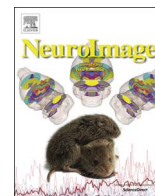




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Dynamic changes of resting state connectivity related to the acquisition of a lexico-semantic skill

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ABSTRACT

The brain undergoes adaptive changes during learning. Spontaneous neural activity has been proposed to play an important role in acquiring new information and/or improve the interaction of task related brain regions. A promising approach is the investigation of resting state functional connectivity (rs-fc) and resting state networks, which rely on the detection of interregional correlations of spontaneous BOLD fluctuations.

Using Morse Code (MC) as a model to investigate neural correlates of lexico-semantic learning we sought to identify patterns in rs-fc that predict learning success and/or undergo dynamic changes during a 10-day training period. Thirty-five participants were trained to decode twelve letters of MC. Rs-fMRI data were collected before and after the training period and rs-fc analyses were performed using a group independent component analysis.

Baseline connectivity between the language-network (LANG) and the anterior-salience-network (ASN) predicted learning success and learning was associated with an increase in LANG – ASN connectivity. Furthermore, a disconnection between the default mode network (DMN) and the ASN as well as the left fusiform gyrus, which is critically involved in MC deciphering, was observed.

Our findings demonstrate that rs-fc can undergo behaviorally relevant changes within 10 training days, reflecting a learning dependent modulation of interference between task specific networks.

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1. Introduction

Learning is based on experience, memory and adaptation. Changes in the way the brain processes new stimuli, accompanied by an improvement in goal-directed performance, are often referred to as ‘neuroplasticity’. Practicing and learning are thought to

both induce and profit from neuroplasticity, which has been described on different levels of neural organization, ranging from synaptic plasticity (Trachtenberg et al. 2002) to changes in complex neural circuitry (van Turennout et al., 2000). Modern brain imaging techniques have enabled the detection of macro-changes in task related brain function associated with various types of learning, such as motor, perceptual and associative learning (Kelly and Garavan 2005). A fairly new approach to the understanding of neuroplastic adaptation is based on the investigation of resting state functional connectivity (rs-fc) and resting state networks, where, in the absence of a task, interregional correlations of spontaneous low frequency BOLD fluctuations are calculated, which are thought to reflect synchronized neural activity (Biswal et al. 1995; Biswal 2012). Using rs-fc analyses a number of networks have been identified that resemble the patterns of activation observed during specific tasks; as such it is likely that rs-fc serves a dynamic role in brain function supporting the integration and consolidation of previous experience (Lewis et al. 2009). The translation of previous experience, e.g. training, into the

Abbreviations: ASN, anterior salience network; BA, brodmann area; BOLD, blood oxygen level dependency; DMN, default mode network; FNC, intercomponent functional connectivity; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; FWE, family wise error; ICA, independent component analysis; iFC, intra-component functional connectivity; IFC, inferior frontal cortex; IPL, inferior parietal lobule; LANG, language network; MC, Morse Code; OTC, occipito-temporal cortex; rs-fc, resting state functional connectivity; SEM, standard error of mean; SMA, supplementary motor area

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modification of resting state networks is currently under extensive investigation and is likely to provide new insights into the neurobiological underpinnings of adaptation.

A number of studies have already demonstrated relationships between behavior and rs-fc measures, such that inter-individual differences in performance or traits are associated with differences in connectivity strength in networks related to the task and/or behavior (Wang et al. 2010). With respect to practicing and learning there is an increasing interest to longitudinally monitor changes in connectivity and network properties during a practicing/learning process, and to identify markers that allow for the prediction of learning success at baseline, i.e. prior to the training period. Some work in this regard has been done on motor and perceptual learning (Lewis et al. 2009; Ma et al. 2011; Baldassarre et al. 2012; Powers et al., 2012; Guidotti et al. 2015; Ventura-Campos et al. 2013; Albert et al. 2009; Sami, Robertson, and Miall 2014). However, only a few studies have looked at “higher” cognitive abilities involving a lexical and/or semantic learning process. Looking at reading competence, Horowitz-Kraus et al., (2015) for example could demonstrate that a specific reading-training program for children with and without reading difficulties, led to increases in rs-fc between the visual and attention network, as well as between the visual and executive function networks that correlated positively with word reading and reading comprehension (Horowitz-kraus et al. 2015). Likewise Murdaugh et al. found that a reading intervention in children with autism led to an increase in rs-fc between Broca's and Wernicke's areas and that the improvement in reading comprehension correlated with the increase in connectivity of these regions with the reading network (Murdaugh, Maximo, and Kana 2015).

To our knowledge rs-fc has not been investigated in the context of semantic and/or lexical learning, where study participants have to learn new stimulus – response associations. In the current study we used fMRI and Morse Code (MC) to investigate changes in rs-fc related to the newly acquired skill to decode sequences of short and long signals as letters. MC, a method of transmitting text information as a series of on-off tones, clicks, or flashes of light with different durations (short and long), provides an interesting model to investigate neural correlates of lexico-semantic learning and to probe the reading network. We recently introduced a learning paradigm using MC to investigate changes in neural activity related to the decoding of three-letter-words. Study participants learned to assign letters to certain sound pattern (pattern-to-letter/phoneme conversion), thereby establishing a link between an acoustic pattern and an already existing letter representation system. Specific brain regions are known to be critically involved in lexical and semantic processing were recruited in the learning process, such as the left inferior frontal cortex (IFC) and the left occipitotemporal cortex (OTC), including the fusiform gyrus.

