

Neural representations of unfamiliar objects are modulated by sensorimotor experience

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Abstract

Sensory/functional accounts of semantic memory organization emphasize that object representations in the brain reflect the modalities involved in object knowledge acquisition. The present study aimed to elucidate the impact of different types of object-related sensorimotor experience on the neural representations of novel objects. Sixteen subjects engaged in an object matching task while their brain activity was assessed with fMRI, before and after they acquired knowledge about previously unfamiliar objects. In three training sessions subjects learned about object function, actively manipulating only one set of objects (manipulation training objects - MTO), and visually exploring a second set (visual training objects - VTO). A third object set served as control condition and was not part of the training (no training objects - NTO). While training-related activation increases were observed in the fronto-parietal cortex for both VTO and MTO, post training activity in the left inferior/middle frontal gyrus and the left posterior inferior parietal lobule was higher for MTO than VTO and NTO. As revealed by Dynamic Causal Modeling of effective connectivity between the regions with enhanced post training activity, these effects were likely caused, respectively, by a down-regulation of a fronto-parietal tool use network in response to VTO, and by an increased connectivity for MTO. This pattern of findings indicates that the modalities involved in sensorimotor experience influence the formation of neural representations of objects in semantic memory, with manipulation experience specifically yielding higher activity in regions of the fronto-parietal cortex.

keywords: fMRI, semantic memory; manipulation; function; DCM

1. Introduction

The representation of semantic knowledge in the human brain is an issue of considerable debate in cognitive neuroscience (see recent reviews by Cappa, 2008, and Binder et al., 2009). Starting from the 1980ies, the description of specific semantic memory deficits for non-living objects (Warrington and McCarthy, 1983) or living things (Warrington and Shallice, 1984) has given rise to a number of different theoretical approaches.

The sensory/functional theory stresses that semantic knowledge is organized in multiple distributed modality-specific subsystems (Warrington and Shallice, 1984). In accordance with the embodied cognition framework (Allport, 1985), neural representations are thought to reflect the history of sensory experience with a given object (Warrington and McCarthy, 1987). Representations of living entities in semantic memory would thus rely more on perceptual features, such as their visual appearance, whereas tool representations would be based on properties related to function and manipulation. In agreement with this hypothesis, functional magnetic resonance imaging (fMRI) studies have consistently shown tool-specific activations in the (pre)frontal and posterior parietal cortex, partly overlapping with the regions involved in active tool use, presumably reflecting the retrieval of action information (Boronat et al., 2005; Canessa et al., 2008; Chao and Martin, 2000; Kellenbach et al., 2003; Lewis, 2006; Martin et al., 1996; Perani et al., 1999).

These findings imply that action-related information becomes part of the object representation: Since action words or sentences involving body parts elicit somatotopic activation patterns in premotor and primary motor cortex (Hauk et al., 2004; Tettamanti et al., 2005), these brain regions – along with areas of parietal cortex – may be automatically recruited when memory representations of tools tightly linked to actions are accessed. It is, however, as yet unclear whether these representations indeed depend on sensory experience with objects, as suggested by the sensory/functional hypothesis.

In contrast to the sensory/functional theory, the domain-specific hypothesis states that category-specific knowledge is stored in distinct brain networks (Caramazza and Shelton, 1998). In this view, the specificity of neural networks associated with particular domains has

developed in accordance with evolutionary pressures, and the role of experience is considered as secondary. The recent finding that blind subjects showed the same category-specific profile of brain response in the ventral temporo-occipital cortex as sighted participants (higher medial fusiform activation for nonliving stimuli and higher lateral occipital cortex for animal stimuli), has been interpreted as evidence that the ventral visual pathway does not require visual experience in order to develop, suggesting the presence of “innately determined domain-specific constraints on the organization of object knowledge” (Mahon et al., 2009).

The role of prior (motor) experience on the neural representations of objects has as yet only rarely been addressed. An obvious limitation in using familiar objects for the study of semantic memory representations is the lack of control over the individual history of object-related sensory experience. To avoid this problem, previously unfamiliar objects have been used. In a recent event-related potentials study subjects underwent different types of extensive training with novel objects (Kiefer et al. 2007). Only objects towards which subjects had performed “functional actions” during training elicited early frontal and later occipito-parietal activations. Creem-Regehr et al. (2007) examined object representations after subjects were trained to skillfully use objects that had a specific function and manipulate “shapes” without any assigned functions. For both viewing and imagined grasping of novel tools vs. “shapes”, higher activity was observed in the premotor cortex and the inferior parietal lobule, suggesting that neural responses to objects which have a specific function and can be manipulated purposefully are not only linked to action affordances. Lesions of both the left frontal and posterior parietal cortex impair the use of familiar and novel tools, with the most severe deficits occurring after combined frontal and parietal lesions (Goldenberg and Spatt, 2009).

