, respectively. **A:** For MFG, significantly higher level of activities for TBF words that are subsequently forgotten during the encoding phase, are observed. **B:** For PCG, SF TBF words elicit significantly less

activations than UF TBF words in the recognition phase. There is no significant difference during the encoding phase. **C:** For IPL, SF TBF words elicit significantly higher BOLD activation in this region during the encoding phase. Significant differences between groups have been indicated with “*” ($P < 0.05$, ** $P < 0.001$). Bars represent SEM. [Color figure can be viewed at wileyonlinelibrary.com]

MFG seed, the instruction to forget significantly modulated functional connectivity with the right middle occipital gyrus (MOG) and middle temporal gyrus (MTG). For the right PCG seed, notably, significant task-specific changes in functional connectivity with several brain regions strongly implicated in memory processes were observed. For instance, the right parahippocampal gyrus, showed active attenuation of functional connectivity under the forgetting instruction (Fig. 5, right panel), whereas the right precuneus showed enhanced coupling. Moreover, modulation of the right cuneus and bilateral occipital and temporal regions also took place. For the right IPL seed, significant task-dependent modulations with the contralateral MFG and the contralateral supramarginal gyrus (SMG) were present. Cognitive decoding of the three functional connectivity maps by Neurosynth all converge to the terms relating to memory processes like “retrieval,” “memory,” and “episodic memory” (See Supporting Information Figure S3).

DISCUSSION

In this study, we explored the behavioral and neural substrates of the intentional forgetting phenomenon in the auditory domain using valenced information (neutral, negative). Behaviorally, an interaction between emotion and instruction was only observed for the recognition but not for the free recall data which is consistent with previous research on the field [Yang et al., 2015]. We also observed a right lateralized brain response to the instruction to forget.

From the subjects’ verbatim report we found that “interference,” a strategy based on the use of distractors to “interfere” with memory in a way that attention was allocated away from the TBF items, was the main forgetting strategy (observed in more than 71% of the participants). Meanwhile 30% of the participants used a strategy based on active inhibition of the TBF words and 29% of the participants used both strategies in parallel. Our findings reinforce previous reports that attentional inhibition mediates

Figure 5.

Modulation of functional connectivity in each DF activated region: **A:** Right MFG, **B:** Right PCG, and **C:** Right IPL. The left side of all panels shows the representative brain areas that revealed a significant change of functional connectivity between the instruction to forget and the instruction to remember (PPI analysis). The middle and right panels show an overview of all brain regions that significantly change their connectivity with the seed regions, overlaid on a brain model, and the representative

plots demonstrating the direction of change in functional connectivity during forgetting versus remembering. An attenuated coupling between the seed region and the plotted regions during forgetting is observed. All images are $P < 0.05$, FWE corrected for multiple comparisons at the cluster level with an underlying uncorrected threshold of $P < 0.001$. [Color figure can be viewed at wileyonlinelibrary.com]

DF [Bastin et al., 2012; Wylie et al., 2008; Zacks and Hasher, 1994; Zacks et al., 1996]. The type of forgetting taking place in the item-method paradigm is believed to be caused by either a passive selective attentional inhibition mechanism prompted by the instruction to forget [Bjork, 1989; Conway and Fthenaki, 2003] or by an active executive process that limits attentional resources and actively suppresses TBF words. Both processes were reported as forgetting strategies by the subjects, suggesting that selective attention during DF is crucial to facilitate the disengagement of TBF word encoding and to strengthen TBR word representation, while actively inhibiting TBF words. In line with this, our fMRI data shows a network of brain regions associated with

response inhibition, working memory and manipulation of attentional resources during both encoding and recognition. These findings conformed to previous literature [Garavan et al., 2002; Nowicka et al., 2011] and are supported by Bayesian analysis using Neurosynth.

We found that regardless of the emotional valence, the attempt to forget elicited the activation of the MFG, the IPL, and PCG on the right hemisphere. Neutral TBF words showed significant activation of both the MFG and the IPL on the right hemisphere, while negative words only recruited the latter.

