

Training Stay Report

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Training Stay Report of Norma Naima Rüter (Grad. School “SFB 874 - Integration & Representation of Sensory Processes” within “International Graduate School of Neuroscience IGSN”), Department of Neuropsychology, Ruhr-University Bochum (Germany) at San Raffaele Scientific Institute, Milan (Italy), Prof. Cappa (Grad. School “School of Molecular Medicine - Section of Neuroscience”).

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The influence of sensory experience on cortical representations of manipulable objects

Human declarative long-term memory system was suggested to be dividable into two theoretical sub-components: episodic memory, storing memories of autobiographical content, and semantic memory, storing general knowledge about the world, including facts and concepts (Tulving, 1972). Over the past years, many studies aimed to investigate how information about concepts, like for example “tools” or “animals”, are represented in the brain. Research on representation of concepts in the brain was motivated by findings in patients suffering from, e.g., neurodegenerative disorders. Some patients showed, on the one hand, specific impairments in their knowledge about inanimate objects like “tools”, but, on the other hand, preserved knowledge about living things (e.g. Moss & Tyler, 2000). Functional neuroimaging studies revealed a fronto-parietal network of brain activation associated with concepts about tools that is active when participants view pictures of, or answer questions about tools. More precisely, activations were (mostly) found in inferior frontal cortex, posterior parietal cortex and middle temporal gyrus / ventral temporal lobes (e.g., Martin et al., 1996, Perani et al., 1999, Johnson-Frey et al., 2003; Creem-Regehr and Lee, 2005; Martin and Chao, 2000). This fronto-parietal network is suggested to be related to automatic access to action knowledge, e.g. like information about grasping and tool-motion. Action knowledge thus seems to be integrated in representation of tool- concepts and can be activated by the mere sight of tool stimuli. This interpretation is also supported by the remarkable overlap of left-hemispheric regions active during tool perception in comparison to active manipulation or pantomime of tool-use (Lewis, 2006). The potential incorporation of information about manipulation, function and usage of tools into their cortical representation suggests that regions active during knowledge acquisition are re-activated during access to semantic representations, as has also been proposed by the Sensory-Motor theory (Martin, 1998; Martin et al., 2000). According to this theory, direct object experience should lead to representations that are modeled by the primarily activated brain regions during knowledge acquisition. However, for humans there is no need of direct object experience (e.g. active tool-manipulation) to acquire knowledge about a concept, as humans are able to learn “to do an action from seeing it done” (Thorndike, 1898). With regard to the Sensory-Motor Theory, the questions arises if an activation of action knowledge-related brain regions occurs as well for objects that have only been observed to be manipulated. The acquisition of semantic knowledge about tools by observation in contrast to active manipulation in form of a training-study that is able to control for prior object-related experience has not been conducted so far, though it can yield important information about the structure of semantic memory. Moreover, it is important to bear in mind that the brain acts as a network of regions active during processing of stimuli. Therefore, it is especially important to consider dynamic approaches inferring how brain regions modulate each other within its cortical network. Using Dynamic Causal Modeling, Bellebaum et al. (2012) have recently shown that active experience with previously novel tools (the study trained participants in active manipulation of tools versus visual exploration of tools) leads to differences in effective connectivity of brain regions within the fronto-parietal tool network of the brain: visually explored novel tool-like stimuli down-regulate, whereas actively manipulated novel tool-like stimuli up-regulate the fronto-parietal tool network. The current study aims to elucidate a) whether observation of manipulation of novel tools leads to activation in a fronto-parietal network when, after observation of manipulation training, the induced tool-representations are incidentally activated and b) how network connectivity between brain regions is modeled depending on the type of stimulus set that participants

incidentally access representations of (observation of manipulation tools vs. visually explored objects).

Preliminary work at “Institute of Cognitive Neuroscience”, Ruhr-University Bochum, Germany

