Connectivity of the hippocampus and Broca's area during acquisition of a novel grammar

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ABSTRACT

Following Opitz and Friederici (2003) suggesting interactions of the hippocampal system and the prefrontal cortex as the neural mechanism underlying novel grammar learning, the present fMRI study investigated functional connectivity of bilateral BA 44/45 and the hippocampus during an artificial grammar learning (AGL) task. Our results, contrary to the previously reported interactions, demonstrated parallel (but separate) contributions of both regions, each with their own interactions, to the process of novel grammar acquisition. The functional connectivity pattern of Broca's area pointed to the importance of coherent activity of left frontal areas around the core language processing region for successful grammar learning. Furthermore, connectivity patterns of left and right hippocampi (predominantly with occipital areas) were found to be a strong predictor of high performance on the task. Finally, increasing functional connectivity over time of both left and right BA 44/45 with the right posterior cingulate cortex and the right temporo-parietal areas points to the importance of multimodal and attentional processes supporting novel grammar acquisition. Moreover, it highlights the right-hemispheric involvement in initial stages of L2 learning. These latter interactions were found to operate irrespective of the task performance, making them an obligatory mechanism accompanying novel grammar learning.

1. Introduction

Acquisition of a new language is a dynamic and multi-layered process. It encompasses various aspects, from developing the lexicon, through mastering the phonology and pronunciation, to acquiring the syntactic and pragmatic competences. Combining linguistic units to form either phonologically, morphologically, or syntactically correct utterances is necessary to achieve proficiency in a second language (L2). However, particularly in case of adult L2 learners, such mastery of the grammatical rules of a language is often burdened by difficulties, and characterised by a great deal of differences between individuals, both in terms of learning rate and the ultimate levels achieved (e.g., Abrahamsson and Hyltenstam, 2009; Antoniou et al., 2016). Investigating the neural aspects of the process of novel grammar acquisition could help in understanding the different learning paths, and provide insights enabling proper training methodologies.

Research into the neural architecture behind grammar acquisition often employs highly controllable paradigms modelling an isolated aspect of language learning. The so-called *artificial grammar learning* (AGL) paradigms (Reber, 1967) can, for example, offer a view on the neurobiological mechanisms of syntax acquisition in real time, without the interference of semantics, phonology or pragmatics, and warrant strict control over prior exposure (cf. e.g., Petersson et al., 2012; Petersson and Hagoort, 2012).

In this line of research, Opitz and Friederici (2003) investigated how the brain modulates the initial stages of acquisition of a new artificial grammar. In a functional magnetic resonance (fMRI) experiment, they employed an AGL paradigm consisting of a number of vocabulary items forming different word categories, combined in ways following rules found in many natural languages. Participants in the study learned this artificial grammar over the course of several learning and test phases. During learning, they were presented with correct sentences formed on the basis of the grammar and were instructed to extract the underlying rules. The test phases consisted of presentation of both grammatical and ungrammatical sentences and participants were asked to assess their grammaticality. The accuracy of these grammaticality judgements served

as an indication of the learning progress. Over the course of learning, Opitz and Friederici (2003) found decreasing activity of the left hippocampus; later stages were coupled with increased activation of Broca's area (left inferior frontal gyrus, left IFG). The authors interpreted these results as supporting the importance for hippocampal–prefrontal interactions during acquisition of language-like rules and suggested that a transition of the roles of the different brain structures critically underlies the process of novel grammar learning. In particular, they argued that hippocampal involvement supporting general, similarity-based learning at the outset of grammar acquisition, with time shifts to the processing system specialised for language localised in the left ventrolateral prefrontal cortex. This process is accompanied by increasing proficiency in the novel grammar, which ultimately results in permanent cortical representations independent of the hippocampal contributions.

As a corollary to this proposal, several studies have provided evidence for contributions of two learning systems to AGL, as well as identified the underlying neural systems. Experiment reported by Opitz and Friederici (2004) tapped directly into the neural signatures of the two learning systems: similarity-based and rule-based learning, during AGL and established that they are supported by the left hippocampal system, and the left ventral premotor cortex respectively. Hauser et al. (2012) extended the study by accounting for individual differences in performance on both rule types and showed that development of similarity knowledge during an AGL task depended on the hippocampus and the right IFG, while activity of the left ventral premotor cortex was related to rule processing. On the other hand, however, Musso et al. (2003) proposed Broca's area to be involved in the acquisition of language rules, and its right-hemisphere homologue to underlie rule acquisition more generally. The role of the right Brodmann's area (BA) 44/45 therefore seems to deserve more elaboration in the context of grammar learning. More recently, in a study concentrating on behavioural measurements, Opitz and Hofmann (2015) underscored the hybrid (rule- and similarity-driven) account of AGL, proposing an interaction of the two learning processes and suggesting a direct link between them to be established in future research. To the best of our knowledge, whether, and, if so, how the two learning systems might interact with each other during AGL remains thus far unclear.

On the neural level, interactions between the hippocampal formation and cortical regions are particularly important for memory encoding, consolidation and storage, as put forward by the hippocampal/neocortical interactions theory of memory formation by Morris (2006) (see also Wang and Morris, 2010). Simons and Spiers (2003) suggested interactions between prefrontal cortex and the medial temporal lobe to be vital for long-term memory. In the domain of language, apart from the studies referred to above, contributions of the hippocampal system and the prefrontal cortex to the initial stages of learning a second language (L2) have also been established for the acquisition of new vocabulary items (e.g., Breitenstein et al., 2005; Davis and Gaskell, 2009); intensive L2 acquisition was further shown to induce cortical (in the left IFG, middle frontal gyrus and superior temporal gyrus) and (right) hippocampal structural plasticity (Mårtensson et al., 2012).

