

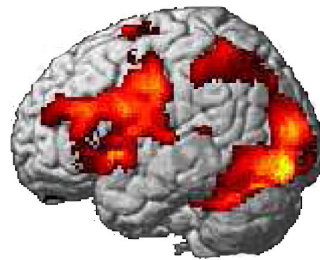


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Inferior parietal activation correlates with verbal learning success in a standardized training paradigm

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Abstract

Word learning is a first fundamental step in language acquisition. Understanding underlying neural correlates during the progress of verbal learning is of interest for improving language therapies for naming disorders. In order to study neural correlates of verbal learning, 14 healthy participants learnt 40 pseudowords each with three belonging semantics in a standardized training program. In three fMRI scans the neural correlates of verbal learning were studied. During the first fMRI scan, accomplished before the pseudoword training started, participants were asked to name 40 black-white drawings plus three associated semantics. The second fMRI scan took place on the first day of the pseudoword training, the last fMRI scan after the end of training. In scan 2 and 3 pseudoword naming and naming of the learnt semantics were requested.

Participants learnt pseudowords successfully during the training. Familiar word naming activated typical neural correlates of speech production as frontal and temporal regions. Interestingly, for pseudoword learning occipital areas and the inferior parietal lobule showed elevated responses next to typical speech production areas. Regarding the change of neural correlates during the learning progress, bilateralized caudate and right cerebellum were more strongly activated during the first acquisition phase. Cerebellar involvement in verbal working memory activity was recently found, while caudate activation could reflect suppression of unwanted responses. When the pseudowords became better consolidated the inferior parietal lobule showed increased activation maybe reflecting phonological storage. Activation of inferior and inferior parietal areas, as well as orbitofrontal areas correlated also with learning success. It will be interesting for future research to compare our findings of neural correlates of verbal learning in healthy subjects with those of aphasic or schizophrenic patients, in order to refine treatment possibilities.

Introduction

Word acquisition is a fundamental step in language acquisition (Veroude, Norris, Shumskaya, Gullberg, & Indefrey, 2010). Word acquisition or access to the mental lexicon can be impaired, e.g. after stroke resulting in aphasia (Breitenstein, et al., 2005), or in schizophrenic patients with formal thought disorder (Barrera, McKenna, & Berrios, 2005). Reacquiring speech is an exhausting challenge for these patients. Thereby, relearning words seems to have priority over relearning syntactical grammar rules, because it facilitates communication in a more profound way. A sufficient mental lexicon is necessary for comprehension, as well as exchange of information (Breitenstein, et al., 2005). In order to facilitate language therapies for patients with naming disorders and adjust therapies to individual needs of different patient groups, it is important to understand biological fundamentals of word learning and reacquisition of speech. In contrast to well-studied neural correlates of word retrieval and speech production, little is known about neural correlates during the course of word acquisition given methodological constraints of long term imaging studies (Meltzer, et al., 2009). Another difficulty in studying the course of natural word acquisition with functional imaging methods is the impossibility for toddlers to stay several minutes motionless in the magnet resonance tomograph, thus leaving only behavioural observations for research of infant word acquisition (Breitenstein, et al., 2005). Recently, several 2nd language studies have been conducted (Cornelissen, et al., 2004; Gronholm, Rinne, Vorobyev, & Laine, 2005), although learning a 2nd language is not identical with mother tongue learning or reacquisition after stroke. Pseudoword trainings have been offered as alternative approach, though still rarely implemented in long trainings and functional imaging. Pseudowords are pronounceable words that do not contain any meaning, but respect phonotactic standards of the specific language. In a recent study a pseudoword pool that resembles an aphasic treatment method was established (Barthel, 2009). We adventured to implement this pseudoword training, which will be described below, into a longitudinal functional imaging study in order to test neural correlates of verbal learning. Before outlining the precise research paradigm I will briefly elucidate the current level of knowledge concerning speech production and verbal learning, and present our hypotheses.

Neural correlates of speech production

Before deepening on verbal learning it seems important to review contemporary research findings on neural correlates of speech production. Levelt, Roelofs, and Meyer, (1999) proposed a modular serial model of speech production. The authors roughly divided the process in four stages: conceptualization, verbalisation, articulation, and constant self-monitoring. During conceptual preparation the content of the utterance is defined keeping in mind prior information about previous discourse, the counterpart, and own intentions. In the following, the speaker has to access the mental lexicon for verbalisation of the information defined before. The mental lexicon consists of lemmata and lexemes. Lemmata are stable representations of syntactical characteristics of the word, while lexemes define the right word form, including its morphological make-up, metrical shape, and segmental make-up. After selecting the right lemmata, phonological encoding of the right lexeme follows. According to Levelt and colleagues (1999) this is a discrete two-step process. Afterwards, the right articulatory gestures have to be initiated for audible expression of the word. During speech articulation the speaker will also listen to his own utterance, simultaneously monitoring what he is saying. This process in total takes not more than 600ms (Inderey, & Levelt, 2004), and stages can merge. Thus, e.g. while the speaker is articulating and monitoring his message, he can already conceptualise the following utterance (Levelt, et al., 1999).

Neural correlates of conceptualization have been explored by usage of categorization tasks (Indefrey, & Levelt, 2004). This has been tested by a go/ no-go event- related potential study, where subjects had to categorize pictures as animate or non-animate. Another approach was using a picture recognition task in order to identify whether the picture corresponded to the previously presented target therewith accessing the lexical concept. This process takes approximately 175ms (Indefrey & Levelt, 2004). On a neuronal level a left lateralized network has been identified, including the inferior frontal gyrus (IFG), the ventral and dorsal medial prefrontal cortex, the posterior inferior parietal lobule (pIPL), the middle temporal gyrus (MTG), the fusiform gyrus, the prahippocampal gyrus, and the posterior cingulate gyrus (Price, 2010). These areas also appear to be activated during speech comprehension tapping the same conceptual system (Price, 2010).

Word retrieval as a second step is tested by tasks that control for articulation, e.g. comparing a word generation task (find, select and produce a word) to reading (producing a word). The right lemmata have to be accessed, which takes

about 75ms. Furthermore form encoding (lexemes) is required, starting with accessing the phonological code and ending when the word is articulated. This can only be calculated by subtraction and lasts approximately 350ms (Indefrey & Levelt, 2004). Regions that are involved in retrieval are the left inferior and middle frontal gyrus, including the pars opercularis (BA 44) and pars triangularis (BA 45) (Fiebach, Friederici, Muller, & von Cramon, 2002; Price, 2010). Further support for the involvement of left IFG activation in word retrieval is derived by Blasi et al. (2002), who identified severe word retrieval problems in patients with left IFG damage.

Thirdly, during articulation the bilateral motor and premotor cortex, supplementary motor area (SMA), cerebellum, supramarginal gyrus, planum temporale (BA 42), STG, anterior insula, and left putamen are activated (Price, 2010). The left anterior insula seems not only to be involved in phonological processing and motor planning, but also during articulation, especially during articulation of pseudowords with novel syllables (Price, 2010; Shuster, 2009; Whitney, et al., 2009). For control and suppression of inappropriate responses the anterior cingulate cortex (ACC) and bilateral nucleus caudatus play an important role (Gronholm, Rinne, Vorobyev, & Laine, 2007; Price, 2010; Whitney, et al., 2009).

Finally, self-monitoring completes the process of speech production. Feedback loops involve auditory, phonological, or somato-sensory routes. For auditory processing the STG, which proved to be also activated in speech articulation, is of relevance (Abel, et al., 2009; Price, 2010). Higher level phonological processing involves the supramarginal gyrus and planum temporale (BA 42) in order to reduce errors, while somato-sensory feedback is derived by left postcentral gyrus and cerebellar activation (Price, 2010). Conspicuously, the same areas are partly involved in several processes, making it impossible to link one area solely to one function.