In the study by Weisberg et al. (2007), the subjects had to learn to manipulate new tool-like objects in three training sessions. Specific activation increases for manipulated objects after training were observed in the left premotor cortex, intraparietal sulcus, and middle temporal gyrus. Together with the findings reported above (Creem-Regehr et al.,

2007), these results show that relatively brief experience of direct interactions with previously unfamiliar objects leads to new neural object representations. However, the emerging object representations cannot clearly be assigned to learning how to manipulate the objects, because subjects also acquired detailed knowledge about the objects' visual appearance.

The present study aimed to further dissect the role of object-related sensory experience in object representations by varying the modalities involved in the training experience with unfamiliar objects. Subjects actively manipulated one set of unfamiliar tools, after the function had been named and the use had been demonstrated. For a second set, information about object function was also given, but the objects were explored only visually. It was hypothesized that learning to manipulate novel objects would yield stronger object representations in fronto-parietal brain regions than mere learning about object function and about visual object features. In addition, effective connectivity was assessed between those brain regions showing training related activation increases by means of Dynamic Causal Modeling (DCM). The prediction was that learning to manipulate objects would lead to an increase in effective connectivity between frontal and parietal brain regions known to be involved in tool representations.

2. Methods

2.1. Subjects

16 healthy volunteers participated in the study (9 females). All subjects were right-handed (Oldfield, 1971). The mean age of the participants was 28.3 years (SD = 3.8; range: 23 - 35), and all subjects had normal or corrected-to-normal vision. All subjects gave written informed consent. The study was approved by the Ethics Committee of the San Raffaele Scientific Institute, Milano, Italy.

2.2. Stimuli and experimental design

2.2.1. Object stimuli

The stimuli and experimental procedures were similar to those described by Weisberg et al. (2007). 36 new objects were created using a children's construction toy (K'NEX™). Each object was designed as a manipulable tool serving one of the six functions "transport", "push", "pull", "move", "destroy" or "separate". These functions could be performed on small objects, like plastic cups or table tennis balls. A separate group of 30 subjects who did not participate in the present study rated colour photographs of the new objects with respect to visual complexity, "singularity" (i.e. how much the object "pops out" from the other objects) and similarity to real objects. Based on these ratings, the objects were divided into three sets of 12 objects each matched for the relevant features. Within each set there were two objects for each of the six functions. Each object was photographed from four different perspectives, both in isolation and with manipulating hands. Pictures with hand manipulation were included following the idea that mirror-like mechanisms (Rizzolatti and Fadiga, 1998) may contribute to semantic processing by facilitating automatic access to action related information (Aziz-Zadeh and Ivry, 2009). In sum, there were eight different pictures for each object (four perspectives, each with and without manipulating hands; see Figure 1 for example stimuli). Scrambled images of the objects served as baseline control stimuli during scanning. For each object, one scrambled image was generated by randomly rearranging 150 equally sized fragments created from one of the object images (see examples in Figure 1).

Insert Figure 1 about here

2.2.2. Training

To induce the formation of neural representations of the novel objects, subjects underwent three training sessions on three separate days, in which they learned about features of the objects. Importantly, the type of training varied between object sets. Each subject received manipulation training for one set of 12 objects (manipulation training objects – MTO), and

visual training for another object set (visual training objects – VTO). For the third set, there was no training (no training objects – NTO). The assignment of the different object sets to the different training conditions was counterbalanced across subjects.

The procedure for manipulation training was similar to the procedure applied by Weisberg et al. (2007). Each single object was initially presented to the subject by placing it onto a table. Then the function of the object was named and the manipulation was demonstrated by the experimenter. In the following 90 seconds, the subject's task was to manipulate the object as often and as accurately as possible.

In visual training, each object was also placed on the table, but subjects were not allowed to touch it. After the function of the object had been named and a detailed description of object manipulation had been read to the subject, he/she was asked to describe the object, and the time was taken. No subject needed more than 90 seconds. If the description took less than 90 seconds, the experimenter asked specific questions about the visual appearance of the object (e.g. "How many yellow parts does the object have?") until 90 seconds had passed. This procedure ensured that visual training for each object took as long as object manipulation training.