With a focus on a network perspective to further analyze the underlying neural correlates of lexico-semantic learning, we now used rs-fMRI and independent component analysis (ICA) to identify characteristics in rs-fc and changes thereof that were related to both the learning process itself and to learning success. ICA allows the identification of a number of distinct resting state networks that have been attributed to various tasks. We hypothesized that there would be an association between task performance (after the learning process) and the connectivity (and changes thereof) between the language network (LANG) and the (anterior) salience network (ASN) on the one hand, and also a disconnection between the LANG and the default mode network (DMN).

2. Methods

2.1. Subjects

Thirty-five healthy, right-handed subjects (mean age 24 years, $SD=2.7$, 14 females) participated in the study. 18 subjects were drawn from the study previously published by Schlaffke et al. (2015) where also rs-fMRI data had been acquired. Another 17 subjects had participated in a new study where exactly the same study design had been used. In the new study participants had also practiced to transmit MC (5 min per session), in addition to the decoding part, which was identical in both groups (see below for details). The task related fMRI of this second group will be reported elsewhere. All subjects had normal or corrected-to-normal vision. Furthermore, no participant had a hearing impairment and all participants were tested for a normal hearing range of 20–20,000 Hz frequencies (Seikel et al., 2009). The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Faculty of Psychology at the Ruhr-University Bochum, Germany. Before the experiment, participants were informed about the testing procedure and gave written informed consent.

2.2. Task and training

Morse Code (MC) is a method of transmitting text information as a series of on-off tones, clicks, or lights. The International Morse Code encodes the ISO basic Latin alphabet, some extra Latin letters, the Arabic numerals and a small set of punctuation and procedural signals as standardized sequences of short and long signals pictured as ‘dots’ (●) and ‘dashes’ (–), where the duration of a dash is three times the duration of a dot.

All participants were naïve to MC prior to the learning intervention. The learning procedure has been described in detail in (Schlaffke et al. 2015). In brief, using an in house developed audio book a subset of 12 letters (day 1: E S N and O; day 2: T and R; day 3: U and D; day 4: A and I; day 5: M and G; day 6: repetition of all letters) was presented and learned at a standardized speed. The audio book was played on a Google Nexus 7 tablet with the implemented “Google Play Music” presentation software. Stereo headphones by Philips (40mm speaker driver, 20–20000 Hz frequency range, 98 dB sensitivity, 32 Ω impedance, 500 mV maximum power input; lightweight comfort with adjustable headband) were used.

Study participants learned 12 letters in a specific order within six supervised learning sessions (duration per session approx. 60 min). In the first training session, participants learned to decipher four letters (E, N, O, S). On all training days, apart from the first, a repetition of the previously learned Morse Code letters was performed, followed by the practice of two new letters and the decoding of three-letter MC-trains. Participants of the second cohort ($n=17$) skipped decoding 30 (of 240) acoustically presented MC letters and practiced to transmit them instead. Except for this difference, both groups followed exactly the same learning protocol (same practicing time). The training was completed within ten days, with an adjournment of one weekend.

2.3. fMRI – sequences

All participants underwent two MRI sessions in a Philips Achieva 3T X-series MR-Scanner, one at the beginning (before the first training session) and one at the end (after the last training session). Using a 32 Ch head coil, in the first session high-resolution T1-weighted data sets (TR 8.3 ms, TE 3.8 ms, FOV 256 × 256, yielding 220 transversal slices with a voxel size of 1.00 × 1.00 × 1.00 mm³ and reconstructed to 0.94 × 0.94 × 1.00 mm³)

were acquired first from all subjects for excluding any anatomical abnormalities. In each session participants underwent a resting state scan followed by a task related fMRI scan, to obtain a

behavioral measure of performance. For the task related fMRI MC were acoustically presented in trains of three letters that made up a word, a non-word or the international emergency signal "SOS". In

