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Changes in Default Mode Network as Automaticity Develops in a Categorization Task

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CHANGES IN DEFAULT MODE NETWORK AS AUTOMATICITY DEVELOPS

IN A CATEGORIZATION TASK

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ABSTRACT

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The default mode network (DMN) is a set of brain regions in which blood oxygen level dependent (BOLD) signal is suppressed during attentional focus on the external environment. Because automatic task processing requires less attention, development of automaticity in a rule–based categorization task may result in less deactivation of the DMN as compared to the learning stage. Furthermore, previous work suggests that DMN changes its functional connectivity with other brain networks depending on task (Spreng et al., 2010). Hence we hypothesize that the functional connectivity of the DMN may change as automaticity develops. We tested these hypotheses by re-analyzing the functional magnetic resonance imaging (fMRI) data of 15 participants who were each trained in rule-based categorization for 20 sessions on consecutive workdays (Helie et al., 2010a). Each participant was scanned on his or her 1st, 4th, 10th, and 20th session. The results show deactivation of some DMN regions in sessions 1, 4 and 10, but not in session 20. In addition, analysis of variance shows a statistically significant decrease in the deactivation of four DMN regions between sessions 1 and 20, suggesting that automatic rule-based categorization does not inhibit DMN regions as much as rule-based category learning. These results provide preliminary evidence

that DMN inhibition is reduced when the rule-based categorization task becomes more automatic. This is in line with the hypothesis that automatic task processing requires less attentional focus. We also investigated changes in functional connectivity pattern by running three seed-based coherence analyses with precuneus (important DMN region), medial prefrontal cortex (important DMN region) and premotor cortex (important in automatic categorization) as seed regions. The results from analyses with precuneus and MPFC as seed regions show that both DMN and non-DMN regions increase their functional connectivity with these two important DMN regions after automaticity developed. Some of the non-DMN regions are involved in task-processing. Likewise, functional connectivity with premotor cortex as the seed shows that the left inferior parietal lobule (a DMN region) increases its functional connectivity with premotor cortex. These results suggest that communication between DMN and task-related regions becomes more efficient with extensive practice. No region decreased its functional connectivity with precuneus or premotor cortex. However, as categorization became more automatic, coherence between MPFC and ventromedial prefrontal cortex decreased. These results bridge the cognitive and neuroscientific conceptions of automaticity in showing that the reduced need for cognitive resources in automatic processing is accompanied by a disinhibition of the DMN and stronger functional connectivity between DMN and task-related brain regions.

INTRODUCTION

Many daily tasks and behaviors are processed automatically. Automatic

activities are usually effortless and are done without the need for conscious monitoring.

For example, for some people playing piano and riding a bike are done automatically.

The ability to categorize objects is necessary in order to function properly in everyday

life. People categorize faces, objects, and scenes every day. In most cases

categorization is done automatically. For example when a driver sees a stop sign, s/he

usually automatically chooses the correct action and operates the brake pedal. This

thesis focuses on changes in brain activity related to automatic categorization.

The work in this thesis focuses on the relationship between the default mode

network (DMN) and automaticity. The DMN is a network of connected regions that is

active when participants are not engaged in an external task and inhibited when

focusing on an attentionally demanding task (Raichler et al., 2001). Because automatic

tasks require less attentional resources than controlled tasks (Shiffrin & Schneider,

1977), it is likely that DMN inhibition is reduced when performing an automatic task

(compared with a controlled task). In addition, Helie et al. (2010a) showed that the

brain areas involved in automatic rule-based categorization are different from those

involved in initial rule-based category learning. Specifically, initial category learning is

processed by a subcortical network centered around the head of the caudate nucleus but

after some practice the learned categories are re-encoded in the ventrolateral prefrontal cortex. Finally after extensive practice this cortical system becomes more caudal and dorsal, centering around the premotor cortex. This suggests that the cognitive task performed by participants changes with practice (Helie & Cousineau, 2011; Logan, 1988). Interestingly, there is also evidence suggesting that default mode network's pattern of functional connectivity changes depending on task (Spreng et al., 2010). Hence, it is likely that functional connectivity of the DMN changes with the development of automaticity.

This thesis focuses on changes in DMN deactivation and DMN functional connectivity as automaticity develops. To explore these topics, the fMRI data from 15 participants who were each trained for 20 sessions (over 10,000 trials) in a simple rule-based categorization task are re-analyzed (Helie et al., 2010a). The reminder of this thesis is organized as follows. First, default mode network's characteristics are discussed. Then a short review on automatic processing from both behavioral and biological perspectives is done. After the introduction on DMN and automaticity, two different studies are done in order to study changes in DMN after automaticity development. A deactivation level analysis in which deactivated regions in each session are identified and level of deactivation among sessions is compared. Then a seed-based functional connectivity analysis is done to compare patterns of functional connectivity between sessions 1 and 20. Finally the results of studying changes in DMN's neural activity after automaticity development are presented and relation between them and previous studies are discussed.

Default Mode Network

Comparing brain activity in control states with task states using PET and fMRI shows task-related increases in brain activity that are often task-specific. However, decreases in brain activity appear to be largely task independent (Raichle, MacLeod, Snyder, Powers, Gusnard & Shulman, 2001; Shulman, Fiez, Corbetta, Buckner, Miezin, Raichle & Petersen, 1997). In addition, studies on resting-state functional connectivity (rs-fMRI) identified a network including the same brain regions that are deactivated during tasks (Anticevic et al., 2012). This led to the idea that there is an organized system in the brain that is present as a default state and deactivated during goal oriented tasks.

Raichle and his colleagues (2001) suggested that the baseline state signals, associated with the default mode network (DMN), may be associated with an essential adaptive function of the brain. Attention to DMN in the scientific community further increased after observations showing changes in DMN activity in neurological and psychiatric diseases (when compared to control population). For example a lack of DMN suppression compared to a control group is observed in people with autism (Kennedy et al., 2006), schizophrenia (Buckner et al., 2008), Parkinson's disease (Eimeren et al., 2009) and depression (Buckner et al., 2008). There is also evidence showing that at the early stages of Alzheimer's disease, glucose metabolism is reduced in some of the DMN regions (Buckner et al., 2008).

Default Mode Network Brain Regions

Laird and his colleagues (2009) performed a meta-analysis of DMN from 840 participants. Nine regions were identified as part of DMN (shown in Figure 1):
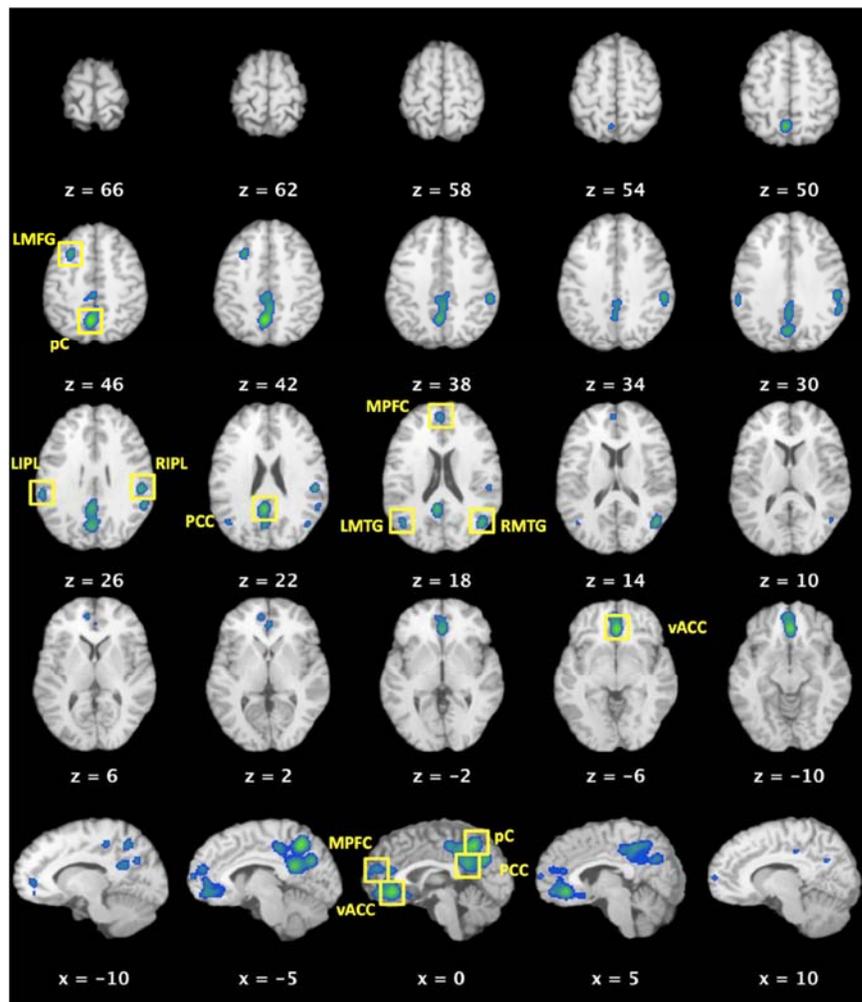
Figure 1. Meta-Analytic Identification of regions in the DMN ($p < 0.005$, corrected).

Regions identified as part of DMN and shown in the figure are: Precuneus (pC),

posterior cingulate cortex (PCC), ventral anterior cingulate cortex (vACC), dorsal

medial prefrontal cortex (MPFC), bilateral inferior parietal lobules (IPL), bilateral

middle temporal gyri (MTG), and left middle frontal gyrus (LMFG) (from Laird et al.,

2009).

Precuneus (pC), posterior cingulate cortex (PCC), ventral anterior cingulate cortex (vACC), dorsal medial prefrontal cortex (MPFC), bilateral inferior parietal lobules (IPL), bilateral middle temporal gyri (MTG), and left middle frontal gyrus (LMFG).

We used Laird et al (2009) results as the reference for the remaining of our analysis and result interpretation since it was a meta-analysis and results of a number of other DMN studies were taken into account for identifying DMN regions. However, it is important to note that results of some other studies are not exactly the same as the one that we introduced. For example Koshino et al (2014) did not identify left middle frontal gyrus (LMFG) as a DMN region but on the other hand hippocampal formation (HF) was identified as a DMN region.

Studies on DMN Function

There is no established view on DMN function. According to preliminary observations, DMN is activated when individuals are left to think by themselves without being disrupted by an external task. Baird and his colleagues (2012) argue that DMN might contribute to creativity. There are studies suggesting that it is associated with functions that have a self-referential component (Buckner & Carroll, 2007). This evidence suggests that DMN is related to simulation of a world not being externally observed and perceiving internal modes of cognition (Buckner & Carroll, 2007). In all cases, however, the DMN functions seem to be related functions that are not triggered by stimuli from the outside world.

<div align="center">Automatic Processing</div>

Even though intuitively automaticity is understood easily, it's hard to rigorously define it from a scientific point of view. There are two ways to define automaticity,

either by features of it or by explaining the cognitive processes underlying it (Helie & Cousineau, 2011). In the review paper by Helie & Cousineau (2011) both approaches are discussed.

Features reviewed and discussed by Helie & Cousineau (2011) include efficiency, inflexibility, need for extensive practice and fast response. Some of the features are more intuitive (e.g. need for extensive practice), but some are more controversial (e.g. inflexibility) and there is not a general agreement on features of an automatic action. Furthermore, it is not even clear if it is possible to define automaticity by behavioral features alone.

One alternative to feature-based approaches are process-based explanations of automaticity. Two possible processes for explaining automaticity are strategy shift and algorithm strengthening. Strategy shift approaches claim that qualitatively different cognitive processes are responsible for automatic and non-automatic actions whereas algorithm strengthening views claim that same algorithm that is used for non-automatic behavior is used at the automatic stage and the difference is that participants get better at using that algorithm after extensive training. The task-related fMRI analyses performed on the data used for this thesis support a strategy-shift approach to automaticity (Helie et al., 2010a).