Last, but not least given our focus on pseudowords it is interesting to note that there is a different activation pattern for pseudoword in comparison to high frequency word retrieval, although differences are still under debate. Fiebach et al. (2002) used a lexical decision task and found stronger activation for pseudowords compared to high frequency words in the nucleus caudatus, thalamus, and left anterior insula, as well as superior pars opercularis (BA 44). Stronger involvement of IFG and insula during pseudoword naming was confirmed by Shuster (2009), who asked participants to repeat pseudowords and real words. Next to activation of IFG and left anterior insula, motor areas and left

superior temporal gyrus (STG) showed increased activation when pseudoword repetition was contrasted with real-word-repetition. Davis, Di Betta, Macdonald, & Gaskell (2009) found similar activation for pseudowords that were learnt with a grapheme monitoring task and tested in the fMRI scan using a pause detection task. On the contrary, familiar words showed stronger activation in the right middle frontal gyrus (MFG) (Shuster, 2009) and left MTG (Fiebach, et al., 2002), as well as supramarginal gyrus, inferior temporal and fusiform gyrus (Davis, et al., 2009). Thus pseudoword naming activated areas known to be involved in articulation, as insula, motor areas and STG. Caudate activity can reflect suppression of unwanted responses (Chein & Schneider, 2000; Gronholm, et al., 2007 ; Whitney, et al., 2009; Price, 2010). Furthermore the IFG seems to be important in pseudoword naming, probably reflecting retrieval processes.

Neural correlates of verbal learning

For successful verbal learning new words have to be encoded correctly, the information has to be stored, and retrieved when demanded. Therefore intact memory processes are of relevance. Atkinson & Shiffrin (1968) suggested a model with three memory systems: a very brief sensory register for visual, auditive and tactile perception, a short-term storage with delimited capacity and dependent on attention, and a long-term storage. For successful learning the information has to be transferred from short-term memory into long-term memory. The longer the information is subvocally rehearsed in the working memory, the higher the chance of entering the long-term memory. Thus in order to facilitate the transition of words into long term storage repeated exposure and facilitation of subvocal rehearsal should be offered within training paradigms. Offering cues in language trainings has been proven to facilitate retrieval and is successfully used in aphasia therapy (Abel, et al. 2003). When learning is successfully assisted, words pass into the long term memory. Long-term memory is divided into implicit and declarative memory. While implicit memory is involved in procedural learning, declarative memory contains knowledge about events (episodic memory) and about facts (semantic memory) (Sturm & Willmes, 1999). The semantic memory is thought to maintain the network of word representations, the mental lexicon (Ullmann, 2004).

A brain structure that is important in episodic and probably also in semantic memory encoding is the hippocampus (Breitenstein, et al., 2005). It is suggested that the hippocampus plays a role in initial binding of multimodal information e.g. associate a picture with word and attributes. This associative

learning contributes to vocabulary acquisition. Associative learning is known to depend strongly on hippocampus activity. The authors found that hippocampus activity during learning predicted overall vocabulary learning success (Breitenstein, et al., 2005). Interestingly, hippocampus activity decreased with increasing vocabulary proficiency, as well as fusiform gyrus activity. Also the fusiform gyrus is thought to be involved in cross modal integration and in phonological processing. Thus after initial binding, activation of neocortical areas, namely the IPL (BA 40), increases. The IPL is involved in phonological storage of the mental lexicon (Breitenstein, et al., 2005). The full integration of words into the mental lexicon needs some time (Gaskell, 2003).

A few studies tried to examine the neuronal processes of verbal learning. Different approaches were used. One study used a second language training (Raboyeau, et al., 2004), while in another study rare objects names of the mother tongue were taught (Gronholm, et al., 2005). Davis et al. (2009) favoured pseudoword learning by means of a phoneme monitoring task and focused on overnight consolidation. Breitenstein and Knecht (2002) developed an implicit pseudoword training, and implemented it into functional imaging analysis (Breitenstein, et al., 2005). Finally I want to present a pseudoword training that is modelling aphasic naming therapy, enabling a direct comparison between healthy subjects and patients (Barthel, 2009). Given the resources that lie in such a comparison, we chose to adopt Barthel's training paradigm in order to implement it in functional imaging.

Starting with second language training for testing word acquisition in adulthood, Raboyeau et al. (2004) taught 10 healthy French participants a 15 minute English computerized training for 5 days a week during 4 consecutive weeks. Graphemic and phonological cues, but no semantic cues, were offered in order to facilitate English learning. Before and after the whole training a PET session was accomplished testing neural correlates of speech production in English and French. Successful naming (French T1 - English T1) activated the left fusiform gyrus, left inferior and middle temporal gyrus (MTG), and left middle frontal gyrus (MFG). In the right hemisphere MTG and STG (BAs 21, 22) and inferior temporal gyrus (BA 20), cerebellum were activated. During English lexical learning ([English T2 - English T1]-[French T2 - FrenchT1]) the ACC, which is important for attentional control processes (Chein, & Schneider, 2000; Gronholm, et al., 2007; Price, 2010), showed elevated responses. Furthermore, the frontal motor cortex BA4/6 involved in speech output, as well as left insular cortex and cerebellum, which are linked to articulatory speech gestures, were activated.

Besides, right parahippocampal temporal gyrus showed increased activation possibly revealing episodic memory activation. Correlations of PET changes and performance measured at PET1 and PET2 revealed activation in right BA 47 and BA 45, hippocampus associated with episodic retrieval, and STG. Furthermore right SMA and left ventral striatum and cerebellum were activated, too, helpful in good pronunciation of foreign words. Correlations of PET changes and performance after PET2 and 2 month follow up indicted activity in left superior temporal sulcus and middle temporal cortex, probably related to semantic storage, while activation in regions linked to episodic memory decreased. Thus, the authors suggest that long delay recall depends on transferring information from episodic to semantic representations. As mentioned above, the difficulty of testing language learning by aid of a second language is grounded in the problematic equalisation of knowledge. All participants had studied English before at school making it impossible to equal the amount of time and effort put into learning English, next to implicit influences of other media as television or music. Furthermore mastering other Germanic languages may have facilitated acquisition of English words.

Grönholm et al. (2005) deployed a modified approach, teaching rare Finish object names for a 4-day period to Finish-speaking subjects. For learning, the participants were asked to read in one condition the name and in another condition the name and the definition of the rare object aloud. The object was presented with power point. Interestingly, there was no difference in learning success between learning names alone or together with semantics, although this could be explained by the fact that the participants reported using self-made semantics on the naming alone condition. During the PET session they should name the object aloud. In line with Raboyeau et al. (2004), Grönholm et al. (2005) found activation in the right cerebellum during naming. Furthermore, left anterior STG (BA 22, BA 38) and the pars opercularis (BA 44) showed an elevated activation pattern for the newly learnt words, probably reflecting retrieval processes. The different activation pattern could be due to the different calculation. Grönholm calculated a simple T1 >/< T2 contrast, while Raboyeau (2004) used an interaction effect to reveal activation in lexical learning and compared it with naming in the mother tongue.

A helpful step in overcoming biases of language pre-exposure is using a set of pseudowords. Davis et al. (2009) implemented a pseudoword paradigm in functional imaging for testing overnight consolidation. The participants learnt half of the words a day before and the other half on the day of the scan, thus making

overnight consolidation comparable to newly learnt words. In order to learn the pseudowords participants got a phoneme-monitoring task with pseudowords. The pseudowords were derived from a base word (e.g. alcohol-alcoholin). In the scan a pause detection task was accomplished, which means that participants had to press a button, when a pause trial was presented. After the scan different tasks were accomplished in order to test the generalization of learning to different tasks. Generalization is a key component that is needed in order to employ knowledge efficiently. Therefore the familiarity of the pseudowords was rated, recognition was tested, and lexical competition was measured by the reaction times of deciding whether the presented word was a no-word or word. Ratings of high familiarity were found for consolidated as well as unconsolidated items. But successful lexical competition was seen only in consolidated items. Lexical competition is an indicator for the integration of words in the mental lexicon, because successful learning is not only marked by recognizing words, but also by distinguishing them from similar sounding competitors. Higher interference means slower reaction times in repeating words, because the word serves as competitor. Here consolidated words (e.g. alcoholin) slowed down the lexical decision (word/non-word) to the base word (e.g. alcohol), indicating integration of the word into the mental lexicon. Also recognition of pseudowords from similar foils (e.g. alcoholid) in a forced choice task was only affected by overnight consolidation. These results stress changes in neural representations after overnight consolidation. For items that were consolidated overnight, areas similar to Grönholm (2005) were activated: the right cerebellum and IFG, bilateral STG, and premotor areas. Items learnt on the same day showed strong hippocampal activation. Moreover, hippocampal activation during initial learning correlated with post-test learning success. The authors suggested a two stage account, with rapid familiarization marked by hippocampal activity, followed by long-time storage in the neocortex (Davis, et al., 2009).