However, relative levels of involvement of different brain structures in a task do not *per se* constitute a functional interaction between them. The question arising is whether the hippocampal and prefrontal contributions to novel grammar learning follow from a direct functional link between them, or whether they are independent from each other in terms of functional connectivity. Interactions between brain regions during a cognitive task (such as those proposed by Opitz and Friederici, 2003) can be explored by investigating temporal correlations between the hemodynamic activity of different brain areas obtained with fMRI. In particular, having prior hypotheses about regions involved, insights into whether and how they are coupled together in performing specific functions can be derived from psychophysiological interaction (PPI) analysis (Friston et al., 1997). Such an approach has been successfully applied to, for example, recent investigations into hippocampal – medial prefrontal interactions during memory integration (Schlichting and Preston, 2016). PPI analyses detect regions whose activity levels can be accounted for by the activation pattern of a predefined seed region in conjunction with a specific cognitive or sensory process. The premise of such investigations is that the MRI signal correlations potentially reveal functional connectivity between regions (Rogers et al., 2007), thus providing information on their common involvement in a task. Interregional correlations of hemodynamic signal fluctuations can moreover be dependent on behavioural measures and thus indicative of skill and performance. For example, Hampson et al. (2006) showed that individuals' reading abilities were associated with their functional connectivity between Broca's area and BA 39.

To the best of our knowledge, no study has tapped directly into the possible interactions between frontal and hippocampal structures during a grammar learning task, by investigating their functional connectivity patterns. The goal of the present experiment was therefore to extend the previous research on the learning-related changes in hemodynamic activity during novel grammar acquisition (Opitz and Friederici, 2003), by employing a PPI analysis and focusing on functional coupling of the crucial hubs in language processing and learning, viz. the hippocampus and Broca's area. Based on previous research (Hauser et al., 2012; Mårtensson et al., 2012), our analysis involved both left and right hippocampal regions, together with Broca's area proper and its right-hemisphere homologue. The present study used fMRI to explore the initial stages of L2 acquisition, employing a paradigm adapted from Opitz and Friederici (2003), and a different, complementary analytical approach to the collected data. Specifically, we asked whether there is a direct functional coupling between Broca's area (left BA 44/45) and the hippocampus during the process of acquisition of novel grammar rules. Furthermore, we set out to explore whether the learning-related connectivity strength of the contributing brain systems can predict how well participants acquire the novel grammar. Based on the previous literature (in particular Opitz and Friederici, 2003), we expected a pronounced functional coupling between Broca's area (left BA 44/45) and the hippocampus during the whole task. Decreasing levels of hippocampal connectivity (with regions other than the ventrolateral prefrontal cortex), along with increasing functional links of the prefrontal cortex over the course of the task, should also be present. Since the left prefrontal cortical activity was suggested to arise with increasing proficiency in the novel grammar and with the formation of permanent cortical representations, we expect its connectivity patterns to be predictive of the ultimate performance.

2. Methods

Data from part of this experiment were described in a previous report (Kepinska et al., 2017a) examining data-driven functional connectivity networks during AGL and how language learning predispositions influence the whole-brain connectivity patterns. The two studies differ in the analytical approach, in that in the previous report we used an Independent Component Analysis approach to investigate brain's networks present during novel grammar learning, whereas here we use a PPI approach to investigate how the hippocampi, Broca's area and its right hemisphere homologue are engaged during the learning experience, and how the connectivity patterns of these predefined ROIs modulate the grammar learning success.

2.1. Participants

Forty-two participants took part in the study. Two data-sets had to be discarded due to technical issues. The remaining 40 participants (10 male) were all right-handed native-speakers of Dutch and with normal or corrected-to-normal vision. They were 19–43 years of age (M = 23.33).

The Medical Ethical Committee of the Leiden University Medical Centre (LUMC) (Leiden, the Netherlands) approved the protocol of the MRI experiment; behavioural testing was also conducted according to the Ethics Code of the Faculty of Humanities at Leiden University.

Participants gave written informed consent prior to the experiment and were remunerated for their time.

2.2. Stimuli and design

The stimulus material was an adapted version of the materials used in Opitz and Friederici (2003), i.e. the BROCANTO AGL paradigm (see Section 1 above). In short, the task consisted of three alternating learning and test phases in which grammatical (learning phases), and grammatical and ungrammatical (test phases) sentences were presented. Six days after the scanning, participants performed a delayed transfer test. For a full description of the design see our previous reports (Kepinska et al., 2017a, 2017b). As in the case of Kepinska et al. (2017a), the present experiment focused on the consecutive learning phases of the AGL task. Fig. 1 contains two example trials from the learning phase.

2.3. Neuroimaging data acquisition and pre-processing

For a description of neuroimaging data acquisition parameters and pre-processing steps see Kepinska et al. (2017a).

2.4. Data analysis

2.4.1. Behavioural data
The behavioural performance data gathered in the three test phases of the AGL task performed in the MRI scanner served as an indication of learning progress, and the delayed transfer test scores as an indication of the retention of the acquired rules and the degree of grammar learning success. For the analysis, the individual hit- and false-alarm rates for each participant were first transformed into d' scores in order to account for response bias (Macmillan and Creelman, 2005). Following previous studies employing similar experimental designs (Brod and Opitz, 2012; Friederici et al., 2002; Hauser et al., 2012; Opitz et al., 2011; Opitz and Friederici, 2007, 2004, 2003), the d' scores were then analysed with a repeated measures ANOVA (alpha level = 0.05) with learning phase (first phase, second phase, last phase, and transfer test) as a within-subject factor. The analysis was performed in SPSS version 22 (IBM SPSS, 2012). Mauchley's test showed violations of sphericity against the factor phase, $\chi^2(5) = 27.310$, $p < 0.001$, therefore Greenhouse-Geisser correction for non-sphericity was applied ($\varepsilon = 0.730$).

