

The developmental neural substrates of Hebb repetition learning and their link with reading ability

Short running title: Developmental neural substrates of Hebb

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ABSTRACT

Hebb repetition learning is a fundamental learning mechanism for sequential knowledge, such as language. However, still little is known about its development. This fMRI study examined the developmental neural substrates of Hebb repetition learning and its relation with reading abilities in a group of 49 children aged from 6 to 12 years. In the scanner, the children carried out an immediate serial recall task for syllable sequences of which some sequences were repeated several times over the course of the session (Hebb repetition sequences). The rate of Hebb repetition learning was associated with modulation of activity in the medial temporal lobe. Importantly, for the age range studied here, learning-related medial temporal lobe modulation was independent of the age of the children. Furthermore, we observed an association between regular and irregular word reading abilities and the neural substrates of Hebb repetition learning. This study suggests that the functional neural substrates of Hebb repetition learning do not undergo further maturational changes in school age children, possibly because they are sustained by implicit sequential learning mechanisms which are considered to be fully developed by that age. Importantly, the neural substrates of Hebb learning remain significant determinants of children's learning abilities, such as reading.

200 words

Keywords: serial order, Hebb repetition learning, learning, language, reading, development, fMRI

INTRODUCTION

Novel sequential information in working memory (WM), such as first new words in infants or a word in a foreign language, can be transformed into a stable long-term memory representation via simple repeated exposure to the information. The principle of learning via repeated exposure is known as Hebb repetition learning. The Hebb repetition learning effect has initially been demonstrated by the observation of a progressive increase in recall performance for repeated versus novel digit sequences over the course of an immediate serial recall task (Hebb, 1961). The ability to learn novel sequential information via mere repeated exposure is considered to be a core learning mechanism of our brain and supports sequential learning in different domains such as vocabulary learning, reading or mathematics (Bogaerts et al., 2016; De Visscher et al., 2015; Ordonez Magro et al., 2018; Szmalec et al., 2009). The transformation of novel sequence information into a stable long-term memory (LTM) representation via Hebb repetition learning is therefore also an important ability contributing to cognitive development. Yet, we currently have very limited knowledge about the cognitive and neural maturation of this fundamental learning ability.

At the behavioral level, we know that children as young as 5 years of age can present Hebb repetition learning but some studies also suggest that Hebb repetition learning may be reduced in young children as compared to adults (Bogaerts et al., 2016; Mosse & Jarrold, 2008). Other studies suggest that children can show similar, or even stronger Hebb repetition learning effects than adults (Smalle et al., 2016, 2018). Hebb repetition learning performance has been shown to predict learning abilities in different domains, such as vocabulary development and reading (Archibald & Joanisse, 2013; Bogaerts et al., 2016; Evans et al., 2009; Mosse & Jarrold, 2008; Ordonez Magro et al., 2018; Smalle et al., 2016; Szmalec et al., 2012). Also, Hebb repetition learning impairments have been observed in adults with reading

disabilities (Bogaerts et al., 2015; Szmalec et al., 2011), as well as in adults with mathematical deficits (De Visscher et al., 2015).

While being a strongly investigated mechanism at the behavioral level, the neural basis of Hebb repetition learning has received relatively little consideration, and this particularly from a neurodevelopmental perspective. The few studies that have investigated the neural substrates of Hebb repetition learning in adults have highlighted the role of medial temporal structures also known to be involved in episodic and semantic long-term memory (Mayes et al., 2007). A first study by Kalm, Davis and Norris (2013) observed that Hebb repetition learning for verbal sequences is associated with global activity decreases in superior and middle temporal regions as well as in premotor cortex. Critically, neural patterns for repeated sequences were shown to become increasingly similar in the left anterior hippocampus as well as in the right supramarginal gyrus and the bilateral insula. These findings are supported by a second study showing more similar neural patterns in the right posterior hippocampus for objects presented in their learned sequential positions than for the same objects presented in random positions (Hsieh et al., 2014). These studies suggest that the anterior and posterior parts of the hippocampus are critically involved in Hebb repetition learning processes. However, it is important to note that other authors found that focal hippocampal lesions (in the bilateral hippocampal head and the tail) do not affect Hebb learning performance (Gagnon et al., 2004). The potential involvement of the hippocampus raises the question of possible neuromaturational processes in children, given that this structure undergoes significant and prolonged neurodevelopmental change. While some studies failed to show clear evidence of a relation between hippocampal volume and age (e.g., Giedd et al., 1996; Yurgelun-Todd, Killgore, & Cintron, 2003), other more recent studies demonstrated that hippocampal volume increases with age (DeMaster et al., 2014; Østby et al., 2009). De Master et al. (2013) showed that 8 to 11-year-old children have a larger right

hippocampal head, bilaterally smaller hippocampal body, and a larger right hippocampal tail compared to adults. Overall, anterior regions of the hippocampus appear to decrease in volume while more posterior regions appear to increase in volume (Gogtay et al., 2006; see also Insausti, 2010). These structural changes in regions potentially critical for Hebb repetition learning could also have an impact on the development of its functional neural substrates and learning efficiency. Although the functional neural substrates of Hebb repetition learning have not been investigated in children so far, studies focusing more specifically on explicit (episodic memory) or implicit learning tasks have indeed shown age-related changes in hippocampal and basal ganglia activity (DeMaster & Ghetti, 2013; Ghetti et al., 2010; Maril et al., 2010; Paz-Alonso et al., 2008; Thomas et al., 2004).

The potential recruitment of hippocampal areas for Hebb learning also raises the question about the nature of the involved learning processes. Hippocampal regions have been mainly associated with explicit, episodic memory rather than with implicit sequential learning processes supported by procedural memory (DeMaster & Ghetti, 2013; Maril et al., 2010; Paz-Alonso et al., 2008). Also, procedural memory is generally considered to reach maturity early in development while episodic memory abilities still progress until adulthood (Amso & Davidow, 2012; Finn et al., 2016; Meulemans et al., 1998). However, note that existing studies did not clearly establish the age at which procedural memory is fully developed. With this in mind, numerous studies in the Hebb learning field have tried to understand the nature of this learning effect. On the one hand, studies observing no age-related increases in Hebb learning performance support the procedural memory view on Hebb learning (Smalle et al., 2016, 2018). On the other hand, studies observing such age effects suggest that there is also a contribution of episodic memory mechanisms in Hebb learning (Bogaerts et al., 2016; Kalm et al., 2013; Mosse & Jarrold, 2008).