Hypothesis

The goal of this study is to explore the alterations in DMN activity after automaticity develops in a categorization task. We re-analyzed data first published in Helie et al (2010a) to study changes in BOLD signals related to automatic categorization. Participants were trained for 20 sessions and acquired automaticity

(Helie et al., 2010b). Since automatic task processing requires less attention than early stages of performing a task, it should result in less inhibition of the DMN (or, in other words, more DMN activity while performing the task). The first step is to identify regions that are deactivated in each of the four sessions and also compare them to see if there are DMN regions which are less deactivated in sessions 4, 10 and 20 compared to the first session (these were the four scanning sessions; other training sessions were performed outside the scanner).

The next step is to go beyond activation levels and explore how functional connectivity of DMN changes as automaticity develops. There are studies (e.g. Spreng et al., 2010) that show that depending on the task, functional connectivity between DMN and other brain regions change. Comparing functional connectivity between early stages of categorization and automatic stage could be interesting because at the automatic stage (unlike early stages of categorization), participants do not need to disrupt whatever they are thinking after stimulus presentation, they can continue their day dreaming, etc. and nonetheless do the task well. This may result in a stronger coupling between DMN and task-related regions. To investigate this hypothesis, we want to identify regions that either strengthen their functional connectivity with precuneus and medial prefrontal cortex (two key DMN regions) or reduce it (the reasons for choosing these regions will be explained later). In addition, there is evidence (Helie et al., 2010a) suggesting that at the automatic level different brain regions are responsible for categorization. Premotor cortex is an important region for categorization at the automatic stage and to investigate the same hypothesis we want to

identify regions that increase or decrease their functional connectivity with premotor

cortex after automaticity development.

DEACTIVATION LEVEL ANALYSIS

Methods

The hypotheses were tested by re-analyzing event-related functional magnetic resonance Imaging (fMRI) data of 15 participants trained for 20 sessions in a rule-based categorization task. The stimuli were circular sine-wave gratings of constant contrast and size as shown in Figure 2. The scanning sessions were conducted at University of California Santa Barbara, Brain Imaging Center using a 3T Siemens TIM Trio MRI scanner (details can be found in Helie et al (2010a)). We analyzed brain scans of participants at 4 different stages of training: 1st session (with no previous practice), 4th session (after 1,680 trials of practice), 10th session (after 5,160 trials of practice) and 20th session (after 11,040 trials of practice).

One group of participants did the simple 1-D condition (Figure 2-c) and another group did the disjunctive rule condition (Figure 2-b). For the simple-1D condition stimuli with frequency smaller than a set value formed category A, whereas stimuli with frequency greater than that set value formed the category B. For the disjunctive rule condition category A was uniformly distributed in two regions divided along the frequency dimension. Category A stimuli were defined as having frequency greater than a set value or smaller than another set value. Category B stimuli were defined as having frequencies between those two set values. Participants responded using two
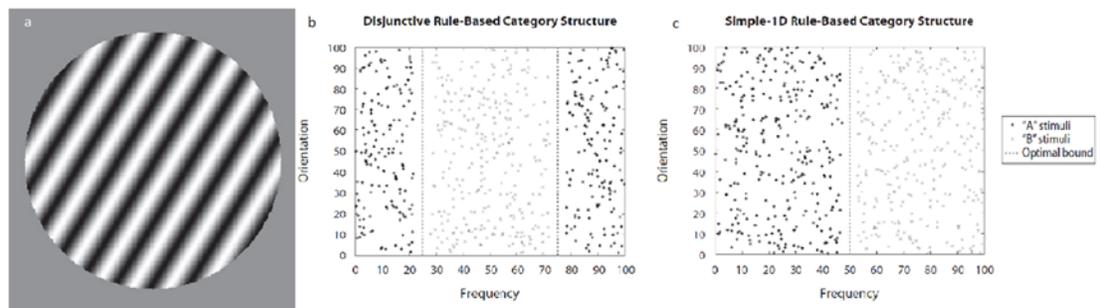
Figure 2. (a) Stimulus and category structures in (b) disjunctive rule and (c) simple 1-D condition (from Helie et al., 2010a).

button boxes: Button box in the left hand for category A and button box in the right

hand for category B.

The experiment was a rapid-event related design with a repetition time (TR) of

2 seconds (Helie et al., 2010a). Each stimulus was presented for 1 TR. Correct

responses were followed by a green check mark displayed for 1 TR. Incorrect

responses were followed by a red "X" mark displayed for 1 TR.

The timing of a trial scaled in TR is shown in Figure 3. The number of blank

TRs between stimulus and feedback was jittered with a truncated geometric

distribution with $p = 0.5$ (maximum 3 TRs), whereas the number of blank TRs between

the feedback and the next stimulus was jittered with a truncated geometric distribution

with $p = 0.5$ (maximum 5 TRs). Jittering is done to decrease the correlation between

the regressors, which increases the efficiency in estimating parameters. When one or

more TR was inserted between the feedback and the following stimulus (48% of the

trials), a crosshair was displayed in the second half of the TR immediately preceding

stimulus presentation. As a result, the mean correlation between two regressors of

interest (i.e., stimulus and crosshair) was 0.07.

Participants in both simple 1-D and disjunctive rule conditions reached a

similar level of accuracy and response time after third and second session of practice

respectively (RTs were compared only between session that were done in the lab,

because for the sessions that were done in the scanner response environment and

response keys were different). Figure 4 shows accuracy of each session for each

condition. However, some behavioral features kept improving. For example, there is

evidence showing that categorizing stimuli that are close to the category boundary is
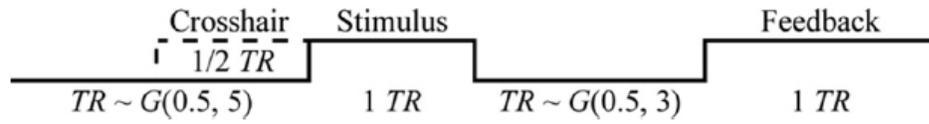
Figure 3. Event structure in experiment (from Helie et al., 2010a).
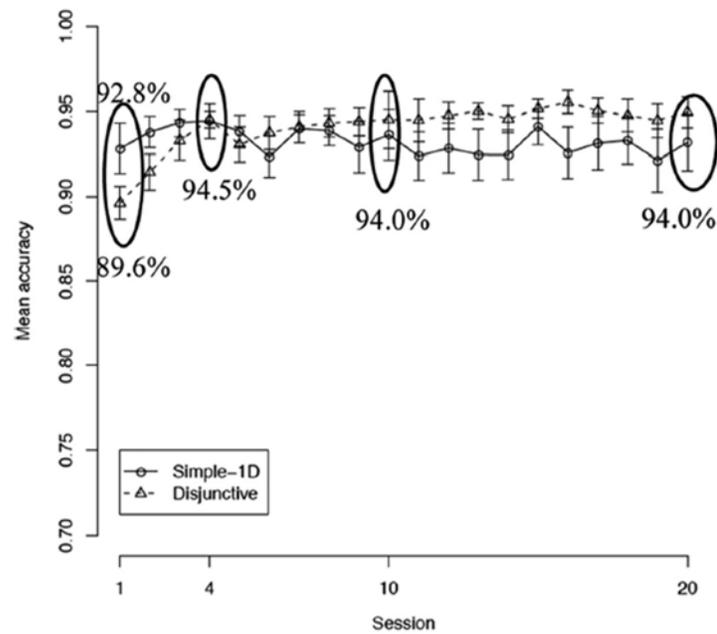
Figure 4. Mean accuracy in each session (from Helie et al., 2010a).

more difficult than categorizing stimuli that are further away (Maddox et al., 1998).

This distance-to-bound effect was initially stronger for simple 1-D condition but after

14 sessions the difference diminished. As a result, Helie et al. (2010b) concluded that

automaticity was fully developed between sessions 10 and 20. Note that only sessions

1, 4, 10 and 20 were completed in the MRI scanner. For the purpose of current study

the data from two rule-based conditions were merged.

Preprocessing fMRI Images

All of the preprocessing and statistical analysis steps were done through the

FMRIB Software Library (FSL) (Jenkinson, Beckmann, Behrens, Woolrich & Smith,

2012).

Spatial Transformation for Motion Correction

We used an affine transformation called "Rigid body transformation" as the

transformation model for motion correction (Poldrack, Mumsford & Nichols, 2011).

The size of each voxel is $3 \times 3 \times 3.51\ mm$, hence we considered scans with more

than 3mm displacement on average as too much motion and eliminated those scans for

analysis (about 8% of data).

Slice Timing Correction

Data acquisition was interleaved, first even slices acquired and after that odd

slices. In order to interpolate time series of slices to the middle of TR, we used a

(Hanning-windowed) Sinc function in FSL.

Spatial Smoothing

Spatial smoothing is done to increase the signal to noise ratio. We used a three dimensional Gaussian filter. The amount of smoothing is determined by the full width at half maximum (FWHM) of the filter. We chose FWHM of filter to be 5mm.

Statistical Analysis

Convolving Model With HRF

When a brain region is engaged during a cognitive task, neuronal firing rate increases, which leads to increased metabolic needs for neurons (Ogawa, Lee, Kay & Tank, 1990). In order to satisfy this metabolic need, cerebral blood flow changes, and this affects the concentration of deoxyhemoglobin in the brain area. This physiological phenomenon corresponds to the (BOLD) signal measured in fMRI.

Since changes in blood flow are relatively slow, hemodynamic response is a low-pass filtered delayed version of actual neural activity (Ogawa et al., 1990). In order to estimate this function, we need to model its characteristics such as peak height, time to peak and width.

There is evidence showing that the transformation from neural activity to BOLD signal is linear time invariant (LTI) (Poldrack et al., 2011), thus we can convolve an explanatory variable pattern (Figure 5) with an Haemodynamic response function (HRF) in order to create a more accurate estimate of shape of the BOLD signal corresponding to that presentation pattern. In our analysis, the HRF is a Gamma function with mean lag of 4 seconds and standard deviation of 3 seconds.
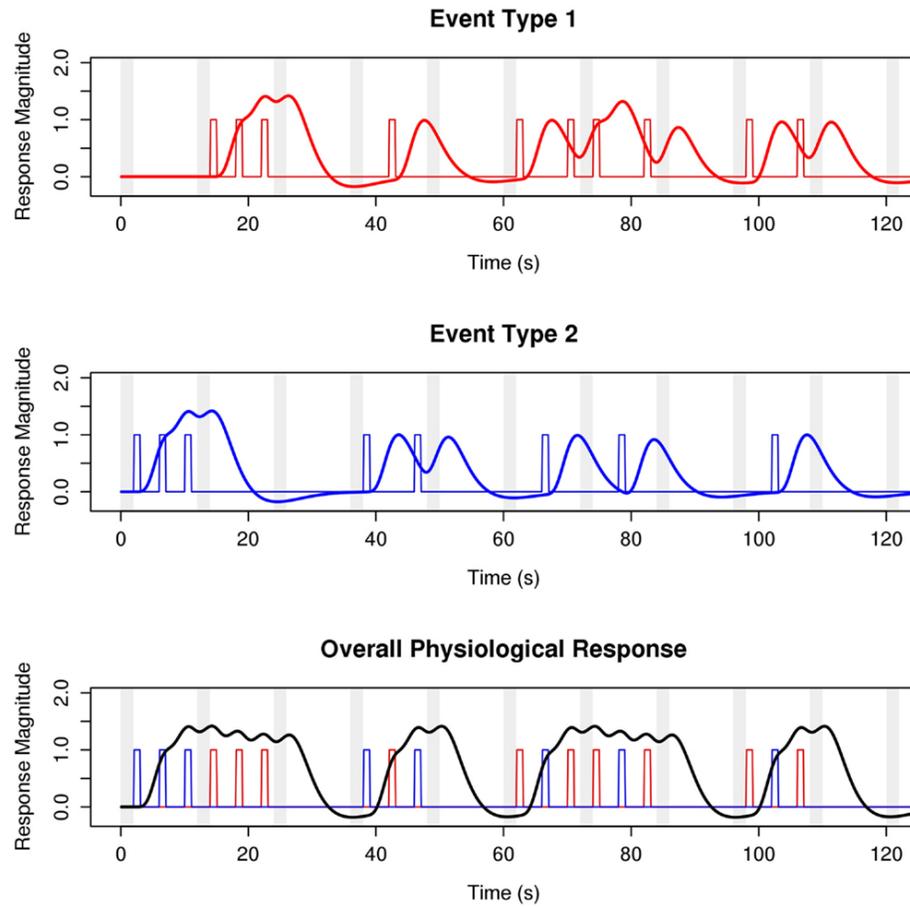
Figure 5. BOLD response (black line) to two events, event A (blue line) and event B (red line) (from Perrachione et al., 2013).