In general, right hemispheric specialization has also been found in experiments with visual stimuli in which TBF words activated the right MFG and parietal regions

TABLE II. PPI analysis for DF task

	Seed region (F > R)	Side	x, y, z	Brain region	Side	x, y, z	T	K
Contrast	MFG	R	42 26 46	Inferior Occipital Gyrus extending to MOG & MTG	R	36 -80 2	4.66	125
F > R	PCG	R	2 -20 36	Lingual Gyrus	L	-26 -80 -6	5.44	121
				Precentral Gyrus	R	32 -18 52	5.30	165
				Fusiform Gyrus extending to Culmen	L	-28 -44 -18	4.93	165
				MOG extending to Angular Gyrus & Cuneus	L	-34 -82 18	4.91	419
				Parahippocampal Gyrus extending to Fusiform Gyrus	R	34 -38 -12	4.89	283
				MOG extending to MTG	R	36 -80 4	4.47	250
				Superior Temporal Gyrus extending to MTG	L	-40 -54 14	4.39	138
				Precuneus extending to Cuneus	R	8 -64 24	4.33	152
				SMG	L	-58 -50 36	4.75	158
				MFG	L	-44 48 -2	4.45	147
NegF > NeuF	Pyramis	R	32 -84 -32	MTG extending to Superior Temporal Gyrus & Angular Gyrus	R	50 -62 24	5.99	156

[Bastin et al., 2012]. Negative TBF pictures activated a mainly right lateralized network, consisting of frontotemporal and parahippocampal areas, precuneus and the bilateral lingual gyrus, while in neutral pictures only increased activation of the right lingual gyrus occurred [Nowicka et al., 2009].

Our results showed a lack of interaction between Instruction and Emotion during the forgetting phase. We proposed two potential explanations for such discrepancies: (i) the Instruction $\times$ Emotion interaction effect is only observed in the recognition task but not the free recall task. In the memory literature there is a long history of investigation on the two tasks and there is common consensus that free recall and recognition reflect two related but differentiable cognitive processes with dissociable neural correlates (e.g., Tsivilis et al., 2008). It is hypothesized that free recall is largely hippocampus dependent while recognition requires the extended hippocampal structures. It is possible that our encoding data are more hippocampal dependent (see the R > F contrast) and resembles free recall more, and thus instruction to forget did not interact significantly with the valence of stimuli; (ii) the alternative explanation is our use of an ecologically valid, cognitively more challenging task for forgetting which could have led to two situations. First, it has been shown that neural processes of neutral words encoded in an emotional context are different from those encoded in a neutral context [Erk et al., 2003, 2005]. The initial instruction to create a meaningful image for each word (regardless of emotional valence to support processing) could have provided an emotional context to neutral words modifying their salience by associating them to an emotional “tag” [Erk et al., 2005] making them in this way more similar to the negative items. Second, due to fewer SF items the interaction between Instruction and Emotion during encoding was underpowered making it difficult to be observed.

Similar to other studies, we observed differences between intentional and incidental forgetting: enhanced activation of the right IPL was revealed, indicating that these processes are different and discernible. In the visual domain, intentionally forgotten words compared with incidentally forgotten words recruited the right IPL and MFG [Bastin et al., 2012], whereas negative words showed no activation. This difference has been attributed to an attentional bias caused by the emotional valence of the negative items, which apparently hinders correct execution of the inhibitory processes necessary for successful forgetting [Yang et al., 2015].