The aim of the present study was to investigate the functional neural substrates of Hebb repetition learning in children aged 6 to 12 years and to examine more specifically the association between Hebb repetition learning and hippocampal activity. The critical question is whether or not the Hebb learning effect is associated with age-related changes in hippocampal activity between the ages of 6 and 12. If the Hebb learning effect in children is exclusively determined by implicit sequential learning mechanisms (procedural memory) considered to be fully developed in preschool children (Amso & Davidow, 2012; Finn et al., 2016; Meulemans et al., 1998), we should expect no developmental increases in Hebb learning ability for the age group studied here, and hence no age-dependent modulation of the link between Hebb learning and hippocampal activity. If, on the contrary, the Hebb learning effect between the ages of 6 and 12 is also supported by episodic memory mechanisms, which mature at a later age (Bauer, 2008; Finn et al., 2016; Ofen et al., 2012, 2007), an age-related modulation of the association between hippocampal activity and Hebb learning ability should be observed. We used an fMRI design in which children were asked to recall syllable sequences, with half of the sequences being repeated in line with the standard Hebb repetition learning paradigm. Neural activity for repeated (Hebb) and unrepeated (filler) sequences was determined and compared to behavioral scores for the Hebb repetition learning task. Moreover, the Hebb sequence learning task is basically an immediate serial recall task which thus also involves a working memory component, responsible for the temporary maintenance and reproduction of the syllables constituting the sequences. These working memory requirements are known to be supported by a fronto-parietal network and are associated with age-related activity increases in school age children (Attout et al., 2019; Kharitonova et al., 2015; Klingberg et al., 2002; Spencer-Smith et al., 2013; van den Bosch et al., 2014). Therefore, we also anticipate a general age-related increase in parietal activity for both the Hebb and the filler sequences.

Finally, in order to further examine the wider relevance of Hebb repetition learning and its developmental neural substrates, we assessed the link between neural markers of Hebb repetition learning and reading ability. Reading has been associated with memory abilities for sequential information, over both the short-term and the long-term (Bogaerts et al., 2016, 2015; Martinez Perez, Majerus, Mahot, et al., 2012; Martinez Perez, Majerus, Poncelet, et al., 2012; Szmalec et al., 2012). Long-term memory for serial order information, as assessed by Hebb repetition learning, has been proposed to be specifically involved in the creation of new and stable orthographic representations, allowing for more proficient and automatized reading (as required for regular and irregular word reading). More specifically, serial order learning abilities may support the creation of a unitary orthographic representation for a given word with its grapheme-phoneme mappings in their correct serial order, and may therefore be involved in the development of the fast, direct-access lexical reading route (Szmalec et al., 2011). If this is true, then we should also expect a link between neural markers of Hebb repetition learning and reading ability, especially for existing (regular and irregular) words, as opposed to nonwords which can only be assembled through letter-by-letter decoding (the latter being supported by short-term serial order memory abilities; e.g., Martinez Perez et al., 2012).

METHODS

The data that support the findings of this study are openly available at https://osf.io/mrkud/?view_only=492cc6170bd54cf29876ab7833558094.

Participants

Fifty-nine right-handed children from 2nd to 6th grade participated in the study. All parents declared that their children were native French speakers and had no history of neurological disorder, sensory impairment, or learning difficulties. Families received a 20

euros gift card for their participation. Data from 10 participants were excluded because of excessive movement in the scanner (see criteria below). The data from 49 participants (27 girls and 22 boys) were retained for analysis (mean age = 9.29 years old, range = 6.7–12.2 years old). Fourteen participants were in 2nd grade, eleven in 3rd grade, eight in 4th grade, four in 5th grade and twelve in 6th grade. Note that the same children also participated in the study reported by Attout et al. (2019). The study has been approved by the ethics committee of the Faculty of Medicine of the University. In line with the Declaration of Helsinki, both the parents and children gave their written informed consent prior to inclusion in the study.

fMRI task

Sequences of meaningless consonant-vowels syllables (/lou/, /mo/, /pi/, /ra/, /vu/) were presented auditorily to the children for immediate serial recall. The order of the syllables was the same for a subset of the sequences (Hebb condition) and varied randomly (filler condition) for the other sequences. All sequences contained 5 syllables to ensure that performance for recall was not at ceiling and that there was room for learning in the Hebb trials. For the different trials, we furthermore ensured that: (1) two (or more) consecutive syllables never resulted in an existing French word, (2) a syllable in one Hebb sequence was never repeated at the same position in the filler sequences within a block (see below), (3) a same syllable in the filler sequences was not presented more than twice in the same position within a block. Three different Hebb sequences were used, each presented in a different block. For each of the three blocks, the Hebb sequence was repeated eight times. A filler sequence was inserted between each Hebb sequence, resulting in three blocks of 16 (=48) sequences in total. All syllables were pre-recorded by a female voice and stored as a high-resolution audio file. The memory sequences were presented at the speed of one syllable per second with an inter-stimulus interval of 100 ms via a high-quality MRI audio system (Serene Sound system, *Resonance Technology Inc*). After each sequence, a screen with a cartoon character and speech bubble

containing a question mark appeared, instructing the children to recall the sequence they just heard. Children had to recall aloud a maximum of syllables in correct serial order within 15000 ms maximum. They had to press a button when they had finished recalling the sequence, thereby initiating the presentation of the next sequence which was separated by an intertrial interval of 3500 ± 250 msec (random Gaussian distribution). The order of presentation of the three blocks was counterbalanced across participants. Recall performance for the sequences was determined based on a method introduced by McKelvie (McKelvie, 1987; Ordonez Magro et al., 2018; Smalle et al., 2016; Staels & Van den Broeck, 2015). This method takes into account the absolute position of the recalled items, but also their relative serial position. First, the number of items recalled in correct position in both ways (from left to right and from right to left up to the first error) is determined. Then, terms recalled in any correct order (in groups of two or more items) are counted (3) from left to right (4) and from right to left. The maximal possible recall score using this procedure was 5. On this basis, we collapsed the scores of trials 1 to 3 into a 1st half score and the scores of trials 6 to 8 into a 2nd half score for each type of sequence (filler, Hebb). 2nd half scores for the Hebb sequences were considered to maximally capture Hebb repetition learning performance, as compared to 2nd half scores for filler sequences (Archibald & Joanisse, 2013; Mosse & Jarrold, 2008; Ordonez Magro et al., 2018; Smalle et al., 2016, 2018). We also computed for each participant the regression slope of performance increase as a function of trial number for Hebb and filler lists. This measure allows to obtain a measure of the gradual nature of the Hebbian learning process (Page et al., 2006). Task reliability was .87 for filler and .89 for Hebb sequences (Cronbach's alpha). Moreover, the correlation between performance for each block (second half) was moderate to high (from .44 to .59 for filler sequences and from .36 to .51). The task was presented on a workstation running Matlab 12 and the Cogent toolbox (UCL, <http://www.vislab.ucl.ac.uk/cogent.php>).

