Neuropsychologia 50 (2012) 2245–2256

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Note

Inside out: A neuro-behavioral signature of free recall dynamics

Irit Shapira-Lichter [a,*], Eli Vakil [c], Yifat Glikmann-Johnston [a], Tali Siman-Tov [a], Dan Caspi [b,d], Daphna Paran [b,d], Talma Hendler [a,d,e]

[a] *Functional Brain Imaging Center, Wohl Institute for Advanced Imaging, Tel-Aviv Sourasky Medical Center, Israel*
[b] *Department of Rheumatology, Tel-Aviv Sourasky Medical Center, Israel*
[c] *Department of Psychology and Gonda Multidisciplinary Brain Research Center, Bar-Ilan University, Israel*
[d] *Sackler Faculty of Medicine, Tel-Aviv University, Israel*
[e] *Department of Psychology, Tel-Aviv University, Israel*

ARTICLE INFO

Article history:
Received 21 September 2011
Received in revised form
20 May 2012
Accepted 25 May 2012
Available online 2 June 2012

Keywords:
Episodic memory
Default mode network
Hippocampus
fMRI
Inter-response time
Memory search

ABSTRACT

Free recall (FR) is a ubiquitous internally-driven retrieval operation that crucially affects our day-to-day life. The neural correlates of FR, however, are not sufficiently understood, partly due to the methodological challenges presented by its emerging property and endogenic nature. Using fMRI and performance measures, the neuro-behavioral correlates of FR were studied in 33 healthy participants who repeatedly encoded and retrieved word-lists. Retrieval was determined either overtly via verbal output (Experiment 1) or covertly via motor responses (Experiment 2). Brain activation during FR was characterized by two types of performance-based parametric analyses of retrieval changes over time. First was the elongation in inter response time (IRT) assumed to represent the prolongation of memory search over time, as increased effort was needed. Using a derivative of this parameter in whole brain analysis revealed the default mode network (DMN): longer IRT within FR blocks correlated with less deactivation of the DMN, representing its greater recruitment. Second was the increased number of words retrieved in repeated encoding-recall cycles, assumed to represent the learning process. Using this parameter in whole brain analysis revealed increased deactivation in the DMN (i.e., less recruitment). Together our results demonstrate the naturally occurring dynamics in the recruitment of the DMN during utilization of internally generated processes during FR. The contrasting effects of increased and decreased recruitment of the DMN following dynamics in memory search and learning, respectively, supports the idea that with learning FR is less dependent on neural operations of internally-generated processes such as those initially needed for memory search.

1. Introduction

Free recall (FR) is an internally guided retrieval operation, dependent on effective utilization of cognitive strategies with minimal support of external cues (Shimamura, 1995). Despite its profound effect on our daily routine and role in major mental declines (Nohara et al., 2000; Schmiedt, Meistrowitz, Schwendemann, Herrmann, & Basar-Eroglu, 2005; Zakzanis, 1998), to date only a limited number of studies have used in-vivo electrophysiological or neuroimaging techniques to study FR operations while most studies have focused on more externally driven modes of retrieval, such as recognition (Spaniol et al., 2009). One explanation for this research bias might be the endogenous nature of FR, which precludes animal studies and imposes a significant methodological challenge in a human brain imaging set-up. Another reason for this bias is that characterization of FR selectivity with respect to other retrieval operations such as cued recall or recognition is confounded by the inherent physical differences between them (e.g., silence in FR versus stimuli in cued recall or recognition).

Several previous studies overcame these difficulties by comparing different types of FR tasks/responses: correct and incorrect FR responses were compared in an intracranial EEG study (Sederberg et al., 2007), supra-span and sub-span FR periods were compared in a PET study (Grasby et al., 1993), and FR responses with and without semantic clustering were compared in an fMRI study (Long, Oztekin, & Badre, 2010). In another fMRI study, the brain activity patterns that preceded the retrieval of items belonging to different semantic categories were classified (Polyn, Natu, Cohen, & Norman, 2005). In the present study an alternative experimental approach was applied, namely, probing the neural signature of FR dynamics in time. To overcome the hurdles associated with the endogenous nature of FR, it was studied via behavioral manifestations of one of the central

---

* Corresponding author. Tel.: +972 3 6974818; fax: +972 2 6973080.
E-mail address: iritlichter@yahoo.com (I. Shapira-Lichter).

0028-3932/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.neuropsychologia.2012.05.028

processes which underlie it—memory search (Wheeler et al., 2006). The minimal availability of external cues during FR makes the process of memory search particularly important. Memory search further captures two important aspects of FR; its emerging property and endogenous nature.

FR memory search was quantified by two behavioral measures: (1) the ***number of items*** retrieved at a certain period, reflecting the efficacy of memory search, and (2) the latency between retrieval of successive items (i.e., ***inter-response time***; IRT), which provides a measure of memory search duration (Wingfield & Kahana, 2002; Wixted & Rohrer, 1994). Additionally, the temporal dynamics of FR memory search was studied on two time scales. One depicts the change in search duration along a designated period of FR attempts, termed here "***within FR blocks***", and is shown by increased IRT over time (Murdock & Okada, 1970; Puff, 1972). The second time scale depicts the change in the efficiency of memory search over repeated encoding-retrieval cycles. This time scale is termed here "***between FR blocks***", and is shown by an increase in the number of items retrieved over time, which can be presented as a learning curve (Tulving, 1962).

In the search for neural correlates of FR memory search, we chose to focus on the Default Mode Network (DMN); a brain system increasingly implicated in internally-based processes including those manifested during rest and memory, for example, self referential processes (Buckner & Carroll, 2007), internal mentation (Buckner, Andrews-Hanna, & Schacter, 2008), autobiographic memory (Andreasen et al., 1995; Svoboda, McKinnon, & Levine, 2006), general mnemonic capabilities (Wig et al., 2008), semantic memory (Binder & Desai, 2011; Wirth et al., 2011), encoding efficiency (Turk-Browne, Yi, & Chun, 2006) and memory search during recognition (Sestieri, Corbetta, Romani, & Shulman, 2011).

FR operations are particularly expected to involve the DMN machinery due to their minimal dependence on external stimuli, the lack of constraints for strategies applied during FR attempts and the centrality of memory search processes during FR. Two central nodes (Buckner et al., 2008) of the DMN are of particular interest in the context of FR memory search: the anterior medial prefrontal cortex (amPFC) which was indicated as the leading mediator of internally-generated mnemonic processes in several studies (Simons, Gilbert, Owen, Fletcher, & Burgess, 2005; Simons,

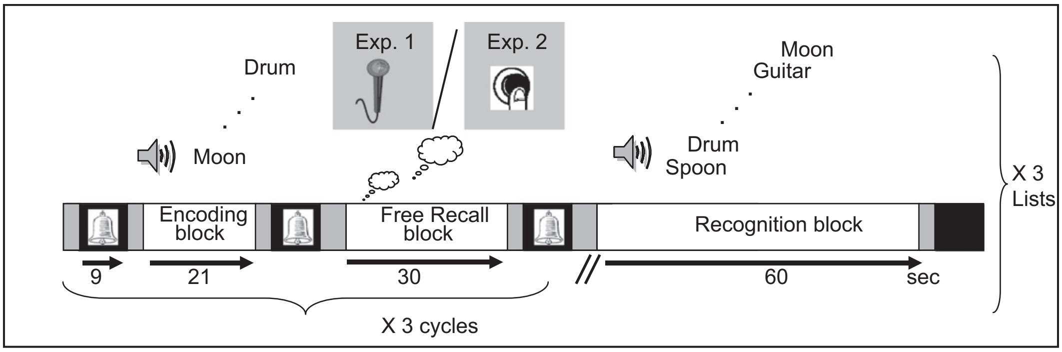

Fig. 1. Experimental paradigm. An fMRI adaptation of a word list learning and recall procedure. Instruction periods are represented by grey bars, baseline periods are represented by black bars, and experimental periods are represented by white bars.