These findings are in concert with Breitenstein et al. (2005). Breitenstein used an implicit learning paradigm though. The participants learnt to associate pseudowords with pictures implicitly with a 10:1 correct, incorrect pairing ratio. The training included 5 training sessions on 1-5 days. Long-term retention was tested 1 and 4 weeks after the implicit training. No feedback was given. Subjects improved significantly confirming that language learning can be modelled in a controlled experimental manner (Breitenstein & Knecht, 2002). As already mentioned above, hippocampus activity increased in the initial learning phase,

and decreased when neocortical regions, as the left inferior parietal lobe (BA 40), became more relevant (Breitenstein, et al., 2005).

Barthel (2009) went a step further by establishing a training paradigm that resembles aphasic language training. Here with he enabled a direct comparison of language acquisition in healthy adults and patients with naming disorders. The pseudowords were learnt in combination with cues, while corrective feedback was given. The cuing method has been proven to be a helpful method for relearning words in aphasic patients by improving word retrieval and lexical access (Abel, et al., 2009; Abel, Schultz, Radermacher, Willmes, & Huber, 2005; Abel, Willmes, & Huber, 2007). But the semantic cues given in Barthel's pseudoword training did not only facilitate learning - at the same time they caused confusion by giving contradicting information, e.g. the picture of a cat was presented with attributes of a dog. This was aimed at imitating mental confusion, which is often seen in aphasic patients (Barthel, 2009). Given the rich potential for future research with aphasic patients, even applicable to other patient group as schizophrenic patients with naming difficulties, we chose to adopt Barthel's pseudowords and his learning paradigm and implemented it into a longitudinal functional imaging study.

Thus going beyond the understanding of word retrieval we are interested in implementing a pseudoword training into functional imaging, allowing a better comparison between patients and healthy controls. Herewith, differences of word acquisition in healthy participants as opposed to patient's word reacquisition can be disclosed and special needs for different patient groups can be divulged in order to refine therapy methods. Thus the aim of our study is to discover areas specific for verbal learning. On a behavioral level we expect to replicate the learning success of Barthel's study. On a functional level we anticipate to find activation in areas typically involved in speech processing, during naming of familiar words (scan 1) as e.g. in the left IFG, STG, and (pre-)motor areas. For pseudoword naming we expect hippocampal activity during learning (Scan 2), which should decrease, while neocortical areas are expected to show higher activation after consolidation (Scan 3). Probably, neural correlates of more consolidated words will resemble those of more familiar words. Furthermore, we were interested in correlations of brain activations and learning success.

Methods

Participants

The sample consisted of 15 healthy adults (4 males; mean age: $M = 26.6$, $SD = 3$; age range, 22-33 years) with an average verbal intelligence, absolving minimal 13 years of education. Because of artefacts in the orbitofrontal cortex participant 3CL had to be discarded, reducing the sample size to $N = 14$. The participants were acquired by mail and bulletins at the University Hospital in Aachen. In a screening interview participants were selected, who were right handed, German native speakers, qualified for fMRI research and without a psychiatric or neurological history. According to these requirements, the Edingburgh Inventory Test tested the right handedness (Oldfield, 1971), the SKID light (Wittchen, Zaudig, & Fydrich, 1997) ruled out psychiatric diseases, and a questionnaire was accomplished in order to check the fMRI exclusion criteria. For the whole screening, German questionnaires were used. Each participant gained an allowance for expenditures after completion of participation.

Procedures

The participants were tested using fMRI three consecutive weeks at the same day (see Table 1). During the first fMRI-measurement, the participants were asked to name objects and also generate three associated semantics (subordinate concept and two attributes). Besides, an anatomical image was measured. Antecedent to the fMRI measurement, a neuropsychological test battery, describing the sample according to their level of intelligence, learning ability, and memory capacity, were conducted and a short written and oral debriefing was given.

In week 2, the fMRI measurement was preceded by three trainings, each followed by a 15 minute break. This time the learnt pseudo-words and newly learned associated semantics were asked in the fMRI scan. The next day, two more trainings were given. The last training followed the day after.

In week 3, again the pseudo-words and learned semantics were requested during the fMRI measurement. Finally, after the 3rd scan a posttest tested whether participants linked the semantics with the pseudoword or with the images. Hence the participant should name the superordinate concept and attributes to the pseudowords, which were read aloud by the tester.

Table 1 Time-line and duration of trainings and scans

| Week | Day | Task | Duration |
|------|-----------|---|----------|
| 1 | Thursday | Neuropsychological tests + Scan 1 | 2 h |
| 2 | Thursday | TRN1 – break – TRN2 – break – TRN3 – break – Scan 2 | 3 h |
| | Wednesday | TRN4 – break – TRN5 | 1 h |
| | Thursday | TRN6 | ¼ h |
| 3 | Tuesday | Scan 3 + post test | 1¼ h |

Material

Neuropsychological tests

The neuropsychological test battery was accomplished previous to the first fMRI scan, consisted of the Mehrfach Wortschatz Test (MWT-B), the Regensburger Wortschatz Test (RWT), the Trail Making Test (TMT-A, TMT-B), and the verbal and nonverbal learning test (VLT, NVLT) and subtests of the Wechsler Memory Scale (WMS-R). The Mehrfach Wortschatz Test determined the crystalline intelligence via lexicon capability (Lehrl, 2005). The Regensburger Wortschatz Test (RWT) served as an indicator for the divergent problem-solving ability measured by the form lexical and semantical word fluency (Aschenbrenner, Tucha, & Lange, 2000). The Trail Making Test (TMT-A, TMT-B) was intended to detect the performance of executive functions in the field of symbol detection and cognitive flexibility (Reitan, 1958; Reitan, 1992). The verbal and nonverbal learning test (VLT, NVLT) revealed the learning ability by recognition (Sturm & Willmes, 1999). Subtests of the Wechsler Memory Scale (WMS-R) were conducted in order to define the efficiency of short-term memory and working memory (Härting, Markowitsch, Neufeld, Calabrese, Deisinger, & Kessler, 2000).

Learning paradigm

The learning paradigm, adopted by (Barthel, 2009), comprised 40 items and associated pseudowords. Standardized black white drawings of Snodgrass and Vanderwart (1980) served as items, which were revised for German usage by Mottaghy (1998). Additionally, the pseudowords were learnt together with phonological and semantical attributes. The phonological attribute was the denomination of the item, while for semantical attributes the superordinate concept and two meaningful features were given. These attributes served as cues in order to facilitate learning, but were also asked to be learned. In order to simulate the mental confusion of aphasia patients the new attributes were derived from an associated item with the same superordinate concept, e.g. the picture of

a cat was combined with attributes of a dog as “bellt” (German for ‘barking’),”in Hütte” (German for ‘in kennel’). One attribute was obligatory (here: barking), the other one was facultative (here: in kennel). The name of the pseudoword had the same number of phonemes as the German name for the related item, e.g. bint for “Hund”, but was further totally unrelated to the German or English original word.

In six trainings these new associations between drawing, pseudoword and new attributes were taught by aid of a cuing method (see Figure1).