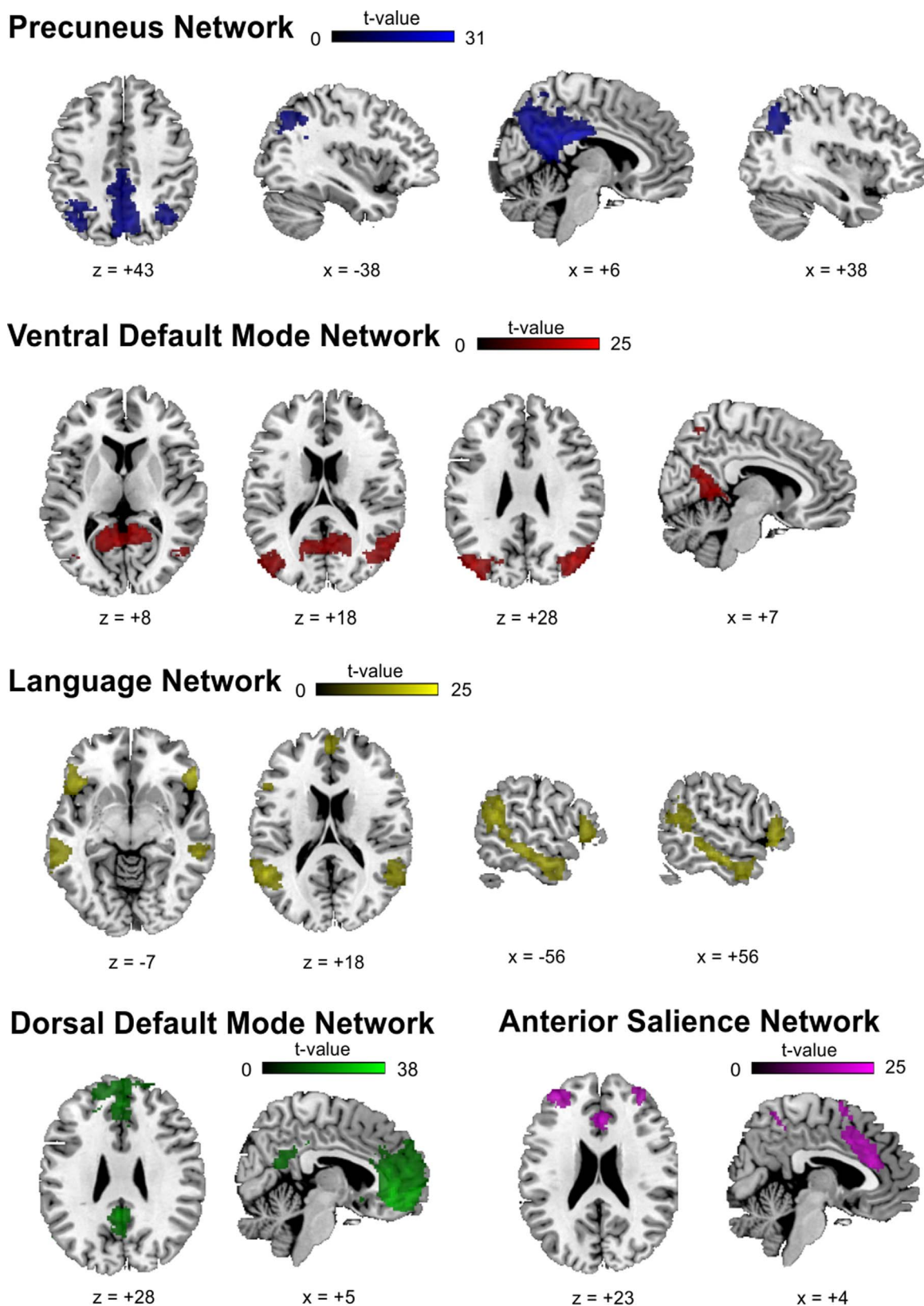


Fig. 1. Resting State Networks of Interest. Five RSNs investigated were the Precuneus, Ventral Default Mode Network (DMN), Language network, Dorsal DMN, and the anterior salience network. Figures depict one-sample *t*-test results of the pre-learning condition ($p < .05$, FDR-cluster corrected), where colored voxels represent the corresponding RSN.

addition, a sine wave tone (“beep”) served as a control stimulus. Participants were required to decide via button press, whether the given stimulus made up a word, a non-word, the “SOS” or the beep control (for details see Schlaffke et al., 2015). All answers were recorded and the assessment of performance as well as correlation analyses between performance and rs-fc are based on performance (assessed as the number of correct answers) in this task at time point 2.

Before the actual task on both days, rs-fMRI data were collected. Participants were instructed to keep their eyes closed and not to think about anything in particular. In a total duration of 8:37 min 205 volumes (including 5 dummy scans) were scanned (single shot EPI with 90° flip angle, TR 2500 ms, TE 35 ms, FOV 224 × 232 mm² with a voxel size of 2 × 2 × 3 mm³ yielding 39 slices in an ascending scan order without gaps).

2.4. fMRI – preprocessing and statistical analysis

Functional images were slice time corrected, realigned, normalized to the EPI template, and smoothed (6 mm FWHM kernel) using SPM8. Data reduction was accomplished using ICA provided by the GIFT toolbox. The first step reduced each subject’s 200 time points (scans) to 70 principle components. In the second step reduced this 70 to 30 principle components and the third from 30 to the final 20 ICS. Infomax was chosen for the group ICA algorithm due to its robustness in a low-order dataset. This was run 20 times (using ICASSO) to improve the independent components’ (IC) stability, which then was confirmed using the Iq measure of stability. Group ICs were then back reconstructed using the GICA algorithm to create subject-specific component maps and time courses. An individual’s back-reconstructed (br) map thus identifies those voxels that are both spatially and temporally most consistent with the group-identified IC. Components were not further scaled due to the preprocessing step of intensity normalization, which returns br maps in units of percent signal change.

Group ICs were visually inspected and then spatially sorted against the network templates provided by the Stanford Resting State Network templates (link:http://findlab.stanford.edu/functional_ROIs.html) (Shirer et al. 2011). This was carried out using the “spatial correlation” function provided by the GIFT toolbox. Of particular interest in this study were the Language, Default Mode, and Anterior Saliency networks, hereafter referred to as LANG, DMN, and ASN, respectively (Fig. 1). Since the DMN is typically represented in three components, the ventral (v-DMN), dorsal (d-DMN), and precuneus (PREC) components were identified and used in the analyses. Only one IC was identified as best representing the respective RSNs, which was that with the highest spatial correlation with the template of interest. This resulted in six RSNs that were further analyzed.

Further analysis included intra-component functional connectivity (iFC) and inter-component functional connectivity (FNC). iFC was calculated as the subject-specific median value of the br maps within a given network. The higher the average component values, the stronger the iFC strength. In addition to the whole-network level analyses of iFC, further analyses were performed on a voxel-wise level to compare changes in the connectivity of each voxel in the brain with a given network. Br maps from each subject’s pre session were compared to the same subject’s post session in paired tests in SPM8 (whole brain analysis). No additional correction for age or gender was included due to the homogeneous age ($SD = \pm 2.7$ years) and balanced gender within the group. No network mask was used, allowing all voxels to be taken into account. The defining voxel-level threshold was set with an uncorrected $p < 0.001$ and cluster significance was set at an FDR cluster-corrected level of $p < .05$.