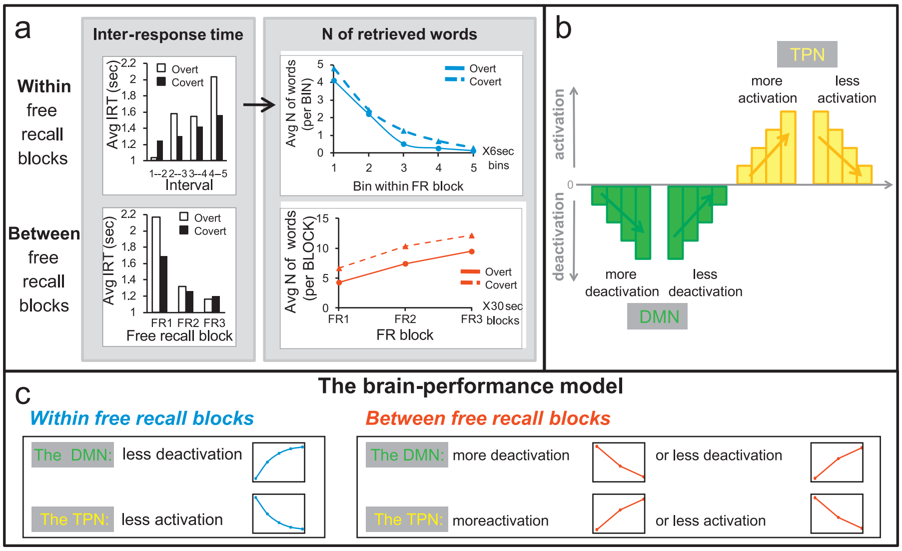

Fig. 2. (a) Behavioral results. Left panel: Changes in inter-response time (IRT) within and between free recall (FR) blocks. IRT significantly increased along FR blocks (averaged across the various leaning blocks). IRT significantly decreased between FR blocks (collapsed over the first four intervals in each FR block). Right panel: Changes in the number of retrieved words within and between FR blocks. Individual changes in retrieval rate within and between FR blocks were used as parametric predictors. (b) Schematic demonstration of the potential activity changes in the default mode network (DMN) and the task positive network (TPN). (c) Schematic demonstration of the model: a conjunction between main effect and an individually behavior-based parametric predictor. A whole-brain conjunction analysis was performed. For each participant and list, changes in retrieval rate within FR block were used as a parametric predictor. As greater recruitment of the DMN was hypothesized within FR blocks, scores were multiplied by minus one, and a conjunction with main effect for deactivation during FR was performed. The TPN was hypothesized to demonstrate the opposite pattern. To explore the neural correlates of changes between FR blocks, the learning curve of each participant and list was used as a parametric predictor. Whole brain conjunction analyses entailed examining the four possible patterns of increase/decrease in activation/deactivation.

Henson, Gilbert, & Fletcher, 2008), and the posterior cingulate (PCC)/precuneus cluster which was implicated in mnemonic memory search (Sestieri et al., 2011). Nevertheless, the role of the DMN in FR-related memory search has not yet been investigated systematically. The present study aims to characterize the emerging properties of FR memory search, probing the neural signature of its temporal dynamics.

To accomplish this aim, we used a verbal learning and memory test involving repeated cycles of encoding and FR of a word list (Fig. 1) during a functional Magnetic Resonance Imaging (fMRI) scan. Two complementary experiments were conducted; in the first experiment, participants overtly responded during the scanning, allowing a reliable behavioral measure of memory search and the identification of DMN modulations associated with it. In the second experiment, participants covertly responded during the scanning, minimizing the noise associated with the articulation of the retrieved words. In both experiments, behavior-based parametric analyses of FR over two time scales were performed: (1) Within FR blocks, representing the ***prolongation of memory search***. This was estimated by the parametric change in measured IRT within 30 s blocks (Fig. 2a–c). We hypothesized that with prolonged memory search the DMN would be recruited to a greater extent (i.e., be less deactivated). (2) Between FR blocks, over consecutive encoding-FR cycles, representing the process of ***learning*** (Fig. 2a). In this regard we tested the two possible options of activation change within the DMN (Fig. 2b–c). One is lowered recruitment of the DMN due to a reduced need for memory-search, mirroring the process referred to the within FR blocks. The other is increased recruitment of the DMN, as retrieval become easier and less resources are required, allowing more resources to be allocated to task-irrelevant internal processes, similar to the practice effect seen in working memory tasks (Mason et al., 2007). Our results point to a unique role of the DMN in FR-related memory search, with altered recruitment of this network with the prolongation of memory search and over learning.

2. Experiment 1—Overt retrieval

2.1. Material and methods

2.1.1. Participants

Eighteen healthy, right-handed, native Hebrew-speaking individuals participated in the study (age range 19–43 years; mean age 26.89 ± 5.58 SD; 9 females). Participants were financially compensated for their time and gave written informed consent that was approved by the Ethics Committee of the Tel Aviv Sourasky Medical Center.

2.1.2. Protocol

The learning and memory task: Participants studied a word list containing 15 concrete, frequently used, and emotionally neutral Hebrew nouns. The list was encoded and freely retrieved in three consecutive steps, followed by a recognition test. During periods of encoding (21 s), participants heard a list of 15 words (1 word per 1400 ms), and tried to remember as many as possible. During periods of FR (30 s), participants were required to overtly retrieve as many words as possible from the encoded list. This encoding-retrieval cycle was repeated three times, with a consistent word order so that participants could use serial encoding strategies. Following the three encoding-retrieval cycles there was a period of recognition (60 s), in which participants heard a 30-word list (1 word per 2 s), and were asked to repeat aloud words that belonged to the original 15-word list. The 30 words in the recognition phase consisted of the original 15 words (i.e., old words) and 15 new words. The new words were frequently used and emotionally neutral Hebrew nouns consisting of six phonologically and nine semantically distracting words. Experimental blocks were separated by 9 s active baseline blocks, where participants pronounced the sound “beep” in respond to a tone. Auditory instructions at the beginning of each block indicated the task to be performed. This procedure (i.e., three encoding-retrieval cycles and a recognition phase) was repeated four times, using four different lists. Three lists were used during scanning and the fourth list was used as a full-length experimental practice prior to scanning. Due to technical problems, two participants have data from two lists only.

Auditory stimuli were presented binaurally through pneumatic headphones. Stimuli presentation was controlled by Presentation software (version 10.3). Participants' verbal responses were recorded via an MR compatible noise reduction audio system (OptoAcoustics Ltd) and analyzed offline using Audacity software (version 1.3.4-beta). EEG was recorded simultaneously with fMRI, however, here we report and relate only to the fMRI data.

2.1.3. Behavioral measures of FR

For the behavioral analysis, performance was averaged for each participant across the three lists studied during the scan, prior to statistical analysis. Two behavioral measures of FR were obtained:

1. ***The number of words retrieved***—the number of responses recorded at each 30 s FR block was measured, separating correct and incorrect (intrusions or repetitions) responses. The change in the number of words retrieved over repeated encoding-retrieval cycles (i.e., learning) was examined using a 1-way analysis of variance (ANOVA) with the variable “cycle” (three levels: the first, second and third FR blocks).
2. ***Inter-response times***—IRT was calculated as the latency between each pair of consecutive articulations, measured from the beginning of each articulation. Both correct and incorrect responses were taken into account while computing the IRT, since ignoring the incorrect responses would have create artificially large IRT. IRT was calculated separately for each FR block, allowing differentiation of changes between and within FR blocks, using a 2-way ANOVA with the variables “cycle” (three levels: the first, second and third FR blocks) and “retrieval order” (four levels, see explanation below), respectively. Statistical analysis requires each participant to have at least one value in each condition. Therefore, in order to include the vast majority of participants in this analysis, we limited the “retrieval order” variable to four levels—examining the IRT in between the first five words retrieved (that is, IRT between the first and second word, between the second and third word, etc).

Statistical Package for the Social Sciences (SPSS) software (version 12) was used to analyze the behavioral effects. To adjust for any non-homogeneity of covariance for the within-subject effects, we used P values that were adjusted according to the Huynh-Feldt method.

2.1.4. MRI data acquisition and analysis

Imaging was performed on a 3T GE Signa Horizon scanner (General Electric, Milwaukee, WI), using an eight channels head coil. The scanning session included three-dimensional spoiled gradient (3D-SPGR) echo sequence [field of view (FOV), 250 mm; matrix size, 256 × 256; axial slices of 1-mm thickness, gap 0], and functional T2$*$-weighted images [FOV, 200 mm; matrix size,

96×96; repetition time, 3000 ms; echo time (TE), 35 ms; flip angle (FA), 90°; 39 axial slices of 3-mm thickness, gap 0].

Function-related signals of blood oxygenation level dependent (BOLD) contrasts were analyzed using the Brain Voyager analysis package (BRAIN VOYAGER QX Version 2.1, Brain Innovation, Maastricht, The Netherlands). Preprocessing of functional scans included 3D motion correction, slice scan time correction, spatial smoothing (a FWHM 4 mm Gaussian Kernel), linear trend removal and high-pass filtering (fast Fourier transform based with a cutoff of 2 cycles/time course). Head movements did not exceed 3 mm, and were in the 2–3 mm range in only 6 of the 52 sessions. All sessions were included in the analysis. The functional images were then superimposed on 2D anatomical images and incorporated into the 3D data sets through trilinear interpolation. The complete data set was transformed into Talairach space (Talairach & Tournoux, 1988). Statistical maps were prepared for each participant using parametric General Linear Models (GLMs) designed to directly explore the activation dynamics within and between FR blocks.