The current study aims to infer training-related changes in brain activation in response to pictures of novel, tool-like object stimuli. Therefore, participants had to complete three training sessions in order to induce experience-dependent representations about previously novel objects. Before and after the training, participants underwent functional magnetic resonance imaging during accomplishment of a visual mismatch task with the aim to compare brain activation in response to seen tool pictures prior to training with post-training. In total, 36 novel (tool-like) objects were invented serving six different functions (transport, push, tag, destroy, separate, move) that were assigned to three different object sets. For the acquisition of object-related brain activation, twenty participants were scanned in a 3 Tesla MRI scanner while they performed a visual matching task that aimed to implicitly activate representations about the presented objects (Weisberg et al., 2007; Bellebaum et al., 2012), since it has been shown that seeing tools is sufficient to activate the fronto-parietal tool network. In this task, pictures were presented showing photographs of the novel objects from four different perspectives. Participants had to indicate whether two pictures presented on a particular trial showed the same object or not. The two pictures always used different perspectives and showed two objects of one training set (observation of manipulation objects vs. visually explored objects). fMRI data was later analyzed with respect to training conditions, since the aim was to illustrate differences in brain activation for observed- in contrast to visually-explored objects. Matching of scrambled pictures served as baseline condition. After the first (pre-training) fMRI session, participants attended three training sessions (1h15 each) on three different days. The training sessions aimed to induce two different kinds of tool representations depending on different types of object-experience: as already stated above, information about one set of objects was intended to be learned only by observation of object-manipulation. Thus, in one half of each training session, participants saw the experimenter using the observation of manipulation tool set (OTOs, observation-trained objects) and hence learned about object functions and object manipulation by observation. During the second half of each training session, a second set of objects was visually explored by describing the objects' form (VTOs, visually trained objects), though information about the tools' general function was also verbally provided (manipulation knowledge, like present in the training observation of manipulation, and functional knowledge about object functions are segregated in the brain, see: Boronat et al., 2005; Canessa et al., 2008). This condition served as a control for familiarity. A third set of objects was not part of the training but of the mismatch task and served as a no-experience control condition (NTOs, not trained objects). After the three training sessions, participants again completed the same matching task in the fMRI scanner by which the semantic representations were aimed to be incidentally accessed.

Dynamic Causal Modeling (DCM) for functional magnetic resonance imaging (fMRI)

Dynamic Causal Modeling is a Bayesian model to estimate effective connectivity of brain regions (Friston et al., 2003). It aims to infer the effective connectivity of brain regions by means of a Bayesian model comparison procedure. It estimates, based on specific hypothesis-driven models, how brain regions are coupled and influenced by experimental changes, e.g. changes in context

variables or a cognitive set (in the current study: experience-dependent representations about object sets) (Friston, 2003). It is not sufficient to infer the temporal course of brain activation from the observed fMRI data (e.g. like Granger causality, inferring dynamic changes from sequences of events and related changes with respect to its temporal order) because fMRI data is only indirectly acquired via BOLD function caused by hemodynamic changes and indirectly identifying neuronal activation. Rather, models of connectivity between cortical nodes are constructed (general bilinear state equation, see “Training stay” section below) and embedded into a framework comprising models of how hemodynamic changes are transformed into the observed BOLD function (e.g. via a “Balloon model”, Buxton et al., 1998). Competing hypothesis-driven models about the influence of external factors (modulating input) on brain-network effective connectivity are then generated and statistically compared by means of Bayesian Model Selection (BMS) for fMRI DCM. The model which describes the actually observed data best is then favored.

Training Stay at San Raffaele Scientific Institute, Milan – Prof. Cappa and Dr. Tettamanti

At the beginning of my training stay at San Raffaele I learned about the theoretical basis of DCM which is composed of different statistical and neuro-computational model assumptions. In order to conduct DCM analyses, it is of particular importance to understand the underlying hypothetical construct of the method since DCM is a highly complex procedure merging a model about the influence of modulatory variables and input parameters in a network of fixed connectivity (general bilinear state equation, figure 1) with a hemodynamic model describing how BOLD response originates in neuronal activity (Hemodynamic Model for fMRI DCM, related to “Balloon model” proposed by Buxton et al., 1998).

$$\frac{dx}{dt} = (A + \sum_{j=1}^m u_j B^{(j)})x + Cu$$

Figure 1 | General bilinear state equation for fMRI DCM. State changes (dx/dt) are described by a term comprised of values for fixed connectivity (A), the sum of parameters of modulation of connectivity (B), the system state (X) and input parameters (C). (Stephan et al., [J Biosc.], 2007)

