The cingulo-opercular network controls stimulus-response transformations with increasing efficiency over the course of learning

Janik Fechtelpeter (janik.fechtelpeter@mailbox.tu-dresden.de)  
Department of Psychology, Technische Universität Dresden  
Zellescher Weg 17, 01069 Dresden, Germany

Hannes Ruge (hannes.ruge@tu-dresden.de)  
Department of Psychology, Technische Universität Dresden  
Zellescher Weg 17, 01069 Dresden, Germany

Holger Mohr (holger.mohr@tu-dresden.de)  
Department of Psychology, Technische Universität Dresden  
Zellescher Weg 17, 01069 Dresden, Germany

Abstract:
We all have experienced that the amount of effort required to perform a task can rapidly decrease over the course of practice. Previous studies have shown that short-term automatization of stimulus-response transformations is associated with a reorganization of functional coupling between different large-scale brain networks. However, it has remained an open question how changing connectivity patterns translate into more efficient stimulus-response processing over the course of learning. Here, we employed a control-theoretic approach to test the hypothesis that the amount of control energy required for stimulus-response processing decreases from early to late practice for networks involved in task control. Using fMRI data from a learning group, N = 70, and a control group, N = 67, stimulus-response transformations were modeled as trajectories of activity starting in the visual network and ending in the sensorimotor network. The stimulus-response trajectories were determined by the functional connectivity matrices derived from the fMRI data plus additional control activation exerted by task-related networks. Based on this analysis approach, we found that the cingulo-opercular network can control stimulus-response transformations with increasing efficiency over the course of learning, while no change in control energy was observed for the fronto-parietal network, highlighting the central role of the cingulo-opercular network for short-term task automatization.

Keywords: control theory; fMRI; instruction-based learning; cingulo-opercular network

Introduction
Transforming novel stimuli into appropriate motor responses typically requires substantial effort at the beginning of practice. However, already within the first few practice trials, the human brain starts to perform stimulus-response transformations with increasing efficiency, as indicated by decreasing reaction times (Ruge and Wolfensteller, 2010; Ruge et al., 2017). Recent neuroimaging studies have shown that these gains in efficiency are enabled by a reorganization of functional connectivity among several large-scale brain networks (Mohr et al., 2016, 2018). Particularly, it was shown that practicing stimulus-response transformations is associated with increasing functional connectivity between the cingulo-opercular network (CON) and other large-scale networks, most prominently the dorsal attention network (DAN) and visual network. This functional integration is accompanied by decreasing activation within the fronto-parietal network (FPN). These findings suggest that stimuli are transformed into motor responses more directly via the DAN and CON over the course of practice, thereby reducing the need for high-level cognitive control provided by the FPN.

However, until now it has remained unclear how the observed reorganization of large-scale functional connectivity contributes to more efficient stimulus-response processing. We address this open question by applying a recently proposed control-theoretical analysis approach (Gu et al., 2015, 2017) to functional connectivity data from a learning group and a control group (Mohr et al., 2016). This analysis approach assumes that the brain can be modeled as a dynamical system (Breakspear, 2017) whose state trajectories evolve not only according to its intrinsic dynamics but also as a function of additional control inputs (see Figure 1). Using this model allows us to compute the control energy required by each network to transform visual stimuli into motor responses, given the current intrinsic dynamics of the brain. We
hypothesized that if a network becomes increasingly efficient in transforming stimuli into responses, this should be reflected by a corresponding decrease in control energy required by the network over the course of learning.

\[ \dot{x}(t) = Ax(t) + Bu(t) \]

where the vector \( x(t) \) represents the state of neural activation at time \( t \), matrix \( A \) describes the intrinsic dynamics of the system, matrix \( B \) defines the control set, and vector \( u(t) \) provides the control input at time \( t \). Here, we modeled neural activations at the network

**Methods**

First, we briefly describe the experimental tasks, data collection and how the connectivity matrices were constructed from fMRI time series. For more details on these points, see Mohr et al., 2016. Then we describe how the connectivity matrices were analyzed using the control-theoretical analysis approach presented in Gu et al., 2015, 2017.

**Experimental tasks** Subjects either performed an instruction-based learning task (learning group, \( N=70 \)) or a 1-back working memory task (control group, \( N=67 \)). In the learning task, subjects were instructed at the beginning of a new block how to respond to four novel stimuli (left or right index finger), see Figure 2. The instruction phase was followed by a sequence of trials in which the subjects had to respond to the presented stimuli as instructed. In the control task, the subjects were presented with the same stimulus material but instead of implementing fixed stimulus-response rules they performed a 1-back task, i.e. they had to indicate whether the preceding stimulus was identical to currently displayed stimulus in each trial.