1. ***Parametric indication of memory search process within FR blocks:*** This model defined five regressors: one parametrically representing FR, two uniformly representing encoding and FR, one representing recognition, and one for instructions. The parametric regressor in this model was created by dividing each 30 s FR block into five equal time bins of 6 s, similarly to the work of Puff (1972). A boxcar waveform of these units was weighted for each individual and wordlist, based on his/her own performance in each bin (i.e., the number of correct verbatim responses in each bin). The transformation from IRT changes to changes in retrieval rate entailed the examination of this measure parametrically. For each participant and each list, the weight of parametric predictor was orthogonalized with respect to the main effect predictor. A conjunction analysis for (1) the parametrically changing, and (2) the uniform (i.e., main effect) FR predictors was used to identify regions whose deactivation during FR decreased with time within the FR blocks (Fig. 2c, the DMN).
   To better and more directly characterize activity changes during prolonged periods of search, regions of interest (ROI) were defined around the peak of activations obtained by this analysis, with an 11-voxel diameter box-shaped volume centered upon peaks of activation. In these ROIs, activity dynamics during relatively prolonged IRT (lasting at least 15 s) were characterized. The average percent signal change from baseline was calculated in each TR along the prolonged IRT. Baseline signal was computed by averaging the activity level in only the last TR of all baseline periods, allowing the signal to decay.
2. ***Parametric indication of learning process between FR blocks:*** This model defined six regressors: one parametrically representing the encoding condition, one parametrically representing the FR condition, two uniformly representing encoding and FR conditions, one for recognition, and one for instructions. The parametric regressors for encoding and FR blocks in this model were created as a boxcar waveform weighted for each individual and each wordlist based on individual learning curve (i.e., the number of correct verbatim responses in each block). This approach is similar to the one applied by Zeineh et al., (Zeineh, Engel, Thompson, & Bookheimer, 2003), however, we weighted regressors individually, unlike the group curve used by Zeineh et al. For each participant, the weights of parametric predictors were orthogonalized with respect to the main effect predictor. A conjunction analysis of (1) the parametrically changing, and (2) the uniform (i.e., main effect) FR predictors was used to identify regions that respond to FR in a learning-dependent fashion. In correspondence with our bidirectional hypothesis (Fig. 2c), two opposite models were constructed: one searching for region showing decrease in deactivation between FR blocks, and the other searching for regions showing increase in deactivation between FR blocks.

In all GLMs, all regressors were modeled as boxcar functions convolved with the hemodynamic response function, assuming a hemodynamic lag of 2 TRs (6 s). The crucial independence of the within and between GLMs employed stems from the averaging across the three FR blocks in the first GLM, which examines changes within FR blocks, and the averaging across an entire FR block in the second and third GLMs, which are focused on the dynamics between FR blocks (i.e., increases and decreases in deactivation over learning).

Single subject analysis was followed by a multi-subject analysis computed with random effects, using a white-matter mask. Brain activation was assessed at an uncorrected statistical threshold of $p < 0.05$. To correct for multiple comparisons, Monte Carlo simulation was used to calculate and apply a cluster-size threshold corresponding to a corrected threshold of $\alpha < 0.05$, using Brain Voyager QX Cluster-level Statistical Threshold Estimator plugin (Goebel, Esposito, & Formisano, 2006). A relatively liberal threshold was chosen owing to the usage of a statistically strict conjunction analysis to produce the maps. A data-driven approach, implemented in the plugin, was applied to estimate the amount of spatial correlations in the map, i.e., the smoothness of the data (Forman et al., 1995). The smoothness parameter obtained was used as the FWHM in the Monte Carlo simulation. Thus, the FWHM parameter was determined not only by the voxel size and smoothing kernel, but was further affected by the actual structure of the data (e.g., the usage of a white matter mask at previous analysis steps). Computation of the minimum cluster threshold was accomplished via 1000 iterations of a simulation.

2.2. *Results*

2.2.1. *Behavioral indices of FR*

As expected, IRT increased on average as time passed within FR blocks (2-way repeated measure ANOVA, main effect for "retrieval order", $F_{(2.33,30.26)}=3.595$, $p < 0.034$; Fig. 2a left upper row, white bars). Similarly to previous studies, repeated encoding-retrieval cycles produced an increase in the number of remembered words (1-way repeated measure ANOVA, main effect for "cycle", $F_{(2,34)}=156.93$, $p < 0.001$, see Fig. 2a, right lower row, circles), indicating that participants learned the wordlists. Overt responding allowed an estimation of error rate. As expected from young healthy participants, errors (intrusions and repetitions collapsed together) were infrequent: 0.58, 0.65 and 1.00 incorrect responses were produced on average in the first, second and third FR blocks, respectively.

To examine the relation between IRT and learning, the changes in IRT over repeated encoding-retrieval cycles (i.e., with learning) were tested. Fig. 2a (lower left panel, white bars) shows a decrease in average IRT over repeated cycles of encoding-retrieval, representing the change in memory search during learning (2-way repeated measure ANOVA, main effect for "cycle", $F_{(1.1,14.24)}=5.038$, $p < 0.039$).

2.2.2. *The neural correlates of the dynamics within FR blocks*

The neural dynamics related to prolonged memory search were identified using the change in IRT within FR blocks as a model for whole brain analysis (Fig. 2c for the hypothesis). The behavioral indices of the IRT change were transformed to fit a brain activation predictor (see Material and methods) and a strict conjunction analysis was used (Random, $N=18$, $p<0.05$ corrected, cluster size 24×3^3 voxels). Whole brain analysis indicated that as expected, the elongation of IRT as time passed within FR blocks (reflected as a reduced number of words retrieved in block-end bins), was associated with greater recruitment (that is, less deactivation) of the DMN. Increased recruitment was seen in the dorsal and ventral aspects of amPFC, bilateral IPL and the PCC/precuneus (Fig. 3a, blue and purple, Table S1a).

To inspect the contribution of the DMN to memory search more directly, we focused on FR responses that were given following a prolonged IRT ($\text{IRT}\geq15$ s), which allows characterization of the evolvement of memory search during IRT. This analysis was conducted in two key DMN regions: the amPFC (Talairach coordinates: −7, 49, 0) and the PCC/precuneus (Talairach coordinates: −7, −50, 27). In each region, a ROI was defined centered on the peaks of activation obtained in the conjunction analysis described above (see details in Section 2.1.4). Fig. 3b shows that, as expected, in both ROIs activity gradually increased with IRT, and then dropped again immediately prior to the FR response.

2.2.3. *The neural correlates of the dynamics between FR blocks*

The neural correlates of FR dynamics over learning were examined next (see Fig. 2c for the hypothesis) using, once again, a strict conjunction analysis (Random, $N=18$, $p<0.05$ corrected, cluster size 29×3^3 voxels). Learning was associated with reduced recruitment (that is, more deactivation) in major parts of the DMN, including dorsal and ventral amPFC, bilateral IPL and the PCC/precuneus, as well as in the left hippocampus (Fig. 3a, red and purple, Table S1b). No region showed the opposite pattern of increased recruitment (that is, decrease in deactivation) between FR blocks (Random, $N=18$, $p<0.05$ corrected, cluster size 24×3^3 voxels).

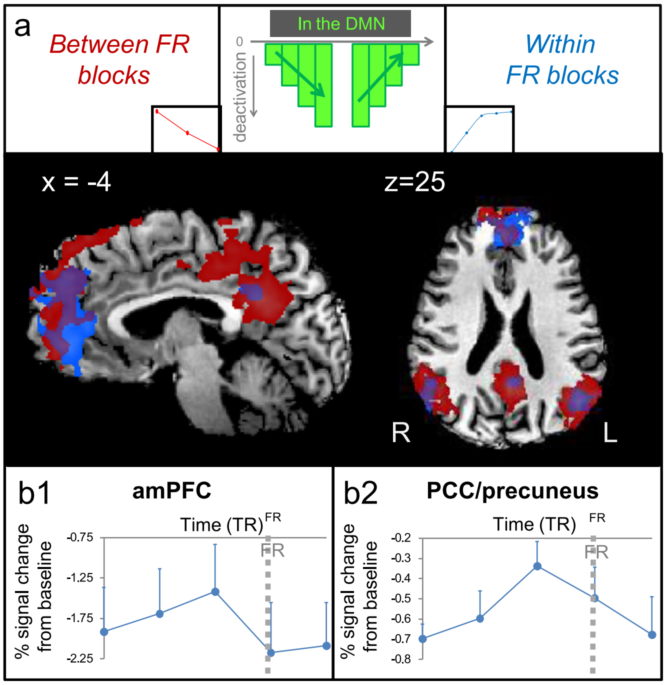

Fig. 3. Performance-related changes in deactivation within (blue) and between (red) free recall (FR) blocks. (a) Parametric whole brain group activation maps of regions showing performance-related changes in deactivation within (blue) and between (red) FR blocks. The overlap is presented in purple. Random, $N=18$, $p<0.05$, cluster size (determined by Monte Carlo correction for multiple comparisons) was 24×3^3 voxels for the within analysis and 29×3^3 voxels for the between analysis. (b) Percent signal changes in deactivation during prolonged IRT were examined in two major ROIs: the anterior medial prefrontal cortex (amPFC) and the posterior cingulate cortex (PCC)—precuneus cluster. The FR response is marked by the dashed line. Note that the expected hrf delay was not incorporated in the figures. DMN—default mode network, amPFC, FR- free recall. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.3. *Interim discussion*

Consistent with previous studies, two FR performance dynamics were evident in Experiment 1 (Murdock & Okada, 1970; Puff, 1972; Tulving, 1962). First, the gradual elongation of IRT within FR blocks (Fig. 2a, upper panel), reflecting an increase in memory-search (Wingfield & Kahana, 2002; Wixted & Rohrer, 1994). Second, the learning of the list of words following repeated encoding-retrieval cycles (Fig. 2a, lower panel, red), which was accompanied by gradual shortening of the IRT (Fig. 2a, lower panel, white bars).