Reading abilities. Reading abilities were assessed for nonwords (reading via general grapheme-to-phoneme conversion rules), regular words and irregular words (accurate reading mainly possible via access to specific long-term sequential knowledge about the grapheme-to-phoneme mappings that characterize each word) (Poncellet, 1999). The nonword reading task was composed of 30 items varying in length (from 2 to 6 syllables) and orthographic frequency (low, medium, high). Note that the 30 nonwords also assessed contextual grapheme-to-phoneme knowledge (e.g., in French, the letter “s” is usually pronounced /s/, but when surrounded by vowels, it is pronounced /z/). The regular and irregular (like *femme* read /fam/ in French) word list included 30 items for each word type, varying in length (from 4 to 10 letters), lexical frequency and imageability level. The (non)words were printed in lowercase letters and were matched for length (number of letters). The experimenter presented the (non)words one by one to the child on a computer screen (typeface: new roman, 16 points), who had to read the words aloud as accurately as possible. The score was the number of (non)words read correctly out of 30 for each task.

Non-verbal intelligence. We also collected an estimate of nonverbal intellectual efficiency by administering Raven’s Colored Progressive Matrices (Raven & Raven, 1998). The raw scores were taken as the dependent measure.

Procedure

A first practice session outside the scanner took place one week before the fMRI session. During this session, children completed the tasks assessing reading abilities as well as the test assessing non-verbal intelligence. The fMRI environment and upcoming experiment was explained in detail with pictures and a book describing a space travel story which was used to introduce the fMRI experiment. The task was presented as a game, the whole fMRI experiment being described as a journey with a space shuttle, and with the child playing the role of an astronaut. Children then practiced the immediate serial recall task for the following

fMRI session. One week later, children came back for the fMRI session which started with the administration of at least 4 practice trials outside the scanner. All participants demonstrated sufficient understanding of the task when being placed in the scanner. To minimize head motion, children were trained not to move their head and cushions were inserted around their head to fill the gap between the head and the coil.

MRI acquisition

Functional MRI time series were acquired on a whole-body 3T scanner (Magnetom Prisma, Siemens Medical Solutions, Erlangen, Germany) operated with a 20-channel receiver head coil. Multislice T2*-weighted functional images were acquired with the multi-band gradient-echo echo-planar imaging sequence (CMRR, University of Minnesota) using axial slice orientation and covering the whole brain (32 slices, multiband factor = 2, FoV = 192x192 mm², voxel size 3x3x3 mm³, 25% interslice gap, matrix size 64x64x32, TR = 978 ms, TE = 30 ms, FA = 90°). The five initial volumes were discarded to avoid T1 saturation effects. A gradient-recalled sequence was applied to acquire two complex images with different echo times (TE = 10.00 and 12.46 ms respectively) and generate field maps for distortion correction of the echo-planar images (EPI) (TR = 634 ms, FoV = 192x192 mm², 64x64 matrix, 40 transverse slices (3 mm thickness, 25% inter-slice gap), flip angle = 90°, bandwidth = 260 Hz/pixel). For anatomical reference, a high-resolution T1-weighted image was acquired for each subject (T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence, TR = 1900 ms, TE = 2.19 ms, inversion time (TI) = 900 ms, FoV = 256x240 mm², matrix size = 256x240x224, voxel size = 1x1x1 mm³). Between 613 and 857 functional volumes were acquired (M = 716.29, SD = 60.79) during the task. The visual stimuli were displayed on a screen positioned at the rear of the scanner, which the participant could comfortably see via a head coil mounted mirror.

fMRI analyses

Image preprocessing

The functional images were preprocessed and analysed using SPM12 software (Wellcome Department of Imaging Neuroscience, www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (Mathworks, Inc., Sherborn, MA). EPI time series were corrected for motion and distortion using the Realign and Unwarp with default settings functions together with the FieldMap toolbox (implemented in SPM12) (Andersson et al., 2001; Hutton et al., 2002). A mean realigned functional image was then calculated by averaging all the realigned and unwrapped functional scans and the structural T1 image was coregistered to this mean functional image (using a rigid body transformation optimised to maximise the normalised mutual information between the two images). After this processing step, all the functional images were normalized to a pediatric template. We created a pediatric tissue probability map template using the CerebroMatic software (Wilke et al., 2017). We used the unified segmentation parameters as described in Wilke et al. (2017) and built a template based on 147 pediatric structural MRI scans (downloaded from <https://www.medizin.uni-tuebingen.de/kinder/en/research/neuroimaging/software/>) that fitted participant age and gender as well as magnetic field characteristics of our study. The warping parameters were then separately applied to the functional and structural images to produce normalised images of resolution $2 \times 2 \times 2 \text{ mm}^3$ and $1 \times 1 \times 1 \text{ mm}^3$, respectively. Finally, the warped functional images were spatially smoothed with a Gaussian kernel of 6 mm FWHM. ArtRepair was used to remove residual motion from the functional images prior to normalization (Mazaika et al., 2009). Volumes with rapid scan-to-scan movements of greater than 1.5 mm were repaired by interpolation of the two nearest non-repaired scans. Each trial with more than 15% of the total number of volumes replaced was removed from the analyses. The mean number of repaired scans was $2.92\% \pm 3.49\%$. The number of repaired scans did not correlate with any

behavioral measures (all $r < .26$, all $BF_{10} > .85$); we nevertheless included the number of repaired scans as a covariate of no interest in every model conducted at the second-level.

For each participant brain responses were estimated at each voxel, using a general linear model with epoch regressors and event-related regressors. We defined regressors to cover the whole trial (encoding and first 2000ms of the recall phase) since the recall phase seems to be particularly important to reactivate the items in WM (see Attout et al., 2019).

First, in order to contrast filler sequences and Hebb sequences but also to isolate the activations associated with the Hebb repetition learning effect, we defined two regressors for each sequence type, filler sequences and Hebb sequences, a first regressor covering the beginning of the repetitions (1st half) and the other, the end of the repetitions (2nd half). On this basis, four linear contrasts were obtained. The resulting contrast images were then entered in second-level analyses, corresponding to random effects models: $y = b_1x_1 + b_2x_2 + b_3x_3 + b_4x_4 + e$ (1st half Hebb + 2nd half Hebb + 1st half filler + 2nd half filler + error).

Second, for each subject, a parametric design was defined in order to assess Hebb repetition learning for the Hebb sequences in the most sensitive manner. This parametric regressor ranged from the onset of each trial until 2000 ms after the end of the presentation of the last word of each sequence and was combined with a learning rate covariate (parametric modulators in SPM) (see also Kalm et al., 2013). The learning rate covariate was determined by computing Levenshtein distances between the presented sequence and the participant's recall obtained for each successive syllables. The Levenshtein distance is the smallest number of edit operations (insertion, deletion, or substitution of a single character) that are necessary to modify one string to obtain another string, the value of 0 corresponding to two identical sequences (Levenshtein, 1966). We then correlated the trial-by-trial Levenshtein distances with the BOLD signal response amplitude in a given brain region. T-contrasts of parameter

estimates from the single-subject models were entered in second-level analyses, corresponding to random-effects models with one-sample t tests.