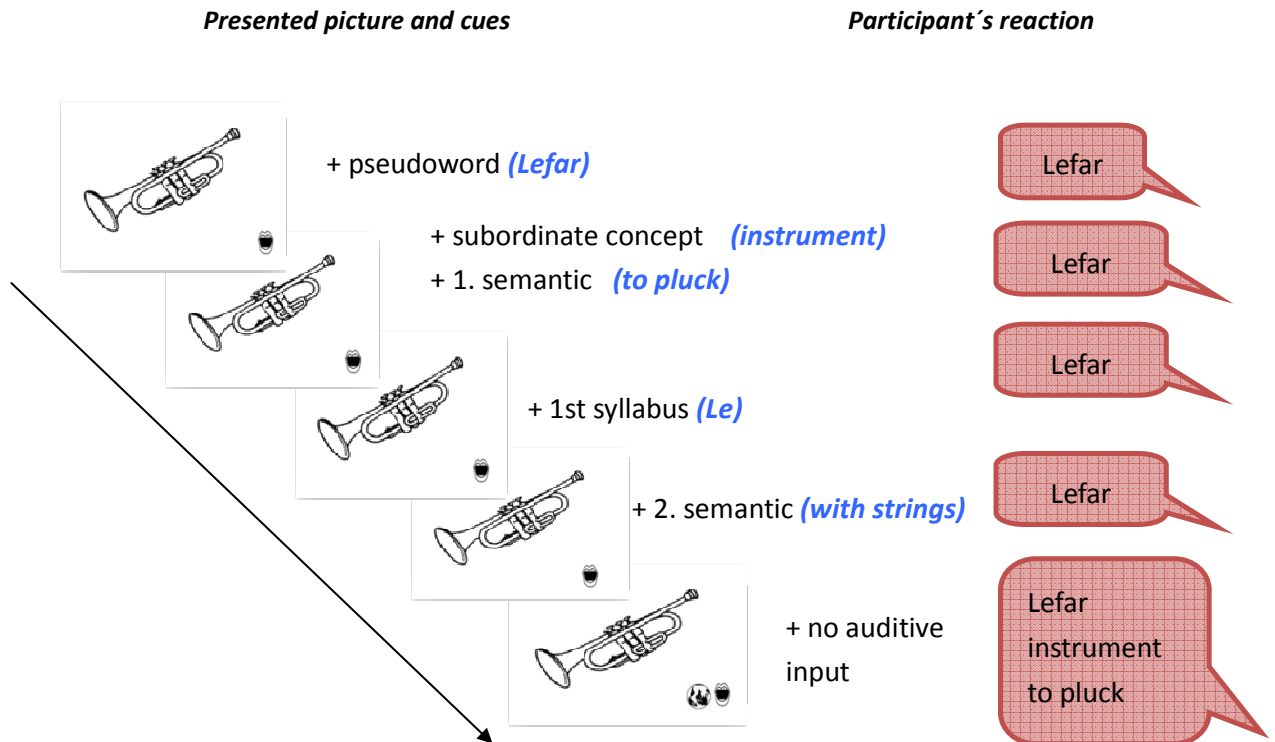


Figure 1 Example of one training trial and the succession of cues, based on Meyer (2012)

In the first training trial the image was followed by the auditive presented pseudoword. Secondly, the subordinate concept and one attribute were given. Then the initial sound of the word was presented. Afterwards the second attribute was introduced. After each trial the participant was asked to name the pseudoword, which was accompanied by corrective feedback. The corrective feedback consisted of a beep tone for a correct response and a repetition of the pseudoword for an incorrect response (including omissions). In the last trial the participant should reproduce all learned information on his own. At this point the corrective feedback was extended by naming all attributes that served as cues additionally to the pseudoword. From the third training on the participant had the chance to name all information after the first presentation of the stimulus. The

learning trials were skipped when the response was correct, while the cues were repeated when the response was incorrect. Herewith we could to test the learning progression. With progression in trainings the number of cues was reduced systematically by leaving out one more cue per training (see Figure 2). Therefore, the duration of the training decreased subsequently from 25 minutes onwards. Overcoming order-effects, the items were presented in a pseudo-randomized order in every training session and in the fMRI scan.

The items were presented in Presentation 14.9 (Neurobehavioral Systems, Inc., Albany, CA, USA), while the pseudowords were auditioned in Adobe® Audition™ 1.5 (2004 Adobe Systems Incorporated, San Jose, CA, USA).

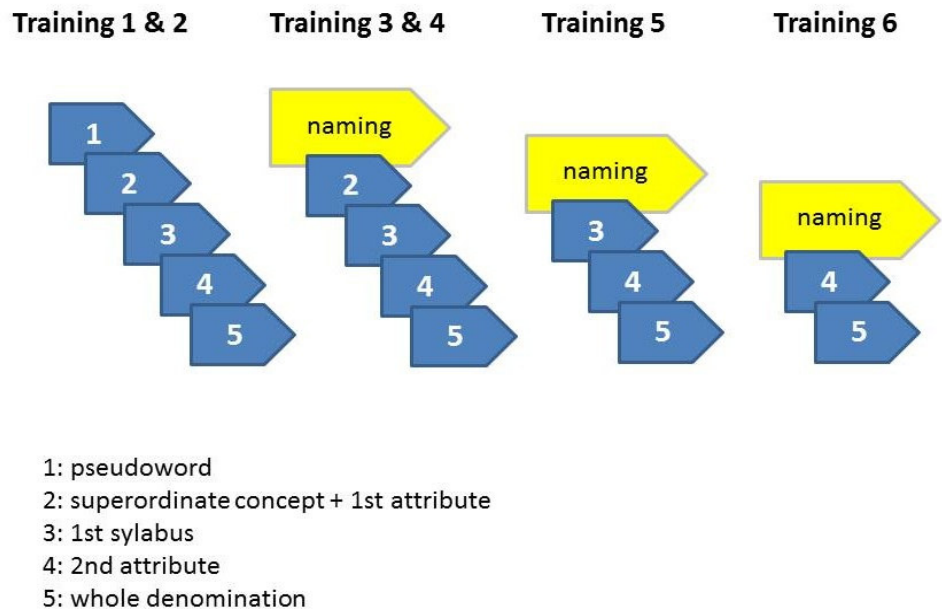


Figure 2. Barthel's training cycle and consequent reduction of cues

Task and design concerning the fMRI measurement

During fMRI measurements participants were asked to name the pseudowords in the first two runs. In the third and fourth run the associated semantics were requested. In case of control stimuli, participants were asked to say "ok". The order of items was presented pseudo-randomized in an event-related design. Each run contained 20 drawings and 5 control images. In total the set of stimuli consisted of 40 objects, which were presented twice, and 20 control stimuli, 5 presented at one run. For the control stimuli images from the item pool were cut into unrecognizable images, by aid of Paint Windows 7 (© 2007 Microsoft Corporation, One Microsoft Way, Redmond, Washington, USA). The images were presented for 10 seconds in run 1 and 2, when only pseudoword

naming was asked, while the duration increased up to 15 seconds in run 3 and 4, when three attributes were demanded. The images were separated by a fixation cross, displayed for 5 seconds. A jitter of +/- 2 seconds was embedded. Furthermore, a fixation cross was presented for four times a run for 10/15 seconds to allow the hemodynamic response to decline. The answers of the participants were recorded with Adobe® Audition™ 1.5 (© 2004 Adobe Systems Incorporated, San Jose, CA, USA). In total the duration of one fMRI measurement with 4 runs was approximately 40 minutes without preparation time, prolonged by additional 10 minutes duration for the anatomical sequence during the first fMRI measurement.

Acquisition of data

For the fMRI measurements the 3T-MRT (3T Siemens Trio MRT System) at the University Hospital was used. In each fMRI measurement 4 functional runs were conducted. The functional images were made by usage of a fast- field-echo (FFE) gradient echo planar imaging (EPI) sequence with a repetition time of 2000 ms, an echoing time of 28 ms, a flip of angel (FA) of 77° and a field of view (FOV) of 224 mm. 32 slices à 3,5mm with an interslice-gap of 0.5 mm were acquired in an interleaved order. 220 pictures were produced in the first 2 runs of pseudoword naming, while 286 pictures were obtained in the 3rd and 4th run of semantic naming. Thus in total 1012 EPI volumes per fMRI measurement were derived. In the first fMRI measurement an anatomical scan was carried out, additionally. A T1 weighted MPRAGE sequence with a repetition time of 9879 ms, an echoing time of 4590 ms, a flip of angel (FA) of 8°, a field of view (FOV) of 256 mm and 176 sagittal slices à 1mm was used for this purpose.