In the training sessions, objects were grouped according to object set. In a given training session, manipulation training was performed first for all 12 objects belonging to the same set, followed by visual training for the 12 objects of the visual training set. Training order (visual and manipulation) was counterbalanced both between subjects and within subjects from session to session. The training procedures in the second and third training sessions were identical to those in the first session, the only difference being that at the beginning of the training session memory of object function was assessed. Each training session lasted between 75 and 90 minutes.

2.2.3. fMRI acquisition: The object matching task

Subjects were scanned before training and after the three sessions had been completed (pre and post training) in order to examine training-induced changes in the neural representations

of the objects. During both scanning sessions, subjects performed an identical object matching task. On each trial, pairs of pictures showing objects from different perspectives or scrambled object images (SCI) were presented on the screen for 3000 ms. Pressing a left or right response button (with the index and middle finger of the left hand), subjects had to decide whether the two pictures showed the same object or not. For SCI, subjects had to decide whether the images were the same or not, without reference to the objects. After an inter-trial interval of 500 ms, a fixation cross appeared for 500 ms, followed by the next pair of object pictures.

The trials were organised in blocks, each block including pictures of one object set only (MTO, VTO or NTO). To emphasize the definition of all objects as manipulable tools, objects were shown with manipulating hands on half of the trials (see Figure 1). Trials with and without hands were grouped in separate blocks. Exploratory analyses of behavioural and fMRI data showed that the factor hands did not differentially affect the effects of the different object-related trainings. Therefore, pictures with and without hands were pooled in all group analyses. Both fMRI acquisition sessions included six sequences of 14 blocks each, four per object set (MTO, VTO, NTO, two with and two without hands) and two for SCI. The blocks consisted of 6 trials each, half of which were matches, showing the same object (or picture for the SCI condition) on both sides. One block lasted 24 s. Each object was shown 24 times during one fMRI acquisition. Given the four different perspectives and the variation with respect to manipulation (hands vs. no hands), each individual picture appeared three times in each acquisition session. Stimulus timing, recording of subjects' responses and the scanner pulses was controlled with Presentation software (Neurobehavioral Systems, Inc., Albany, California, USA).

The mean time period between the first and the second fMRI acquisition was 19 days (SD = 12 days). The training sessions were completed within two weeks in most of the subjects, and the average time period between the last training session and the second fMRI acquisition was 3 days (SD = 4 days).

After subjects had completed the second fMRI acquisition, a recognition test was performed. Subjects had to indicate for each object whether a) it was part of the training and – if subjects answered positively – b) if they had actively manipulated the object or visually explored it during training.

2.3. Behavioural data analysis

Memory of object function before the third training session was compared between MTO and VTO by means of a t-test. Response accuracy and reaction times (RTs) in the object matching task were analyzed with a repeated measures ANOVA with factors stimulus type (MTO vs. VTO vs. NTO vs. SCI) and time (pre vs. post training). For the analysis of the accuracy of the object assignments to the appropriate object set in the recognition test after the second fMRI acquisition a repeated measures ANOVA with the factor object set (MTO vs. VTO vs. NTO) was performed.

2.4. Imaging parameters and analysis

Anatomical T1-weighted and functional T2*-weighted MR images were acquired with a 3 Tesla Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands), using an 8-channel Sense head coil (sense reduction factor = 2). For both fMRI acquisitions, functional images were acquired using a T2*- weighted gradient-echo, echo-planar (EPI) pulse sequence with 30 interleaved slices parallel to the anterior commissure-posterior commissure line covering the whole brain. Time repetition [TR] was 2000 ms, time echo [TE] 30 msec (flip angle = 85, field of view= 240 x 240 mm, no gap, slice thickness = 4 mm, in-plane resolution 2 x 2 mm). During both fMRI acquisitions, subjects underwent six functional scanning sequences. Each scanning sequence comprised 202 sequential volumes, preceded by 6 dummy scans, which did not enter data analysis. Following the first fMRI acquisition, a high resolution T1-weighted anatomical scan (3D, spoiled-gradient-recalled sequence, 124 slices, TR = 600 ms, TE = 20 ms, slice thickness = 1 mm, in-plane resolution 1 x 1 mm) was acquired for each subject.

SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, London, UK) was used for pre-processing and statistical analysis. EPI images were realigned within each fMRI acquisition relative to sequence 1. Then EPI images were unwarped (Andersson et al., 2001), spatially normalized to the Montreal Neurological Institute (MNI) standard space and smoothed by a 8 mm FWHM Gaussian kernel, and General Linear Model statistical analysis was used (Friston et al., 2002). We adopted a two-stage random-effects approach to ensure generalizability of the results at the population level (Penny and Holmes, 2003).

2.4.1. First-level General Linear Models

The time series of each participant were high-pass filtered at 128 s. No global normalization was performed. To allow a direct comparison of pre and post training activations, data were analyzed across both acquisitions, six sequences pre and six sequences post training. As outlined above, a block design was used. At the first level, single-subject fMRI responses were modeled with a canonical hemodynamic response function aligned to the onset of a block of trials belonging to one experimental condition. A 4 x 2 factorial design comprising all 12 sessions was applied, with the factors stimulus type (MTO, VTO, NTO, and SCI), and time (pre vs. post training). First level t-Student contrasts were specified, each contrasting the stimuli for one object set pre or post training with the respective SCI baseline (e.g. MTO pre vs. SCI pre). This procedure yielded six contrasts for each subject, each representing the activation evoked by one object set relative to the SCI baseline pre or post training (MTO pre, VTO pre, NTO pre, MTO post, VTO post and NTO post).

2.4.2. Second-level General Linear Model

The contrast images obtained for each of the object sets relative to SCI at the single-subject level entered the second level analysis at the group level including all 16 participants. ANOVA with the factors object set (MTO vs. VTO vs. NTO) and time (pre vs. post training) was performed in a full factorial design. The levels of both factors were modeled as not

independent and with equal variance. In the first analysis, regions showing specific activation increases from pre to post training were identified for each set of objects (MTO, VTO and NTO). More specifically, a T-contrast was run for each object set comparing post training and pre training activations (e.g. VTO post > VTO pre). We expected to see activation increases from pre to post training in a similar fronto-parieto-temporal network as was described by Weisberg et al. (2007).

In analogy to the procedures applied by Weisberg et al. (2007), the second analysis aimed at identifying brain regions which were significantly more activated for a particular object set relative to the other object sets after but not before training. For this purpose, direct T-contrasts between object sets were performed for all possible combinations, separately for the pre and post training fMRI assessment. We predicted increased fronto-parietal activations following active manipulation compared to visual training.

If not stated otherwise, all comparisons were carried out with a statistical threshold of $p < .001$ uncorrected and an extent threshold of > 10 voxels. For the direct contrasts between object sets after training, an inclusive mask for the contrast post > pre with a liberal threshold of $p < .05$ uncorrected was used to make sure that the identified brain regions also showed some evidence of activation increase from pre to post training. We are aware that the use of uncorrected statistical thresholds may lead to false positive results. Therefore, small volume correction (SVC; Worsley et al., 1996) was applied, based on 10 mm radius spheres around tool related activations reported in previous studies, to further confirm the activations obtained. The main conclusions drawn from the present pattern of findings are based on significant activations surviving SVC. A further reason for applying liberal thresholds was that the present study mainly aimed to identify the functional interactions between regions representing newly acquired tool knowledge. fMRI thus mainly aimed at identifying regions which were somehow involved in learning about object features.

For SVC, the activation peaks observed by Weisberg et al. (2007) in the frontal, parietal and temporal cortex were used. With respect to the frontal cortex, however, we considered activations not only in the premotor cortex but also in a more anterior region

coding more abstract action representations (Bach et al., 2010). If necessary, coordinates were transformed from Talairach to MNI space before SVC was applied (www.mrc-cbu.cam.ac.uk). For the anatomical localization of activation peaks in MNI space, the SPM Anatomy toolbox Version 1.3b was used (Eickhoff et al., 2005).

2.5. Dynamic Causal Modeling: preparatory analyses and extraction of volumes of interest

DCM (Friston et al., 2003) is a confirmatory technique that relies on a priori hypotheses of anatomo-functional connectivity to infer inter-regional causality effects. Based on the results of the second-level GLM analysis on activation increases from pre to post training (see Results section for details), we tested the hypothesis that object training induced a positive increase of functional coupling between brain regions with a multisensory semantic role (i.e. with activation increase for manipulation and visual training), and modality specific semantic nodes (i.e. the brain regions activated for manipulation or visual training). The included brain regions were, respectively, the left inferior parietal lobule (LIPL), as a region commonly activated by MTO and VTO after training; the left posterior parietal cortex (LPPC) and the left inferior frontal gyrus (LIFG), both as regions specifically activated by MTO; the left middle temporal gyrus (LMTG), as a region specifically activated by VTO (and possibly also by MTO at subthreshold significance; see Results section for the analyses yielding these activations and for the coordinates of activation peaks).