![Figure 2: Instruction screen (a) and sequence of trials (b) in the learning task and control task. Figure reproduced from Mohr et al., 2016.](image)

**Data collection and processing pipeline** For each subject, fMRI data from 20 task blocks were collected using a 3T scanner with TR = 2 s. Each task block had a length of approximately 90 s (at least 32 trials, depending on errors). The raw fMRI data were preprocessed using a standard pipeline in SPM8. A general linear model was estimated to remove task-related activity at the single-subject level. Residual time series were extracted from 222 regions of interest using the MNI coordinates published in Power et al., 2011. For each task block, the time series were cut into three equidistant parts, with the first part representing the early learning phase and third part representing the late learning phase. Pearson correlation values were calculated separately for early and late learning for all pairs of regions, resulting in 222 x 222 connectivity matrices for the two learning phases. The 222 regions were assigned to the 10 large-scale functional networks reported in Cole et al., 2013. The set of networks consisted of the default-mode network (DMN), fronto-parietal network (FPN), sensorimotor network (SMN), visual network, subcortical network, cingulo-opercular network (CON), salience network (SAN), ventral- and dorsal attention networks (VAN and DAN) and auditory network. Using this assignment, mean values for between- and within-network connectivity were calculated for all network pairs, resulting in connectivity matrices \( A_{early}, A_{late} \) of size 10 x 10 that were subsequently used in the control-theory based analysis.

**Control theory** In the control-theoretical framework proposed by Gu et al., 2015, 2017, brain activation states \( x \) evolve according to the following differential equation:

![Figure 1: Control-theoretical analysis approach. Initially, stimuli are represented within visual cortex. To transform the stimuli into appropriate motor responses, a certain amount of control energy is required (right trajectory).](image)
level, i.e. $x(t)$ was a 10-dimensional vector.

We assumed that stimulus-response transformations started in the visual network and ended in the SMN, hence we defined

$$x(0) = e_{\text{visual}} \quad \text{and} \quad x(T) = e_{\text{SMN}},$$

that is, activation within the visual network was set to 1 and activation within all other networks to 0 at time $t = 0$, whereas at time $t = T$, only the SMN was set to 1 and all other networks set to 0. The control set consisted of all task-related networks except the visual network and SMN, since they were defined as start and target networks. The DMN was also excluded from the control set, as the DMN's decoupling from task-related networks over the course of learning indicates that the DMN is not involved in stimulus-response processing (Mohr et al., 2016, 2018).

As proposed in Gu et al., 2015, 2017, we optimized the control input $u(t)$ required to get from the initial state $x(0)$ to the target state $x(T)$ by minimizing the control energy $E_u$:

$$E_u = \int_0^T |x(t) - x(T)|^2 + \rho |u(t)|^2 dt$$

Following Betzel et al., 2016, we set $\rho = 100$ and $T = 1$. For each subject, the minimal control energy required to traverse from the initial state to the target state was estimated for the early and late conditions, using the connectivity matrices $A_{\text{early}}$, $A_{\text{late}}$ respectively.

**Statistics** As we were interested in learning-related effects, we tested for the interaction effect ‘group’ × ‘learning phase’ for each network of the control set. That is, we calculated for each subject the difference between the amount of control energy required for stimulus-response processing during the early and late practice phase, and compared these changes from early to late practice across groups. Before being submitted to statistical tests, control energy values were log-transformed, resulting in normally distributed values. As the control set contained 7 networks, we corrected the resulting p-values for 7 tests using Bonferroni-correction.

**Results**

The results are shown in Figure 3 and Table 1. After correcting for multiple comparisons, only the CON showed a significant interaction effect group (learning vs. control) × learning phase (late vs. early). In this network, the amount of control energy required for transforming stimuli into responses decreased from early to late learning in the learning group but slightly increased in the control group. At the uncorrected level, the VAN showed an interaction effect in the opposite direction ($t = 2.2$, $p = 0.028$ uncorrected). There was no significant interaction effect found for the other networks, in particular for the FPN there was no significant interaction effect at the uncorrected level ($t = 0.5$, $p = 0.61$ uncorrected). Moreover, since the control-theoretical analyses were conducted at the network level, numerical instabilities as discussed in Tu et al., 2018 and Pasqualetti et al., 2019 did not occur.
Table 1: Statistical results for the interaction effect group (learning vs. control) × learning phase (late vs. early). P-values were Bonferroni-corrected for 7 tests.

| Network | T-value | P-value |
|---------|---------|---------|
| FPN     | 0.5     | 1       |
| Subcortical | 1.5   | 0.99    |
| CON     | -3.2    | 0.013   |
| SAN     | 2.2     | 0.20    |
| VAN     | 1.5     | 1       |
| DAN     | -1.2    | 1       |
| Auditory| 0.8     | 1       |

Discussion

Our results show that gains in efficiency observed across the first few practice trials can be primarily attributed to more efficient control of stimulus-response processing by the CON. This finding corroborates the notion that the reorganization of large-scale functional connectivity is centered around the CON as the main catalyst of short-term task automatization (Mohr et al., 2016, 2018).

The presented findings also shed light on the question whether the FPN's activation decrease indicates that stimulus-response processing is more efficiently controlled by the FPN, or alternatively, that less cognitive control is required by the FPN over the course of learning. Since no significant reduction in control energy was found for the FPN, our results speak for the latter case.

From a more general perspective, our results show that the control-theoretic analysis approach proposed by Gu et al., 2015, 2017 can be employed to uncover interesting relationships between large-scale connectivity patterns and control costs that would remain undiscovered without this analysis framework.

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