Research literature refers to the MFG as an important piece for regulating inhibitory processes especially in the initiation of inhibitory modulation of cognitive, emotional and motor responses [Benoit and Anderson, 2012; Depue et al., 2007, 2016; Garavan et al., 1999; Nowicka et al., 2011]. Right frontal function appears critical for control of encoding and retrieval, during a DF task patients with right frontal lobe injuries were neither able to selectively modulate rehearsal nor could they intentionally stop retrieval of the unwanted information. This suggests that right frontal areas are fundamental for assisting intentional control of retrieval [Conway and Fthenaki, 2003] and regulation of attentional processes including control of exogenous-endogenous attentional shifts [Japee et al., 2015]. The functional interactions observed in the PPI analysis during DF between MFG, right MOG and right MTG may be the reflection of the combined efforts among these areas to aid memory formation [Buckner et al., 1999; Wylie et al., 2008]. Increased BOLD activity in prefrontal areas has been observed in conjunction with occipital and medial temporal lobes during retrieval practice [Buckner et al., 1999; Wimber et al., 2008]. The majority of our participants chose to redirect their attention to either the TBR items or (in a few cases) to external cues to improve the chances of successful future recalling. It is known that

during volitional learning to encode information active rehearsal is required to strengthen its representation in memory. It is possible that the activation of the right MFG mediates the beginning of an inhibitory process while prompting other areas involved in tasks such as retrieval to support intentional forgetting [Conway and Fthenaki, 2003]. This is coherent with our decoder analysis in which the MFG-based functional connectivity map revealed “retrieval,” “memory,” and “episodic memory” as main themes. Retrieval and practice of TBR or non-task related items enabled by the instruction to forget may bring as a consequence a decrease in rehearsal of the TBF items and limited access to memory.

The PCG, however, has been regarded as an important piece in correct cognitive function. PCG has been linked to memory retrieval [Cabeza and Nyberg, 2000; Maddock et al., 2001], attentional processes [Bonnelle et al., 2011, 2012; Leech and Sharp, 2014], future planning [Leech and Sharp, 2014], mental stimulation and strategic decision making [Gerlach et al., 2011]. PCG has been identified as an important element assisting efficient allocation of attentional focus [Hahn et al., 2007; Leech and Sharp, 2014; Leech et al., 2011], its activation occurs during environmental cognitive changes and it has a proactive role by adjusting subsequent behavior [Pearson et al., 2011]. Task-dependent functional connectivity patterns were observed between PCG and a widely distributed network of brain areas involved in memory. Connections with medial temporal regions and parahippocampal areas suggest a key role in memory function [Kim, 2010; Kim et al., 2010, 2012; Maddock et al., 2001; Pearson et al., 2011], whereas interactions between PCG and occipital cortices have been linked to sensory/perceptual processing of stimulus information [Kim et al., 2010]. Connectivity changes in regions coupled with the PCG during the forgetting phase were seen in both directions. Decreased connectivity may reflect the shift of attention and disengagement of the TBF word. While the enhanced connectivity with regions such as right precuneus and cuneus, known to be involved in memory search [Makino et al., 2004] may support retrieval and successful encoding of the TBR words by helping find the internal mnemonic representations [Kim et al., 2010]. In agreement with this, decoding the PCG-based connectivity maps, converged to the main theme of “retrieval” and includes terms such as “episodic memory” among the main topics. PCG has been associated with functional flexibility to implement modifications in strategy when circumstantial changes are detected [Pearson et al., 2011]. The fact that it interacts with a broad network may be one of the reasons for such flexibility. During the DF paradigm once the instruction has been delivered, in order to forget it is necessary to swiftly stop encoding of the TBF words, and unattend the TBF items to prevent further encoding and to suppress TBF word’s representation to avoid retrieval [Gamboa et al., 2017; Hahn, et al., 2007; Zacks and Hasher, 1994]. In this scenario, the intervention of the

PCG network could be crucial supporting the release of task engagement by means of self-directed cognition [Mason et al., 2007; Pearson et al., 2011] and a rearrangement of functional activities that allow the establishment of a new strategy [Pearson et al., 2011].