The FNC (network-to-network) comparisons were ‘despiked,

detrended, and filtered,’ as per default in the GIFT Toolbox. The low-pass filter cutoff used was 0.1 Hz.

FNC was calculated within the MANCOVAN Toolbox, as provided by Gift. Individual IC time courses were log-transformed to obtain a normal distribution before statistical analyses.

The average functional connectivity between the six networks was extracted for each subject.

STATISTICA (StatSoft, Inc. version 10) was used to analyze changes in performance (i.e. number of correct responses) in the Morse Code task and functional connectivity measures (iFC, FNC). Simple correlations compared post performance (i.e. a measure of how well subjects learned Morse Code) with pre, post, and changes in functional measures (i.e. iFC and FNC for the five RSNs). Significance was set at $p < .05$.

3. Results

3.1. Performance

All participants completed the learning phase and the scanning sessions (no dropouts). For the task related scans there was a significant effect of time for the performance during the task ($F_{1,34} = 165.34$; $p < 0.0001$). Post hoc *t*-tests revealed that study participants performed significantly better in the task after learning as compared to before learning, showing a gain in accuracy from 44.46% ($SEM \pm 1.06$, chance level), to 74.43% ($SEM \pm 1.83$, $p < 0.001$) in the task. The given values are relative scores of correct answers, e.g. words/non-words for the task (sum of correctly identified words and non-words divided by all words and non-words) (Fig. 2). There were no differences in performance between the two cohorts for the task ($p > 0.75$) after learning.

3.2. ICA analyses – component to component

All resting state networks of interest could be associate with one of the 20 independent components. By spatially correlating components with the RSN templates (see Section 2.4), IC 1 was defined as the PREC ($r = .62$), IC 3 as the dDMN ($r = .64$), IC 10 as the ASN ($r = .46$), IC 16 was defined as the LANG ($r = .38$), and IC 19 as the vDMN ($r = .44$).

Paired *t*-tests comparing pre and post sessions revealed that

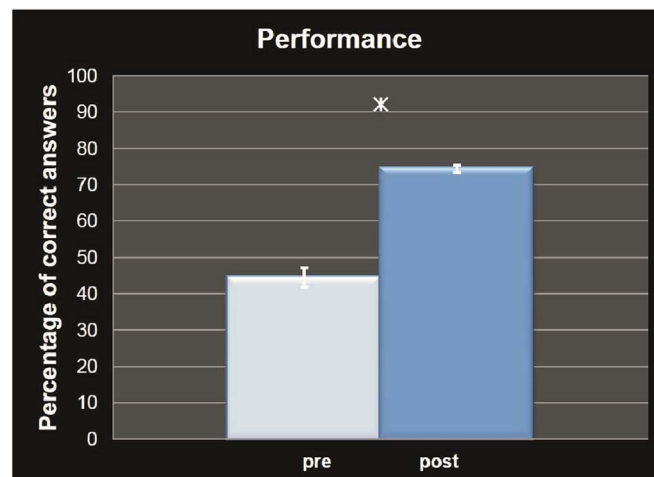


Fig. 2. Morse Code Learning Performance. Relative scores and standard error of means (SEM) of task performances. Light blue: lexico-semantic pre-learning performance. Dark blue: lexico-semantic post-learning performance. There was a significant increase in performance in both tasks $p < 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Overview of analyzed network components and the between network connectivity.

Network comparison	PRE	POST	<i>t</i>	<i>p</i>
PREC - dDMN	0.28 ± 0.18	0.29 ± 0.19	-0.10	0.920
PREC - ASN	0.28 ± 0.19	0.21 ± 0.21	2.19	0.035
PREC - AUD	0.14 ± 0.22	0.17 ± 0.20	-0.69	0.498
PREC - LANG	0.00 ± 0.14	0.00 ± 0.12	0.06	0.949
PREC - vDMN	-0.04 ± 0.14	-0.04 ± 0.17	0.01	0.990
dDMN - ASN	0.52 ± 0.18	0.40 ± 0.21	3.73	0.001*
dDMN - AUD	0.38 ± 0.15	0.37 ± 0.20	0.30	0.767
dDMN - AUD	-0.01 ± 0.11	-0.02 ± 0.12	0.49	0.624
dDMN - vDMN	0.11 ± 0.15	0.09 ± 0.19	0.84	0.405
ASN - AUD	0.42 ± 0.26	0.34 ± 0.24	1.74	0.091
ASN - LANG	0.09 ± 0.13	0.15 ± 0.12	-2.59	0.014
ASN - vDMN	0.23 ± 0.13	0.22 ± 0.14	0.63	0.532
AUD - LANG	-0.04 ± 0.12	-0.08 ± 0.13	1.44	0.159
AUD - vDMN	0.03 ± 0.19	-0.01 ± 0.18	1.23	0.228
LANG - vDMN	0.09 ± 0.15	0.11 ± 0.12	-0.83	0.414

* Significant following bonferonni correction $p=0.05/15=0.0033$.

inter-component connectivity strength, or FNC, was reduced between the PREC-ASN (mean ± SD, pre: 0.28 ± 0.19 , post: 0.21 ± 0.21 , $t=2.19$, $p < .05$), and the dDMN-ASN (pre: 0.52 ± 0.18 , post: 0.40 ± 0.21 , $t=3.73$, $p < .001$), and increased between the ASN - LANG (pre: 0.09 ± 0.13 , post: 0.15 ± 0.12 , $t = -2.59$, $p < .05$) in the post session, as compared to the baseline session. There were no significant changes in intrinsic functional connectivity strength in any of the networks ($p > .3$). See Table 1 for detailed information of all analyzed components.