Our parametric fMRI analysis implicates the DMN in FR memory search. As expected, the elongation of the IRT within FR blocks, representing the sustained memory search, was accompanied by decreased deactivation in the DMN. In contrast, shortening of the IRT over learning (i.e., between FR blocks) was accompanied by increased deactivation in the DMN. To note, the dynamics in the recruitment of the DMN (particularly its posterior aspects: the PCC/precuneus and Angular gyri) seem to be larger between FR blocks as compared to within blocks. The gradual increases in DMN recruitment during relatively long IRT (Fig. 3b) further corroborate its role in memory search, suggesting that with time, the process of memory search becomes deeper or more internally oriented.

The transient decrease in DMN recruitment that immediately preceded FR responses may however imply that the retrieval response interferes with the process of memory search. To reduce such interference which might be partly associated with articulation, and to minimize the head movements and noisy effects of the articulation, in Experiment 2 the same protocol was used, however, participants were asked to covertly retrieve the words and respond by a key-press when retrieval occurred during the FR block.

3. Experiment 2—Covert retrieval

This experiment replicates and extends the analyses conducted in the overt responding experiment in a cleaner setting, minimizing the noisy and interfering effects of articulating the recalled words. In addition, in the present experiment the neural hypotheses and the resulting analysis were extended to include:

(a) The hippocampus which is known to play a key role in episodic memory (Eichenbaum, 2000). Owing to the robust correlation seen between the hippocampi and posterior components of the DMN, both at "rest" and during directed recollection (Greicius, Srivastava, Reiss, & Menon, 2004; Vincent et al., 2006), the hippocampi are considered a subsystem of the DMN (Buckner et al., 2008). The left hippocampus was examined due to the verbal nature of the memory task.

(b) The task positive network (TPN)—This network typically exhibits activity increases during tasks, showing an opposite pattern of activation to the DMN (Fox et al., 2005). The TPN network includes regions such as the intraparietal sulcus (IPS) and the Frontal Eye Field (FEF) of the precentral sulcus. It has been suggested that the anti-correlation between these networks reflects competition between two modes of information processing, which differ in the direction of attention focus; when attention is mainly directed internally, the DMN is more activated and the TPN is less activated, whereas these roles are reversed when attention is mainly directed externally (Buckner et al., 2008; Fox et al., 2005; Fransson, 2005). Thus, the balance between the DMN and TPN during FR memory search is of interest.

3.1. Material and methods

3.1.1. Participants

Fifteen healthy, right-handed, native Hebrew-speaking individuals participated in the study (age range 19–44 years; mean age 27.4 years ± 6.93 SD; 8 females). Participants were financially compensated for their time and gave written informed consent that was approved by the Ethics Committee of the Tel Aviv Sourasky Medical Center.

3.1.2. Protocol

The Learning and Memory Task: Participants performed the same task described in Experiment 1, however, without overtly responding in the scanner. During encoding, participants pressed a key immediately following the presentation of each word. During FR periods, participants indicated when they covertly retrieved previously heard words by pressing a key each time a word was retrieved. During the recognition block, participants pressed a key for words recognized as "old". During the baseline period, participants pressed a key whenever they heard a tone. The full-length experimental practice run prior to scanning involved overt responding, providing overt behavioral data in the same group of participants. The data collected during practice and the data collected during the recognition blocks were used to confirm that participants indeed learned the word lists.

Motor responses were recorded using a 4-button response box (Current Designs, Philadelphia; the covert responding experiment). Stimuli presentation and participants' responses were controlled by Presentation software (version 10.3). Due to technical problems, two participants have data from two lists only.

Localizer Task: To localize the DMN and the TPN, a subgroup of 7 participants performed an additional *N*-back task during the fMRI scanning. In this task, participants were presented with a sequence of numbers (at a rate of one number every 2s) and were asked either to press a button when presented with the number "9" (0-back condition), or to indicate when the current stimulus matched the one from two steps earlier in the sequence (2-back condition). The task included four blocks of each condition, each lasting 18 s. Experimental blocks were separated by 6–9 s baseline fixation blocks. This experimental scan was used as an external localizer for DMN by contrasting the fixation blocks with the most demanding task (i.e., fixation $>$ 2-back). To identify the TPN, the most demanding task was contrasted with the least demanding task (i.e., 2-back $>$ 0-back).

3.1.3. Behavioral measures of FR

The number of words retrieved and the IRT measures were defined and analyzed as in Experiment 1, using the button presses instead of articulation responses. In addition, to compare covert retrieval in the scanner to overt retrieval during practice, 1-way repeated measure ANOVA with the variable "setting" (two levels: practice, scan) was conducted.

3.1.4. MRI data acquisition and analysis

Imaging was performed on a 3T GE Signa Horizon scanner (General Electric, Milwaukee, WI), using a standard quadrature head coil. The scanning session included conventional anatomical MR images (T1-WI, T2-WI, and T2-FLAIR), three-dimensional spoiled gradient (3D-SPGR) echo sequence [field of view (FOV), 250 mm; matrix size, 256 × 256; axial slices of 1-mm thickness, gap 0], and functional T2*-weighted images [FOV, 200 mm; matrix size, 64 × 64; repetition time, 3000 ms; echo time (TE), 35 ms; flip angle (FA), 90°; 45–46 axial slices of 3-mm thickness, gap 0].

Function-related signals of blood oxygenation level dependent (BOLD) contrasts were analyzed using the Brain Voyager analysis package (Brain Innovation, Maastricht, The Netherlands). Image preprocessing was performed with BRAIN VOYAGER 2000, and advanced analyses were performed with BRAIN VOYAGER QX (Version 2.1). Preprocessing of functional scans included 3D motion correction, slice scan time correction, spatial smoothing (a FWHM 4 mm Gaussian Kernel), linear trend removal and high-pass filtering (fast Fourier transform based with a cutoff of 3 cycles/time course). Head movements did not exceed 1 mm. The functional images were then superimposed on 2D anatomical images and incorporated into the 3D data sets through trilinear interpolation. The complete data set was transformed into Talairach space (Talairach & Tournoux, 1988). Statistical maps were prepared for each participant using the same parametric GLM models described in Experiment 1, again, aiming to independently explore the activation dynamics within and between FR blocks. In the present experiment, however, in addition to the changes in deactivation, changes in activation were also examined (Fig. 2c, TPN). As in Experiment 1, the regressors were modeled as boxcar functions convolved with the hemodynamic response function, assuming a hemodynamic lag of 2 TRs (6 s). Single subject analysis was followed by a multi-subject analysis computed with random effects, using a white matter mask. Brain activation was assessed at an uncorrected statistical threshold of $p < 0.05$. To correct for multiple comparisons, a cluster-size threshold corresponding to a corrected threshold of $\alpha < 0.05$ was calculated and applied using the Monte Carlo simulation, as described in more details in Experiment 1.

3.1.5. ROI analysis

ROIs were defined using the peak of activations obtained in the *N*-back localizer task, with an 11-voxel diameter box-shaped volume centered upon each peak of activation. In the hippocampus, manual segmentation of the left hippocampi was performed for each participant, producing individually defined ROIs in this region. The boundaries of the hippocampus were defined using previously described and validated anatomical landmarks established by Watson et al. (1992).

For all analyses, the average percent signal change from baseline was calculated and a delay of 2 TRs (6 s) was incorporated. Baseline signal was computed by averaging the activity level in only the last TR of all baseline periods, allowing the signal to decay. For the ***within*** blocks analysis, in each ROI, the percent signal change was calculated for each TR relative to baseline, and averaged across FR blocks, resulting in the time courses presented in Fig. 4 (see the far right column colored blue) and S3 (blue). For the ***between*** blocks analysis, in each ROI, the percent signal change was calculated for each FR block relative to baseline, and averaged across TRs within the block, resulting in the bar-graphs presented in Fig. 4 (see the far left column colored red) and S3 (red). Two-way repeated measure ANOVA was used to test the statistical significance of the presented signal changes within and between blocks. In the ROIs that showed both effects, percent signal changes were calculated for each TR and each FR block separately, allowing demonstration of the interaction between the ***within*** and ***between*** effects, (Fig. 4 & S3).