Analysis of behavioural data

In order to evaluate the learning progress, the correct pseudoword denominations were counted from training 3 (TRN3) on for every training and fMRI measurement. Training 1 (TRN1) and 2 (TRN2) were skipped, because no self-employed naming in the beginning was possible. The acquired data were statistically analyzed with IBM SPSS 20.0 using a repeated measurement ANOVA with correct pseudoword naming on these 6 points in time as factor. Subsequently a paired samples t-test specified when a significant learning increase took place. Tests are reported significant Bonferroni corrected at a threshold of $p < 0.003$.

Imaging analysis

The functional imaging data were analyzed with SPM8 (Statistical Parametric Mapping: The Wellcome Trust Centre for Neuroimaging, GB) on a basis of Matlab 7.2 (The MathWorks, Naticks, USA). Preprocessing included slice timing correcting for different acquisition times and realignment correcting for head movements. Furthermore, coregistration with the participants' own anatomy, normalisation into MNI space via the segmentation algorithm, and smoothing with a smoothing kernel of 12 mm³ (FWHM) was accomplished. For first level analysis, a linear model was used to estimate BOLD (blood oxygen level dependent) signal amplitudes during each experimental condition for each participant. Each stimulus was modelled using the onset of stimulus presentation as onset. This onset was convolved with a standard canonical hemodynamic response function as implemented in SPM8. Realignment parameters were included as regressors of no interest. Averaging of the estimated parameter maps for conditions of interest resulted in nine parameter maps for each participant, one for each experimental condition: naming of objects/pseudowords, naming of semantical attributes, and control condition in Scan 1, 2, and 3. Because of our focus on pseudowords, only three parameters were implemented in the group analysis. The conditions were fed into a flexible factorial second level group analysis using an ANOVA (factor: condition; blocking factor: subject). The factor condition encompassed 3 levels: naming objects (Scan 1), naming newly learnt pseudowords (Scan 2), and naming more consolidated pseudowords (Scan 3). The main effect for normal word naming (Scan 1) was calculated, as well as conjoint activation for pseudoword naming (Scan 2 \cap Scan 3). The results were reported as FWE corrected, at a significance level of $p < 0.05$ with a minimal cluster size of 15 voxel. For a closer look at activation changes within the learning progress we compared activation of newly learnt pseudoword naming and better consolidated pseudoword naming in both directions ([Scan2 - Scan 3] and [Scan 3 - Scan2]). Contrasts are reported uncorrected at a threshold of $p < 0.001$, with a minimal cluster size of 15 voxel. Structures were labelled using the anatomy toolbox (Eickhoff, Paus, & Caspers, 2007; Eickhoff, Stephan, & Mohlberg, 2005). Additionally, the wfupick atlas (Maldjian, Laurienti, Burdette, 2004; Maldjian, Larueinti, Burdee, & Kraft, 2003) and a neuro-anatomy atlas (Trepel, 2004) were used.

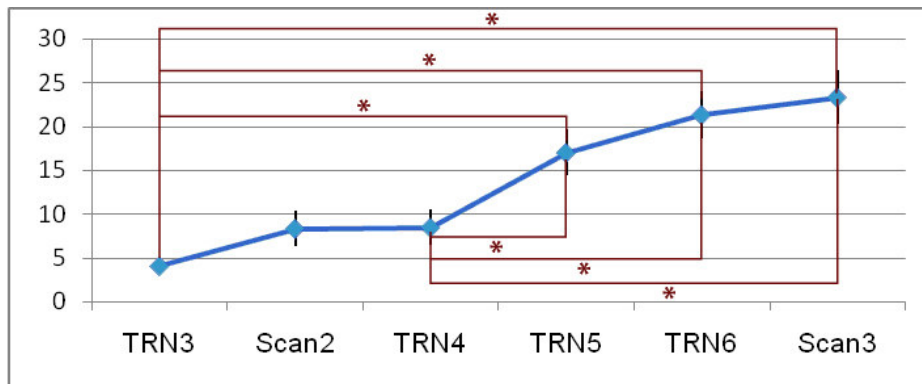
In a covariance analysis we wanted to test how the general naming ability combined with the learning success covaried with brain activation during pseudoword learning. Learning success was calculated by counting the right

pseudoword denominations for scan 2 and 3. For a correct pseudoword naming we gave 3 points, while a 2/3 resemblance with the pseudowords delivered 2 points. Less resemblance was accredited with only 1 point, and a total omission gave no points. For a 2/3 resemblance, 2/3 phonemes should be similar. The points of all items of scan 2 and scan 3 were summed up, telling us how successful the participant had learnt the pseudowords. This score was integrated as covariate in the flexible factorial group analysis, explained above, in order to explain how much variance was explained by learning success.

Results

Behavioural data

Regarding the learning progress, a significant linear increase was evident [$F(2, 27.982) = 19.965$; $p < 0.001$]. A paired samples t-test revealed a significant effect from training 3 to training 5 (TRN3-TRN5: $t(1.953) = -6.622$, $p < 0.003$), to training 6 (TRN3-TRN6: $t(2.269) = -7.611$, $p < 0.003$) and to Scan 3 (TRN3-Scan3: $t(2.787) = -6.914$, $p < 0.003$). Training 4 to training 5 (TRN4-TRN5: $t(4.565) = -7.24$, $p < 0.003$), to training 6 (TRN4-TRN6: $t(1.838) = -6.999$, $p < 0.003$) and Scan 3 (TRN4-Scan3: $t(2.552) = -5.825$, $p < 0.003$) showed also a significant improvement. Participants learnt on average 23.33 pseudowords after 6 trainings.



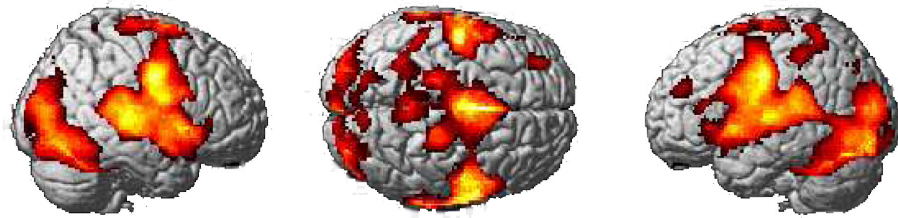
Figur. 3 Progress of correct pseudoword denomination (significant increases are marked with a *)

Functional imaging data

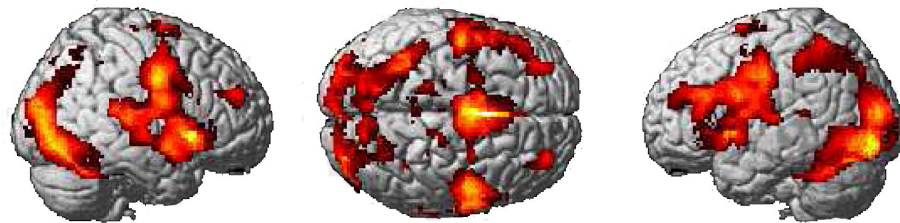
Naming familiar words (Scan 1) involved a large network, encompassing the postcentral gyrus (BA 3b) bilaterally, right precentral gyrus (BA 4a), and left SMA (BA 6), further left middle cingulate cortex (MCC, BA 23), left pars opercularis (BA 44), left fusiform gyrus, and left STG. Also the left middle frontal Gyrus (MFG), was activated.

Conjoint activation during (Scan 2) and after pseudoword learning (Scan 3) activated a big occipital cluster extending from the bilateral lingual gyrus (BA 18) into right calcarine gyrus (BA 17), left inferior occipital gyrus, bilateral fusiform gyrus, left SMA (BA 6) and right MCC. Furthermore activity in the right MFG and right inferior parietal lobule was found.