2.4.2. First-level analysis of imaging data
We conducted a PPI analysis to examine the functional interaction between specific ROIs (seed ROIs) and the rest of the brain. Four seed ROIs were defined anatomically. Masks of left BA 44/45 (Broca's area) and right BA 44/45 were defined using the Jülich Histological Atlas, as implemented within FSLVIEW, part of FSL (www.fmrib.ox.ac.uk/fsl). The probabilistic maps of BA 44 and BA 45 in each hemisphere were thresholded at 50%, summed and binarised (cf. Flöel et al., 2009). Masks of left and right hippocampus were defined on the basis of the Harvard-Oxford Subcortical Structural Atlas as implemented within FSLVIEW, part of FSL (www.fmrib.ox.ac.uk/fsl). Again, the probabilistic maps of the left and right hippocampus were thresholded at 50% and binarised.

Each ROI was projected on the pre-processed functional images (three

data sets per participant). The time series of BOLD activity was extracted using *fslmeants* utility by averaging across all voxels within each ROI, for each individual data set. The PPI analysis was conducted for every ROI separately using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The design matrix of the first-level statistical analysis comprised of three regressors: the first two were the psychological variable (task design) convolved with a double gamma hemodynamic response function, and the physiological variable (the time-course of the seed ROI); the interaction between the physiological and psychological variables (PPI) was the third regressor. Brain regions showing significant PPI effects were determined by testing for a positive slope of the PPI regressor. Time-series statistical analysis was carried out using FILM (Woolrich et al., 2001).

2.4.3. Subject-level analysis of imaging data
Individual contrast images (corresponding to the three learning phases of the AGL task performed during the MRI) were entered into the subject-level analysis. Two separate subject-level analyses were performed: in the first, mean functional connectivity maps of the three phases of the task per subject were calculated; in the second analysis, we tested for significant linear increases and decreases in functional connectivity over the course of the task. In both cases, data were processed with FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The three phases of the experiment were not enough for a mixed effects model, hence a fixed effects model was used, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004). Again, both subject-level analyses were performed separately for each seed ROI.

2.4.4. Group-level analysis of imaging data
Finally, the contrast images generated on the two subject-level analyses were entered into group-level statistical analyses. Following the subject-level analyses, two separate analyses were performed. In the first the mean, i.e. time-invariant functional connectivity of the four seed ROIs during the whole task was investigated. Additionally, we examined whether the magnitude of functional connectivity during the AGL task predicted individual attainment of the presented grammar rules (operationalized by the transfer test scores).

Data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann et al., 2003; Woolrich, 2008; Woolrich et al., 2004) (cf. Eklund et al., 2016). Pre-threshold masking was applied and a grey matter mask was used to mask out non-grey matter regions. Subsequently, the Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z > 2.3 and a (corrected) cluster significance threshold of $p = 0.05$ (Worsley, 2001), with a Bonferroni correction for the number of investigated ROIs.

The second analysis explored whether the functional connections strengthened or weakened progressively as participants learned the task, and whether the changes in connectivity were coupled with the individual performance. The same analysis steps were taken as in the case of the time-invariant functional connectivity analysis described above, the difference being the subject-level contrast images processed.
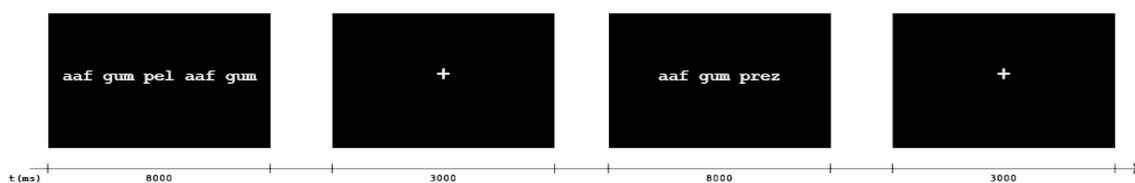

Fig. 1. An example of two trials from the learning phase of the AGL task: the grammatical BROCANTO sentences were presented one by one, for 8 s each, and were followed by a fixation cross (3 s).

3. Results

3.1. Behavioural data

The analysis of the behavioural data revealed that the d′ scores on the AGL task increased over the course of the experiment (see Fig. 2): there was a main effect of learning phase, $F(2.189, 85.386) = 34.898$, $p < 0.001$, $\eta_p^2 = 0.472$, and a significant difference between the mean d′ scores on the first and second phase ($F(1, 39) = 32.417$, $p < 0.001$, $\eta_p^2 = 0.454$), and second and third phase ($F(1, 39) = 22.197$, $p < 0.001$, $\eta_p^2 = 0.363$). The difference between the d′ scores on the third phase and the subsequent transfer test was not significant ($F(1, 39) = 3.196$, $p = 0.082$, $\eta_p^2 = 0.076$).

3.2. PPI results

Two separate analyses were performed. The first, concentrated on mean, i.e. time-invariant functional connectivity of the four seed ROIs during the whole task. Apart from group mean connectivity, modulation of the strength of the functional connections of each ROI by the individual attainment of the presented grammar rules (operationalized by the transfer test scores) was investigated. The results of this analysis are described in Section 3.2.1 and presented in Table 1, Figs. 3 and 4.

The second analysis examined whether the functional connections strengthened or weakened progressively as participants learned the task, and whether the changes in connectivity predicted the individual performance, see Section 3.2.2, Table 2 and Fig. 5.