Linear Modeling

To find active voxels we applied linear modeling to each voxel. We had four events presented to participants when they were in the scanner: Stimulus (S), Feedback (FB), Blank (B), Crosshair (C). In this case linear modeling can be formulated as follows:

$$y(t) = a_1 S(t) + a_2 FB(t) + a_3 C(t) + a_4 B(t) + b + e \quad (1)$$

where $y(t)$ is the data (time series for a certain voxel), and $S(t), FB(t), C(t)$ and $B(t)$ are model events. A model event is 1 at time t if it is present at that time and it is 0 otherwise. For example $S(t)$ is 1 if the stimulus is present at time t and 0 otherwise. b corresponds to rest intensity of the voxel and e is error. In this model, if a specific voxel responds for example to stimulus, a_1 will be a large value.

For each voxel value a_1, a_2, a_3, and a_4 will be estimated. In order to convert parameter estimates (PEs) to statistical maps, the PE are divided by an error estimate corresponding to that PE value. PE divided by its error estimate results in a *t* value. This *t* value is calculated for each voxel and can be transformed into a *z* values.

The goal of this study was to compare activation in Crosshair (C) with Stimulus (S). The reason to choose Crosshair (over Blank, for example) is that in Crosshair, a fixation point is shown on the screen which makes the brain activity in primary visual regions similar to when Stimulus is shown on the screen and as a result the difference would be due to task related brain activity. The contrast of interest was $a_3 - a_1$. The two PEs were subtracted from each other, and a pooled standard error was calculated.

Dividing $a_3 - a_1$ by the pooled standard error resulted in a value that could be transformed to produce z-images.

Visualization and Higher Order Analysis

Image Registration

For visualization and higher level analyses the functional images of each participant are aligned to their structural image, and the resulting image is aligned on a standard brain image. We used the MNI152, a widely used standard image. This standard registration is required for visualization and for higher-level analyses.

Higher Order Analyses

There were 15 participants in the experiment and each of them was scanned for four sessions. Each scanning session of each participant consisted of 6 blocks and there were three missing sessions in our data so 342 separate low-level analyses were performed. After analyzing each block of each session for each participant separately and aligning brain images on the standard brain (MNI 152), we performed within-session averaging in each session for each participant in order to have a single statistic map of each session for each participant (57 separate analyses). Next, between-participant averaging was done for each session (4 separate analyses). Thus, we end up with 4 statistical maps corresponding to DMN activity at 4 different stages of category learning.

For within session averaging we used fixed effect modeling. Fixed effect modeling ignores cross-session and cross-participant variance and so reported activation is with respect to the group of sessions or participants present, and not representative of the wider population.

Between-participant averaging was done using mixed effect modeling. We used the FLAME 1+2 algorithm (Beckmann, Jenkinson & Smith, 2003), a sophisticated two-stage process using Bayesian modeling and estimation. We used *z*-threshold of 2.81 (significance level of 0.0025) for voxel wise significance and statistic images were assessed for cluster-wise significance using a cluster-defining threshold with significance level of 0.01.

Comparing Deactivation Level in Different Sessions

In order to see the effect of training on suppressing DMN activity, we computed a linear model with these regressors:

$$S_1, S_2, S_3, \dots, S_{15}, D_2, D_3, D_4$$

where S_i is participant i and D_2, D_3, D_4 corresponds to session 4, 10 and 20. Session 1 is not included as a regressor (it will be taken into account as baseline). Participants are considered to be regressors to model additional variance due to individual differences.

$$y(t) = a_1 S(t) + a_2 S_2(t) + \cdots + a_{15} S_{15}(t) + a_{16} D_2(t) + a_{17} D_3(t)$$
$$+ a_{18} D_4(t) + b + e \quad (2)$$

To explore which brain region levels of deactivation are decreased, each session was contrasted with session 1. Since session 1 is not a regressor, and it is taken into account in the baseline term (b), the contrast matrix to compare levels of deactivation between sessions 4, 10 and 20 with session 1 is simply composed of the negative of the

estimated regressors, i.e., $(-a_{16})$, $(-a_{17})$, and $(-a_{18})$ for sessions 4, 10 and 20 (respectively; see bottom of Figure 6).

The resulting design matrix is shown in Figure 6 (top part). In Figure 6 (top part), columns are regressors (participants 1,...,15 and sessions 4, 10 and 20). Each regressor (column) is labeled at the bottom of the design matrix. There are 56 rows, each corresponding to a participant in one of the four sessions. In the matrix, light gray bars indicate affiliation to a regressor (i.e., a value of 1 in the matrix) and each dark gray bar correspond to a 0 in the design matrix. For example, the first row corresponds to participant 2. Because there is no light gray bar in any of the last three columns of the matrix, this row corresponds to session 1 data (of participant 2.) As can be seen from the matrix, there are four missing sessions: session 1 of participant 1, and session 3 of participants 9, 11 and 108. The contrasts are shown at the bottom of the design matrix. C1 is used for identifying regions which were less deactivated in session 4 compared to session 1, C2 and C3 are similar for comparing session 1 with sessions 10 and 20.

We used z-threshold of 1.645 (significance level of 0.05) for voxel wise significance and statistic images were assessed for cluster-wise significance using a cluster-defining threshold with significance level of 0.05.

Deactivation Level Results

DMN Deactivation Level on Each Session

As a first step, the mean of each session for the contrast of Baseline>Stimulus is computed to produce a separate brain map for each session. In analyzing fMRI images, we only considered the correct categorization trials.
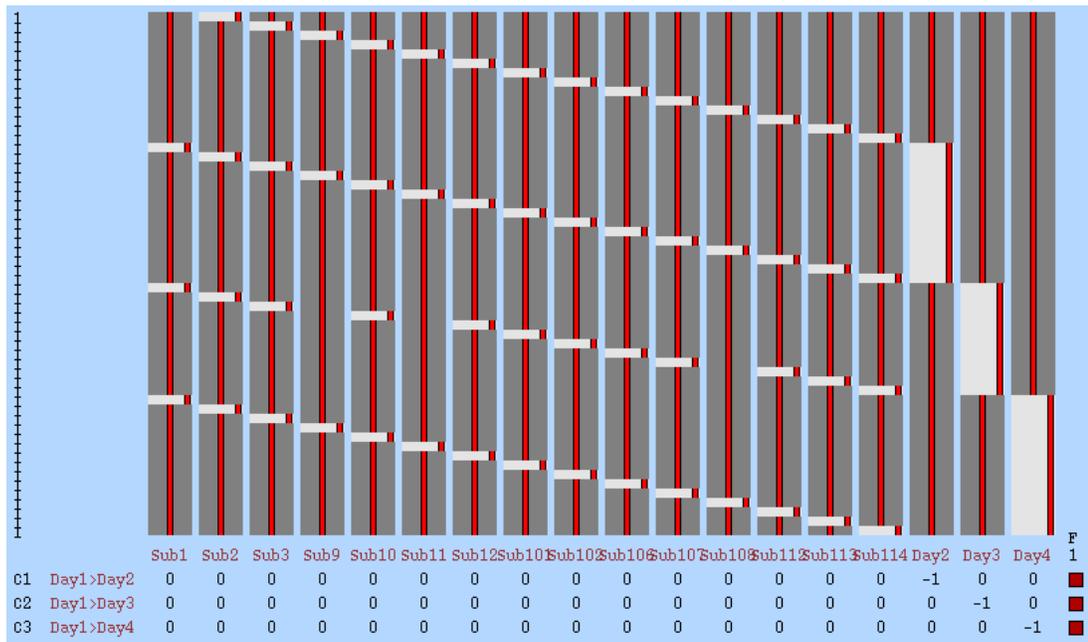
Figure 6. Design matrix for comparing degree of deactivation in different sessions.

Baseline > stimulus in session 1. Figure 7 shows the results in Session 1. Two regions were found in which level of activity was higher in crosshair compared to stimulus. These two regions were medial prefrontal cortex (MPFC) and left inferior parietal lobule. These areas are both part of the DMN.

Baseline > stimulus in session 4. Figure 8 shows the results in Session 4. Four regions were found in which level of activity was higher in baseline compared to stimulus. These four regions were medial prefrontal cortex (MPFC), left inferior parietal lobule (lIPL), right inferior parietal lobule (rIPL) and precuneus (pC). As in Session 1, these regions are all part of the DMN.

Baseline > stimulus in session 10. Figure 9 shows the results in Session 10. Four regions were found in which level of activity was higher in baseline compared to stimulus. These four regions were left inferior parietal lobules (IPL), precuneus (pC), left middle temporal gyrus (lMTG) and right middle temporal gyrus (rMTG). Again, all of these regions are part of DMN.

Baseline > stimulus in session 20. No regions were found in this session. This suggests that no brain region suppressed while participants were doing task.

Comparing Deactivation Level in Different Sessions

After obtaining separate statistical maps for each session, we compared voxel-wise levels of deactivation in the first session with other sessions. There was no statistically significant difference between levels of deactivation of session 1 and sessions 4 and 10. However, two clusters were found in which deactivation was lower in session 20 when compared to session 1. One of the clusters contained medial prefrontal cortex and anterior cingulate cortex, and the other cluster contained
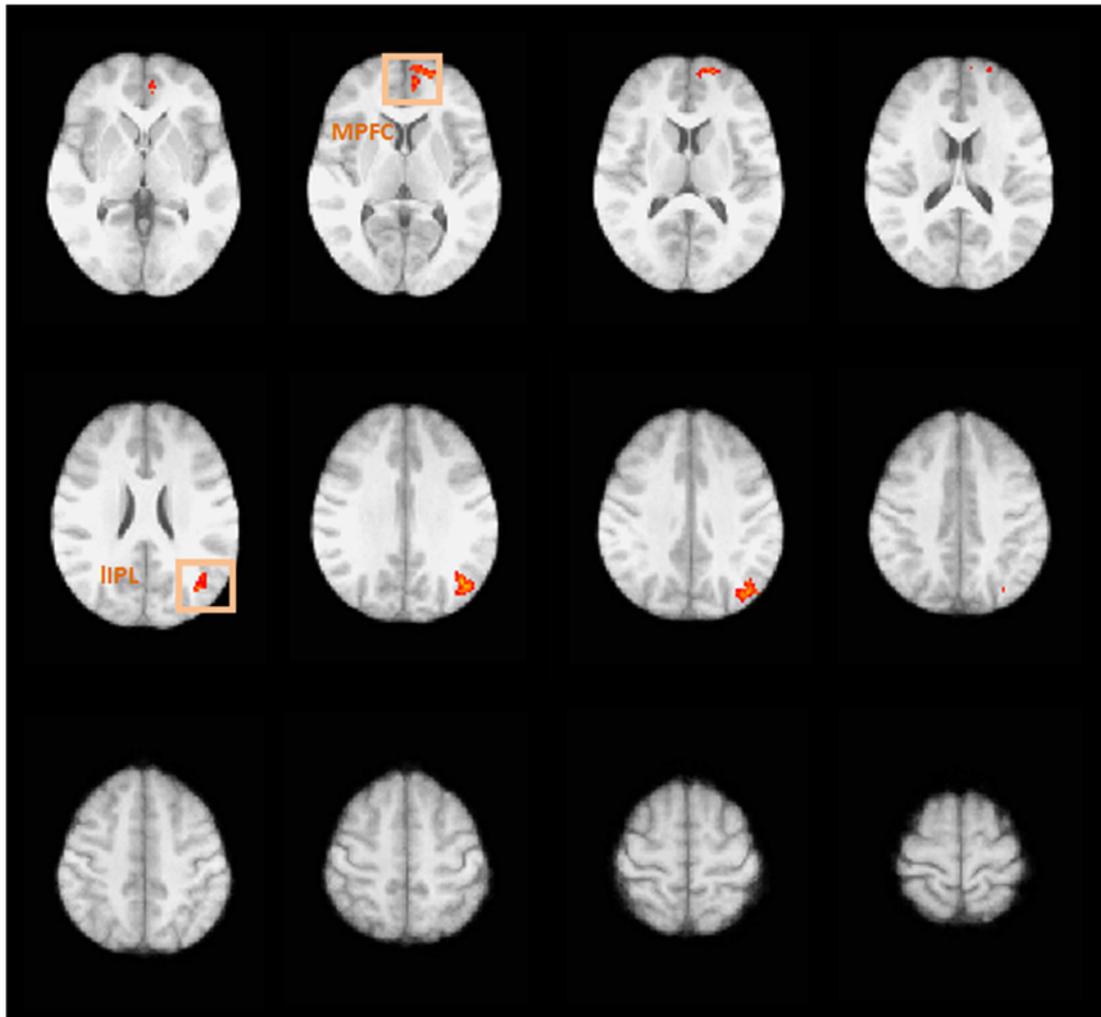
Figure 7. DMN regions deactivated in first session: medial prefrontal cortex (MPFC),