For each model, the design matrix also included the realignment parameters to account for any residual movement-related effect. A high-pass filter was implemented using a cutoff period of 128 seconds in order to remove the low-frequency drifts from the time series. Serial autocorrelations were estimated with a restricted maximum likelihood algorithm with an autoregressive model of order 1 (+ white noise). Statistical inferences were performed at the cluster level at $p < .05$, with familywise error (FWE) corrections for multiple comparisons across the entire brain volume; a cluster-forming threshold of $p < .001$ uncorrected was used in order to minimize the likelihood of false positives (Eklund et al., 2016). For the ROI analyses, the threshold was defined at $p < .05$ with small volume corrections based on Gaussian random field theory.

ROI Analysis

We extracted ROIs using the anatomical WFU PickAtlas Toolbox (Wake Forrest University 312 PickAtlas, <http://fmri.wfubmc.edu/cms/software>). As the Hebb repetition learning paradigm is based on an immediate serial recall task that at its root involves the maintenance and recall of serial order information in WM, we first selected several ROIs considered to support general task performance. These ROIs were based on functional activity foci that had been reported to be involved in verbal serial order WM and more generally WM tasks in children (Attout et al. 2019; Siffredi et al., 2017). We created a parietal ROI including the IPS (44, -30, 48; -42, -30, 44) and the postcentral gyrus [50, -20, 50; -44, -26, 50]. We also considered a frontal ROI including the bilateral superior frontal gyrus [24, 16, 56; -22, 5, 55], the bilateral middle frontal gyrus [46, 36, 22; -44, 24, 32], the bilateral inferior frontal gyrus [42, 12, 22; -54, 6, 18] and the supplementary motor area (SMA) [-3, 8, 54]. For Hebb repetition learning per se, we focused on three functional activity foci that had been shown to

be involved in Hebb repetition learning in adults (Kalm et al., 2013) and/or in implicit sequential learning in children studies (Ghetti et al., 2010; Maril et al., 2010; Urbain et al., 2016). The selected ROIs were the bilateral hippocampus [27,-15, -23; -28, -14, -19; -30, -18, -28; -28, -12, -19], the bilateral insula [32, 24, 0; -30, 28, 8], the left cingulate [-16, 36, 24] and the right caudate [12, 4, 16]. The sphere generated via the WFU PickAtlas was of 10 mm radius.

Age related analyses

To explore the developmental trajectory of the Hebb repetition learning effect, we first conducted regression analyses between age and neural activity for each measure of the Hebb repetition learning effect (2nd half of the Hebb sequences and the learning rate parametric regressor) (see Results section for further details). Moreover, given the uneven distribution of age across participants, we also explored age effects by contrasting the children from 6 to 7 versus those from 10 to 12 years old, leading to two distinct age groups with N=15 for the younger group and N=15 for the older group. This analysis may therefore have been biased by the uneven distribution of age across the entire sample.

Correlational analyses with reading ability

A further analysis examined correlations between behavioral/neural measures of Hebb repetition learning and reading ability. We regressed behavioral results of the reading tasks (response accuracy of nonword reading, regular and irregular word reading) on neural activity linked to the Hebb repetition learning effect (2nd half of the Hebb sequences and the learning rate parametric regressor).

Bayesian analyses

For the analysis of the behavioral data and brain-behavior associations based on beta-values, we used a Bayesian model comparison approach. Relative to frequentist statistics, the Bayesian approach has the advantage of relying on a model comparison rationale including

the null model, thus allowing to quantify the strength of evidence associated *with* as well as *against* each model (Dienes, 2011; Morey & Rouder, 2011; Wagenmakers, 2007). The Bayesian approach is thus particularly useful when interpreting null results, which, in the present case, could concern associations between behavioural and neural markers of Hebb learning as well as age. For the main fMRI analyses, we however used the more common frequentist approach in order to allow comparability with the few previous studies that explored the nature and spatial extent of the neural substrates of Hebb learning in either adult or children populations.

For interpreting the Bayes factors, indicative guidelines proposed by Jeffreys (1961) were used: $BF < 1$ = no evidence, $1 < BF < 3$ = anecdotal evidence, $3 < BF < 10$ = moderate evidence, $10 < BF < 30$ = strong evidence, $30 < BF < 100$ = very strong evidence and $BF > 100$ = extreme/decisive evidence for the presence (or absence) of a given effect. When reporting BFs, BF_{10} indicates evidence in favour of a specific variable/model against the null model, and BF_{01} indicates the reverse evidence. Bayesian analyses were conducted with version 0.9.0.1 of the JASP software package, using default settings for the Cauchy prior distribution (JASP Team, 2017).

RESULTS

Behavioral analyses

First, we ran a 2 (Sequence type: filler vs. Hebb) x 8 (Repetition) Bayesian repeated measures ANOVA on recall performance in the Hebb repetition learning task as a function of sequence type and trial repetition. We observed decisive evidence for both main effects of Sequence type, of Repetition as well as for their interaction (see Table 1 for detailed results). The interaction reflected better performance for later trials, and this specifically for Hebb trials (see Figure 1). These results were confirmed by an analysis of specific effects ($BF_{\text{Inclusion}}$: type = ∞ ; repetition = $9.38E+9$; interaction = 99904).

Moreover, a Bayesian paired t-test on the regression slopes for the two conditions showed, as expected, very strong evidence in favor of a higher regression slope for Hebb as compare to filler lists ($BF_{10}=46.63$). Finally, in order to check that learning was equivalent across the three repeated lists, we conducted a Bayesian repeated measures ANOVA on the regression slopes as a function of type of Hebb lists. We observed moderate evidence *against* an effect of type of Hebb lists ($BF_{01}=5.27$).

<INSERT FIGURE 1 HERE>

<INSERT TABLE 1 HERE>

fMRI analyses of the Hebb repetition effect

A first 2 (Sequence type: Hebb vs. filler) x 2 (Half: 1st half vs. 2nd half) ANOVA explored the neural activity peaks associated with the different sequence types as a function of sequence half. A significant main effect of Half was observed at the left insula ROI's level ($z=3.89$, $k=37$, $p<.05$), with a more significant activation for the 1st than the 2nd half, whatever the kind of sequence type. However, no significant effect of sequence type or interaction was observed. Both filler and Hebb sequences activated a wide network including bilateral postcentral cortices, bilateral inferior parietal cortices, the left superior anterior parietal lobe, the left middle temporal gyrus, the middle and inferior occipital gyri, insula cortices, hippocampal cortices and the posterior and anterior cingulate cortices (see Table S1 and Figure 2). These results are in line with neural activity foci associated with tasks involving the maintenance and recall/retrieval of sequences of verbal information (Attout et al., 2019; Majerus et al., 2007, 2010). Like in previous studies on Hebb repetition learning, no specific neural activity foci were associated with second half versus first half trials (Kalm et al., 2013).