3.2.1. Time-invariant functional connectivity

During the whole AGL task, functional connectivity for the whole group, irrespective of task performance was found for only one of the four investigated seed ROIs, namely the left BA 44/45. The cluster exhibiting functional connectivity with the left BA 44/45 was localised in the occipital lobe, with a peak in the left occipital pole, see Fig. 3a (in green) and Table 1. Furthermore, the pattern of functional coupling of Broca's area also modulated the task performance, see Fig. 3a (in red), Fig. 4a and Table 1. The higher the ultimate rule knowledge, the more functionally connected the left BA 44/45 was during the task with areas immediately adjacent to it. The peak of this effect was localised in the middle frontal gyrus, and the voxels forming the cluster extended further to the paracingulate, precentral, and the superior frontal gyri.
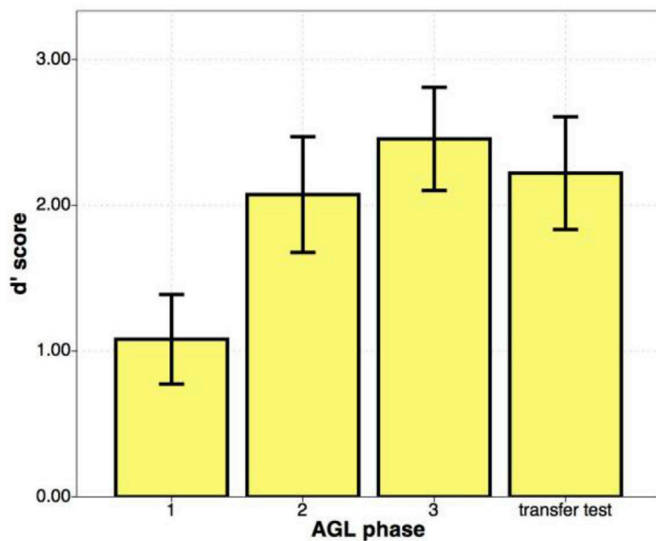

Fig. 2. Performance (d′ scores) across all participants during the three AGL test phases (performed in the scanner) and the subsequent transfer test. Error bars stand for 95% Confidence Intervals.

Table 1
Brain areas exhibiting functional connectivity during the three learning phases of the AGL task with the four ROIs: (a) Left BA 44/45 (Broca's region), (b) Right BA 44/45, (c) Left Hippocampus, (d) Right Hippocampus. Per each ROI, functional connectivity both irrespective of performance (group mean), and modulated by the ultimate task performance are reported. The x, y and z coordinates (in mm) are in MNI space, regions were labelled according to Harvard-Oxford Cortical and Subcortical Structural Atlases and Jülich Histological Atlas (all implemented within FSLVIEW, part of FSL).

Cortical region (peak)	Size (voxels)	p-value	Z max	L/ R	Peak location (mm)		
					X	Y	Z
(a) Seed ROI: Left Broca's region							
Connectivity irrespective of performance (group mean):							
Occipital Pole/ Lateral Occipital Cortex, superior division	610	$p = 0.005$	4.99	L	−34	−90	8
Performance-related connectivity:							
Middle Frontal Gyrus	1370	$p < 0.001$	4.41	L	−42	14	38
(b) Seed ROI: Right Broca's region							
Connectivity irrespective of performance (group mean):							
–	–	–	–	–	–	–	–
Performance-related connectivity:							
–	–	–	–	–	–	–	–
(c) Seed ROI: Left Hippocampus							
Connectivity irrespective of performance (group mean):							
–	–	–	–	–	–	–	–
Performance-related connectivity:							
Occipital Fusiform Gyrus	1089	$p < 0.001$	4.44	R	16	−90	−16
(d) Seed ROI: Right Hippocampus							
Connectivity irrespective of performance (group mean):							
–	–	–	–	–	–	–	–
Performance-related connectivity:							
Precuneus Cortex/ Cuneal Cortex	1432	$p < 0.001$	3.95	R	14	−68	26
Occipital Fusiform Gyrus	860	$p < 0.001$	3.69	L	−18	−86	−16
Temporal Occipital Fusiform Cortex	698	$p < 0.01$	3.53	L	−32	−58	−20

The strength of functional coupling of both left and right hippocampi was greatest for participants who performed best on the transfer test. The left hippocampal connectivity modulated by the task performance was found in the occipital cortex, with a peak in the contralateral (right) occipital fusiform gyrus, and voxels localised in the left occipital fusiform gyrus, see Fig. 3b, Fig. 4b and Table 1. The right hippocampus exhibited increased functional connectivity with three clusters: (1) the right precuneus/cuneal cortex, extending to the right occipital pole and the lateral occipital cortex; (2) the contralateral (left) occipital fusiform gyrus extending to the right occipital fusiform gyrus, right lateral occipital cortex, and the left lingual gyrus; and (3) the temporal occipital fusiform cortex extending to the cerebellum (left crus I, II and left VI), see Fig. 3c, Fig. 4c and Table 1.

3.2.2. Time-varying functional connectivity

Functional connections of both left and right BA 44/45 strengthened progressively as participants learned the task. These changes in connectivity were not affected by task performance, see Fig. 5 and Table 2. Over the course of the AGL task the left BA 44/45 increased its functional coupling with two clusters: (1) a right parieto-temporal cluster with its peak in the angular gyrus/supramarginal gyrus, encompassing the superior and middle temporal gyri as well; (2) the right posterior cingulate gyrus extending to the left anterior cingulate gyrus and the right precuneus (Fig. 5, in red). The right BA 44/45 exhibited increasing functional connectivity with the following areas: (1) a cluster with a peak in the juxtapositional lobule (supplementary motor cortex) with voxels extending to the left paracingulate gyrus and the right posterior cingulate gyrus; (2) right temporal areas encompassing middle temporal gyrus,