left inferior parietal lobule.
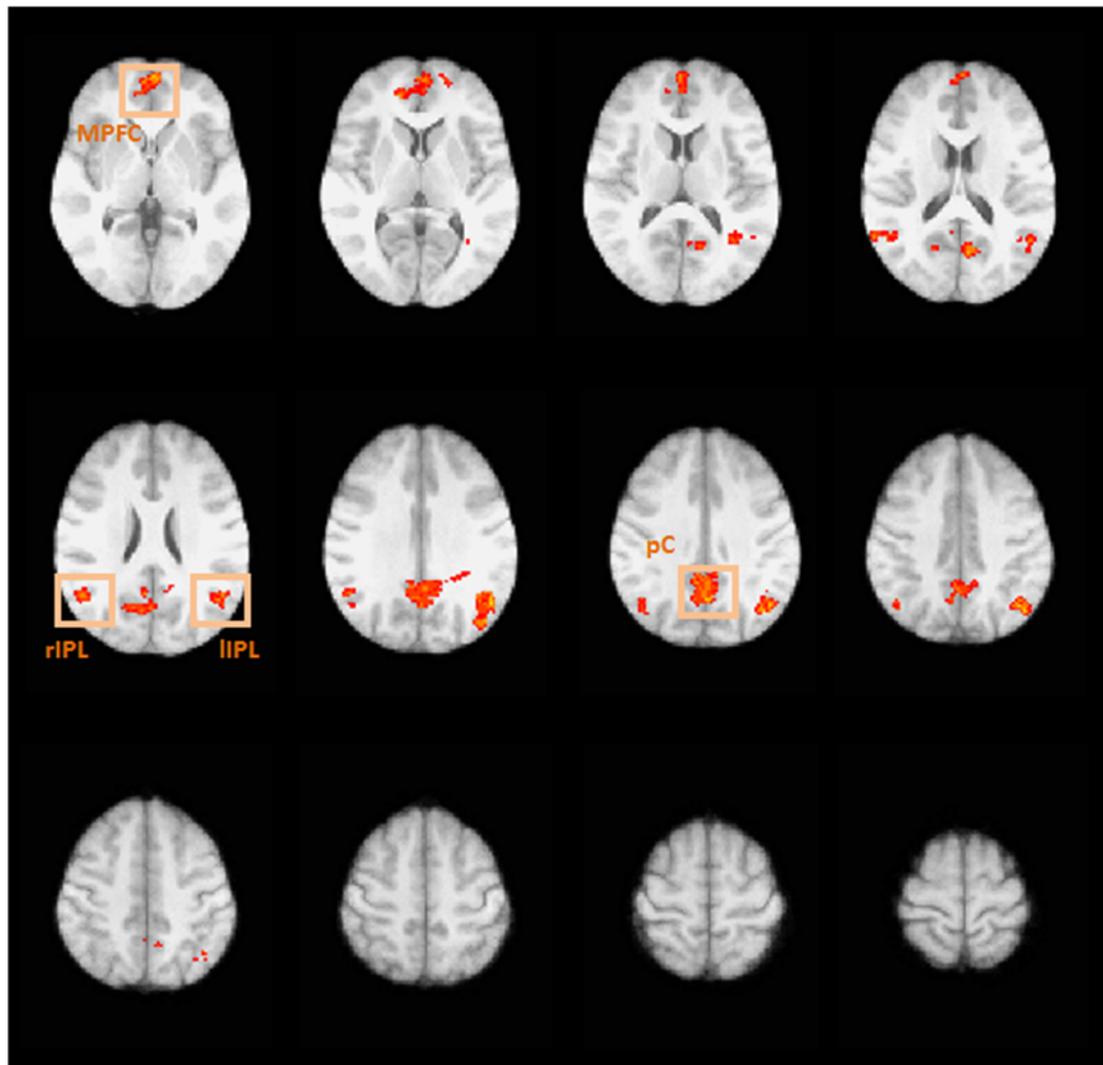
Figure 8. DMN regions deactivated in fourth session: medial prefrontal cortex (MPFC), bilateral inferior parietal lobules (IPL) and precuneus (pC).
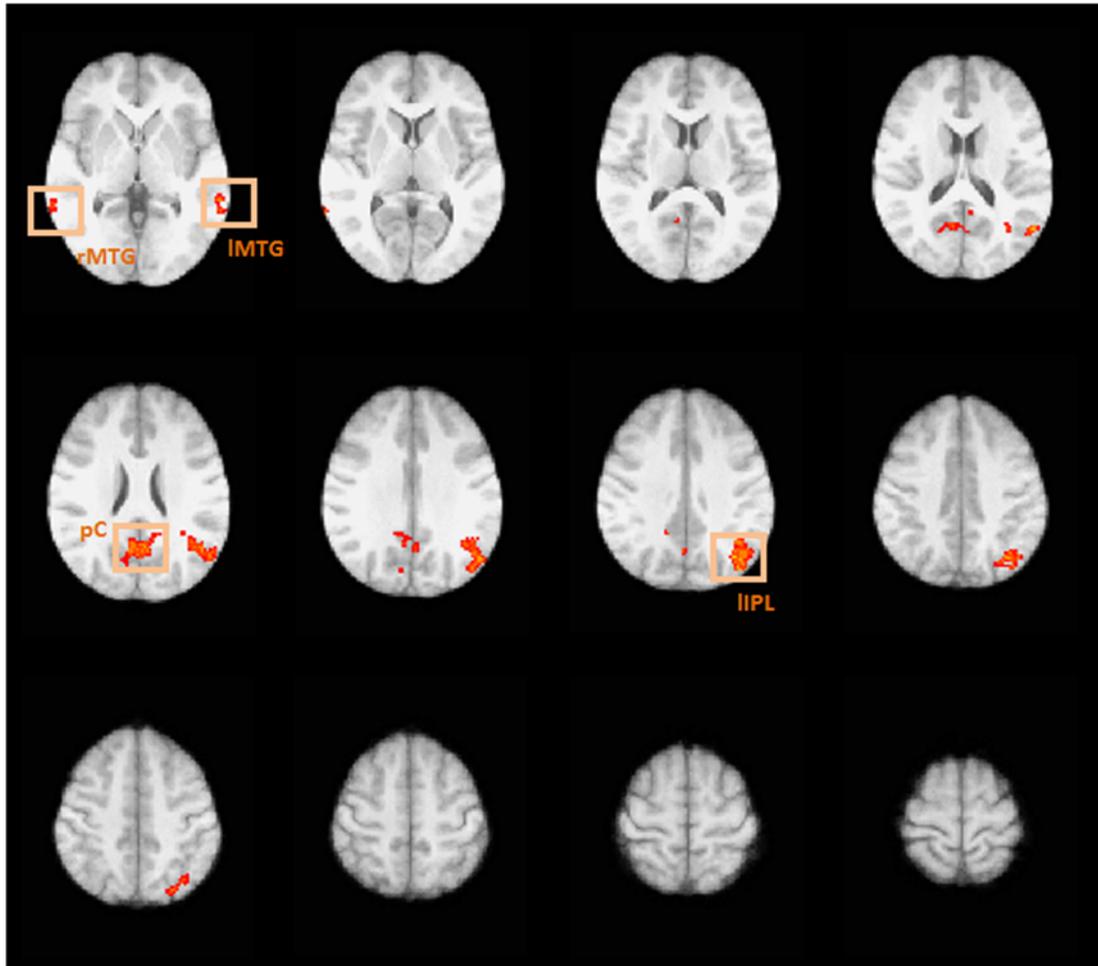
Figure 9. DMN regions deactivated in tenth session: bilateral inferior parietal lobules (IPL), precuneus (pC), bilateral middle temporal gyri (MTG) and left middle frontal gyrus (LMFG).
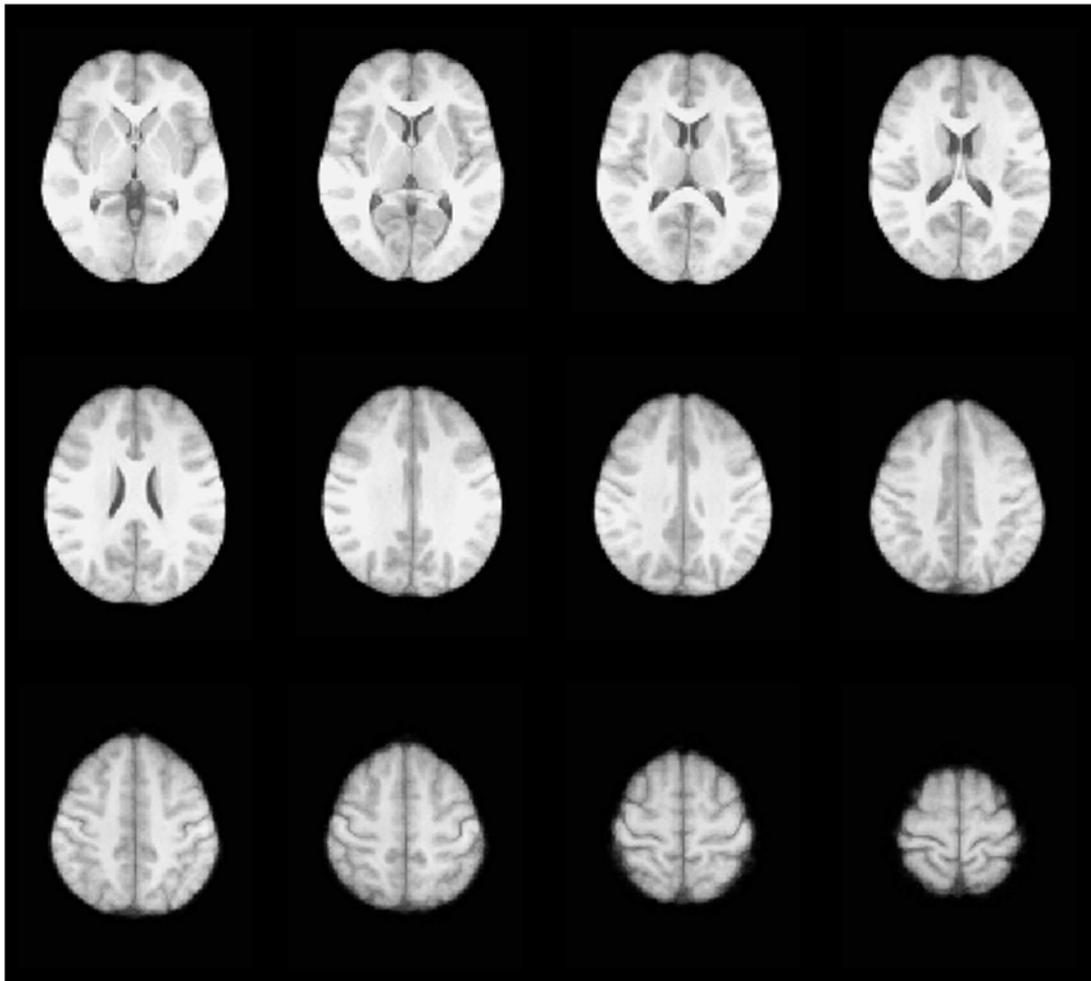
Figure 10. No region identified as being deactivated in session 20.
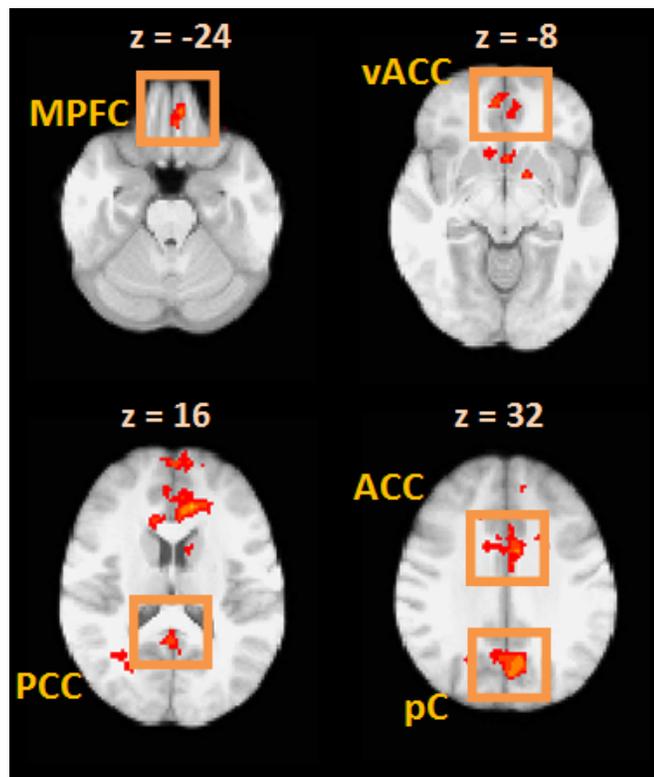
Figure 11. DMN regions deactivated more in the first session than in the last session:

the first cluster includes medial prefrontal cortex and anterior cingulate cortex. The

second cluster includes the precuneus and the posterior cingulate cortex.

precuneus and posterior cingulate cortex. There is a small portion of the more anterior cluster (which include anterior cingulate cortex) that is not part of the DMN, but the larger portion and the other cluster are both DMN regions.

Discussion on Deactivation Levels

There are DMN regions that were found to be deactivated while participants were completing the task in sessions 1, 4 and 10. The results are in accordance with how DMN was originally characterized, which is deactivation when focus is on the external world. However, no regions (DMN or non-DMN) were identified as being deactivated while participants were doing the task in session 20. This is consistent with the hypothesis that at the automatic stage there is less need to pay attention to the task. Comparing sessions 4 and 10 to session 1 showed no difference in deactivation but there are four DMN regions that were more deactivated in session 20 compared to session 1, which shows that DMN's pattern of activation changes as automaticity develops. Changes can be attributed to automaticity development since comparisons are made on the contrast between Crosshair and Stimulus, therefore they cannot be due to the fact that partcipants get more familiar with lab equipment.

While these results suggest that DMN deactivation is reduced with extensive practice, it is unclear whether these changes are accompanied by changes in functional connectivity both between DMN regions and between task-related and DMN regions. In order to investigate other aspects of changes that may occur in DMN after the development of automaticity, a functional connectivity analysis was conducted to observe which areas of the brain change their functional connectivity with the precuneus and the medial prefrontal cortex (two key DMN regions). In addition, there

is evidence suggesting that the premotor cortex is the most important region involved in automatic categorization (Helie et al., 2010a), so another functional connectivity analysis was conducted with premotor cortex as a seed region to see if any of the DMN regions change their functional connectivity with premotor cortex as automaticity develops.

FUNCTIONAL CONNECTIVITY

Results from studying deactivation in different stages of category learning and comparing them suggest that DMN activation patterns change as automaticity develops. In deactivation level analysis single voxels' activity were compared without looking at relations between them. Functional connectivity analysis aims to look at functional interactions between spatially remote neurophysiological events, so instead of looking at how one single voxel's activity changes, the relation between them is compared. Using particular seed regions allows for looking into the hypotheses more specifically than deactivation level analysis. As a result, the next step was to study how functional connectivity of precuneus, medial prefrontal cortex (two important DMN regions) and premotor cortex (an important region for categorization at the automatic level) changes after extensive practice. Results from deactivation level comparison showed that level of deactivation in session 20 is less than session 1, but no difference was detected when session 1 was compared to sessions 4 and 10. So in the functional connectivity analysis only sessions 1 and 20 are compared.

Precuneus was chosen as a seed region because there is evidence suggesting that it is the functional core of DMN (Utevsky et al., 2014). Utevsky et al (2014) studied brain networks to see how they interact and how behavior is orchestrated. They showed that precuneus is the only region that during rest increases its functional

connectivity with DMN network (compared to task state) and also increases its functional connectivity with task dependent regions during task (compared to rest). The mask was created by using voxels that have a probability of 70% or more of being part of the precuneus according to the Harvard-Oxford cortical structural atlas. The mean time-series of the mask was used as the seed for coherence analyses.

Medial prefrontal cortex is another important DMN region. A study by Uddin et al (2009) on resting state data suggest that MPFC may have a role in modulating visual spatial and temporal attention networks. This is an interesting finding and it is related to the hypothesis that we want to test. Specifically, if we find that MPFC couples more strongly with task related regions, this may indicate that the modulatory role of MPFC discussed in Uddin et al (2009) increases with the development of automaticity. The mask was created by using voxels that have a probability of 70% or more of being part of the medial prefrontal cortex according to the Harvard-Oxford cortical structural atlas. The mean time-series of the mask was used as the seed for coherence analyses.

Finally, premotor cortex was chosen since it is considered to be the most important region for categorization at the automatic level (Helie et al., 2010a). Functional connectivity analysis with premotor cortex as seed was conducted to see if there is any DMN region that changes its functional connectivity pattern with premotor cortex at the automatic level. The mask was created by using voxels that have probability of 70% or more of being part of the premotor cortex according to the Juelich histological atlas. The mean time-series of the mask was used as the seed for coherence analyses.

Methods

We took the mean of all of the voxels in each seed region at each point of time, formed a time series and then computed the coherence of all the other voxel's time series with the time series of the seed region.

Functional Connectivity Measure: Coherence Versus Correlation

Coherence is a measure to test the strength of association between two time series. It calculates a value in frequency domain, similar to what is calculated by correlation in time domain. Since it is depended on similarity of simultaneous values in frequency domain (and not time domain), it takes into account leaning, lagging and smoothed relationships. Coherence has a number of advantages over correlation as a functional connectivity measure. First, the lag in functional connectivity between two time series is not known and, unlike correlation, coherence is not sensitive to the lag. Second, the hemodynamic response function (HRF) may be different in various parts of the brain (Schacter 1997). Different HRF reduces correlation between two regions even if they have identical neural activation. However, it can be shown that coherence remains unchanged (Ashby 2011). Third, the effect of adding noise can be reduced in coherence compared to correlation. Noise affects high frequency components more than low frequency components and since the hemodynamic response function contains information only in frequencies between 0 and 0.15 Hz (Sun et al., 2004), coherence is computed only in this frequency band, and therefore the effect of noise is reduced.

However, one advantage of correlation over coherence is that correlation allows for both positive and negative values so that positive and negative values can be

interpreted differently. In contrast, coherence of time series will always be positive. As

a reminder, the hypothesis in this study is based on changes in functional connectivity

between DMN and other brain regions depending on tasks (e.g. Spreng et al., 2010). If

the participants are performing the automatic task differently (as suggested by the

deactivation results above and those from Helie et al., 2010a), then it is possible that

functional connectivity also changes. However, we do not have strong hypotheses

related to the sign of the changes. More specifically, the goal of functional connectivity

analyses with precuneus and MPFC (two important DMN regions) as seed regions is to

test the hypothesis that these brain regions strengthen their associations with regions

that might be involved in task. Similarly for premotor cortex we want to see if this

region strengthens its association with DMN regions after automaticity development.

However, we do not have strong hypotheses as to whether these regions should activate

or inhibit one another. For this reason, the benefits of coherence over correlation

outweigh the limitations and coherence was chosen as our measure for functional

connectivity.

Nuisance Model

A possible approach to compute functional connectivity is to first remove

unwanted variance from the functional connectivity analysis (e.g., task-related

variance). The first step is to fit a model to the data that includes all sources of

variance. This is the same as the model that we used to find deactivated regions

(equation(1)), but since it is used to remove unwanted variances, in this context it is

called a nuisance model (Poldrack, Mumsford & Nichols, 2011).

As our first step in the functional connectivity analysis we fit this model to take into account systematic variations in our data that we are not interested in for our analysis. So we used the "e" of each time series to compute our functional connectivity measure. In this way we exclude all of the unwanted variance that we would not want affecting functional connectivity.

Coherence

We computed coherence between the precuneus and other voxels in the brain as the measure of functional connectivity. Coherence is used to measure linear time invariant relationships between time series.

To compute coherence, we first define cross-spectrum and power spectrum. Cross-spectrum $f_{xy}(\lambda)$ of x and y is the Fourier transform of the cross-covariance between the two time series while the power spectrum $f_{xx}(\lambda)$ of a time series is the Fourier transform of its auto-covariance:

$$f_{xy}(\lambda) = \sum_u Cov_{xy}[u]e^{-j\lambda u} \quad (3)$$

$$f_{xx}(\lambda) = \sum_u Cov_{xx}[u]e^{-j\lambda u} \quad (4)$$

In the above equations u is the lag in which cross covariance (or auto-covariance is calculated):

$$Cov_{xy}(u) = E\{(x[t] - \mu_x)(y[t + u] - \mu_y)\} \quad (5)$$

Coherence is computed in the same way as cross-correlation:

$$Coh_{xy}[\lambda] = \frac{|f_{xy}(\lambda)|^2}{f_{xx}(\lambda)f_{yy}(\lambda)} \quad (6)$$

In order to obtain a single value from this function to form brain maps of functional connectivity, the frequency domain that will be used to determine the functional connectivity needs to be selected. As mentioned before, hemodynamic response function contains information only in frequencies between 0 and 0.15 Hz (Sun et al., 2004). This frequency band was thus selected.

Computing coherence in a specific frequency domain. Any linear time invariant operation on a time series makes changes in non-zero components in frequency domain of the time series. On the other hand other types of operations like sampling and windowing lead to changes in frequency domain that might create new frequency components. The phenomenon 'spectral leakage' usually refers to changes resulted by windowing and it refers to localized spreading of the frequency domain. To reduce spectral leakage, estimates of cross-spectrum and power spectrum are used instead of the values themselves. Cross-spectrum and power spectrums for discrete time series were estimated by Welch's modified periodogram averaging method (Welch 1967) through Matlab (Matlab, 2012).

In order to obtain brain maps of functional connectivity we need a single value measure for the functional connectivity in each voxel. To do so, we used (Andrew and Pfurtscheller 1996):

$$\widehat{Coh}_{xy}(\bar{\lambda}) = \frac{\left|\sum_\lambda \widehat{f_{xy}}(\lambda)\right|^2}{\sum_\lambda \widehat{f_{xx}}(\lambda) \sum_\lambda \widehat{f_{yy}}(\lambda)} \quad (7)$$

where $\widehat{f_{xy}}$, $\widehat{f_{xx}}$ and $\widehat{f_{yy}}$ are estimates of cross-spectrum of x and y and power

spectrums of x and y respectively and the sum is over all the frequencies that we want

to include in measure.

Binomial Testing

The goal of this analysis is to compare session 1 and session 20 to explore

whether the coherence of different brain regions with seed areas change as automaticity

develops. A standard paired t-test was not possible because the distribution of

coherence values did not appear to be normal. We thus ran two series of one-tail

binomial tests on each voxel. First, a one-tail binomial test was done to identify brain

regions that show stronger coherence with the seed region after extensive practice.

Second, another test was done to identify regions that reduced their coherence with the

seed region after extensive practice.

We defined success for a voxel as having a stronger coherence in session 20

compared to session 1. The null hypothesis was no change in coherence after

automaticity development. In our binomial test terminology this was translated as

having probability 0.5 of success.