3.3. ICA and performance (whole-network)

Post-performance was significantly correlated with the connectivity between the ASN and LANG network at baseline ($r = -.53$, $p = .001$, Fig. 3). Post-performance was additionally correlated with the change in connectivity between the ASN and LANG network ($r = .37$, $p = .03$, Fig. 3) as well as the change in connectivity between the LANG network and the vDMN ($r = -.44$, $p = .009$, Fig. 4). Additionally, performance was related to intrinsic connectivity of the vDMN, both with connectivity at the post time point ($r = .35$, $p = .04$, Fig. 5) and the change in connectivity over time (post-pre: $r = .35$, $p = .04$, Fig. 5).

3.4. Language network - component-to-voxel

Since intranetwork connectivity within the vDMN was related to performance (see above), this network was further analyzed for changes at a voxel level. Paired *t*-tests revealed a reduced connectivity between the vDMN and left fusiform (-32 , -24 , 70 mm, $t=5.45$, $k=81$) and the left precentral cortex (-44 , -58 , -8 mm, $t=4.44$, $k=64$) after learning (See Fig. 5).

4. Discussion

Using MC as a model to investigate neural correlates of lexico-semantic learning we sought to identify patterns in rs-fc that either predict at baseline learning success, or undergo dynamic changes during the training period. LANG - ASN connectivity was predictive of learning, such that weaker connectivity at baseline predicted better performance after learning. There was an overall increase in LANG - ASN connectivity following learning and the change in LANG - ASN connectivity additionally correlated with learning success, such that greater increases in LANG - ASN connectivity were associated with better performance. A concurrent disconnection in DMN - ASN connectivity was observed.

Furthermore, there was a relationship between the degree of DMN - LANG disconnection and performance after learning, such that study participants with a higher degree of DMN - LANG disconnection performed better after learning. During the learning process, DMN connectivity was specifically reduced with the left fusiform gyrus, a region which has been shown to be critically involved in both visual letter processing (Thesen et al. 2012) as well as MC deciphering (Schlaffke et al. 2015). Finally, we found that the increase in intrinsic connectivity (within component) of the DMN correlated with performance. In summary, we find a withdrawal of the DMN from the LANG and from the left fusiform and left precentral gyrus, with a concurrent increase in LANG - ASN connectivity.

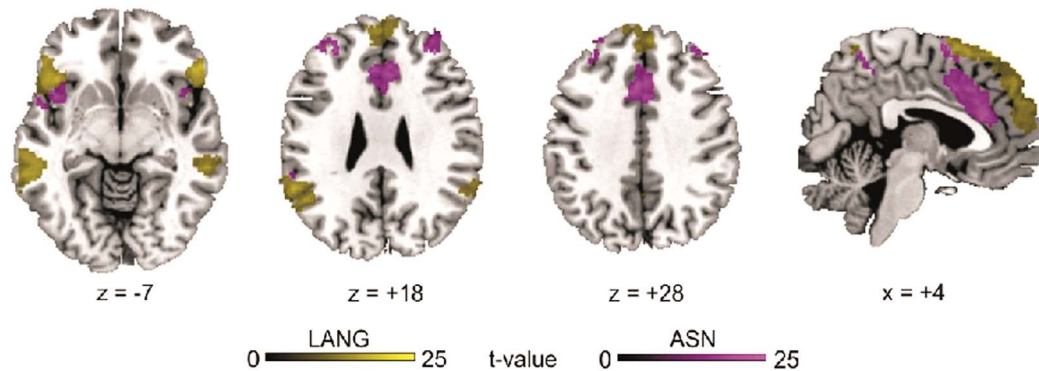
Only recently scientists have begun to investigate rs-fc to predict learning success and to identify changes in rs-fc related to the improvement of a preexisting skill or to the acquisition of a new skill. For perceptual learning, Baldassarre et al. could demonstrate that pre-existing rs-fc both within the visual cortex and between the visual cortex and prefrontal association areas was related to the improvement rate in a novel visual discrimination task (Baldassarre et al. 2012). Furthermore, Lewis et al. found that perceptual learning in a visual task (shape identification) was associated with a modification of rs-fc between the visual cortex and fronto-parietal brain regions, which are thought to be critically involved in spatial attention (Lewis et al. 2009). In the acoustic domain, Ventura-Campus et al. reported that rs-fc between the left insula/frontal operculum and left superior parietal lobule predicted the learning ability to identify foreign sounds (Palomar-García et al. 2015). Interestingly, learning itself was associated with a reduction in rs-fc, such that there was a disconnection between the left insula/frontal operculum and the left superior parietal cortex in favor of a strengthened connection between the left insula/frontal operculum and the salience network (Palomar-García et al. 2015).