Thereafter, Dr. Marco Tettamanti of the Department of Neuroscience and I more specifically evaluated how DCM can be applied to the fMRI data on observation of manipulation and visual exploration of novel objects. At first, brain regions were selected that could form a network and should enter DCM analysis. It is important to keep in mind that during the second fMRI session, pictures of trained objects, i.e. pictures OTOs, VTOs or NTOs, were shown during the visual mismatch task. As regions of interest one region commonly activated by all stimulus types was selected (common region). In addition, one region selectively activated by a specific semantic stimulus type (semantic region for: OTOs or VTOs) was selected for VTOs and OTOs each. On single-subject level, volumes of interest (VOI) were extracted from fMRI data corresponding to the common region or semantic regions – therefore, a sphere of 8mm was set on the coordinates of interest to extract maximum peak activation for every single participant in the brain region of interest (common, OTO or VTO). Bayesian Model Selection for DCM was used to find the best model explaining the fMRI data (Penny et al., 2010). Hypothesis-driven models were designed and DCM model space comprised parameters of fixed connections (which brain regions are connected with each other? → synaptic connections of neuronal populations), of modeling of connectivity (how do neuronal interactions

change depending on external manipulations or endogenous activity → how do modulatory inputs render strength of coupling between brain regions?) and of input (which region get stimulus-specific input?).

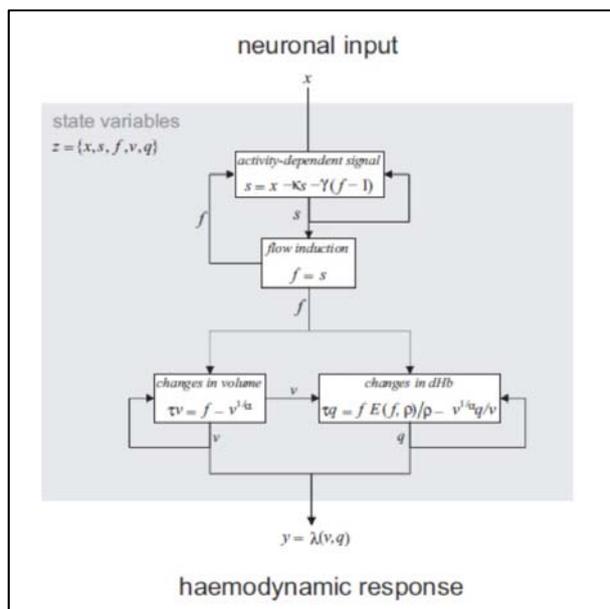


Figure 2 | Hemodynamic model for fMRI DCM. The hemodynamic response is generated by activity-dependent signals increasing blood flow. The change in blood flow leads to changes in volume and deoxyhemoglobin, leading to the predicted BOLD response. Originally proposed by Friston et al., 2003; adapted from Stephan et al., 2007.

The search for the optimal model was defined as the model with the highest fitting accuracy but lowest complexity. DCM models were clustered into 9 families defined by general influence of modulatory input on specified network connections (figure 3) (method proposed in Stephan et al., 2009). Each family of modulatory input configuration consisted of ten different intrinsic connection configurations (figure 4) (9 families à 10 fixed connection possibilities each = 9 families * 10 fixed connection configurations * 17 participants → 1530 models). Input parameters were kept stable within this procedure by directing input of all conditions (OTOs, VTOs and NTOs) onto the common region. Finally, a random effects BMS analysis was used to identify the winning family and model.

Future prospects

A second group of participants is currently acquired at Ruhr-University Bochum in Bochum (Germany) that actively manipulates a set of novel objects. In cooperation with Prof. Cappas Lab and Dr. Tettamanti in particular, DCM will be applied on this data set as well with the aim to later compare network connectivity for actively manipulated objects with objects where manipulation has only been observed. A direct comparison will hint at possible differences within the fronto-parietal tool network processing actively manipulated-, observed- and visually explored tools in comparison to novel un-trained objects. Furthermore, a project using DCM in a multimodal integration study is considered in cooperation with Dipl. Psy. Robert Lech from the Department of Neuropsychology, Institute of Cognitive Neuroscience in Bochum.