We defined $Coherence_i^{20}$ and $Coherence_i^1$ as coherence of ith voxel at

session 20 and 1 respectively. Then D_i was defined as difference between coherence at

session 20 and session 1 for i^{th} voxel:

$$D_i = Coherence_i^{20} - Coherence_i^1 \quad (8)$$

$$i = 1,2,\ldots,13,14$$

Values of $D_i > 0$ were translated to 'success' in our binomial test and $D_i < 0$ were translated to 'failure'. For each voxel two binomial tests were done. In the first test voxels that showed 12, 13 or 14 successes (yellow shaded region in Figure 12) were marked (i.e. voxels showed stronger coherence with precuneus after practice in 12, 13 or 14 participants) and in the second test voxels with 0, 1 or 2 successes (shown in Figure 13) were marked (i.e. voxels showed weaker coherence with precuneus after practice in 12, 13 or 14 participants). Probability of rejecting the null hypothesis would be 0.0065 for each test and after correction for multiple testing it is 0.0130.

Cluster Size Correction

When considering a set of statistical inferences simultaneously, the 'multiple testing problem' occurs (Miller 1981). In this situation null hypothesis is more likely to get rejected. This makes comparing significance levels of single multiple tests difficult. There are techniques called 'multiple testing correction' that address problems associated with multiple testing.

When dealing with fMRI data one possible solution is cluster size correction. There are different standards for making clusters, in three dimensions there are 6-connected, 18-connected and 26-connected neighboring standards. We chose 26-connected neighboring standard which means that a voxel is connected to another voxel if it touches one of its faces, edges or corners. Clusters were formed using voxels that were statistically significant according to the binomial testing described above.
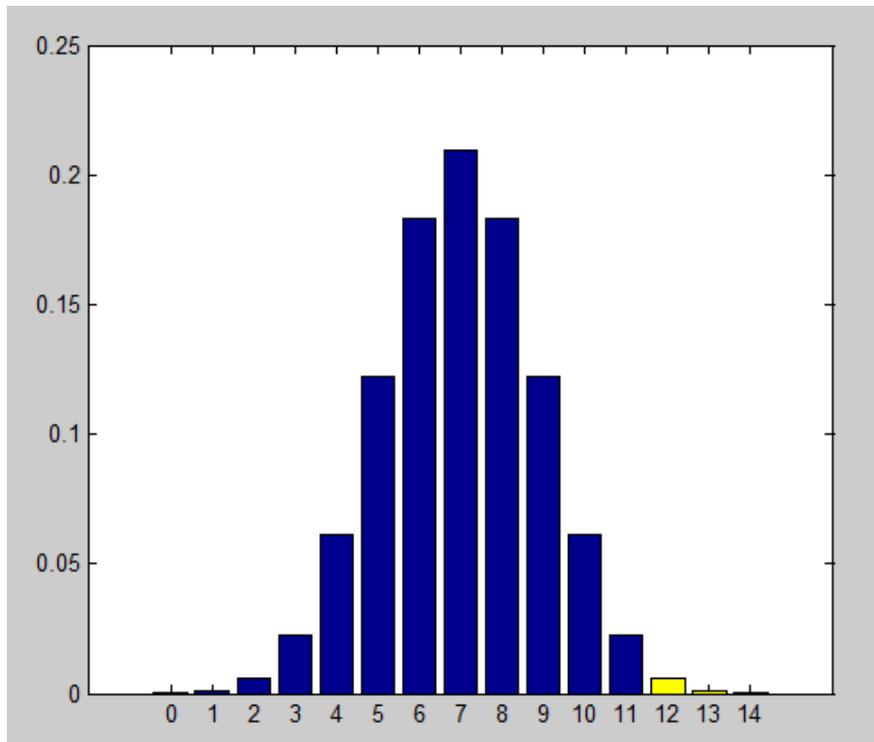
Figure 12. A binomial distribution with 14 trials and success probability of 0.5. Voxels

with greater coherence value in 12 or more participants after practice were marked.
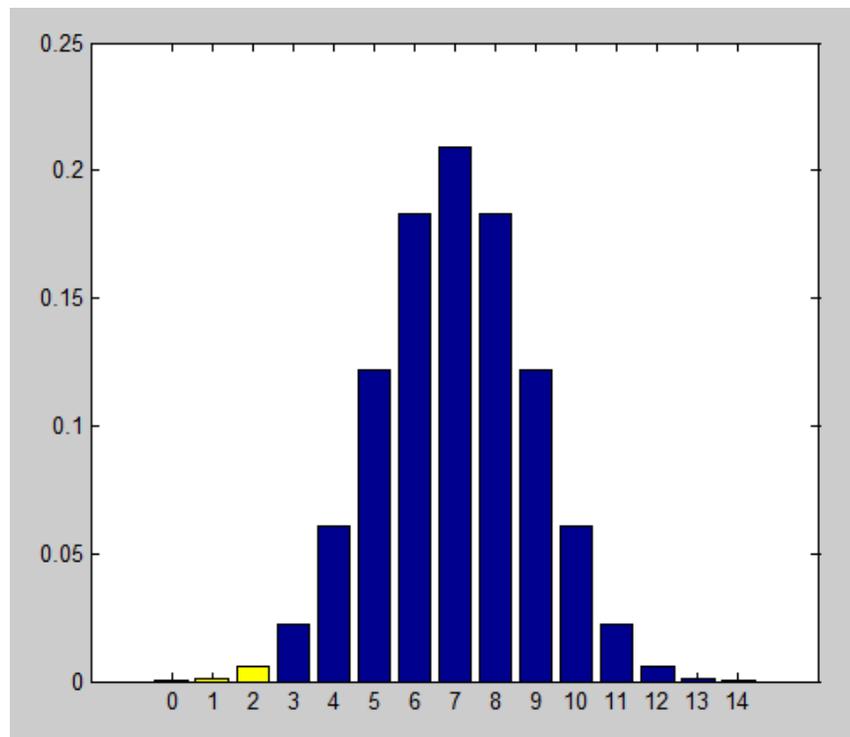
Figure 13. A binomial distribution with 14 trials and success probability of 0.5. Voxels with weaker coherence value in 12 or more participants after practice were marked.

After forming clusters, we set a threshold and retained clusters that have a size bigger than the set threshold. The way to choose the threshold is by bootstrapping techniques.

Bootstrapping. Bootstrapping is a subset of resampling methods. It is usually used to estimate variation of a statistic. The distribution of the statistic of interest is obtained by artificially creating a large number of data sets and computing the statistic on each of the new data sets.

Our aim was to have an estimation of the cluster size distribution to distinguish small clusters that formed due to type I errors when marking 'active' voxels from clusters that were formed because of an actual change in coherence in that brain region between sessions 1 and 20.

In order to create new data, we repeated the whole procedure, with a change at the beginning of our computations. For example, coherence was computed between precuneus of a certain block and the whole-brain of another block at the same session of the same participant. Since the initial design was jittered (stimulus presentation timing relative to TR was varied randomly), our new data reflect a general outcome that might have occurred if there were no effect of practice on coherence. We took the new brain maps of coherence of all the fourteen participants, ran the same two binomial tests that we ran on our actual data and identified 'active' voxels and formed clusters. We kept record of cluster sizes and repeated the procedure 6 times. At last there were about 5200 identified clusters. Small clusters were more likely to appear and about 56% of the clusters were single voxel clusters and about 95% of clusters had less than ten voxels. We chose 0.001 as our threshold for accepting a cluster which
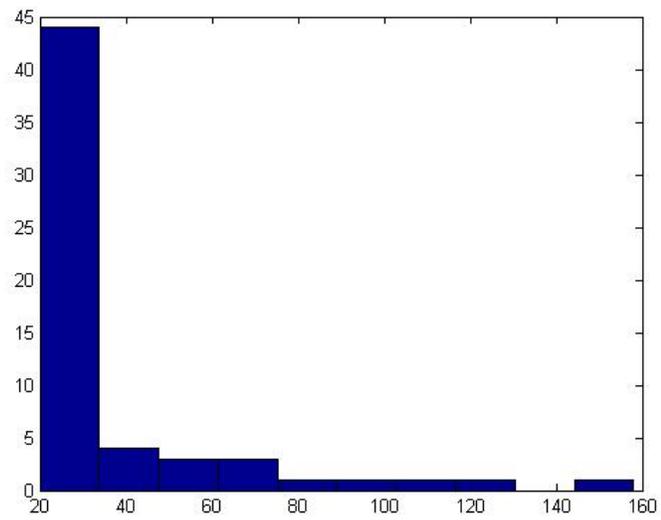
Figure 14. Histogram of cluster size for precuneus. Clusters with less than twenty are not shown on the figure.

corresponds to a cluster size of 69. Figure 14 shows the histogram of cluster size distribution.

The same procedure was done for MPFC and Premotor and resulted in 15 and 73 as threshold for cluster significance respectively.

Functional Connectivity Results

Comparing Head Movement Between Sessions 1 and 20

There are studies (Power et al., 2012 & Van Dijk et al., 2012) that show how subtle head movements can affect resting state fcMRI. Results caused by head movements could be mistaken for neural effects, so it is important to be cautious about head movements.

Studies mentioned above were done on resting state fcMRI and their measure of connectivity was correlation. But it is possible that head movements affect coherence as well, so we looked at basic statistics of head movement parameters for participants in sessions 1 and 20.

We calculated mean and standard deviation of relative displacements for all 14 participants in two sessions and plot difference of each pair:

Based on these plots it seems that at least mean and standard deviation of relative displacement is not affected by number of sessions that participants spent in scanner. Paired t-test on both mean and standard deviation showed no significance (p-value of 0.1731 for mean and p-value of 0.3815 for standard deviation). Hence, changes in functional connectivity detected by the following analyses were likely not caused by changes in head motion.
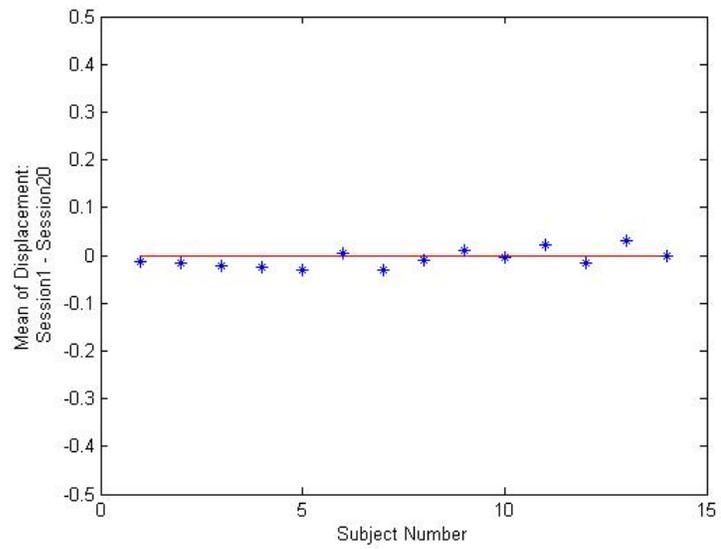
Figure 15. Difference between mean of relative displacement in session 1 and session
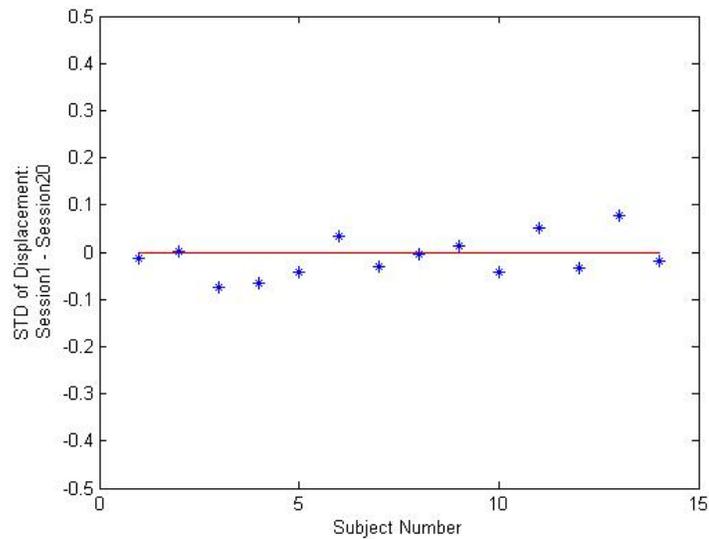
20 in millimeters.