The volumes of interest extracted from these brain regions were used for the specification of the dynamic causal models of interest (all technical details are described in Appendix 1). Importantly, in order to investigate how learning (manipulation or visual exploration) differentially modified the effective connectivity within the parieto-frontal/temporal brain system, only the parametric modulation regressors contrasting pre and post training for MTO, VTO (and NTO as a control condition) were entered as modulatory inputs to the system. In the context of the DCM analysis, we will therefore refer to parametric learning

effects (p.l.e.) for each condition, namely: MTO-p.l.e., VTO-p.l.e. (and NTO-p.l.e. as a control).

2.6. Dynamic Causal Modeling: Bayesian Model Selection

We used Bayesian Model Selection (BMS) for Dynamic Causal Models (software version: DCM10 implemented in SPM8) for the choice of the best model fitting our data, following a model space partitioning approach (Penny et al., 2010). The model space (see Figure 2) resulted from the combination of 9 different intrinsic connection configurations, with 4 different configurations of, respectively, modulatory and direct inputs ($9 \times 4 \times 4 = 144$ dynamic causal models per subject, giving a total of 2304 models for the group of 16 subjects). The combinatorial principles underlying the creation of a model space for BMS were guided by the search of the optimum model, as a best compromise between fitting accuracy and complexity. Thus, the intrinsic, modulatory and direct parameters in the specified models ranged from maximal complexity (risk of parameter overfitting) to a progressive increase of parsimony (all technical details are described in Appendix 2).

Insert Figure 2 about here

The set of 144 models was subdivided into 16 families, consisting of all possible combinations of the 4 modulatory input with the 4 direct input configurations. Each family thus comprised 9 models, consisting of all the specified intrinsic connection configurations. In other words, this allowed us to first focus our inferences at the hierarchically higher family level, abstracting away from model-specific configurations of intrinsic connections. Subsequently, we focused our inferences at the hierarchically lower model level, by taking into account all three bilinear model components, i.e. intrinsic connections, direct and modulatory inputs.

A random effects BMS analysis was performed to identify the winning family and the winning model (see also Appendix 2). Once we identified the best family and the best model, we also identified the second-best family and second-best model in the respective rankings (Stephan et al., 2009). In order to provide formal support to a higher evidence in favor of the second-best family and model with respect to lower-ranked families and models, we used the BMS calculated in the first step and we reduced the model space. The reduced model space was then submitted to family and model level inferences (see also Appendix 2).

3. Results

3.1. Behavioural data

3.1.1. Pre and post training performance in the object matching task

As described in the Methods section, accuracy and speed (RTs) of image matching performance were analyzed. Analysis is based on 15 subjects; data of one subject had to be excluded because of technical problems in response recording during the second fMRI acquisition. Figure 3 shows mean accuracy and mean RTs for the different sets of stimuli in the pre and post training fMRI acquisitions. For accuracy data, ANOVA with the factors stimulus type (SCI vs. VTO vs. MTO vs. NTO) and time (pre vs. post training) revealed a main effect of TIME, with significantly higher accuracy post compared to pre training ($F(1,14) = 15.563$, $p = .001$). The main effect of STIMULUS TYPE and the interaction between both factors did not reach significance (all $p > .125$).

Insert Figure 3 about here

For RTs, ANOVA also yielded a significant main effect of TIME ($F(1,14) = 7.181$, $p = .018$) ($F(1,14) = 7.504$, $p = .016$), indicating that responses were faster after compared to before training. The main effect of STIMULUS TYPE ($F(3,42) = 15.929$, $p < .001$) was further examined in follow-up paired comparisons. The matching of SCI took significantly longer than the matching of object images of each individual object set ((VTO: $t(14) = 4.610$; $p < .$

001); MTO: $t(14) = 5.560$; $p < .001$); NTO: $t(14) = 4.767$; $p < .001$)). No significant differences were found for the comparison of object matching RTs related to the different sets of objects (all $p > .836$). The interaction between TIME and STIMULUS TYPE did not reach significance ($p = .111$).