<INSERT FIGURE 2 HERE>

Next, we assessed the neural substrates more specifically associated with Hebb repetition learning using the learning rate parametric regressor. A significant modulation of brain activity was observed as a function of individual differences in learning rate at the level of the left insula and the bilateral hippocampus, as well as in the right inferior frontal cortex, the left cingulate cortex and the right caudate nucleus (see Table 2 and Figure 3).

<INSERT TABLE 2 HERE>

<INSERT FIGURE 3 HERE>

Age effects

First, we examined age effects at the behavioral level, by conducting correlational analyses between age and different measures of the Hebb repetition learning task (2nd half of filler sequences, 2nd half of Hebb sequences and regression slope for Hebb lists). No robust association with age was observed for any of these measures (all $BF_{10} < 1$) (see Table 4). Given the uneven distribution of age across participants, we further examined age effects by contrasting subgroups of younger (<8 years old) and older children (>10 years old), given the uneven distribution of age across participants (see Method section). When running a 2 (type of sequence: Filler vs. Hebb) x 2 (Half: first vs. second) x 2 (young vs. old children) ANOVA, we observed no evidence in favour of a main effect of group ($BF_{Inclusion} = 0.61$) but a moderate evidence in favour of an interaction between group and task ($BF_{10} = 3.57$), the older group of children showing a more significant increase of performance in the Hebb task, relative to the Filler task than the younger group. This suggests that the Hebb repetition learning effect was higher in older children and this independently of their WM performance.

When conducting correlation analyses between age and neural activity foci associated with the Hebb repetition learning task, no voxels survived for any contrasts, 2nd half of filler sequences, 2nd half of Hebb sequences or learning rate parametric regressor.

Finally, given that this analysis may have been biased by the uneven distribution of age across the entire sample, we further examined age effects by contrasting subgroups of young (<8 years old) and older children (>10 years old) with equal sample sizes (N=15) (see Methods section). When running a 2 (2nd half of Hebb sequences vs. 2nd half of filler sequences) x 2 (young vs. old children) ANOVA, we observed a main effect of Group where older children exhibited greater activity at the right insula, the right inferior frontal cortex, the right parietal cortex and the left anterior cingulate cortex area, in line with an age-related increase of the parieto-frontal network associated with serial order WM (Attout et al., 2018); at the same time, age did not interact with sequence type (see Table S2). We also conducted a t-test on neural activity associated with the learning rate parametric regressor as a function of age group and again, no age effect was observed.

Associations with reading ability

The descriptive statistics for reading ability are detailed in Table 3.

<INSERT TABLE 3 HERE>

We examined the association between behavioral measures of Hebb repetition learning and reading abilities (Bayesian partial correlations are showed in Table 4). First, Bayesian correlation analyses showed robust associations between the three reading scores (nonwords and regular words: $r=.74$, $BF_{10}=35.07E+6$; nonwords and irregular words: $r=.62$, $BF_{10}=17.93E+1$; regular words and irregular words: $r=.83$, $BF_{10}=26.56E+10$). We conducted Bayesian partial correlation analyses controlling for age, sex and nonverbal intelligence. For

nonword reading, we observed no evidence in favor of a link with 2nd half of filler or Hebb lists. For regular word reading, we observed anecdotal evidence in favor of a link with the 2nd half of the filler lists but no evidence for a link with the Hebb lists. Finally, for irregular word reading, we observed moderate evidence for a link with both the 2nd half of filler and Hebb lists. Moreover, the evidence for a link with the 2nd half of Hebb lists was still moderate after controlling for the 2nd half of filler list performance ($r=.53$, $BF_{10}=4.07$), demonstrating a robust link between irregular word reading and the Hebb learning. However, with regard to the regression slope for Hebb lists, no link was observed with reading abilities.

<INSERT TABLE 4 HERE>

Next, we explored the relationship between the functional neural substrates for Hebb repetition learning and reading abilities by correlating the different reading scores with neural activity during 2nd half Hebb sequences, 2nd half filler sequences and the learning rate parametric regressor. Nonword reading scores showed no association with the different measures. On the other hand, regular word reading abilities showed a negative association in a slightly more extended left hippocampal cluster ($z=3.84$, $k=33$, $p<.05$), and this as expected for 2nd half Hebb sequences only. Similar results were observed for irregular word reading, with a negative association with a relatively large left hippocampal cluster for 2nd half Hebb sequences ($z=4.73$, $k=108$, $p<.05$), and a smaller left hippocampal cluster for 2nd half filler sequences ($z=4.31$, $k=38$, $p<.05$). In order to examine the specificity of these associations beyond the effect of age, we extracted individual beta values for each of the significant clusters and their sequence condition. We then predicted, using multiple Bayesian regression, the respective beta values by both the reading scores and age. For the left hippocampal clusters which showed a negative association with regular (for 2nd half Hebb sequences) and irregular (for both

sequences) word reading scores, for regular word reading, the association with the 2nd half Hebb betas was still best predicted by a model including only regular word reading score ($BF_{10} = 4.73$; $R^2 = .13$) as compared to a model including in addition age ($BF_{10} = 1.62$; $R^2 = .13$); for the association with irregular word reading scores and beta values in 2nd half Hebb sequences, the same was observed, the best model included the irregular word reading score only ($BF_{10} = 42.08$; $R^2 = .22$) as compared to a model including in addition age ($BF_{10} = 23.03$; $R^2 = .24$) or including only age ($BF_{10} = 0.89$; $R^2 = .06$); for the association with irregular word reading scores and beta values in 2nd half filler sequences, however, the best model included the irregular word reading score and age ($BF_{10} = 14.01$; $R^2 = .23$) as compared to a model including only the irregular word reading score or age alone (model with irregular reading score only: $BF_{10} = 1.35$; $R^2 = .08$; model with age only: $BF_{10} = 0.30$; $R^2 = .00$).

In sum, irregular and regular word reading scores showed a negative association with left hippocampal activity specifically during 2nd half Hebb sequences, and this effect remained after taking into account the age differences within the children sample.

DISCUSSION

This study examined the developmental functional neural substrates associated with Hebb repetition learning and their association with reading abilities in children aged 6 to 12 years. We observed that Hebb repetition learning was associated with modulation of brain activity in the hippocampus, cingulate cortex and inferior frontal cortex, in line with the few studies that have explored this learning mechanism in adults. Importantly, for the age range studied here, no age-related changes were observed, neither in the behavioral markers, nor in the functional neuroanatomy of Hebb repetition learning. At the same time, neural markers of Hebb repetition learning predicted developmental changes in reading abilities, and this specifically for regular and irregular word reading.