3.2. Results

3.2.1. Behavioral indices of FR

The results of the covert responding experiment replicated those obtained in the overt responding experiment. Specifically, repeated encoding-retrieval cycles were accompanied by an

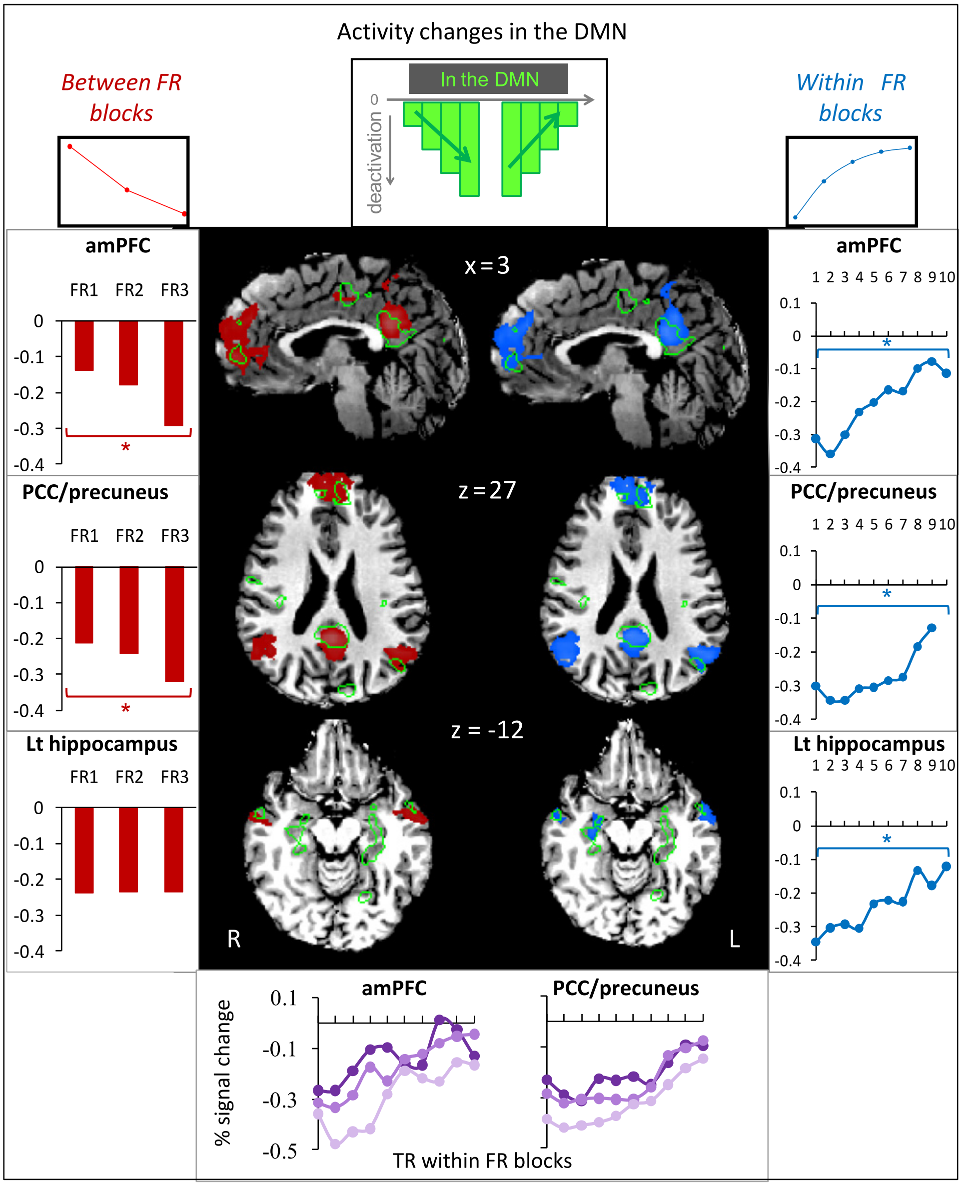

Fig. 4. Parametric whole brain group activation maps of regions showing performance-related changes in deactivation within (blue) and between (red) free recall (FR) blocks. The regions correspond to an external localizer of the default mode network (DMN, outlined in green). Random, $N=15$, $p<0.05$, cluster size (determined by Monte Carlo correction for multiple comparisons) $=24\times 3^3$ voxels. Percent signal changes in deactivation were examined in three externally defined ROIs: the anterior medial prefrontal cortex (amPFC), the precuneus, and the left hippocmpus. Percent signal changes were separately examined within FR blocks (averaged across learning, far right column, blue) and between FR blocks (averaged across time within each block, far left column, red). Statistically significant main effects are marked with asterisks. At the bottom, percent signal changes in activation are presented for each TR and FR block (first block in the darkest purple, third block in the lightest purple), demonstrating the interaction between changes within and between FR blocks. Note that the expected delay of 6 s was incorporated in the figures. DMN— default mode network, amPFC— anterior medial prefrontal cortex, PCC - posterior cingulate cortex, Lt-left, FR- free recall. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

increase in the number of remembered words (1-way repeated measure ANOVA, main effect for “cycle”, $F_{(2,28)}=168.771$, $p<0.001$, see Fig. 2a, lower panel, broken red line), indicating that participants learned the wordlists. Importantly, participants exhibited a similar pattern of performance during overt FR prior to scanning and covert FR during scanning (1-way repeated measure ANOVA, insignificant effect for “setting”, $F_{(1,14)}=2.685$, $p=0.124$; see Fig. S1) and this pattern was similar to the one obtained in the overt responding experiment (Fig. 2a, right lower, broken and continuous lines). These similar patterns validate the covert approach during scanning as representing the FR process.

Similar to the results of the overt responding experiment, IRT increased within FR blocks (2-way repeated measure ANOVA, main effect for “retrieval order”, $F_{(2.36,32.96)}=4.300$, $p<0.017$; Fig. 2a, left upper row, black bars) and decreased over repeated cycles of encoding-retrieval, representing the change in memory search during learning (2-way repeated measure ANOVA, main effect for “cycles”, $F_{(1.22,17.03)}=11.910$, $p<0.002$). Again, the similarity to IRT results obtained during overt responding (white and black bars in Fig. 2a) reinforces the reliability of our covert FR approach.

3.2.2. *Localizing the networks*

Brain activation was analyzed in correspondence to results obtained from a separate localizer scan using the *N*-back task to identify the DMN and the TPN. A typical DMN related deactivation

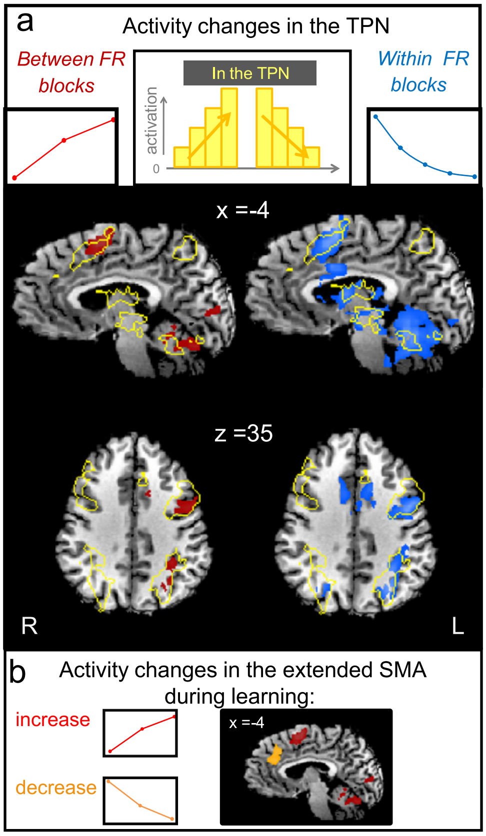

Fig. 5. Activity changes in the task positive network. (a) Parametric whole brain group activation maps of regions showing performance-related changes in activation within (blue) and between (red) free recall (FR) blocks. The regions correspond to an external localizer of the task positive network (TPN, outlined in yellow). Random, $N=15$, $p<0.05$, cluster size (determined by Monte Carlo correction for multiple comparisons)$=24\times3^3$ voxels. (b) Activity changes in the extended supplementary motor area (SMA) during learning. As learning proceeded, activity in the anterior part of the SMA decreased, and activity in its posterior aspect increased, resulting in a posterior shift in activation. TPN - task positive network, SMA—supplementary motor area, (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was obtained by comparing periods of baseline fixation with the most demanding task condition of 2-back (Fig. S2, green; Fig. 4, see green outline). In contrast, the TPN presents increased activation during the most demanding condition of the *N*-back relative to the least demanding condition of 0-back (Fig. S2, yellow; Fig. 5, see yellow outline). These network activations were used for defining ROIs in the DMN in one of the three clusters obtained in the amPFC (Talairach coordinates: 120,79,101) and in the PCC/precuneus (Talairach coordinates: 138,175,101) and in the TPN in the supplementary motor area (SMA, Talairach coordinates: 135,124,77), pre-SMA (Talairach coordinates: 132,106,89), and left IPS (L-IPS, Talairach coordinates: 156,187,89) (see Section 3.1.5 for details).