Figure 16. Difference between standard deviation of relative displacement in session 1

and session 20 in millimeters.

Connectivity With Precuneus

Regions With Stronger Coherence in Session 20 Compared to Session 1

There were both DMN and non-DMN regions that showed greater coherence with precuneus after the development of automaticity. Specifically, the regions were left Middle Frontal gyrus (DMN), left Inferior Parietal lobule (DMN), right Middle Temporal gyrus (DMN), Premotor Cortex (non-DMN), anterior Prefrontal Cortex (non-DMN) and left Superior Parietal lobule (non-DMN). These regions are shown in Figure 15.

Regions With Stronger Coherence in Session 1 Compared to Session 20

No region was identified after cluster-size correction.

Connectivity With Medial Prefrontal Cortex

Regions With Stronger Coherence in Session 20 Compared to Session 1

There were both DMN and non-DMN regions that showed greater coherence with MPFC after the development of automaticity. Specifically, the regions were left Middle Frontal gyrus (DMN), Precuneus (DMN), anterior Prefrontal Cortex (non-DMN), Superior Parietal lobule (non-DMN) and Secondary Visual Cortex (non-DMN). These regions are shown in Figure 15.

Regions With Stronger Coherence in Session 1 Compared to Session 20

There is only one cluster that showed weaker coherence with MPFC after automaticity development. This cluster contains parts of ventromedial orbitofrontal cortex.
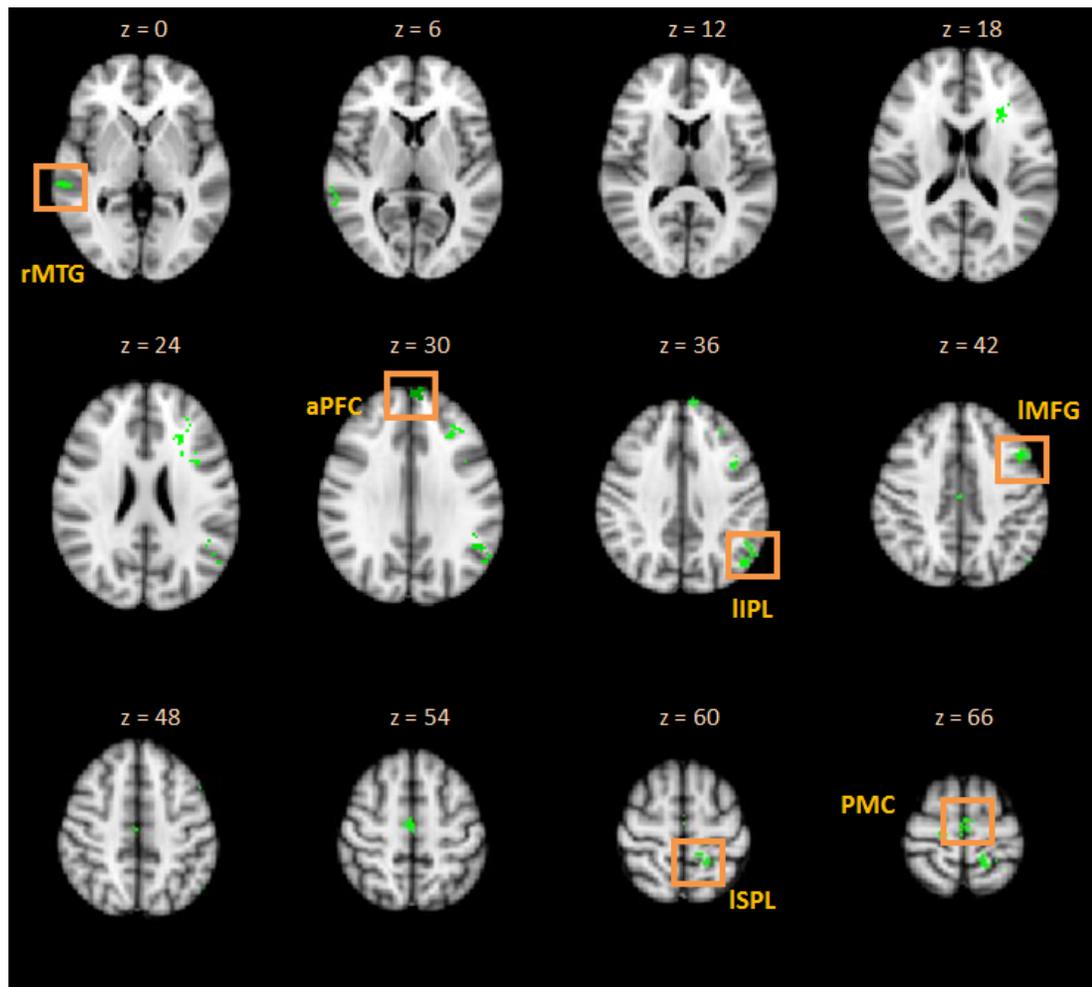
Figure 17. Regions having stronger coherence with precuneus in session 20 compared to session 1.
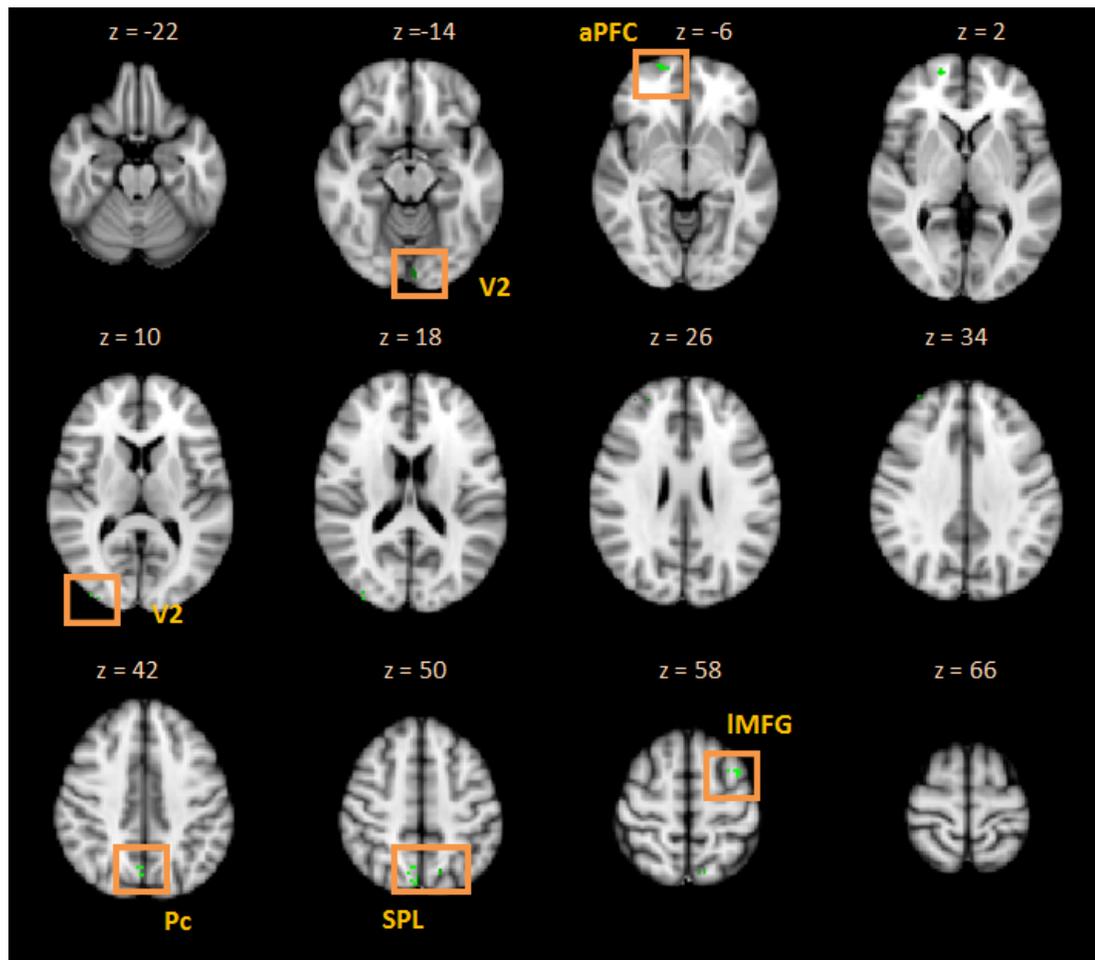
Figure 18. Regions having stronger coherence with MPFC in session 20 compared to session 1.
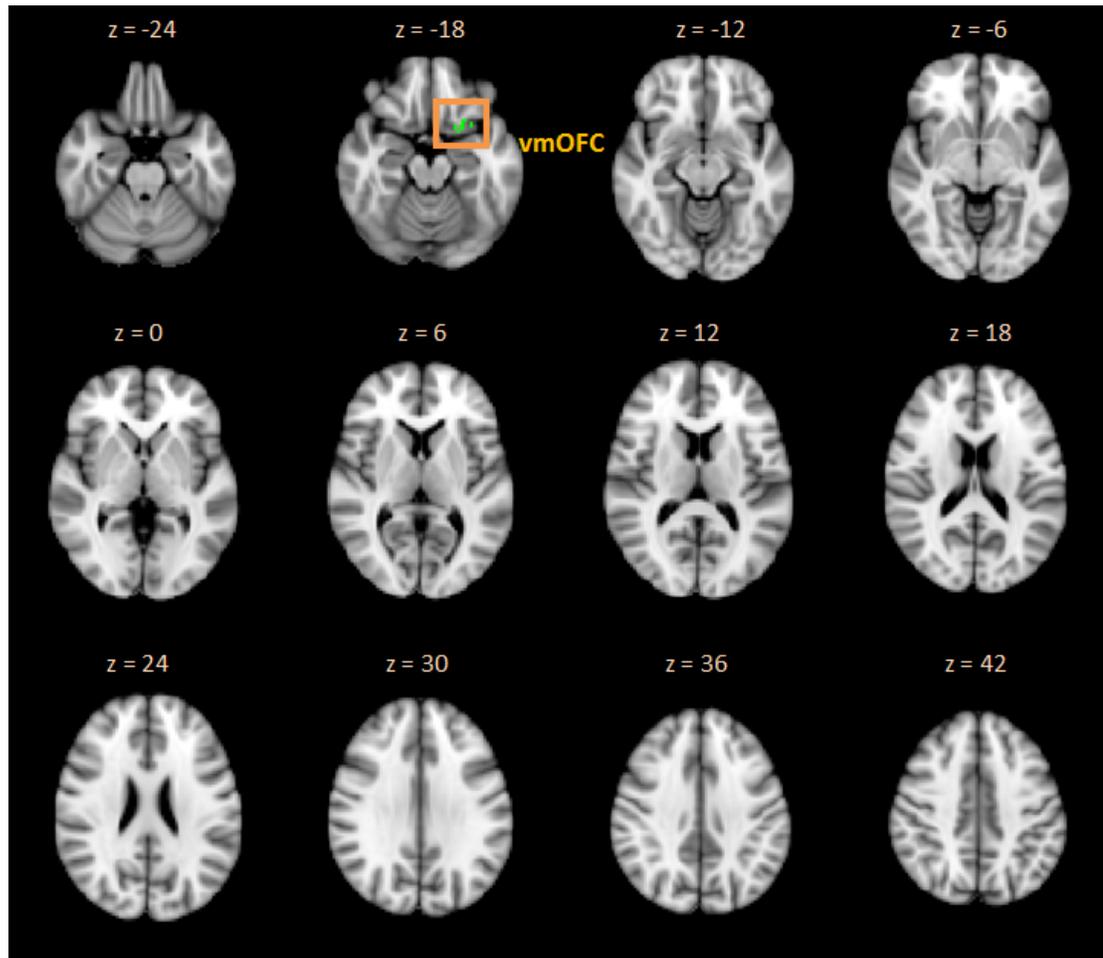
Figure 19. Ventromedial prefrontal cortex shows weaker coherence with MPFC cortex in session 20 compared to session 1.
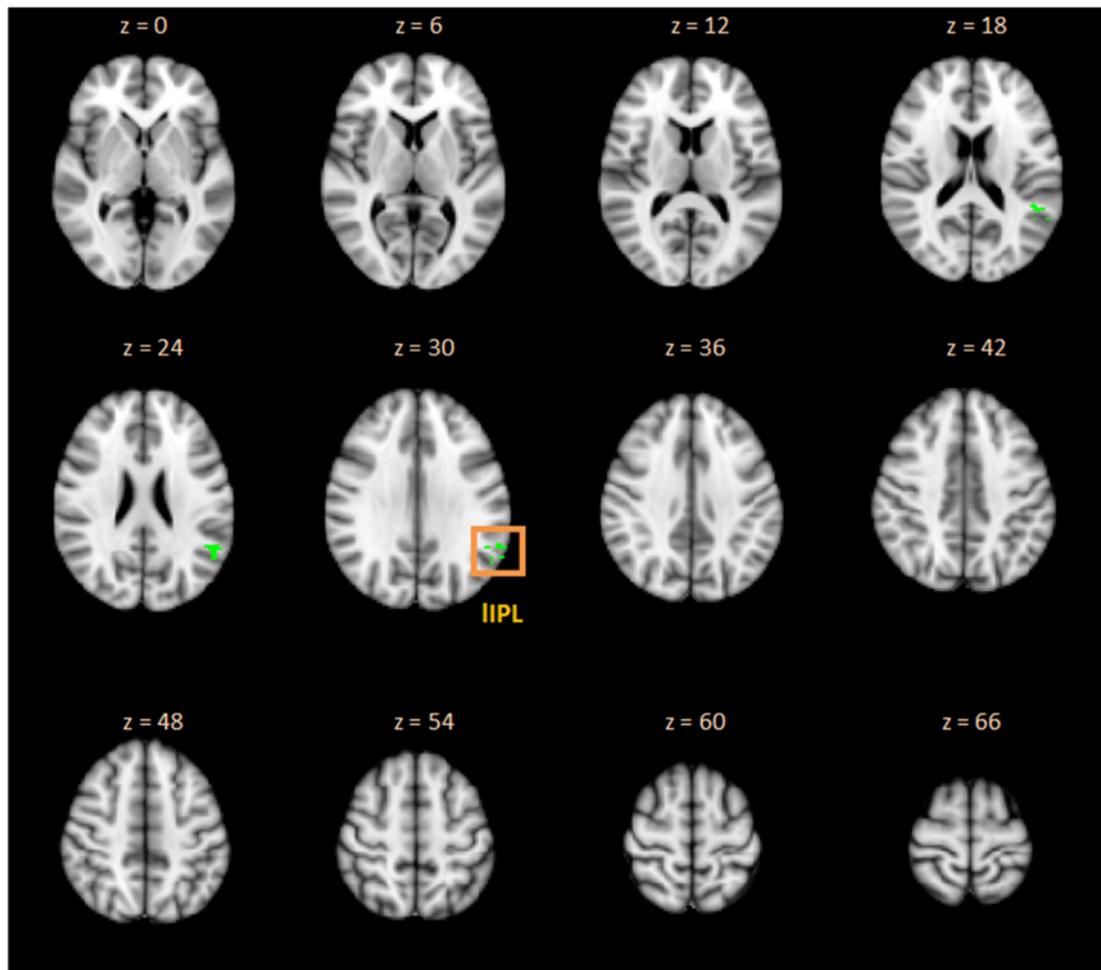
Figure 20. Left Inferior Parietal lobule shows stronger coherence with premotor cortex in session 20 compared to session 1.