Naming of words (FWE: $p = 0.05$; $k > 15$)

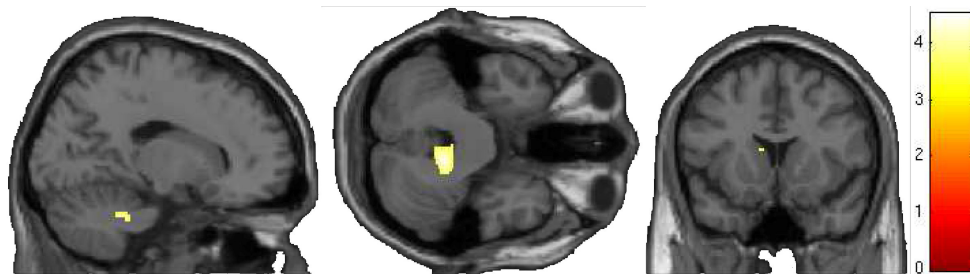


Naming of pseudowords (FWE: $p = 0.05$; $k > 15$)

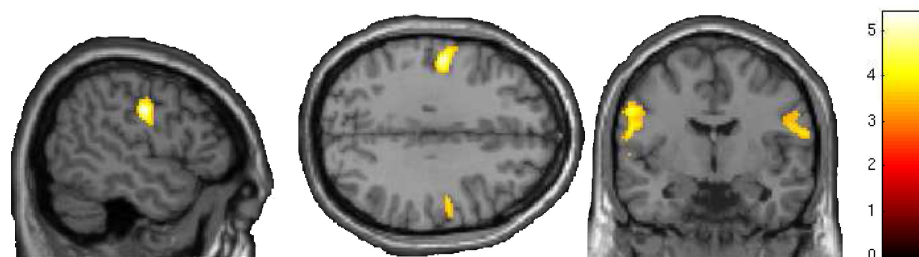


Increased activation during training phase in comparison to consolidation phase was found in the right part of the cerebellum and the bilateral caudate nucleus, while more consolidated pseudoword naming activated the bilateral postcentral gyrus (BA 4p, BA 3b) and mainly left sided STG (BA 22, BA 41), extending into the left pars opercularis (BA 44) and pars triangularis (BA 45).

Learning of pseudowords > Consolidated pseudowords ($p = .001$; $k > 15$)



Consolidated pseudowords > Learning of pseudowords ($p = 0.01$; $k > 15$)



| Contrast | MNI | | | k | t-value | p-value | Side | Region |
|-------------------|-----|-----|-----|-------|---------|---------|------|------------------------|
| | X | Y | Z | | | | | |
| ME_familiar words | -50 | -12 | 34 | 57103 | 15.7 | <0.001 | B | Postcentral Gyrus (3b) |
| | -30 | 46 | 24 | 147 | 6.54 | <0.001 | L | MFG |
| | 4 | -34 | 26 | 84 | 6.3 | <0.001 | R | Cingulate Gyrus (BA23) |
| ME_Pseudowords | -10 | -84 | -8 | 48230 | 7.41 | <0.001 | L | Lingual Gyrus |
| | 32 | 50 | 24 | 236 | 6.72 | <0.001 | R | MFG |
| | 28 | -2 | 56 | 54 | 4.89 | <0.001 | R | MFG |
| | 36 | -46 | 44 | 34 | 5.46 | <0.001 | R | IPL |
| Learning> | 16 | -42 | -34 | 118 | 4.52 | <0.001 | R | Cerebellum |
| Consolidated | 8 | 8 | 16 | 84 | 4.32 | <0.001 | R | Nucleus Caudatus |
| Pseudowords | -8 | 2 | 20 | 65 | 4.16 | <0.001 | L | Nucleus Caudatus |
| Consolidated > | -52 | -10 | 34 | 359 | 5.4 | <0.001 | L | Postcentral Gyrus (3b) |
| Learning | 64 | -4 | 18 | 143 | 4.14 | <0.001 | R | Postcentral Gyrus (4p) |
| Pseudowords | -60 | -12 | 4 | 64 | 3.71 | <0.001 | L | STG |
| | -54 | 6 | -4 | 38 | 3.57 | <0.001 | L | STG (BA 41) |
| | -42 | -32 | 12 | 29 | 3.65 | <0.001 | L | STG (BA 22) |
| | 56 | -2 | -4 | 25 | 3.75 | <0.001 | R | STG (BA 22) |

Table 2. This table includes MNI coordinates of the main peaks of significant cluster, the number of significant voxel (k), the p -values that are FWE-corrected 0.05 ($k > 15$) for the main effects (ME) and not corrected 0.001 ($k > 15$) for the contrasts, the hemisphere (L=left, R=right, and B=bilateral), and the localization name of the main peak activation. Cluster extensions are reported in the text. Abbreviations: MFG=middle frontal gyrus; IPL=inferior parietal lobule; STG=superior temporal gyrus.

In a further covariance analysis, we examined the covariance between learning success and brain activation. We found a wide spread cluster in the first acquisition phase (Scan 2) encompassing left lateralized orbital, superior frontal regions and bilateral middle frontal regions. Right MTG extending into angular gyrus of the IPL also covaried with learning success. Left supramarginal gyrus, superior occipital gyrus and bilateral cuneus (BA 18) were also activated. Besides, the postcentral gyrus (BA2, BA3b) showed elevated responses as well as left anterior and middle cingulate cortex.

When the pseudowords became better consolidated (Scan 3), better learners exhibited more left inferior parietal lobule (IPL) and angular gyrus activation, next to activity in the MCC and right orbitofrontal areas, as the super medial gyrus.

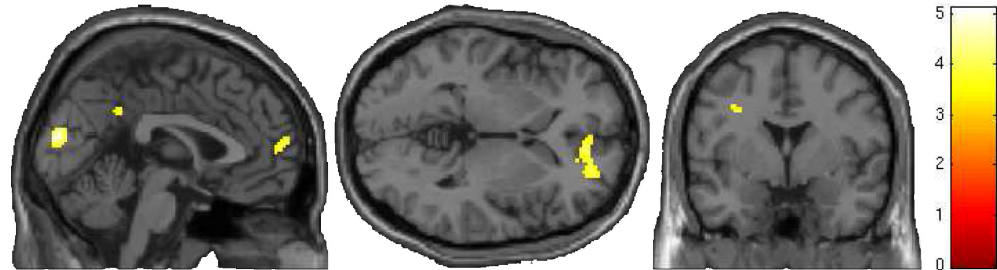
| Contrast | MNI | | | | k | t-value | p-value | Side | Region |
|-------------------|-----|-----|-----|-----|------|---------|---------|-----------------------------|--------|
| | X | Y | Z | | | | | | |
| <i>Pseudoword</i> | 24 | 32 | -10 | 637 | 4.74 | <0.001 | R | Orbitofrontal gyrus (BA 47) | |
| <i>Learning</i> | -2 | -90 | 18 | 318 | 5.11 | <0.001 | B | Cuneus (BA 18) | |
| <i>(Scan2)</i> | 46 | -34 | 54 | 275 | 4.22 | <0.001 | R | Postcentral Gyrus (BA 3b) | |
| | -42 | -44 | 34 | 246 | 4.64 | <0.001 | L | Supramarginal gyrus | |
| | -38 | 16 | 38 | 134 | 3.93 | <0.001 | L | MFG | |
| | 52 | -54 | 20 | 125 | 3.89 | <0.001 | R | MTG | |
| | 22 | 28 | 40 | 92 | 4.37 | <0.001 | R | MFG | |
| | -60 | -8 | -22 | 78 | 3.87 | <0.001 | L | MTG | |
| | | | | | | | | Superior Occipital Gyrus | |
| | -26 | -88 | 24 | 74 | 4.31 | <0.001 | L | (BA 18) | |
| | -36 | 52 | -8 | 55 | 4.31 | <0.001 | L | Middle Orbital Gyrus | |
| | 40 | 8 | 36 | 52 | 4.14 | <0.001 | R | MFG | |
| | -16 | 62 | 14 | 52 | 3.93 | <0.001 | L | SFG | |
| | -2 | -48 | 34 | 52 | 3.76 | <0.001 | L | MCC | |
| | -20 | 22 | 52 | 46 | 4.00 | <0.001 | L | MFG | |
| | -6 | 36 | -8 | 46 | 3.8 | <0.001 | L | ACC | |
| | -42 | -30 | 54 | 32 | 3.86 | <0.001 | L | Postcentral Gyrus (BA3b) | |

| | | | | | | | | |
|---------------------|-----|-----|----|----|------|--------|---|----------------------|
| <i>Consolidated</i> | -62 | -44 | 38 | 61 | 3.82 | <0.001 | L | IPL |
| <i>Pseudowords</i> | -46 | -54 | 30 | 52 | 4.12 | <0.001 | L | Angular Gyrus |
| <i>(Scan 3)</i> | 2 | -46 | 34 | 39 | 3.66 | <0.001 | R | MCC (BA 31) |
| | 4 | 58 | 10 | 32 | 3.63 | <0.001 | R | Medial Frontal Gyrus |
| | 16 | 48 | 2 | 31 | 3.8 | <0.001 | R | Medial Frontal Gyrus |