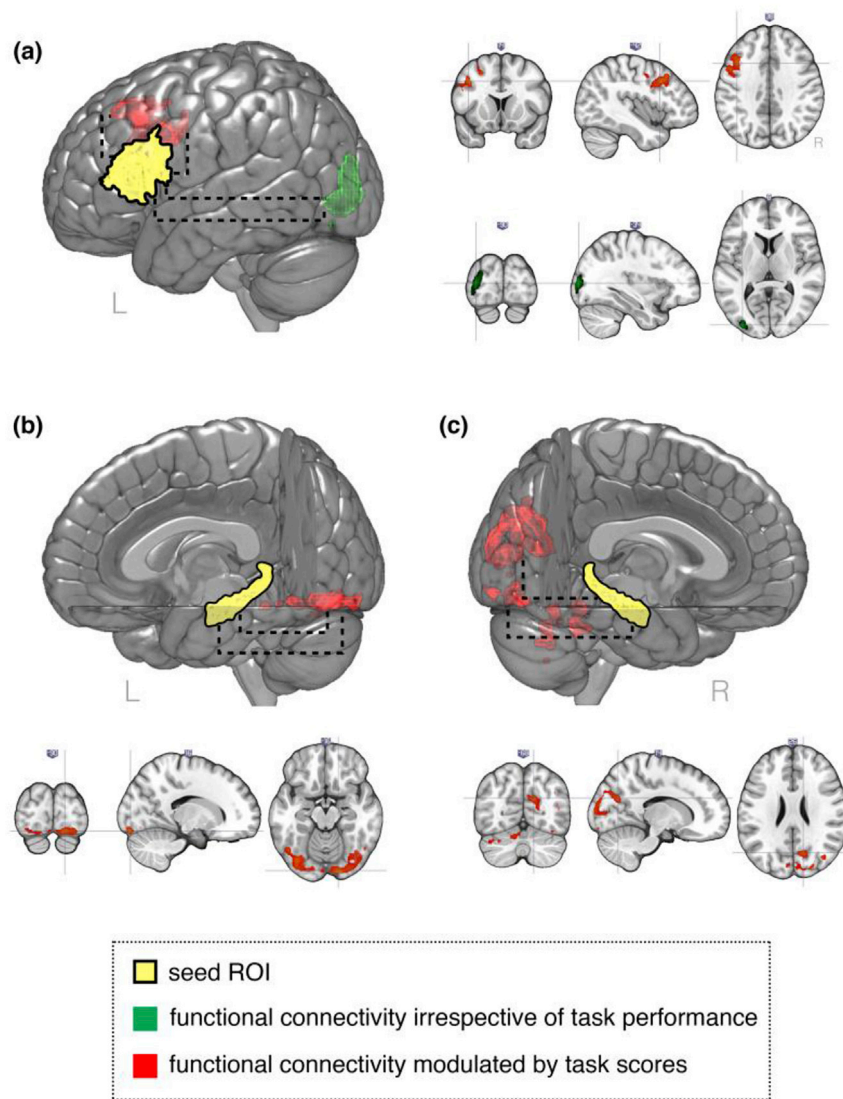## TIME-INVARIANT FUNCTIONAL CONNECTIVITY

Fig. 3. Results of the PPI analysis investigating time-invariant functional connectivity of the four seed ROIs. Represented are the mean connectivity maps (Z (Gaussianised T/F) statistic images) of each seed ROI: (a) Left BA 44/45 (Broca's region), (b) Left Hippocampus, (c) Right Hippocampus; the seed ROI localised in the right BA 44/45 did not yield any significant clusters. Results are displayed at $p < 0.05$, Bonferroni-corrected. In yellow, the seed ROIs are marked; in green results of the contrast testing for mean functional connectivity of the whole group irrespective of task performance; in red, the connectivity modulated by the task performance is shown. Brain activations are displayed using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/).

lateral occipital cortex, planum temporale and supramarginal gyrus (Fig. 5, in green). No time-varying effects on the hippocampal connectivity were found.

4. Discussion

The main goal of the present study was to investigate whether there are direct functional links between the hippocampus, and Broca's area and its right-hemisphere homologue during acquisition of grammar rules. To this end, an fMRI experiment was performed in which participants were exposed to a novel grammar (BROCANTO, Opitz and Friederici, 2003) and were instructed to extract its rules on the basis of example sentences presented one by one over the course of three learning phases. Participants' progress was measured by means of test phases (following each learning phase) in which they were providing grammaticality judgements to both correct and incorrect sentences. Their

sensitivity to the grammatical structure of BROCANTO (operationalised by means of d′ scores) increased over the course of the task and did not significantly decrease until a delayed transfer test performed six days after the initial learning task.

Previous research suggested that over the course of an AGL task hippocampal involvement shifts to brain areas specialised for language processing in Broca's region (Opitz and Friederici, 2003). Following this proposal, we performed a set of analyses on the fMRI data collected during the three successive learning phases of the BROCANTO task, tapping directly into the functional couplings of four pre-defined regions of interest. The premise of our approach was that correlated time-courses of BOLD activity of two or more regions during a cognitive task point to their functional integration in performing the task in question (Friston, 2011; Friston et al., 1997). We thus investigated the functional connectivity patterns of the left and right hippocampi, and left BA 44/45 (Broca's area) and right BA 44/45. We expected Broca's area to be

PERFORMANCE-RELATED FUNCTIONAL CONNECTIVITY

(a) left BA 44/45 seed:

Z statistic in
**middle frontal
gyrus**

(c) right HC seed:

Z statistic in
**precuneous /
cuneal cortex**

Z statistic in
**occipital
fusiform gyrus**

(b) left HC seed:

Z statistic in
**occipital
fusiform gyrus**

Z statistic in
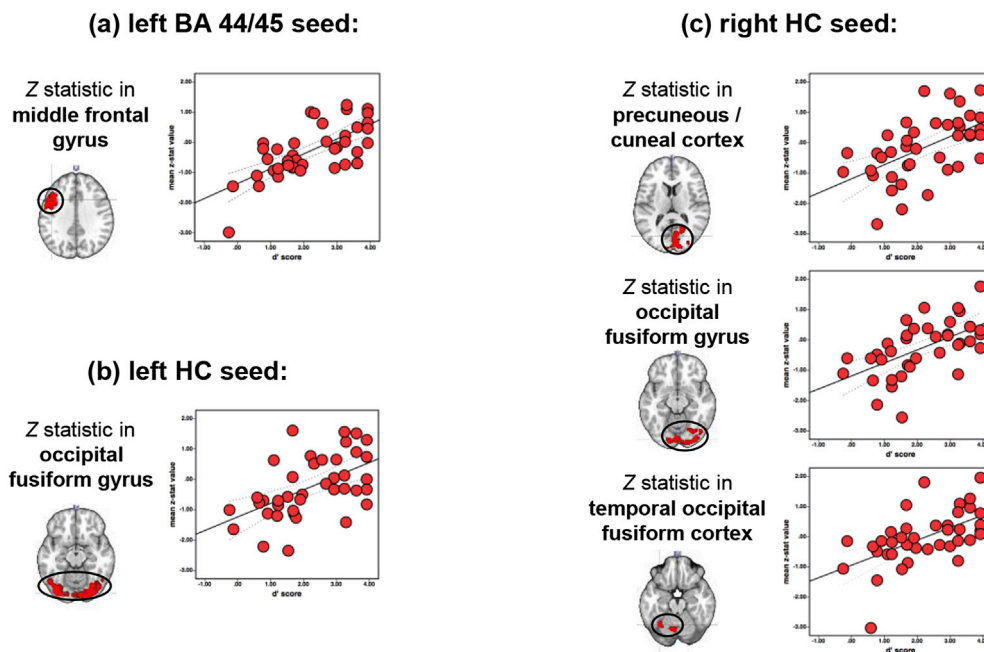**temporal occipital
fusiform cortex**

Fig. 4. Time-invariant functional connectivity modulated by task scores. The scatter plots represent the mean z-score values in relation to the respective d' scores within the clusters determined by the group-level analysis for each seed ROI: (a) Left BA 44/45 (Broca's region), (b) Left Hippocampus, (c) Right Hippocampus. The anatomical descriptions of the clusters refer to clusters' peaks.

functionally coupled with the hippocampus during the learning process. Since L2 learning is a dynamic process, we furthermore examined the changes in functional connectivity of the seed ROIs over time. Here, our prediction was that since hippocampal contributions are most prevalent in the initial stages of learning, and the ventrolateral prefrontal cortex activity arises with increasing proficiency in the novel grammar, the functional connectivity patterns of both should be modulated by time. In particular, we expected a decrease in hippocampal connectivity (with regions other than the prefrontal cortex) over time, and an increase of the connectivity of the left BA 44/45. The delayed transfer test scores were predicted to be modulated by the connectivity patterns of Broca's region.

4.1. Interactions of the hippocampal system and the prefrontal cortex?

The expected interactions, i.e. functional coupling, of the hippocampal system and the prefrontal cortex in learning novel grammar have not been borne out by the present results. Our data suggest that the processes governed by Broca's region and the hippocampus seem to operate in parallel and complement each other, but not in a direct way to be functionally connected with one another. As such these results are in line with the notion of two separate learning systems present during grammar learning: the similarity-based and rule-based learning mechanisms as proposed by Opitz and Friederici (2004), and Hauser et al. (2012). On the basis of our experiment, such a hybrid model accounting for involvement of both surface knowledge and knowledge of grammatical rules in AGL could be extended, by underscoring the autonomous nature of these mechanisms. We note that null effects in neuroimaging analyses should be interpreted with great caution, and that the possibility of a direct functional coupling of the hippocampus and Broca's area during acquisition of novel grammar rules merits further investigations. One possibility of investigating the existence of such direct interactions would be a later stage of learning, past the initial encoding phase (cf. e.g., Tambini et al., 2010). Another way of approaching the question of a functional coupling between Broca's region and the hippocampus during

AGL would be an investigation into interactions between subparts of the regions in question. For example, the hippocampus could be further segmented into sub-regions, following the idea about its functional specialisation along the anterior - posterior axis (Poppenk et al., 2017; Ranganath and Ritchey, 2012). Smaller ROIs might moreover have the advantage of capturing more localised BOLD signal fluctuations, albeit introducing the risk of neglecting the region's activation peak for some subjects, due to inter-individual variations.

4.2. Connectivity of the hippocampus and Broca's area during the whole task

Over the course of the task we observed functional connections of left and right hippocampi, and Broca's region to modulate the grammatical knowledge acquired by the participants. Additionally, Broca's connectivity was found to be present irrespective of the performance: the region was functionally coupled with left occipital areas (see Fig. 3a). Since the stimuli in the current experiment were presented visually, a coupling of the core syntactic processing area (cf. Friederici, 2006; Musso et al., 2003) with regions underlying visual processing seems necessary for attending to the task at hand. Furthermore, such a functional connection most probably follows from structural connectivity of the left inferior frontal areas, in particular in the form of the inferior fronto-occipital fasciculus (IFOF) (Anwander et al., 2007). This fibre track runs ventrally between the frontal regions and the posterior temporal and occipital lobe (Catani et al., 2002) and has been implicated in, among others, such functions as reading (Epelbaum et al., 2008), and semantic processing of language (Duffau et al., 2014; Wu et al., 2016). Whether and how the IFOF is involved in novel grammar learning deserves additional examination.