Likewise, in our study a disconnection of the LANG from the DMN in favor for the ASN was observed. The DMN has been attributed to various functions such as mind wandering, introspection, and theory of mind (Mars et al. 2012; Schlaffke et al. 2015). During the processing of external stimuli and/or goal-directed behavior, a deactivation of the DMN is commonly observed and the degree of deactivation has been shown to correlate with task performance (Weissman et al. 2006). It has also been demonstrated (in adults) that stronger negative rs-fc of the DMN with other networks (functional segregation) as well as strong intranetwork connectivity of the DMN is favorable for task performance (Kelly et al. 2008; Hampson et al. 2006). Sala-Llonch et al., for example, showed that individuals with stronger negative connectivity between the DMN and working memory networks performed better in a working memory task (Sala-Llonch et al. 2012). In the current study, a DMN disconnection was observed in adults from both the LANG and the ASN as well as the left fusiform gyrus within ten days. Given that brain maturation is still occurring in young adults, but is negligible on this narrow time scale, our findings support the notion that learning is associated with reorganization of neural macro-circuitry, including DMN decoupling.

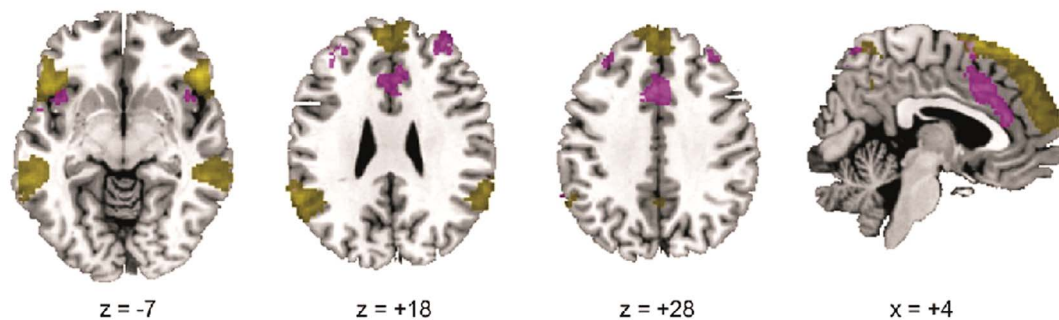
We also observed an increase in rs-fc between the LANG and the ASN, which we interpret in terms of an increased allocation of attention resources to stimuli that have gained informational content, and therefore assume a greater processing complexity, during learning. Study participants with initially low LANG - ASN connectivity performed better after training and the change in LANG - ASN connectivity correlated with learning success. This suggests that the relative increase in LANG - ASN connectivity is relevant to the learning process. Interestingly, Lewis et al. report an opposite effect for perceptual learning in a task, where participants had to visually identify a specific target in the left lower quadrant. Specifically, a decoupling in rs-fc of the visual cortex from higher order visual areas (frontal eye

A. LANG - ASN Connectivity

Pre-learning



Post-learning



B. Correlation with Learning

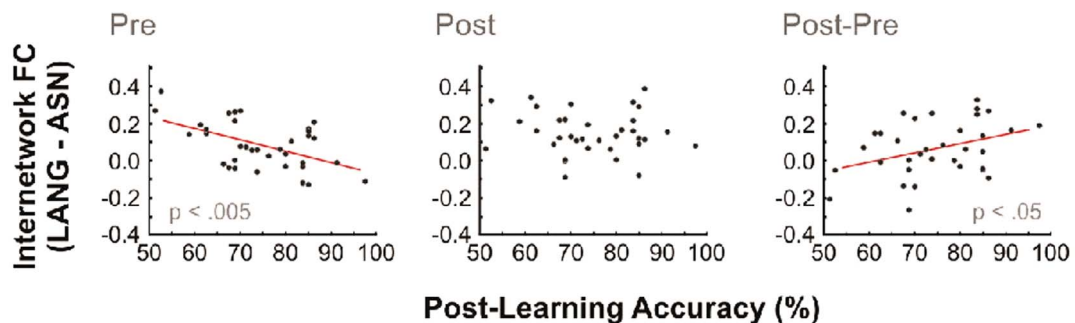


Fig. 3. LANG-ASN Connectivity. (A) Voxels included in LANG (yellow) and ASN (violet) at pre- and post-learning time points. (B) Correlation between post-learning accuracy and LANG-ASN connectivity pre-learning, post-learning, and the change (post-pre). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

fields) was observed. Interestingly, the authors report that after extensive training the participants performed the task rather effortlessly (“as if the target popped out from the background”). They argue that early in training, subjects detected the target only by paying close attention, whereas during the learning process a target template was developed that allowed for more automatic processing, required less top-down control, and resulted in effortless discrimination. In our case, the study task remained cognitively demanding, binding attention resources throughout the learning process, and thus likely necessitating the continued involvement of the salience network.

Apart from a scaffolding process that allows for more efficient information transfer, rs-fc could also reflect offline processing of task-related information, analogous with spontaneous reactivation

observed in the hippocampus during slow wave sleep (Albert et al. 2009). In either case, resting state reorganization can be thought of as the formation of a “system memory”, recapitulating the history of experience-driven coactivation (Lewis et al. 2009).