3.2.3. *The neural correlates of the dynamics within FR blocks*

The neural dynamics related to memory search were identified using the change in IRT within FR blocks as a model for whole brain analysis, using the same parametric approach used in Experiment 1, but now examining changes both in activation and in deactivation (Random, $N=15$, $p<0.05$ corrected, cluster size 24×3^3 voxels). Two patterns of activation were obtained: (a) less deactivation in main components of the DMN (as determined by the external localizer), including the dorsal and ventral aspects of amPFC, bilateral IPL, bilateral Superior Temporal Gyrus/Sulcus (STG, STS) and the PCC/precuneus, as well as in the right hippocampus (Fig. 4, blue color, Table S2); (b) less activation in various parts of the TPN (determined by the external localizer), including the SMA, left medial frontal gyrus (MFG) and FEF and bilateral IPS (Fig. 5 & S3, blue color, Table S2).

These results could potentially reflect the non-specific large transient deflection that typically takes place at the beginning of blocks, represented here by the sharp decrease modeled at the beginning of each FR block (Fig. 2c). To rule out this possibility, we applied a focused analysis on the a priori defined ROIs, and examined the time course of activity changes within FR blocks. Fig. 4 (right column) and S3 show that activity changes within FR blocks were prolonged and gradual, ruling out the transient deflection explanation for the whole brain analysis. In all ROIs examined, activity changes within FR blocks were significant (amPFC $F_{(9,108)}=6.02$, $p<0.001$, PCC/precuneus $F_{(9,108)}=8.01$, $p<0.001$, L-hippocampus $F_{(9,108)}=2.3$, $p<0.027$, SMA $F_{(9,108)}=24.83$, $p<0.001$, L-IPS $F_{(9,108)}=20.79$, $p<0.001$).

3.2.4. *The neural correlates of the dynamics between FR blocks*

We subsequently used an independent GLM model focused on the neural correlated of FR dynamics between FR blocks, as done in Experiment 1, but this time examining changes both in activation and deactivation (Random, $N=15$, $p<0.05$ corrected, cluster size 24×3^3 voxels). Using the parametric model of the between FR blocks, whole brain analysis revealed four activation patterns that accompanied learning: (a) more deactivation in core parts of the DMN, including dorsal and ventral amPFC, bilateral IPL and the PCC/precuneus (Fig. 4, red color, and Table S3); (b) more activation in major components of the TPN, including the SMA, bilateral FEF, the left MFG and left IPS (Fig. 5, red color, Table S3); (c) less deactivation in the primary motor area of the right hand (that pressed the button), representing the increased number of button presses over learning (not shown, Table S3); (d) less activation in the anterior pre-SMA, right inferior frontal gyrus (IFG)/insula and left lateral anterior PFC (Fig. 5b, orange activation; Table S3).

An ROI oriented analysis in the a-priori defined DMN, TPN and the hippocampus regions demonstrate the magnitude and dynamics between FR blocks (Fig. 4 and S3, the far left columns. amPFC $F_{(2,24)}=21.88$, $p<0.001$, PCC/precuneus $F_{(2,24)}=26.10$ $p<0.001$, L-hippocampus $F_{(2,24)}=0.012$, $p<0.98$, i.e., no effect in hippocampus, SMA $F_{(2,24)}=18.61$, $p<0.001$, L-IPS $F_{(2,24)}=16.12$, $p<0.001$).

A unique pattern of activity change during learning was observed in the SMA complex (SMA-proper and pre-SMA): its posterior aspect (SMA proper) showed increased activity between FR blocks, while its anterior aspect (pre-SMA) showed the opposite pattern (see Fig. 5b). Taken together, these results suggest a posterior shift in activation in the extended SMA region over learning. Control analysis ruled out the possibility that this shift is the result of an increased number of key-presses with learning (see details in Supplementary material Text S1 and Fig. S4).

3.2.5. *Interaction in the dynamics within and between FR blocks*

Integration of results obtained from the independent parametric analyses (Figs. 4 and 5) revealed great similarity between activation patterns obtained within FR blocks, representing the prolongation in memory search, and the pattern obtained between FR blocks. In both, regions confined within the DMN and the TPN present varying recruitment over time. The latter is rather a mirror image of the former, with the DMN showing a decrease in deactivation within FR blocks, and an increase in deactivation between FR blocks, and the TPN showing decreased activation within FR blocks, and increased activation between FR blocks (Figs. 4 and 5). The dynamics of this interaction are demonstrated in the percent signal changes calculated for each FR block separately, thus showing its change over learning (Fig. 4 lower panel, Fig. S3).

3.3. *Interim discussion*

Overall, the behavioral results of the covert responding experiment replicate those of the overt responding experiment, corroborating the reliability of the covert retrieval approach. The pattern of activity changes in the DMN within and between FR blocks (Fig. 4) considerably resemble the pattern that emerged in the overt responding experiment (Fig. 3, Experiment 1) with increased recruitment as time passes within FR blocks and decreased recruitment between FR blocks. The replication of these patterns of activation in two experiments using either covert or overt FR performances ruled out confounders such as mind wandering (i.e., not performing the task) in the former, and the effects of head movements due to vocalization in the latter. Owing to the complementary nature of the overt and covert FR experiments and the considerable similarities between their results, the results of the two studies will be jointly discussed in more details in the next section; the relatively minor differences between the two experiments are discussed in the Supplementary material section (Text S2).

4. General discussion

Consistent with previous studies (Murdock & Okada, 1970; Puff, 1972; Tulving, 1962), two FR performance dynamics were evident in the present experiments: first, the gradual elongation of IRT within FR blocks (Fig. 2a, upper panel), reflecting a sustained memory-search (Wingfield & Kahana, 2002; Wixted & Rohrer, 1994); and second, the learning of the list of words following repeated encoding-retrieval cycles (Fig. 2a, lower panel, right), which was accompanied by gradual shortening of the IRT (Fig. 2a, lower panel, left), possibly representing a reduction in memory search. The common behavioral measures used in the present study entailed the quantification of various processes that underlie FR despite its endogenous nature. The emerging property of FR allowed overcoming the requirement for contrast with other experimental conditions. Our parametric fMRI analysis revealed that the elongation of the IRT representing increased memory search was mediated by decreased deactivation in the DMN, while increased deactivation in the DMN, accompanied by reduction of the IRT, emerged during learning. The findings of the current study extend the rule of internality to FR memory search and demonstrate, for the first time, varying recruitment of the DMN during gradual ecological changes in the processes underlying FR, despite constant external demands. To the best of our knowledge, this is the first demonstration of a relationship between FR indices and the DMN activation changes.

4.1. *Involvement of the DMN in FR memory search dynamics*

The IRT-based parametric analysis of the within FR blocks dynamics was designed to identify brain regions associated with memory-search. As expected, this analysis revealed less deactivation in a set of regions identified by an external localizer as the DMN (Figs. 3 and 4, marked in blue, Table S1, S2), as memory search became more prolonged. The DMN has been largely implicated in episodic memory (Andreasen et al., 1995; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Svoboda et al., 2006; Turk-Browne et al., 2006) and in non-mnemonic internally driven processes (Buckner & Carroll, 2007; Buckner et al., 2008). Moreover, it was previously suggested that the recruitment of specific components of the DMN is affected by the need to access internal sources of information during recognition (Simons et al., 2008; Vinogradov et al., 2006), and by the quality of retrieval (Henson et al., 1999). Decreased deactivation in the DMN was further demonstrated regionally in the amPFC, PCC/precuneus and hippocampus (time course analysis, Fig. 4, blue), corresponding to previous evidence on the involvement of the DMN or its components in memory search (Ciaramelli, Grady, Levine, Ween, & Moscovitch, 2010; Polyn & Kahana, 2008; Sestieri et al., 2011; Wheeler et al., 2006).

The present results demonstrate a level of homogeneity in the dynamics of recruitment of the DMN nodes during FR memory search. This contrasts with the clear dissociation reported between anterior and posterior nodes of the DMN during recognition memory search (Sestieri et al., 2011). This dissimilarity, likely reflecting the different utilization of memory search processes in different retrieval tasks, demonstrates the previously suggested flexibility of the DMN.

In the present study, at the beginning of FR blocks, short search periods yielded retrieval responses, while later memory search was less successful, with longer search periods required to produce a retrieval response. The prolongation of memory search represents an increased memory search effort as gradually fewer and weaker items remain to be recalled. These prolonged search periods possibly allow search to become more internal, reflected as greater recruitment of the DMN, shown here as less deactivation during the task. This interpretation is also corroborated by our finding of gradual increase in DMN activity along relatively longer periods of memory search (Fig. 3b).

Notably, the behavioral (IRT measures) and neural (DMN activity levels) dynamics may further represent distinct processes guiding memory search at the beginning and at the end of the FR period. Specifically, greater deactivation later in the FR block may reflect greater contribution of long-term memory search as compared to short-term memory processes to word retrieval. In line with this interpretation, deactivations in the hippocampi – structures associated with long term memory – were attenuated as time passed within FR blocks (parametric and time course analyses, Fig. 4, blue). This idea is consistent with the greater recruitment of the hippocampus previously seen as the delay before recognition was prolonged, indicating greater allocation of long-term memory processes (Huijbers, Pennartz, & Daselaar, 2010).