The strength of functional connectivity of Broca's area was also correlated with the transfer test scores (see Fig. 4a), thereby confirming our hypothesis concerning its connectivity patterns to be predictive of the ultimate performance. Participants who scored highest on the delayed

Table 2
Brain areas whose functional connectivity progressively changed during the three learning phases of the AGL task with the four ROIs: (a) Left BA 44/45 (Broca's region), (b) Right BA 44/45, (c) Left Hippocampus, (d) Right Hippocampus. The x, y and z coordinates (in mm) are in MNI space, regions were labelled according to Harvard-Oxford Cortical and Subcortical Structural Atlases and Jülich Histological Atlas (all implemented within FSLVIEW, part of FSL).

Cortical region (peak)	Size (voxels)	p-value	Z max	L/ R	Peak location (mm)		
					X	Y	Z
(a) Seed ROI: Left Broca's region							
Increasing connectivity over time:							
Angular Gyrus/ Supramarginal Gyrus, posterior division	2326	$p < 0.001$	5.09	R	56	−48	36
Cingulate Gyrus, posterior division	873	$p < 0.001$	3.95	R	6	−26	38
Decreasing connectivity over time:							
–	–	–	–	–	–	–	–
(b) Seed ROI: Right Broca's region							
Increasing connectivity over time:							
Juxtapositional Lobule Cortex (Supplementary Motor Cortex)	930	$p < 0.001$	4.26	–	0	2	62
Middle Temporal Gyrus	526	$p = 0.01$	3.69	R	56	−58	10
Decreasing connectivity over time:							
–	–	–	–	–	–	–	–
(c) Seed ROI: Left Hippocampus							
Increasing connectivity over time:							
–	–	–	–	–	–	–	–
Decreasing connectivity over time:							
–	–	–	–	–	–	–	–
(d) Seed ROI: Right Hippocampus							
Increasing connectivity over time:							
–	–	–	–	–	–	–	–
Decreasing connectivity over time:							
–	–	–	–	–	–	–	–

transfer test, exhibited the strongest functional coupling of the left BA 44/45 with areas immediately adjacent to it, in the posterior, superior, as well as medial direction (see Fig. 3a). Previous research has provided evidence for the importance of activity of regions bordering on Broca's area to the acquisition of novel grammar rules (e.g., Bahlmann et al., 2008). Moreover, the sites found to be functionally linked with the left BA 44/45 in our study have been previously implicated in executive functions, including working memory (superior frontal gyrus, cf. Du Boisgueheneuc et al., 2006), executive attention (middle frontal gyrus, cf. Andersson et al., 2009), verbal fluency and spatial working memory abilities (paracingulate gyrus, cf. Fornito et al., 2004). The results point to the conclusion that involvement of a broader network surrounding Broca's area in an AGL task is advantageous to the learning process. Such a coherence of activity of left frontal areas extending outside the traditionally defined core linguistic processing region, results in a higher retention of the newly acquired grammar rules. This dense interconnectivity is further in line with investigations into the structural organisation of the region in the form of the frontal aslant tract and short U-shaped fibres connecting adjacent gyri (Catani et al., 2012; Ford et al., 2010; Lemaire et al., 2013). Whether the microstructure of these tracts would reflect the behavioural performance in a similar way as the functional connectivity patterns established in our data do, remains open to further investigations.

Successful learning of the grammatical rules of BROCANTO was further modulated by the functional connectivity patterns during the task of both left and right hippocampi (see Fig. 3b and c, and Fig. 4b and c). Hippocampal interactions with cortical regions seem critical for declarative memory formation, as the region has been proposed to underlie the initial binding of new associations formed from various aspects of an event processed in different neocortical areas (cf. Breitenstein et al., 2005; Eichenbaum and Cohen, 2004). Indeed, functional connectivity of the hippocampus has been shown to drive successful memory formation in previous studies (Gagnepain et al., 2011; Ranganath et al., 2005). Furthermore, the fact that the majority of areas exhibiting a functional connectivity with the hippocampal ROIs were localised in the occipital cortex highlights the role the hippocampus plays in similarity-based
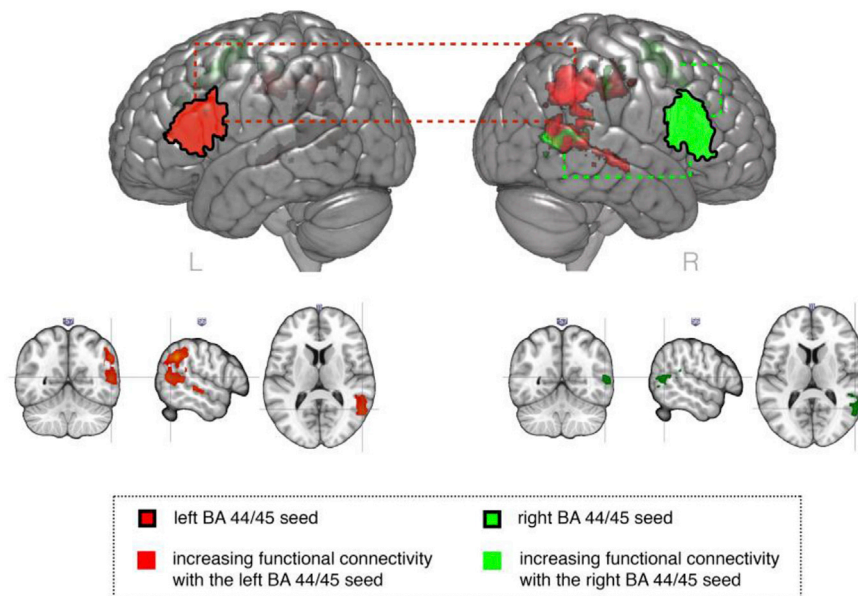