While spontaneous neural activity consumes a considerable amount of energy, its precise function remains to be fully elucidated (Raichle et al. 2001), which is also true for the corresponding BOLD fluctuations, upon which rs-fc is based. It has been demonstrated that rs-fc between brain regions reflects the structure of the underlying anatomical connections (Hagmann et al. 2008). However, changes in rs-fc that reflect a dynamic reorganization of task-specific networks on account of learning can even occur without temporally-concurrent changes in structural connectivity. With respect to the underlying

LANG - vDMN

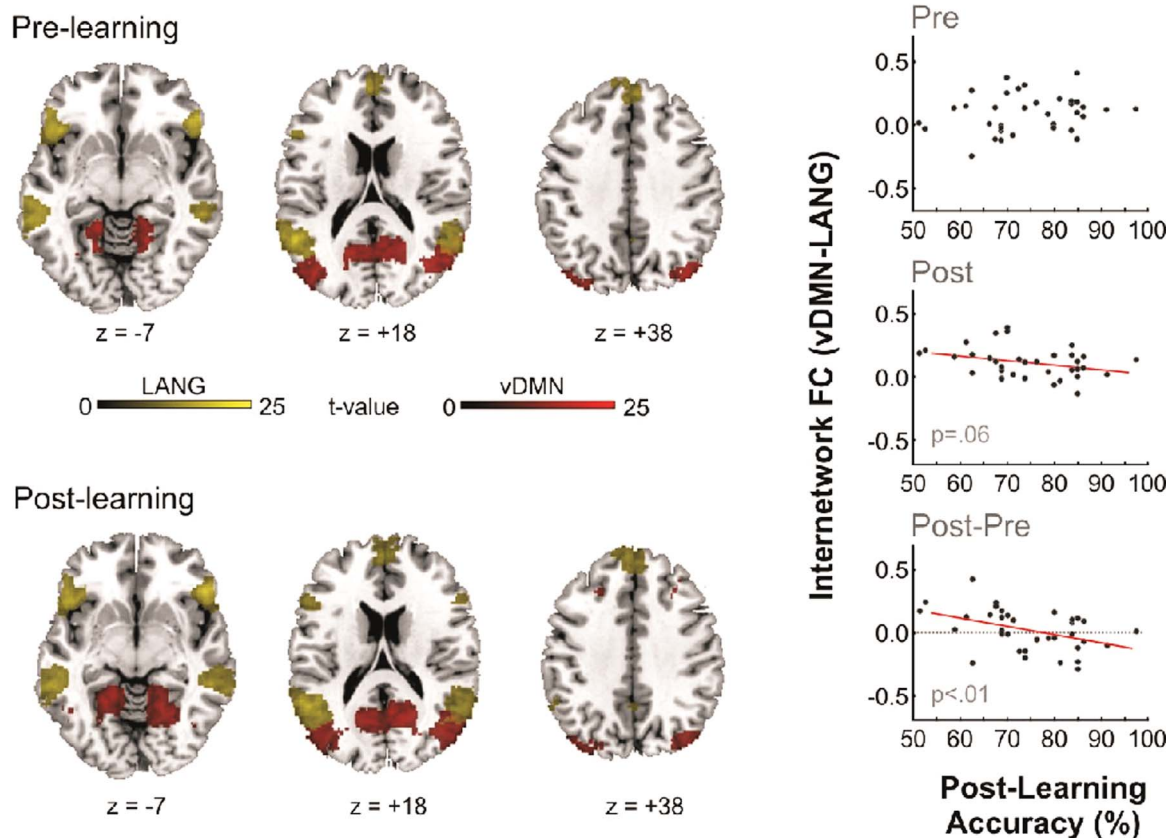


Fig. 4. LANG-vDMN Connectivity. (Left) Voxels included in LANG (yellow) and vDMN (red) at pre- and post-learning time points. (Right) Correlation between post-learning accuracy and LANG-vDMN connectivity pre-learning, post-learning, and the difference (post-pre). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

neural activity it has been hypothesized that correlations in spontaneous BOLD fluctuations are based on changes in slow cortical potentials and also relate to neural activity in the gamma range (He et al. 2008). Multi-modal imaging studies in which BOLD rsfMRI is combined with either EEG or MEG have provided valuable insight into the relationship between spontaneous BOLD fluctuations and neural activity. Overall, the relationship between BOLD fluctuations and neural activity, as assessed by EEG and MEG, is rather complex. Some studies suggest regional specificity (Laufs et al. 2003) while others have suggested that BOLD fluctuations are likely best represented by a 'signature' combination of frequencies, including a wide range of neural activity from 2 to 128 Hz, rather than a single frequency band (Hipp and Siegel 2015; Mantini et al. 2007). In this light, the relationship we find between individual learning success and baseline rs-fc can be extended to a relationship between lexico-semantic learning and underlying neural fluctuations within the LANG, ASN and DMN. Furthermore, the dynamic nature of rs-fc following learning is in line with known plastic changes that accompany learning at the neural level. The specific neural fluctuations contributing to this relationship, however, require further studies using a multi-modal approach.

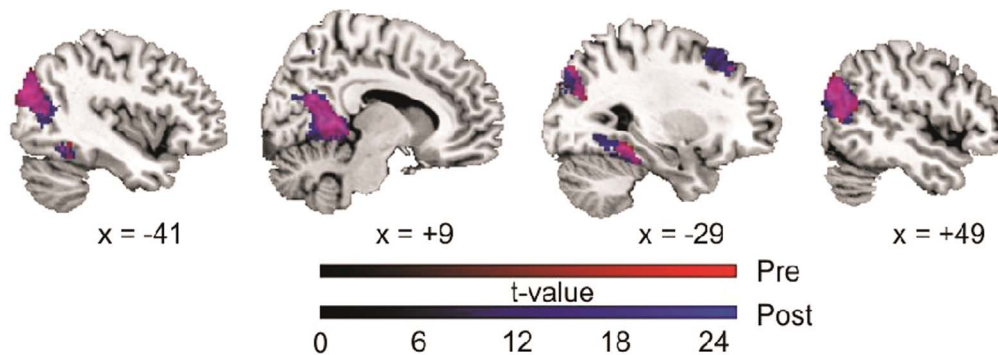
5. Conclusions

Our findings demonstrate that rs-fc undergoes specific behaviorally-relevant changes within 10 days of training, reflecting a learning-dependent modulation of interference between brain regions