By definition, the behavioral measure of IRT is coupled with retrieval successes, i.e., with the number of words retrieved in each time unit (bin) within periods of FR attempts. Thus, the dynamics demonstrated in the DMN within FR blocks could potentially reflect a decreased rate of retrieval success rather than increased memory search. However, the PCC and the precuneus components of the DMN typically show *increased* activity in correspondence with successful retrieval (Henson, Hornberger, & Rugg, 2005). Here accordingly, the time course analysis (Fig. 4 low panel) showed *reduced* activity at the beginning of FR blocks when retrieval success rate was the highest. Furthermore, while the number of FR responses (and the potential associated confounds of motor responses and/or response selection attempts) only slightly changes at the second part of the FR period (Fig. 2a, bins 3 and on), changes in the neural time course obtained from three regions continues throughout the period (Fig. 4, compare to TRs 4 and on, respectively). This pattern fits a gradually emerging process such as memory search and cannot be explained by the minor change in the number of retrieved items. Also, the gradual increases in DMN regional recruitment during prolonged IRTs (Fig. 3b) cannot be explained by motor responses or response selection, as there were no articulation responses within the studied periods. Therefore, we suggest that the increased recruitment of the DMN within FR periods represents changes in memory search which seems to dominate and conceal the more subtle effects of reduced retrieval success.

Another explanation for the reduced deactivation in the DMN is increased mind wandering as participants completed retrieval of all the words they could easily remember (Christoff, Gordon, Smallwood, Smith, & Schooler, 2009; Mason et al., 2007). However, as evident in our overt-experiment, the production of correct FR responses throughout the whole FR period, even towards the end (though at a lower incidence), indicates that participants were continuously engaged with the task, probably precluding the possibility of mind wandering.

In addition to its elongation within FR blocks, IRT reduced between FR blocks. The shortening of IRT as learning is established could reflect a reduction in memory-search effort, mirroring the process referred to the within FR blocks. Alternatively, it might represent an easier and less demanding retrieval. Intriguingly, these two possibilities predict opposite deactivation dynamics in the DMN: either an increase due to reduced need for memory-search, a typical internally-generated process (Buckner et al., 2008); or a decrease representing allocation of more resources to task-irrelevant internal processes, similar to the practice effect seen in working memory task (Mason et al., 2007). Learning-based parametric analysis through repeated encoding-retrieval cycles revealed more deactivation in the DMN (Figs. 3 and 4, red Tables S1, S3). This corresponds to previous findings showing decreased activity in DMN components during learning procedure (Petersson, Elfgren, & Ingvar, 1999; Petersson, Sandblom, Gisselgard, & Ingvar, 2001) and when retrieving well-learnt as compared to new words (Velanova et al., 2003). The increase in deactivation between FR blocks supports the former assertion and points to a unique role for the DMN in episodic memory. Thus, we suggest that with learning FR requires less internally focused memory search also manifested in shortening of the IRT. Changes in organization may underlie the shortening of memory search as learning proceeds: Tulving (1962) demonstrated changes in organization of the retrieved items through the process of learning, while changes in organization (in a context other than learning) have been shown to affect memory search during FR, and coincide with changes in IRT (Polyn, Norman, & Kahana, 2009).

4.2. The relation between DMN and TPN during FR

Our parametric model analyses revealed a set of regions becoming less active within FR recall blocks (Fig. 5, blue) and more active with learning (Fig. 5, red). These regions include the FEF and left medial IPS—two central components of the dorsal attention network which have been implicated in goal directed top-down attention (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002). The contribution of left medial IPS to encoding is probably mediated via attention mechanisms (Uncapher, Hutchinson, & Wagner, 2011). Left IPS was also implicated in retrieval processes. It has been proposed that this region is activated before and after retrieval, allocating top-down attention toward the maintenance of goal states, monitoring and evaluating the products of retrieval (Hutchinson, Uncapher, & Wagner, 2009). The opposite pattern of activation between DMN and dorsal attention network may reflect the competition between internally and externally directed attention. Accordingly when attention is mainly directed internally (here towards the end of FR blocks), the DMN is more activated and the dorsal attention network is less activated; when attention is mainly directed externally (here at the beginning of FR blocks—when retrieval relies more on short term memory, and when learning was established), the DMN is deactivated and the dorsal attention network is more activated (Buckner et al., 2008; Fox et al., 2005; Fransson, 2005). Uniquely, in the present study the opposing effect between the DMN and dorsal attention network is clearly demonstrated despite the lack of change in the external attention requirements.

To note, an additional opposing effect was evident in the SMA complex during learning. The increased activation in the SMA-proper with learning coincided with a parallel decrease in activation in the pre-SMA, producing a posterior shift in activation in the SMA complex as learning proceeded (Fig. 5b, red and orange). Control analyses support a cognitive role to the SMA–pre-SMA activations in this task (see details in Supplementary material). In view of the previously implicated role of this region in internally-generated mnemonic search (Volz, Schubotz, & von Cramon, 2004), the observed posterior shift in activation may reflect less reliance on memory search as learning is enhanced. Several neuroimaging studies (Crosson et al., 2001; Tremblay & Gracco, 2006) support this assertion by indicating a posterior-anterior distribution within the SMA complex, on the processing axis of source of initiation (external–internal, respectively). In language tasks in particular, activation distribution within this region has been related to the extent of internally inherent processes; greater activation in the anterior aspect of the pre-SMA was indicated during internally- as opposed to externally-guided, word generation tasks (Crosson et al., 2001; Tremblay & Gracco, 2006). Overall, the current results can be seen as a generalization of the same phenomena to the field of memory.

5. Conclusions

We characterized the neural correlates of FR memory search, while taking into account two scales of process dynamics: alongside continuous recall attempts (within) and over repeated cycles of encoding-retrieval (between). Our results showed decreased deactivation in the typical regions of the DMN with the prolongation of memory search within FR blocks, and increased deactivation with the establishment of learning over repeated cycles of encoding-retrieval (Fig. 3a & Fig. 4). The behavioral results in terms of the IRT changes (Fig. 2a, left panel) and the posterior shift in activation in the SMA complex during learning (Fig. 5b) are consistent with the possibility that the activation dynamics in the DMN over learning reflect reduced reliance on internally-driven memory search.

Findings from the current study may explain the coexistence of FR impairments and abnormalities in the DMN manifested in several clinical conditions, the most prominent of which is AD. Memory impairments are the leading symptoms of AD, with FR impairments predicting its subsequent development (Grober, Lipton, Hall, & Crystal, 2000). Abnormalities in the DMN were also observed in this condition (Buckner et al., 2005), even at preclinical stages. Further studies with a wider age range and diverse profiles of memory impairments are required to provide greater insight into the criticality of the DMN for effective FR memory search. Such studies should aim to further characterize early biomarkers of impending memory decline in neurodegenerative pathologies and in the elderly.

Acknowledgments

We thank Orit Stern, Eti Ben Simon, Vicki Myers, Ilana Podlipsky and Fabrizio Esposito for helpful comments on this manuscript and Oren Levin, Keren Rosenberg and Noga Oren for technical and data analysis assistance. The study was supported by a post-doctoral fellowship and a Young Investigator Research Grant from The National Institute for Psychobiology in Israel to I-S.L. Corresponding author: Irit Shapira-Lichter, Functional Brain Imaging Unit, Wohl Institute for Advanced Imaging, Tel-Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 64239, ISRAEL.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2012.05.028.

References

Andreasen, N. C., O'Leary, D. S., Cizadlo, T., Arndt, S., Rezai, K., Watkins, G. L., et al. (1995). Remembering the past: two facets of episodic memory explored with positron emission tomography. *The American Journal of Psychiatry*, *152*, 1576–1585.

Binder, J. R., & Desai, R. H. (2011). The neurobiology of semantic memory. *Trends in Cognitive Sciences*, *15*, 527–536.

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function and relevance to disease. *Annals of the New York Academy of Sciences*, *1124*, 1–38.

Buckner, R. L., & Carroll, D. C. (2007). Self-projection and the brain. *Trends in Cognitive Sciences*, *11*, 49–57.

Buckner, R. L., Snyder, A. Z., Shannon, B. J., LaRossa, G., Sachs, R., Fotenos, A. F., et al. (2005). Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. *Journal of Neuroscience*, *25*, 7709–7717.

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of The National Academy of Sciences of the United States of America*, *106*, 8719–8724.

Ciaramelli, E., Grady, C., Levine, B., Ween, J., & Moscovitch, M. (2010). Top-down and bottom-up attention to memory are dissociated in posterior parietal cortex: neuroimagingand and neuropsychological evidence. *Journal of Neuroscience*, *30*, 4943–4956.

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The reorienting system of the human brain: from environment to theory of mind. *Neuron*, *58*, 306–324.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Review Neuroscience*, *3*, 201–215.

Crosson, B., Sadek, J. R., Maron, L., Gokcay, D., Mohr, C. M., Auerbach, E. J., et al. (2001). Relative shift in activity from medial to lateral frontal cortex during internally versus externally guided word generation. *Journal of Cognitive Neuroscience*, *13*, 272–283.