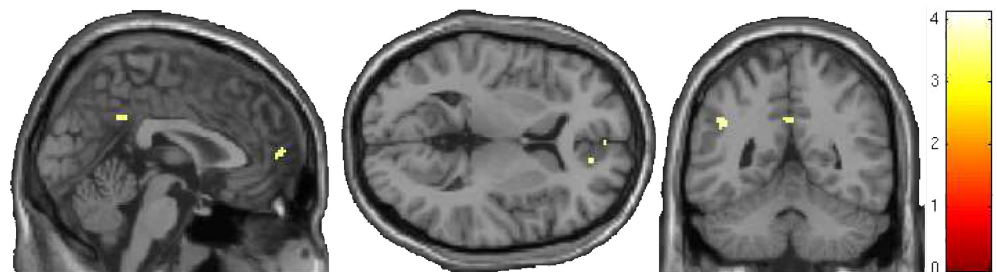
Table 3. Covariance with successful learning

This table includes MNI coordinates of the main peaks of significant cluster, the number of significant voxel (k), the p -values that are not corrected 0.001 ($k > 30$), the hemisphere (L=left, R=right, and B=bilateral), and the localization name of the main peak activation. Cluster extensions are reported in the text. Abbreviations: IFG=inferior frontal gyrus; MFG=middle frontal gyrus; SFG=superior frontal gyrus; IPL=inferior parietal lobule; MTG=middle temporal gyrus; ACC=anterior cingulate cortex; MCC=middle cingulate cortex.

Covariance of brain data with learning success during learning ($p = 0.001, k > 30$)



Covariance of brain data with learning success during consolidation ($p = 0.001, k > 30$)



Discussion

The aim of our study was to discover neural correlates of verbal learning. This was accomplished by teaching the participants pseudowords in a specially developed training paradigm (Barthel, 2009) and testing the learning success in the fMRI. The participants learnt the pseudowords successfully. Although it has to be noted that our participants learnt on average 10 words less than Barthel's. This deviation could be due to variability of the sample due to the small sample size in Barthel's study.

Naming of real words encompassed a large network, which was well in line with previous research (Gronholm, et al., 2005; Price, 2010; Raboyeau, et al., 2004). As expected, frontal and temporal areas were activated next to post- and precentral motor areas and middle cingulate gyrus. The left MFG is known to be involved in lexical selection, while STG seems to be involved in word-form retrieval, self-monitoring (Price, 2010), and in storing phonological representations (Ullman, 2004). Also pars triangularis activation has been shown to be involved in word retrieval (Gronholm, et al., 2005). Besides, we found activation in areas involved in speech articulation as BA 4/ BA 6 (Price, 2010; Raboyeau, et al., 2004). Cingulate cortex is important for attentional and executive control (Chein & Schneider, 2000; Gronholm, et al., 2007; Whitney, et al., 2009; Price, 2010). Interestingly though is the shift to the mid cingulate cortex, while in the literature the anterior cingulate cortex is more extensively described (Chein & Schneider, 2000; Breitenstein, et al., 2005; Fiebach, et al., 2002; Gow, 2012; Raboyeau, et al., 2004; Raettig & Kotz, 2008). But, in a more detailed analysis of specific regions and functions of the cingulate cortex, Torta and Cauda (2011) dedicated semantic and language tasks to the MCC. The MCC seemed to be involved in response selection, error detection, and competition monitoring, next to working memory functions. Strong reciprocal interconnectivity with the parahippocampal gyrus argued for an involvement in episodic memory retrieval (Raettig & Kotz, 2008; Torta & Cauda, 2011). The anterior cingulate cortex on the contrary is involved in reward related tasks, and emotions (Raettig & Kotz, 2008; Torta & Cauda, 2011), next to attentional control, conflict monitoring and error detection as described by several studies (Chein & Schneider, 2000; Gronholm, et al., 2007; Whitney, et al., 2009; Price, 2010; Torta & Cauda, 2011). Thus the ACC is involved in a broad variety of tasks, while the MCC is more specific for language (Torta & Cauda, 2011). Interestingly no insular

activity, known to reflect articulation, was visible. Even though there were no high articulatory task demands this was unexpected.

For pseudoword learning (Scan 2 and Scan 3) we hypothesized to find activation in speech relevant areas, similar to those in familiar word naming. Besides increased hippocampal activity was expected during the first acquisition phase (Scan 2), while neocortical areas were involved after consolidation (Scan 3), therewith resembling more familiar word naming activation. Indeed, activated regions in pseudoword and familiar word naming were partly overlapping, e.g. in the bilaterally fusiform gyrus and left SMA (BA 6). Activation of the fusiform gyrus is unsurprising, given that it is known to be activated in naming studies (Gronholm, et al., 2005) of pronounceable pseudowords as ours and in foreign language learning (Proverbio, Zani, & Adorni, 2008). The fusiform gyrus seems to play an important role in crossmodal integration of information, similar to the hippocampus (Breitenstein, et al., 2005). Breitenstein et al. (2005) found a decrease of fusiform activity as well as hippocampal activity after the first learning phase, when neocortical areas became of greater relevance. Because of our conjoint analysis for pseudoword naming we cannot specify whether fusiform activity decreased.

Furthermore the inferior parietal lobule (IPL) was activated in pseudoword naming, probably reflecting phonological processing and storage (Breitenstein, et al., 2005; Lopez-Barroso, et al., 2011; Zhao, et al., 2011). Activation in visual areas as the lingual gyrus (BA 18) and calcarine gyrus (BA 17) reflect visual processing (Gronholm, et al., 2005, Zhao, et al., 2011), although it is surprising that we did not find this activation in familiar word naming. Maybe these areas have a role beyond visual processing.

Regarding the learning progress, we saw an elevated activation of right cerebellum and caudate nucleus in the first acquisition phase of pseudowords (Scan2 > Scan3). Caudate nucleus is known to be involved in suppression of competing responses (Chein & Schneider, 2000; Gronholm, et al., 2007; Whitney, et al., 2009; Price, 2010) probably stronger activated during newly learnt pseudoword retrieval (Fiebach, et al., 2002). When the right lateralized caudate nucleus was damaged, patients exhibited neglect symptoms. Left lateralized damage caused speech deficits and prolonged response latencies (Kumral, Evyapan, & Balkir, 1999), further supporting the role of caudate in speech and in response selection. Furthermore, patients with caudate damage showed poor control over cognitive sequencing of individual actions, leading to abnormal speech production (Pickett, Kuniholm, Protopoulos, Friedman, & Lieberman,

1998). Next to the caudate nucleus the cerebellum was activated in the first acquisition phase of pseudoword learning. The cerebellum was previously thought to be primarily involved into motor coordination, balance and motor speech (Baillieux, De Smet, Paquier, De Deyn, & Marien, 2008), but recently a broader task domain of the cerebellum has been discovered. Of relevance was its role in associative and implicit learning beyond procedural motor-task learning important for word acquisition (Baillieux, et al., 2008; Price, 2010); in verbal working memory (Baillieux, et al., 2008; Price, 2010; Ullman, 2004), probably during initial phonological encoding; as well as in word generation and auditory self-monitoring (Baillieux, et al., 2008; Price, 2010). Furthermore the cerebellum seems to be involved in mental coordination, control of attention and in error-based learning (Ullman, 2004).