A first important finding of this study is that the hippocampal areas that have been shown to support Hebb sequence learning in adults (Kalm et al., 2013) also characterize school aged children, suggesting that the neural substrates of Hebb repetition learning are not substantially different in children and in adults. Indeed, in the study of Kalm et al. (2013) in adults, the authors found a left activation of the posterior hippocampus during a verbal Hebb learning task while we found exactly the same area, posterior hippocampus, but bilaterally. This raises the question of the role of this hippocampal area in Hebb repetition learning. As hippocampal activity has been mainly shown to be involved in episodic learning mechanisms in children and adults (DeMaster & Ghetti, 2013; Maril et al., 2010; Paz-Alonso et al., 2008), this finding could suggest that Hebb repetition learning of verbal sequences also involves an episodic memory component in children although the task is thought to reflect incidental learning. Other elements however speak against this interpretation of results. First, there was no age-related modulation of hippocampal activity in the Hebb learning task and there were no age-related increases in Hebb learning performance either (for the correlation analysis). Hippocampal activity associated with episodic memory is generally characterized by age-related changes, and episodic learning performance increases throughout childhood (Bauer, 2008; Finn et al., 2016; Ofen et al., 2012, 2007). On the other hand, implicit learning and procedural memory are generally considered to be fully developed at an early age (Amso & Davidow, 2012; Finn et al., 2016; Meulemans et al., 1998). The absence of age effects in the present study therefore more strongly supports the dominant involvement of procedural memory in Hebb sequence learning in children. This interpretation is also in line with other behavioral studies demonstrating no difference between children (8 and 12 years old) and adults in Hebb repetition learning performance (Smalle et al. 2018; 2016). Hence, Hebb repetition learning may be largely based on implicit, procedural memory abilities (Guérard et al., 2011; Reber et al., 1991). Note that this interpretation is only valid for the age range being

studied here. Indeed, when we considered two extreme groups in terms of age (<8 years old and >10 years old), we observed higher Hebb repetition learning for the older children group. However, this result needs to be considered with caution since no age effect was observed for any other behavioral or for neuroimaging analyses. Increased Hebb learning performance for the oldest children group may potentially reflect the additional intervention of strategic processes such as grouped rehearsal of portions of the list, further facilitating the learning process as the sequences are fed to the hippocampal learning system in a more structured manner. This type of grouping process is known not to be spontaneously used in children aged 8 years or less (Lehmann & Hasselhorn, 2007; Naus et al., 1977). A more extensive use of chunking strategies during a Hebb learning task has indeed been shown in adults as compared to children (Smalle et al., 2016). Moreover, Thomas et al. (2004) observed age differences in hippocampal areas (parahippocampal and lateral geniculate) in an incidental learning task when comparing a group of 7-to-11-year-old children to a group of adults. A recent study furthermore suggested that the impact of a specific memory system on Hebb learning may vary depending on age by showing that adults may rely to a larger extent on episodic memory processes during incidental verbal learning, but also that disruption of these episodic memory processes via transcranial magnetic stimulation actually improved learning performance (Smalle et al., 2017).

This also raises the critical question of the more specific role of hippocampal activity in Hebb learning if it does not (only) reflect explicit, episodic memory mechanisms. Hsieh et al. (2004) have suggested that the right posterior hippocampus supports the identification of repeated sequences of information, whether explicit or implicit (Hsieh, et al., 2014).

Hippocampal cells have also been assumed to implicitly code the temporal order information of elements and the temporal regularities between them (see Davachi & DuBrow, 2015, for a recent review). Furthermore, Schapiro et al. (2017) recently showed via computational

modelling that the learning episodes and the (implicit) detection of regularities may be handled by separate anatomical parts within the hippocampus (supported respectively by the posterior hippocampus and the anterior hippocampus). Hebb repetition tasks indeed involve both of these components: the detection of within-list regularities (e.g., Majerus & Oberauer, 2020), and the creation of episodes distinguishing between the different Hebb lists. Therefore, it could be possible that both kinds of memory sustain Hebb learning, particularly when a larger number of Hebb lists have to be learnt. In the present study, three different Hebb sequences had to be learnt but in succession, probably minimizing the reliance on episodic markers for each list, as compared to conditions where different lists are learnt simultaneously.

Although we did not observe age-related changes in hippocampal areas associated with Hebb learning, we observed, as expected, age effects in other brain areas associated with general task performance. More specifically, older children (>10 years old) exhibited stronger activity in a fronto-parietal network for both Hebb and filler sequences (e.g. Attout et al., 2019; Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006). This result is likely to reflect the recruitment of WM and attentional processes involved in the encoding, maintenance and recall of the verbal sequences presented during the Hebb learning task, independently of the status (filler versus Hebb) of the sequences. At a secondary level, this study also shows that the age-related increase in fronto-parietal activity observed during WM tasks is not task or modality specific, as the present study used a full immediate serial recall paradigm for auditory-verbal information while previous studies used probe recognition paradigms for auditory-verbal or visuo-verbal material (Attout et al., 2019; Kharitonova et al., 2015; Klingberg et al., 2002; Thomason et al., 2009; van den Bosch et al., 2014). It is also important to highlight that this effect was not observed at a behavioral level. Indeed, we did not observe a link between performance in filler lists and age but given the specific task

design, this is not completely surprising. In this study, we used a Hebb learning task with nonsense syllables furthermore drawn from a highly restricted pool of syllables which could lead to smaller performance differences as a function of age. Previous studies using nonwords (nonsense syllables) in WM tasks observed overall reduced performance as compared to word stimuli and, importantly, smaller age-related performance increases (Gathercole et al., 1999; Hulme et al., 1991, 1995; Roodenrys et al., 1993); performance for nonword list recall also quickly reaches a plateau (see for example Poncelet & Van der Linden, 2003). At the same time, it is interesting to note that despite the lack of an age effect at the behavioral level for the repetition of filler lists, there was such an effect at the neuroimaging level, suggesting that the neural substrates associated with filler list repetition may be more sensitive age effects than the behavioural outcome measures. This situation indicates that brain imaging methods provide useful tools for developmental psychology as they show that neural substrates involved in a specific cognitive function can change with age while there is not (yet) a measurable impact at the level of age-related behavioural changes (see also Ellis & Turk-Browne, 2018).

Another important question addressed in this study was the link between Hebb repetition learning performance and reading abilities in children. Brain-behavior correlations demonstrated a relationship between regular and irregular word reading performance and left hippocampal activity specifically during Hebb learning trials. Importantly, this association was negative, meaning that the children with the best reading performance outside the scanner showed the lowest increase of activity in the left hippocampus during the Hebb learning condition. Hence good readers needed less recruitment of the left hippocampus for learning and/or retrieving Hebb sequences, potentially indicating that their hippocampal learning system shows a better neuronal efficiency. In this context, the correlation observed between lower levels of hippocampal activity and word reading but not nonword reading suggests that

a better neuronal efficiency for Hebb sequence learning supports word but not nonword reading. This is indeed what we would expect given that the retrieval of acquired letter sequences will support reading for regular and irregular words but not nonwords (except if the nonwords are very wordlike which was not the case in the present study). Note that the regression slope for Hebb lists did not correlate with any reading abilities. This measure, used to obtain a behavioral measure similar to the parametric regressor used in the present and a previous fMRI study (Kalm et al., 2013), is not exempt of criticism (Staels & Van den Broeck, 2015) due to participants starting with different initial performance levels. If a participant starts with a reasonably high baseline score on the first presentation of the Hebb list, this measure does not leave much room for improvement over subsequent repetitions. Accordingly, in the majority of developmental studies focusing on the Hebb effect, the ‘list halves’ measure has been used and considered to provide a more precise behavioral estimation of Hebb learning (Archibald & Joanisse, 2013; Gould & Glencross, 1990; Mosse & Jarrod, 2008; Ordonez Magro et al., 2018; Smalle et al., 2018). At the same time, and despite these criticisms, it is interesting to observe that the learning rate measure is nevertheless sufficiently sensitive to highlight the neural mechanisms associated with Hebb learning.