Eichenbaum, H. (2000). A cortical–hippocampal system for declarative memory. *Nature Review Neuroscience*, *1*(1), 41–50.

Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., & Noll, D. C. (1995). Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magnetic Resonance in Medicine*, *33*(5), 636–647.

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of The National Academy of Sciences of the United States of America*, *102*, 9673–9678.

Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. *Human Brain Mapping*, *26*, 15–29.

Goebel, R., Esposito, F., & Formisano, E. (2006). Analysis of functional image analysis contest (FIAC) data with brainvoyager QX: from single-subject to cortically aligned group general linear model analysis and self-organizing group independent component analysis. *Human Brain Mapping*, *27*, 392–401.

Grasby, P. M., Frith, C. D., Friston, K. J., Bench, C., Frackowiak, R. S., & Dolan, R. J. (1993). Functional mapping of brain areas implicated in auditory-verbal memory function. *Brain*, *116*, 1–20.

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings of The National Academy of Sciences of the United States of America*, *101*, 4637–4642.

Grober, E., Lipton, R. B., Hall, C., & Crystal, H. (2000). Memory impairment on free and cued selective reminding predicts dementia. *Neurology*, *54*, 827–832.

Henson, R. N., Hornberger, M., & Rugg, M. D. (2005). Further dissociating the processes involved in recognition memory: an FMRI study. *Journal of Cognitive Neuroscience*, *17*, 1058–1073.

Henson, R. N., Rugg, M. D., Shallice, T., Josephs, O., & Dolan, R. J. (1999). Recollection and familiarity in recognition memory: an event-related functional magnetic resonance imaging study. *Journal of Neuroscience*, *19*, 3962–3972.

Huijbers, W., Pennartz, C. M., & Daselaar, S. M. (2010). Dissociating the "retrieval success" regions of the brain: effects of retrieval delay. *Neuropsychologia*, *48*, 491–497.

Hutchinson, J. B., Uncapher, M. R., & Wagner, A. D. (2009). Posterior parietal cortex and episodic retrieval: convergent and divergent effects of attention and memory. *Learning and Memory*, *16*, 343–356.

Long, N. M., Oztekin, I., & Badre, D. (2010). Separable prefrontal cortex contributions to free recall. *Journal of Neuroscience*, *30*, 10967–10976.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering minds: the default network and stimulus-independent thought. *Science*, *315*, 393–395.

Murdock, B. B., & Okada, R. (1970). Interresponse times in single-trial free recall. *Journal of Verbal Learning and Verbal Behavior*, *86*, 263–267.

Nohara, S., Suzuki, M., Kurachi, M., Yamashita, I., Matsui, M., Seto, H., et al. (2000). Neural correlates of memory organization deficits in schizophrenia. A single photon emission computed tomography study with 99mTc-ethylcysteinate dimer during a verbal learning task. *Schizophrenia Research*, *42*, 209–222.

Petersson, K. M., Elfgren, C., & Ingvar, M. (1999). Dynamic changes in the functional anatomy of the human brain during recall of abstract designs related to practice. *Neuropsychologia*, *37*, 567–587.

Petersson, K. M., Sandblom, J., Gisselgard, J., & Ingvar, M. (2001). Learning related modulation of functional retrieval networks in man. *Scandinavian Journal of Psychology*, *42*, 197–216.

Polyn, S. M., & Kahana, M. J. (2008). Memory search and the neural representation of context. *Trends in Cognitive Sciences*, *12*, 24–30.

Polyn, S. M., Natu, V. S., Cohen, J. D., & Norman, K. A. (2005). Category-specific cortical activity precedes retrieval during memory search. *Science*, *310*, 1963–1966.

Polyn, S. M., Norman, K. A., & Kahana, M. J. (2009). Task context and organization in free recall. *Neuropsychologia*, *47*, 2158–2163.

Puff, C. R. (1972). Temporal properties of organization in recall of unrelated words. *Journal of Experimental Psychology*, *92*, 225–231.

Schmiedt, C., Meistrowitz, A., Schwendemann, G., Herrmann, M., & Basar-Eroglu, C. (2005). Theta and alpha oscillations reflect differences in memory strategy and visual discrimination performance in patients with Parkinson's disease. *Neuroscience Letters*, *388*, 138–143.

Sederberg, P. B., Schulze-Bonhage, A., Madsen, J. R., Bromfield, E. B., Litt, B., Brandt, A., et al. (2007). Gamma oscillations distinguish true from false memories. *Psychological Science*, *18*, 927–932.

Sestieri, C., Corbetta, M., Romani, G. L., & Shulman, G. L. (2011). Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. *Journal of Neuroscience*, *31*, 4407–4420.

Shimamura, A. P. (Ed.). (1995). Cambridge: MIT press.

Simons, J. S., Gilbert, S. J., Owen, A. M., Fletcher, P. C., & Burgess, P. W. (2005). Distinct roles for lateral and medial anterior prefrontal cortex in contextual recollection. *Journal of Neurophysiology*, *94*, 813–820.

Simons, J. S., Henson, R. N., Gilbert, S. J., & Fletcher, P. C. (2008). Separable forms of reality monitoring supported by anterior prefrontal cortex. *Journal of Cognitive Neuroscience*, *20*, 447–457.

Spaniol, J., Davidson, P. S., Kim, A. S., Han, H., Moscovitch, M., & Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia*, *47*, 1765–1779.

Svoboda, E., McKinnon, M. C., & Levine, B. (2006). The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia*, *44*, 2189–2208.

Talairach, J., & Tournoux, P. (1988). *Co-planar Stereotaxic Atlas of the Humen Brain*. New-York: Thieme.

Tremblay, P., & Gracco, V. L. (2006). Contribution of the frontal lobe to externally and internally specified verbal responses: fMRI evidence. *Neuroimage*, *33*, 947–957.

Tulving, E. (1962). Subjective organization in free recall of "unrelated" words. *Psychological Reviews*, *69*, 344–354.

Turk-Browne, N. B., Yi, D. J., & Chun, M. M. (2006). Linking implicit and explicit memory: common encoding factors and shared representations. *Neuron*, *49*, 917–927.

Uncapher, M. R., Hutchinson, J. B., & Wagner, A. D. (2011). Dissociable effects of top-down and bottom-up attention during episodic encoding. *Journal of Neuroscience*, *31*, 12613–12628.

Velanova, K., Jacoby, L. L., Wheeler, M. E., McAvoy, M. P., Petersen, S. E., & Buckner, R. L. (2003). Functional-anatomic correlates of sustained and transient processing components engaged during controlled retrieval. *Journal of Neuroscience*, *23*, 8460–8470.

Vincent, J. L., Snyder, A. Z., Fox, M. D., Shannon, B. J., Andrews, J. R., Raichle, M. E., et al. (2006). Coherent spontaneous activity identifies a hippocampal–parietal memory network. *Journal of Neurophysiology*, *96*, 3517–3531.

Vinogradov, S., Luks, T. L., Simpson, G. V., Schulman, B. J., Glenn, S., & Wong, A. E. (2006). Brain activation patterns during memory of cognitive agency. *Neuroimage*, *31*, 896–905.

Volz, K. G., Schubotz, R. I., & von Cramon, D. Y. (2004). Why am I unsure? Internal and external attributions of uncertainty dissociated by fMRI. *Neuroimage*, *21*, 848–857.

Watson, C., Andermann, F., Gloor, P., Jones-Gotman, M., Peters, T., Evans, A., et al. (1992). Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. *Neurology*, *42*, 1743–1750.

Wheeler, M. E., Shulman, G. L., Buckner, R. L., Miezin, F. M., Velanova, K., & Petersen, S. E. (2006). Evidence for separate perceptual reactivation and search processes during remembering. *Cerebral Cortex*, *16*, 949–959.

Wig, G. S., Grafton, S. T., Demos, K. E., Wolford, G. L., Petersen, S. E., & Kelley, W. M. (2008). Medial temporal lobe BOLD activity at rest predicts individual differences in memory ability in healthy young adults. *Proceedings of The National Academy of Sciences of the United States of America*, *105*, 18555–18560.

Wingfield, A., & Kahana, M. J. (2002). The dynamics of memory retrieval in older adulthood. *Canadian Journal of Experimental Psychology*, *56*, 187–199.

Wirth, M., Jann, K., Dierks, T., Federspiel, A., Wiest, R., & Horn, H. (2011). Semantic memory involvement in the default mode network: a functional neuroimaging study using independent component analysis. *Neuroimage*, *54*, 3057–3066.

Wixted, J. T., & Rohrer, D. (1994). Analyzing the dynamics of free recall: an integrative review of the empirical literature. *Psychonomic Bulletin & Review*, *1*, 89–106.

Zakzanis, K. K. (1998). The subcortical dementia of Huntington's disease. *Journal of Clinical and Experimental Neuropsychology*, *20*, 565–578.

Zeineh, M. M., Engel, S. A., Thompson, P. M., & Bookheimer, S. Y. (2003). Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science*, *299*, 577–580.