Connectivity With Premotor Cortex

Regions With Stronger Coherence in Session 20 Compared to Session 1

The only region that is identified to have stronger coherence with Premotor cortex after automaticity development is left Inferior Parietal lobule, which is a DMN region. This is showed in Figure 15.

Regions With Stronger Coherence in Session 1 Compared to Session 20

No region was identified after cluster-size correction.

Discussion on Functional Connectivity

Result of functional connectivity analysis when we used precuneus and MPFC (two important DMN regions) as seed regions show that both of these regions strengthen their functional connectivity with other DMN regions as well as some of the non-DMN regions after practice. Two of non-DMN regions (anterior prefrontal cortex and superior parietal lobule) show up in both analyses. Function of both of these regions may be related to the task: Anterior prefrontal cortex is involved in 'cognitive branching' (Koechlin & Hyafil, 2007) which refers to the ability of holding a task in mind while preforming another task. Superior parietal lobule showed finger movement related activity (Bedard & Sanes, 2009). This further supports the interpretation that the relation between the default mode network and task-related network changes at the automatic stage. Premotor cortex, which is considered to play an important role in categorization at the automatic stage, strengthens its functional connectivity with left inferior parietal lobule (a DMN region) after extensive practice. These results are all in line with the hypothesis that at the automatic stage DMN plays a more important role for doing the task and is coupled stronger with task related regions. Interestingly, there

are no regions that show weaker functional connectivity with precuneus and premotor cortex in session 20 compared to session 1. But there is one region (ventromedial orbitofrontal cortex) that reduces its coherence with MPFC after practice. Interestingly, this region plays a role in feedback processing based on a study by Elliot et al (1997). This can be explained by the inflexibility feature of automatic processing which implies that at the automatic stage, participants do not pay attention to feedbacks they receive as much as they do in the early stages of learning a task.

GENERAL DISCUSSION

A deactivation level analysis and a functional connectivity analysis were done to study changes in DMN after automaticity development. Deactivation level analysis showed that for sessions 1, 4 and 10 there are DMN regions that are deactivated while participants were performing the task but no region was deactivated in session 20. Moreover, comparing deactivation level of different sessions showed that there are DMN regions that are less deactivated in session 20 compared to session 1, but no difference detected between sessions 1, 4 and 10. Functional connectivity analysis showed that two important DMN regions (precuneus and MPFC) increase their coherence with both DMN and non-DMN regions after automaticity development. Furthermore, premotor cortex (a key region for automatic categorization) increases its functional connectivity with left inferior parietal lobule (a DMN region) after extensive practice.

Deactivation

The results for each session's statistic maps for Baseline>Stimulus are clear: In Sessions 1, 4 and 10 we have found regions that are parts of DMN, suggesting that these areas were deactivated while doing the task. This result was as expected from recent studies; DMN regions were deactivated when there is a need to focus on the external world. Analysis of behavioral results of the same experiment (Helie et al.,

2010b) suggests that participants acquire automaticity between sessions 10 and 20 and the fact that no active clusters were found in session 20 suggests that there is no deactivation while participants are doing the task automatically in comparison to baseline.

The results presented above are static snapshots of deactivation in a given session. Because the hypotheses are also related to the development of automaticity, additional analyses were done to directly compare levels of voxel deactivations between different sessions (which can be interpreted as different stages of learning). Two clusters were less deactivated in session 20 than in session 1. The first cluster consists of the precuneus and the posterior cingulate cortex and the other cluster consists of the medial prefrontal cortex and the anterior cingulate cortex. Among these regions, medial prefrontal cortex, precuneus, posterior cingulate cortex, and ventral anterior cingulate cortex are part of the DMN. However, dorsal anterior cingulate cortex is not part of the DMN. It is shown (Swick & Jovanocic, 2001) that damage to mid-dorsal anterior cingulate cortex inhibits automatic responses, so the appearance of dorsal anterior cingulate may be due to its activation in automatic tasks, instead of less deactivation in automatic processing than category learning.

Functional Connectivity

The second set of analyses focused on functional connectivity. Three seed-based functional connectivity analyses with precuneus, MPFC and premotor cortex were done. Both DMN and non-DMN regions increased their functional connectivity with precuneus and MPFC (two important DMN regions). Increase of functional connectivity between DMN regions at the automatic stage may be due to the fact that at

the automatic stage participants tend to do mind wandering more often than first session in which they are focusing on the external stimuli to learn the task. Precuneus and MPFC also increase their functional connectivity with non-DMN regions. The possible roles of these non-DMN regions in the categorization task are discussed below:

Anterior Prefrontal Cortex (with both precuneus and MPFC): The function of this region of the brain is one of the least understood among all brain regions (Ramnani & Owen, 2004). Although its function is poorly understood, Koechlin and Hyafil (2007) suggest that the main function of this region is 'cognitive branching'. Cognitive branching refers to the ability of maintaining a running task in a pending state to retrieve it after completion of another task. DMN regions are activated when people are day dreaming. The reason that this region shows stronger coherence with precuneus might be due to the fact that participants are day dreaming and each time a stimulus appears they put their day dreaming on hold and continue it after responding to the stimulus.

Superior Parietal Lobule (with both precuneus and MPFC): This cluster which also includes parts of primary somatosensory cortex plays a role in movement-related actions. Bedard and Sanes (2009) identified this region as one of the regions that shows finger-movement related activation. Our participants pressed buttons in response to

stimuli, so stronger coherence with this region may correspond to altered functional connectivity pattern between DMN and task-related regions after automaticity.

Premotor Cortex (with precuneus): A study by Helie et al (2010a) on the same data set suggests that a cortical system gradually replaces an initial subcortical neural system in automatic processing (also: Helie et al., 2015). The study also suggests that after extensive practice this cortical system becomes more caudal and dorsal, and finally centers on premotor cortex. The increase of functional connectivity between precuneus and premotor cortex may be an evidence of DMN getting involved in task at the automatic stage.

Secondary Visual Cortex (with MPFC): This region is one of the primary regions that responds to simple visual characteristics, among them orientation and spatial frequency (Anzai et al., 2007, Hegde & Van Essen, 2000). These two are the features that vary between stimuli, therefore V2 is involved in categorization task, so similar to the explanation for premotor cortex above this may be evidence of the DMN getting more involved in the task at the automatic stage.

There is no region that reduces its functional connectivity with precuneus and premotor cortex after the development of automaticity. However, this is not the case for MPFC. Ventromedial orbitofrontal cortex (vmOFC) reduces its functional connectivity with MPFC after extensive practice. This region plays role in feedback

processing (Elliot et al., 1997). It is reasonable to assume that at the automatic stage of categorization participants do not pay attention to feedbacks that they receive as much as they do in the primary stages of categorization (this is also a criterion for habit learning; Helie & Cousineau, 2011). Since MPFC has a modulatory role in visual spatial and temporal attention networks (Uddin et al., 2009), it is not unexpected that vmOFC reduces its functional connectivity with MPFC.

In addition to increase in functional connectivity between two important DMN regions and task related regions, premotor cortex (an important region for automatic categorization) also increases its functional connectivity with left inferior parietal lobule, a DMN region. Therefore, altogether these results show that after automaticity development DMN regions and task related regions are more strongly coupled when compared to early stages of category learning.

Theoretical Implications and Future Work

This study provides further evidence for three hypotheses: First, a strategy-shift happens at the automatic stage (Helie & Cousineau, 2011; Logan, 1988). In accordance with Helie et al. (2010a), the results of this study show that neural activity is different at the automatic stage. Specifically, patterns of functional connectivity between DMN and task-related regions change with practice. Second, the results presented herein largely support the hypothesis that DMN's pattern of functional connectivity is task dependent. Other studies (e.g. Spreng et al., 2010) suggest that there is not a simple task-independent relation between DMN and the external attention system (EAS). Because there is a strategy-shift in automatic categorization, the functional connectivity of the DMN also changes. Third, the result of the functional connectivity analyses is

also in line with the hypothesis that at the automatic stage the task can be done without interrupting internalized thinking. This would explain the increase in coupling of DMN and task-related regions.

Future work should focus on the generality of these findings. For example, would DMN deactivation diminish after the development of automaticity in other tasks? Also, work should be devoted to exploring whether the changes in functional connectivity between task-related and DMN regions are specific to the areas found in this task (e.g., premotor cortex) or if they are task-specific. For example, different task-related regions could couple more strongly with the DMN after the development of automaticity in, e.g., the serial reaction time task. Another possible next step is to investigate changes in DMN's pattern of activity after automaticity development using alternative techniques such as Granger causality. More importantly, future work needs to focus on bringing together the cognitive and neuroscience literature on automaticity and habit learning to ensure that the concepts and methods used are compatible and consistent. The results in this thesis suggest that they are.

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