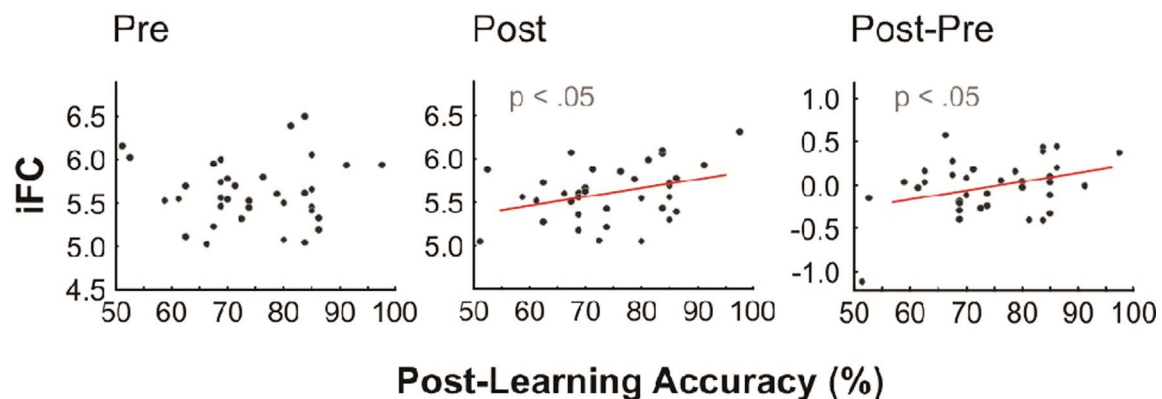
subserving the same task. We hypothesize that these changes are not limited to MC learning, but may also be relevant in other types of higher cognitive learning. Furthermore, we could show that rs-fc can be used to predict learning success, suggesting that both baseline rs-fc as well as adaptive changes in rs-fc seem to be relevant to learning and/or practicing. While other studies investigating changes in rs-fc have concentrated on the improvement of preexisting skills/knowledge, making it likely that optimization and automation of preexisting analysis strategies play a critical role, learning in our study required the establishment of new stimulus-target associations, which were not existent prior to study enrollment.

Overall it needs to be acknowledged that in the current literature studies investigating the reorganization of resting state activity and connectivity within a learning process are far from being conclusive. This can be attributed to the different types of learning (motor vs perceptual vs lexical/semantic), but also other factors such as differences in learning protocols (duration/intensity of training, period between resting state scans, etc.) likely play a role. Apart from multimodal approaches, an important step to further explore the adaptation of resting state networks in future studies will be to investigate more closely the dynamics of these changes. Ma et al., for example, could show that rs-fc between the right postcentral gyrus and the right supramarginal gyrus increased in healthy volunteers learning a sequential finger movement over the period of several weeks. This increase was only found during the improvement period (first 2 weeks), whereas when no further improvement took place, rs-fc decreased, despite ongoing practice

A Ventral DMN iFC



B Learning and network-level iFC



C Changes in vDMN iFC following learning

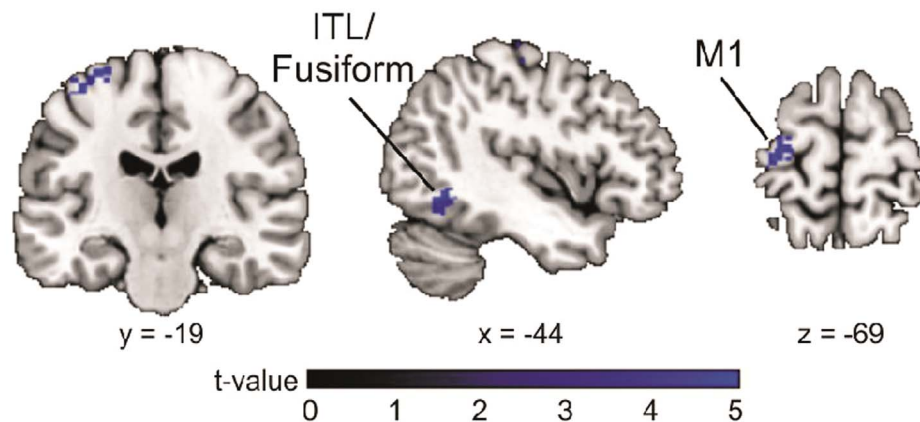


Fig. 5. Intrinsic Connectivity of the vDMN. (A) Voxels included in the pre-learning (red) and post-learning (blue) vDMN mask. Purple voxels represent those voxels included in both masks. (B) Correlation between post-learning accuracy and intrinsic vDMN connectivity pre-learning, post-learning, and the difference (post-pre). (C) Voxelwise changes (post-pre) in vDMN connectivity following learning (paired t -test, $p < .05$, FDR-cluster corrected, unmasked). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(Ma et al. 2011). Therefore, practicing seems to be an initial driver of both reorganization and behavioral improvement, but future studies are needed to further investigate the extent to which changes in rs-fc are related to practicing, to learning (operationalized as improvement), and to automation.

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