Moreover, our results also support the hypothesis of sequential processing and learning deficits in reading disabled children (Bogaerts et al., 2015; Majerus et al., 2004; Martinez Perez, Majerus, Mahot, et al., 2012; Szmalec et al., 2011). The present study shows that the neural substrates involved in learning of sequential information showed a higher neuronal efficiency in those children presenting the highest reading scores. This is in line with a previous study showing not only a difference between poor readers and typically developing children at hippocampal level during a lexical decision task (with pseudowords) but also showing increased activation in hippocampal regions in poor readers after a morpheme-based

spelling intervention (Gebauer et al., 2012). Finally, a recent study provides an additional perspective on the link between hippocampal activity and reading abilities (Skeide et al., 2018). The authors of this study found that children exhibiting a co-occurrence of low reading and mathematical abilities (without having a formal reading or mathematical learning disability) showed reduced cortical folding of the right parahippocampal gyrus. The authors suggested that co-occurrence of lowered reading and mathematical abilities may be functionally related to mapping difficulties between new symbolic/visual features and phonological representations, as required in the learning of reading and mathematical abilities. This mapping could be supported by associative learning mechanisms in hippocampal regions. This interpretation is not incompatible with our own interpretation considering that hippocampal areas are involved in sequential learning via the learning of associations but between temporally co-occurring events. The interpretations forwarded by Skeide et al. and by ourselves could be considered as specific cases of the more general hypothesis of hippocampal associative learning mechanisms.

In sum, the present fMRI study examined the developmental neural substrates of the Hebb repetition learning effect in school-aged children and their implication in the development of sequential learning abilities such as reading. For the first time, we showed the modulation of hippocampal activity as a function of Hebb repetition learning rate in children. This modulation however was age invariant for the range studied here (6-to-12-years of age). Furthermore, we confirmed the specific link between word reading and Hebb repetition learning at both the behavioral and the neural level, stressing the importance of Hebb repetition learning mechanisms in reading acquisition.

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TABLES

Table 1. Results for the Bayesian repeated measures ANOVA on performance in the in-scanner task

Models	P(M)	P(M/data)	BFM	BF10	Error %
Sequence type	0.2	7.10E-11	2.84E-10	9.43E+14	1.04
Repetition	0.2	4.53E-21	1.811E-20	60094.159	0.36
Sequence type + Repetition	0.2	4.0 E-5	1.60E-4	5313E+20	1.14
Sequence type + Repetition + Sequence type * Repetition	0.2	1	99903.69	1.327E+25	1.41

Table 2. Brain activity peaks for the learning rate parametric regressor of the Hebb sequences. If not otherwise stated, all regions are significant at $p < .05$, corrected for whole brain volume.

Anatomical region	No. voxels	Left/ right	x	y	z	BA area	SPM Z - value
Learning rate parametric regressor							
Hippocampus	29	B	-36	-26	-10	20	4.25*
	10		36	-12	-18		4.13*
Cingulate Cortex	2	L	-6	36	24	32	3.30*
Caudate nucleus	8	R	8	8	24	48	3.85*
Insula	89	R	32	24	10	48	3.69*

* $p < .05$, small volume corrections

Table 3. Descriptive data and statistics of demographic and reading measures (N=49).

Tasks	Mean (SD)	Range
Sex	27 Girls – 22 Boys	/
Age (in months)	111.47 (18.89)	78-146
Nonword reading (max.30)	24.67 (3.51)	15-30
Regular word reading (max.30)	27.81 (3.54)	13-30
Irregular word reading (max. 30)	22.08 (7.09)	3-30

Table 4. Results for the Bayesian correlations between different measures of the Hebb repetition learning task, age and the reading tasks at behavioral level.

	2 nd half of the Filler sequences	2 nd half of the Hebb sequences	Regression slope for Hebb lists
Age	$r=.08$ ($BF_{10}=0.21$)	$r=.23$ ($BF_{10}=0.59$)	$r=-.07$ ($BF_{10}=0.20$)
Nonword reading	$r=.09$ ($BF_{10}=0.18$)	$r=.07$ ($BF_{10}=0.17$)	$r=-.26$ ($BF_{10}=0.39$)
Regular word reading	$r=.41$ ($BF_{10}=2.47$)	$r=.24$ ($BF_{10}=0.39$)	$r=-.17$ ($BF_{10}=0.23$)
Irregular word reading	$r=.54$ ($BF_{10}=3.56$)	$r=.54$ ($BF_{10}=4.53$)	$r=-.11$ ($BF_{10}=0.14$)

FIGURE LEGENDS

Figure 1. Mean proportion of items correctly recalled (with standard errors) for Hebb and filler sequences as a function of trial repetition and regression slopes for each kind of lists.

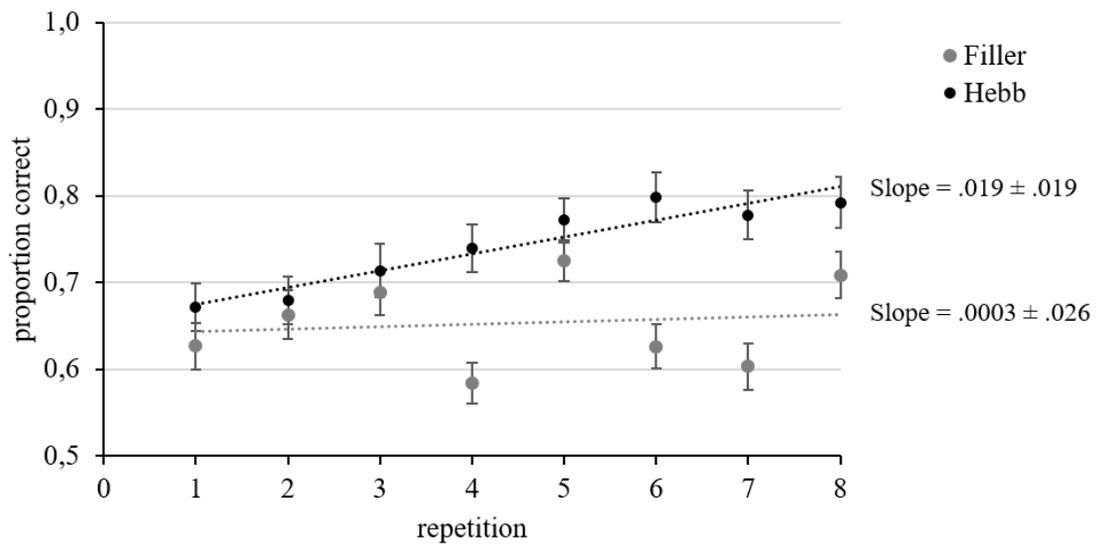


Figure 2. Activity foci for the filler and Hebb conditions. All activity foci displayed here are significant at $p < .001$ (uncorrected) and are mapped onto an inflated brain template using caret 5.64 with the PALS-B12 atlas (Van Essen et al., 2001).