For more consolidated pseudowords (Scan3 > Scan2) activation was found bilaterally in the postcentral gyrus, involved in monitoring (Price, 2010), and STG regions, involved into articulation as well as monitoring (Abel, et al., 2009; Price, 2010). The activation shaded into the pars opercularis (BA 44) known to be involved in retrieval (Fiebach, et al., 2002; Price, 2010). As expected activation of better consolidated pseudoword naming approximated activation of regions of normal word naming. Next to these areas involved into normal naming, the right IPL for phonological storage (Breitenstein & Knecht, 2002; Lopez-Barroso, et al., 2011; Zhao, et al., 2011) was more strongly activated, thus making the role of memory obvious again.

No hippocampus activation during learning

Surprisingly, during learning in comparison with consolidation we could not find any hippocampal activity at a cluster level of $k > 15$. The repeated presentation of stimulus material before testing initial learning in the fMRI scan (scan 2) could have led to habituation minimizing the effect of initial encoding, the task of the hippocampus (Gronholm, et al., 2005). Furthermore the setting of Scan 2 could have been mistaken. For tapping hippocampus activity the right point in time has to be met. As Gronholm et al. (2005) discovered that hippocampal activity first increases before it declines and neocortical areas take memory processes over. We did find IPL activity in Scan 3. Another possible explanation can be derived by the complexity of the task and the complexity of speech production in general. More detailed analysis could have refined the picture.

Next to these potential explanations, it is interesting to report a preceding experiment, which compared hippocampal activation in semantical vs. phonological verbal fluency tasks. Whitney, et al. (2009) discovered that hippocampal activity depends on the sort of retrieval process. Only semantical and associative retrieval resulted in hippocampal activity, phonological retrieval not, offering a solution why we did not find any hippocampal activity during phonological retrieval of pseudoword naming. It would be interesting to check whether hippocampal activity would have been found for our semantical attribute naming task but this calculation goes beyond the aim of this paper.

Covariance of brain data with learning success

Learning success was marked by medial frontal and temporal activity during the acquisition phase (Scan 2). Frontal regions are known to be involved in retrieval processes and phonological processing (Blasi, et al., 2002b; Fiebach, et al., 2002; Liakakis, et al., 2011; Price, 2010), though orbitofrontal regions are known to rather represent goals for action (Rolls & Grabenhorst, 2008; Torta & Cauda, 2011). Temporal activity in the left MTG also could reflect retrieval processes (Fiebach, et al., 2002; Indefrey & Levelt, 2004; Raboyeau, et al., 2004). Thus frontal and temporal areas known to be involved in retrieval were more highly activated in participants who learnt more pseudowords in the end.

Next to frontal and temporal regions, occipital gyrus, cuneus, angular gyrus and supramarginal gyrus were activated. Occipital gyrus and cuneus are known to be involved in visual processing (Kiyosawa, et al., 1995). The angular gyrus is more specific for attention (Kiyosawa, et al., 1995), while the supramarginal gyrus is involved in subvocal articulation in challenging contexts and self-monitoring (Price, 2010) or even in storage of phonological forms (Veroude, et al., 2010). Interestingly, the occipital or lingual gyrus (BA 18) was also elevated in the conjoint analysis of pseudoword naming. It could be speculated that lingual gyrus and occipital regions hold a function beyond visual processing, but this has to be further tested.

Another region that was active in participants with good learning success during the acquisition phase was the postcentral gyrus (BA 2, BA 3b). This could reflect articulatory demands. Participants who could name more words were demanded to articulate unfamiliar pseudowords, while participants with poor learning progress just answered “I don’t know”.

Cingulate cortex, especially the mid posterior part, seemed to play an important role in as well newly learnt words as in better consolidated words (Scan

2 and Scan 3), unsurprisingly given that MCC is involved in language, response selection and error detection.

When retrieving more consolidated words, better learners showed elevated responses in similar regions as during the acquisition phase, namely in the MCC, orbitofrontal regions and the angular gyrus. Uniquely though was the IPL activity for consolidated pseudoword naming. The IPL was also for the whole group of great relevance for consolidated pseudoword naming. This is in line with previous research which suggested a role of phonological storage for the IPL (Breitenstein & Knecht, 2002; Breitenstein, et al., 2005; Lopez-Barroso, et al., 2011; Zhao, et al., 2011). Our findings confirmed the importance of IPL activity for learning success.

Limitations

Despite of highest attempts our study is not free of limitations. It has been questioned whether an increasing or decreasing cueing hierarchy is more valuable for patients with aphasia. Although we were able to find a considerable progress in pseudoword acquisition, there is still room for improved efficiency. Maybe a different method could help relearning words in a less time-consuming manner. On the contrary, there is a high advantage of this method by the easy administration of the computer-based learning paradigm.

A critical point as mentioned above is the timing of scan 2. The aim was to meet a point in time, where first learning was accomplished and no overnight consolidation had yet taken place. A different timing of scan 2 or less prior exposure to the stimulus material could have been superior. However the missing hippocampal activity could have been also due to the phonological nature of pseudoword learning.

Another debatable point is the choice of our control stimuli, which failed to be effective. Brain activity for giving a stereotyped response as “ok” to pixelated pictures evoked higher brain activity than baseline should do. Similar control stimuli had been used in a previous study (Meltzer, Postman-Caucheteux, McArdle, & Braun, 2009). However, several participants reported to have tried to interpret the pictures and eventually discovered some of the objects. This is a highly cognitive process and could explain the strong activity. To overcome this problem it could be useful to develop new control stimuli for future research.

Last but not least, it should not be forgotten that speech production is a very complex process, tapping many different processes in a very brief time, while fMRI has a low temporal resolution. Furthermore, there is not one area that is uniquely dedicated to one task in the speech learning and production process,

but one area is involved in many different tasks (Ullman, 2004), therewith making it sensible to task specific variations and slightly different demands.

Conclusion

Verbal learning of pseudowords demands especially caudate and cerebellar activation in the first acquisition phase before consolidation has taken place, probably reflecting suppression of competing responses (Chein & Schneider, 2000; Baillieux, et al., 2008; P. Gronholm, et al., 2007) and verbal working memory (Price, 2010; Ullman, 2004; Whitney, et al., 2009). This could be valuable information for the design of learning tasks. In order to optimize the learning success, the level of working memory capacity of the learner could be analyzed and the tasks demands adapted to the optimal level. Also suppression of other items could be facilitated by composition of an intelligent item pool. In general our method of decreasing cues was successful. Interestingly, no hippocampus activity was found in the first acquisition phase, which could be due to task demands.

For consolidated items the inferior parietal lobule seems of special relevance as sort of phonological storage (Breitenstein & Knecht, 2002; Lopez-Barroso, et al., 2011; Price, 2010; Zhao, et al. 2011), next to areas found in familiar word naming. Interestingly activation of visual areas, as lingual gyrus and occipital gyrus, were seen in pseudoword naming, but not in familiar naming. This information should be kept in mind for comparison with data of patient groups. If patients would activate a different network, stimulation of IPL and visual areas could facilitate learning by approximating neural correlates of verbal learning in healthy subjects.

Also good learners showed increased activation in visual areas, as well as orbito frontal regions, which are involved in phonological processing and retrieval (Blasi, et al., 2002a; Fiebach, et al., 2002; Liakakis, et al., 2011; Price, 2010). Furthermore more cingulate activity reflecting control (Chein & Schneider, 2000; P. Gronholm, et al., 2007; Price, 2010; Whitney, et al., 2009) was increased in good learners as well as stronger IPL activity, which probably represents phonological storage for consolidated words.

Future directions

Our findings give valuable insight in the process of pseudoword learning, probably generalizable to ordinary word acquisition. To further advance these findings, a comparable patient study would be eligible by unfolding specialized

requirements and needs for these different groups. Of special interest are patients with word retrieval problems, like aphasic and schizophrenic patients. If patients would use a different neural network attempts of stimulating inferior parietal, cerebellar and caudate areas could support their learning success. Also task demands and the administration of language learning could be adapted to the special needs of different patient groups by e.g. varying the level of working memory load.

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