Fig. 5. Results of the analysis investigating changes in functional coupling of the four seed ROIs over time: both left and right areas BA 44/45 increased their functional connectivity over the course of the task. The Z (Gaussianised T/F) statistic images displayed at $p < 0.05$, Bonferroni-corrected. In red, areas whose functional connectivity progressively increased during the three learning phases of the AGL task with the left BA 44/45 (Broca's region) are shown, in green with the right BA 44/45. Brain activations are displayed using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/).

learning mechanisms. Interestingly, the right hippocampus exhibited a pattern of connectivity more dispersed than the left. Apart from with left occipital areas, it was functionally linked with the precuneus, a region implicated in a number of highly integrated tasks, such as mental (visuo-spatial) imagery, episodic memory retrieval, self-processing and consciousness (Cavanna and Trimble, 2006). This finding complements recent results from Sormaz et al. (2017) who showed the left hippocampus to display increased functional connectivity at rest with the left precuneus/cuneus as a result of better semantic memory. Together with our results, these findings might point to a division of labour between left and right hippocampus, and semantic versus syntactic processing. Moreover, hippocampal connectivity modulating the ultimate task performance was found for cerebellar structures, previously put forward to underlie spatial memory (Iglói et al., 2015) and spatial and temporal processing (Yu and Krook-Magnuson, 2015). Since both areas (precuneus and cerebellum) bear significance for visuo-spatial processing, these results seem to further emphasise the importance of the development of surface knowledge for successful learning and memorisation of novel grammar rules.

4.3. Dynamics of functional connectivity during novel grammar learning

Contrary to our expectations, the hippocampal connectivity with regions other than the prefrontal cortex did not decrease over the course of the task. In terms of time-related effects, the consecutive stages of encoding of the new grammatical rules of BROCANTO were found to be associated with increasing functional connectivity of both left and right BA 44/45. The fact that this time effect was not modulated by task performance, might point to the obligatory nature of the involvement of Broca's area and its right-hemisphere homologue to the grammar learning process, extending the idea that syntax processing in the left IFG is automatic and involuntary (Musso et al., 2003). In other words, it seems to be the case that attending to AGL stimuli will over time increase the functional links of the ventrolateral prefrontal cortex bilaterally, no matter the actual level of attainment. Furthermore, the increasing functional connectivity of both our prefrontal regions of interest is in line with the view that the rule-based processing in AGL evolves gradually over time (Opitz and Hofmann, 2015). In addition, given the common topography of the connectivity patterns of both ROIs, it seems to be the case that both areas subserve similar rule-related processing systems.

The areas with which both left and right BA 44/45 progressively strengthened their functional coupling were partly overlapping and were localised in the right hemisphere and in the medial cortex. The sites in which the time-dependent functional links of both left and right BA 44/45 converged was the right posterior cingulate gyrus, along with the right middle temporal gyrus, extending to the angular gyrus, and the right supramarginal gyrus, corresponding to the right temporo-parietal junction (TPJ).

These results point to the importance of both intra- and inter-hemispheric functional connectivity of the prefrontal cortex with the right parieto-temporal areas and the posterior cingulate gyrus during novel grammar learning. The latter has been previously proposed to be involved in controlling attentional focus (Leech and Sharp, 2014), memory consolidation of complex events (Bird et al., 2015), and binding semantic representations on a multi-modal level (Jessen et al., 1999). Our data suggest that the region can also be seen as a site underlying encoding of grammatical rules, be it through its involvement in attentional processes or memory consolidation. The regions in and surrounding the right TPJ are particularly important for multimodal processing. The importance of the inferior parietal lobule for language learning has been previously established by our group (Kepinska et al., 2017b), as well as by others (Barbeau et al., 2016; Goranskaya et al., 2016; Prat et al., 2016). The TPJ itself has been associated with reorienting of attention, theory of mind (Krall et al., 2015) and in more general terms, with updating internal models of the environment (Geng and Vossel, 2013). The importance of attentional and multimodal

processing in acquisition of novel grammar rules seems to be emphasised by the results of the present experiment. Moreover, the findings support claims of Kirchhoff et al. (2000) who postulated that prefrontal modulation of posterior cortical representations is central to encoding. In more general terms, Jung and Haier (2007) have proposed the interactions between frontal and parietal cortices to underpin individual differences in reasoning abilities in humans. Viewed in the context of their Parieto-Frontal Integration Theory of Intelligence, the present results might also suggest increasing reasoning demands over the course of the task.

Finally, it remains to be noted that the patterns of increasing connectivity over time of both left and right BA 44/45 were constrained to the right hemisphere. We argued elsewhere (Kepinska et al., 2017b) that engagement of the right hemisphere in adult L2 learning seems advantageous for the learning process, contrary to the idea that suppression of contralateral activity benefits language performance (Antonenko et al., 2012; Thiel et al., 2006). The findings of the present experiment appear to highlight the supporting role the right hemisphere might play in processes related to language learning, especially in its initial stage.

5. Conclusion

The present study examining the functional connectivity of bilateral BA 44/45 and the hippocampus aimed at exploring the possible interactions between the medial temporal and prefrontal cortex. Our results demonstrated parallel contributions of both regions to the process of novel grammar acquisition, instead of the expected interactions. The functional connectivity pattern of Broca's area underscores the importance of coherent activity of left frontal areas around the core language processing region for successful grammar learning. Furthermore, the encoding of novel linguistic rules driven by the interplay of the visual (occipital lobe) and memory (hippocampus) hubs of the brain seems to be a strong predictor of successful grammar acquisition. Finally, increasing functional connectivity over time of both left and right BA 44/45 with the right posterior cingulate cortex and the right temporo-parietal areas points to the importance of multimodal and attentional processes supporting novel grammar acquisition. Moreover, it highlights the right-hemispheric involvement in initial stages of L2 acquisition. These latter interactions seem to operate irrespective of the task performance, making them an obligatory neural mechanism accompanying novel grammar learning.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2017.09.058.

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