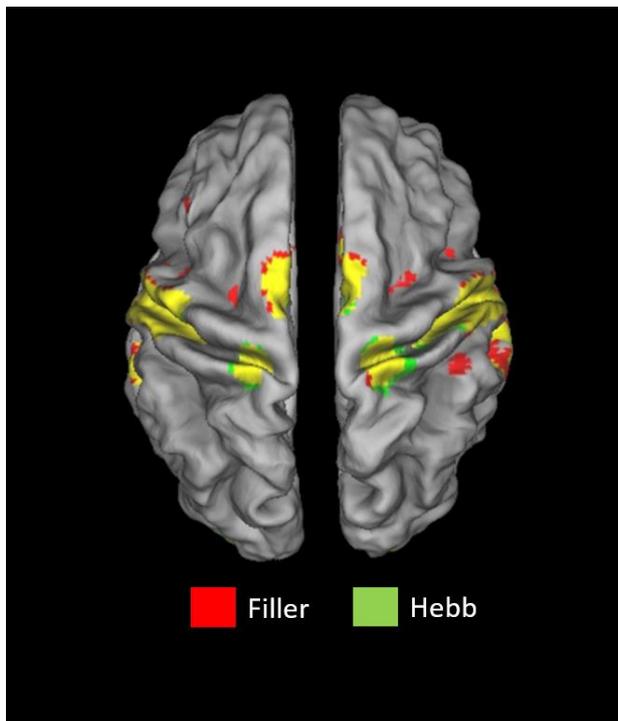
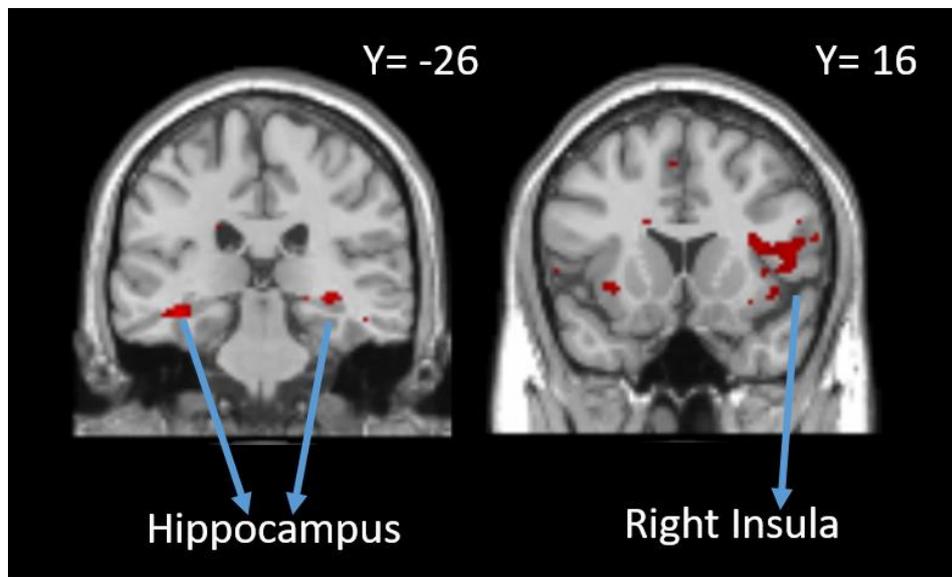


Figure 3. Activity foci for associated with the learning rate parametric regressor. All activity foci displayed here are significant at $p < .001$ (uncorrected).



SUPPORTING INFORMATION

Table S1. Brain activity peaks for the immediate serial recall task, as a function of encoding and retrieval. If not otherwise stated, all regions are significant at $p < .05$, corrected for whole brain volume.

Anatomical region	No. voxels	Left/ right	x	y	z	BA area	SPM Z -value
Hebb repetition task – global activations							
Superior frontal gyrus	23	L	-12	26	66	8	7.29
Superior frontal gyrus	87		-18	56	38	9	6.25
Middle frontal gyrus	25	B	-40	12	26	46	4.25*
Middle orbital frontal gyrus	896	B	-42	50	-4	46	>7.80
	303		36	38	34		7.03*
Inferior frontal gyrus	334	B	-44	-4	16	48	>7.80
	109		46	-4	14	48	6.70
	27		42	20	10		5.80*
Inferior orbital frontal gyrus	62		-40	22	-14	38	7.26
Insula	281	B	-30	18	8	48	>7.80*
	309		32	16	10		>7.80
Postcentral gyrus	23693	B	-44	-16	40	3	>7.80
			46	-12	40		>7.80
Paracentral lobule	691	L	-18	-28	66	4	>7.80
Precentral gyrus	156		-38	-26	68	4	5.96
Intraparietal sulcus	116	L	-38	-38	40	40	5.98
	711	R	42	-36	54		4.51*
Middle temporal gyrus	15444	L	-52	-24	-10	20	>7.80
Occipital inferior	171	L	-26	-96	-10	18	7.36
Caudate nucleus	663		-4	16	14		>7.80
Caudate nucleus	179	R	18	4	12	48	>7.80*
Anterior cingulum cortex	5316		-2	32	4	25	>7.80
Posterior Cingulum cortex	128	R	4	-36	22	26	7.61
Cingulate cortex	268	L	-24	32	26	48	7.74*
Hippocampus	47	B	-38	-4	-20	48	7.11
	63		34	-18	-22	20	>7.80

Lingual	261	R	26	-94	-6	18	>7.80
Cerebellum 6	17		40	-56	-22		6.11

* $p < .05$, small volume corrections

Table S2. Activation peaks for the immediate serial recall task, as a function of two age groups. If not otherwise stated, all regions are significant at $p < .05$, corrected for whole brain volume.

Anatomical region	No. voxels	Left/ right	x	y	z	BA area	SPM Z -value
Older – younger group							
Parietal gyrus	9	R	48	-14	52	4	3.41*
Inferior Frontal gyrus	28	R	42	12	12		3.81*
Insula	20	R	34	28	-8	48	4.39*
	52	R	34	18	2		3.86*
Cingulate cortex	4	L	-22	36	22	32	3.26*

* $p < .05$, small volume corrections