Finally, the IPL has been recognized as an important piece in the ventral attention network. It is involved with attentional reorienting in a broad spectrum, including reorienting between externally and internally mental representations [Bastin et al., 2012; Cabeza, 2008; Uncapher and Wagner, 2009]. The activation of the right IPL during the DF process may indicate an attempt to prevent successful encoding by diverting the attention away from the TBF items and reorienting the attention towards internal representations [Cabeza, 2008; Uncapher and Wagner, 2009]. The PPI analysis showed significant task-specific changes between the right IPL and the SMG and the MFG on the contralateral hemisphere. This frontoparietal interaction has been widely associated with attentional processes and successful retrieval [Hutchinson et al., 2009; Iidaka et al., 2006]. In line with the above, our decoder analysis for the IPL-based connectivity maps gave as main themes “episodic memory” and “retrieval.” It is possible that the function of the parietal network in DF is to facilitate successful retrieval by supporting attentional shifts toward TBR or non-task related items that as a result will obstruct successful remembering by limiting encoding and active representation of the TBF words [Cabeza, 2008; Uncapher and Wagner, 2009].

Moreover, using the results from the recognition test to classify the presented TBF words as SF or UF, we noticed a segregation of roles between these three brain regions. Contrasting the average BOLD response of SF and UF words with the ROIs, there were significantly higher activities in the MFG and IPL for SF words during the encoding phase. This pattern seems to fall in line with the attention reorienting role of right frontoparietal regions, active during encoding when attention is diverted from the TBF items. However, significantly lower activities in the forgetting network MFG-PCG-IPL occurred during the recognition phase. This suppression may indicate obstruction of retrieval processes to avoid activation of unwanted memories [Nowicka et al., 2011; Zacks and Hasher, 1994].

The lack of decline in BOLD activity observed in all three ROIs for the unsuccessfully remembered TBR words reinforces the claim that intentional and incidental forgetting are two different processes [Bastin et al., 2012; Nowicka et al., 2011; Yang et al., 2015]. The former caused by inhibitory and attentional processes and the latter by lack of encoding.

To the best of our knowledge this is the first fMRI study related to auditory DF. We acknowledge several limitations of our study: first, aiming to ensure encoding, our experimental design included an explicit instruction to create a personally meaningful image for each word (negative/neutral). The effects of this instruction may have

affected the discriminative power of the factor Emotion in the fMRI analyses, which led to a lack of interaction between Instruction and Emotion. Second, seeking a more realistic DF approach and a robust DF response, we used a relatively small amount of items (20/condition) in order to render DF more difficult. This led to a relatively low number of SF TBF words, which could also have affected the power of our fMRI results. Despite these limitations we consider that our goals have been largely achieved.

CONCLUSION

Coherent with visual DF studies, we found that DF in the auditory domain is a complex mechanism that goes beyond passivity or simple suppression and has a neural signature different from incidental forgetting. We suggest that each observed region in the MFG – PCG – IPL network is linked to a series of processes, which seem to act in synchrony at several levels of memory to support inhibition. However, although necessary and sufficient to cause forgetting, it seems that a certain level of efficiency should be achieved. Apparently each area associated with the forgetting network can purposefully modulate the connectivity patterns of various brain regions, to target different stages of memory. We proposed that (1) MFG triggers inhibition to discontinue the rehearsal of TBF items and to obstruct their access to working memory, (2) PCG facilitates disengagement of the task previous to the TBF instruction and supports the change of strategy, and (3) IPL enable selective attentional processes (attentional shift) to facilitate disengagement of unwanted items. Each of these three mechanisms however, seem to converge to the modulation of memory processes such as retrieval and episodic memory.

These results provide valuable information to advance the development of therapeutic approaches with possible clinical applications related to unwanted memories. In future studies, it could be interesting to consider the use of non-invasive transcranial stimulation techniques to further assess the role of the regions participating in the DF process and as a powerful tool to develop nonpharmacological neuromodulation therapies related to this disorder.

COMPETING FINANCIAL INTEREST

The authors declare no competing financial interests

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