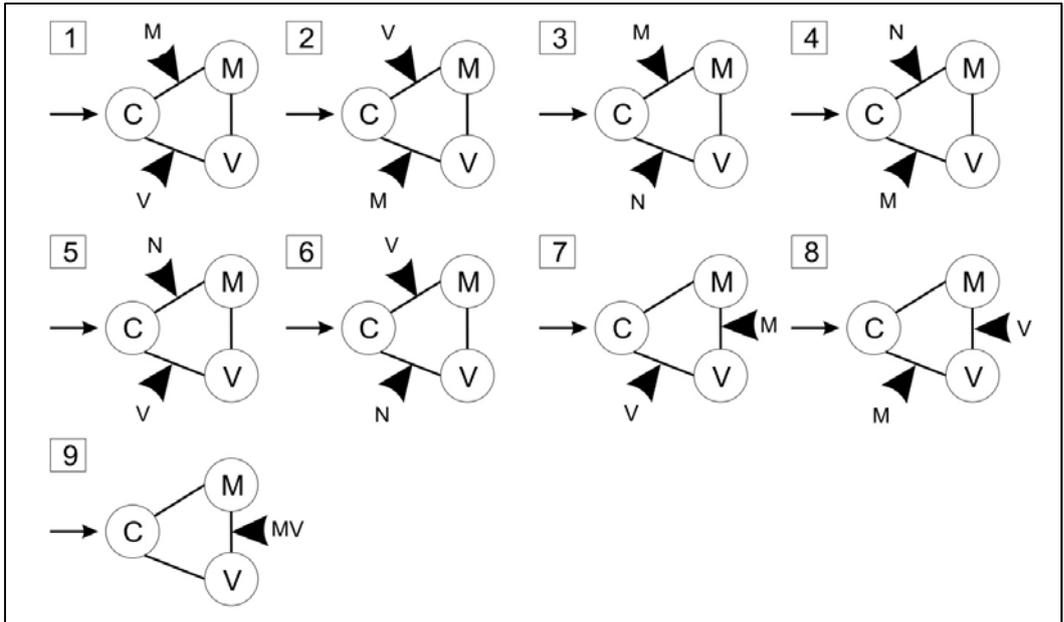


Figure 3 | Families of models for fMRI DCM. Nine different possible combinations of modulatory input onto connections between brain regions were defined, independent of fixed connectivity patterns. Bold errors represent modulatory input on a certain connection. M = stimulus set of observed manipulated objects; V = stimulus set of visually explored objects; N = stimulus set of not trained objects during fMRI data acquisition post. Please note that to avoid false model selections due to the tendency of DCM to pick out the simplest model to explain the observed data (balance between accuracy and complexity), only two modulatory parameters were chosen for each model. After selecting the best modulatory model (family), BMS was used to select the best model fitting the data with respect to fixed connections under the assumption of the chosen modulatory family.

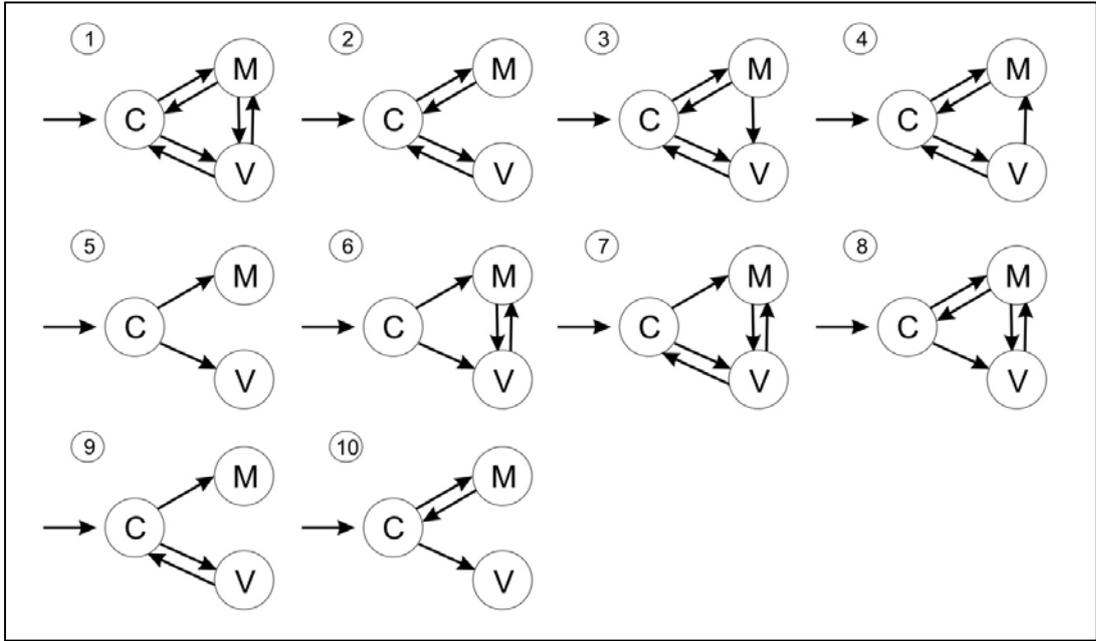


Figure 4 | Models of connectivity within each modulatory family. Ten different models of fixed connections were included into BMS model selection. M = stimulus set of observed manipulated objects; V = stimulus set of visually explored objects; N = stimulus set of not trained objects during fMRI data acquisition post.