3.1.2. Learning about object function during training

Subjects were given information about the function of each object during training, irrespective of whether the object was actively manipulated or visually explored during training (see Methods section). In the third training session, subjects on average recalled the function of 11.63 of the 12 MTO ($SD = 0.62$) and of 10.88 of the VTO ($SD = 1.31$). This difference in object function recall approached significance ($p = .054$).

3.1.3. Object recognition following the second fMRI acquisition

In the recognition test following the second fMRI acquisition subjects on average classified 11.19 of the 12 MTO correctly ($SD = 0.83$). Of the VTO, 11.44 ($SD = 0.73$) objects were identified, and 11.75 ($SD = 0.45$) objects on average were correctly classified as NTO. There was no significant difference between the object sets with respect to classification performance ($p = .138$).

3.2. *Imaging data*

3.2.1. Training-related activation increases relative to scrambled image matching

Table 1 lists those brain regions showing significant training-related activation increases, separately for MTO, VTO and NTO. Relative to SCI, the presentation of MTO objects was accompanied by activation increases in a network mainly consisting of regions in the bilateral prefrontal and posterior parietal cortex. When only the significantly activated clusters ($p < .05$ corrected on the cluster-level) were considered, MTO-related activity was larger post compared to pre training in the left inferior parietal lobule and in the left middle frontal gyrus, with the activation for the latter cluster extending into the inferior frontal gyrus and covering

parts of area 44. In the right hemisphere, the peak parietal activation was found in the angular gyrus in the inferior parietal cortex. In the right frontal cortex, the peaks of both significant activation clusters were located in the middle frontal gyrus (see also Figure 4A for significant activation differences between the pre and post training fMRI assessment).

Insert Table 1 about here

For VTO, the pattern of activation increases from pre to post training was similar to the pattern for MTO. The strongest activations, however, were seen in the left hemisphere, in the inferior parietal cortex and the middle frontal gyrus. The posterior parietal and middle frontal VTO activations partly overlapped with the left hemisphere activations seen for MTO, but the peaks for VTO were located more anteriorly (see Table 1 for a complete list of regions with activation increases, Figure 4A shows the activations significant on the cluster level).

Finally, activation increases from pre to post training were also found for NTO. Activations were most pronounced in the right hemisphere. Activations in the right angular gyrus overlapped to a large extent with the right parietal MTO cluster described above. Further, strong NTO-related activation increases were found in the right middle and inferior frontal gyrus. However, compared to the right frontal MTO cluster, the middle frontal NTO cluster was more anterior and extended into the superior orbital gyrus (see Table 1 and Figure 4A).

Insert Figure 4 about here

3.2.2. Specificity of training-related activation increases

After training, activity was higher for MTO than for NTO in the left inferior/middle frontal gyrus, with peak activation at the transition between the pars opercularis and pars triangularis ($x = -36$, $y = 16$, $z = 32$, $Z = 3.35$, cluster size 14 voxels; see Figure 4B). In the same region, MTO-related activity was also larger compared to VTO ($x = -36$, $y = 18$, $z = 28$,

$Z = 3.94$, cluster size 27 voxels). Both activations were corroborated by SVC based on a left middle frontal gyrus activation observed by Bach et al. (2010) for abstract action representations (both $p < .05$, false discovery rate (FDR) corrected). Moreover, clear activation increases from pre to post training were seen in this region, as shown by SVC ($p < .05$, FDR-corrected). For $MTO > VTO$, a second activation cluster emerged in the right inferior frontal gyrus pars triangularis ($x = 46$, $y = 26$, $z = 24$, $Z = 3.28$, cluster size 25 voxels; see Figures 4C). None of the other contrasts yielded significant activations ($VTO > MTO$, $VTO > NTO$, $NTO > VTO$ and $NTO > MTO$).

In the parietal cortex, activation differences between MTO and NTO or MTO and VTO were found only with a slightly more liberal statistical threshold ($p < .002$). Activations were found near the transition between the inferior parietal lobule and the middle occipital gyrus (see Figure 4D; $MTO > NTO$: $x = -30$, $y = -66$, $z = 36$, $Z = 3.11$, cluster size 15 voxels; $MTO > VTO$: $x = -28$, $y = -64$, $z = 36$, $Z = 3.01$, cluster size 19 voxels). As outlined in the Methods section, we had strong a-priori hypotheses to see specific training effects not only in the frontal, but also in the parietal cortex. We therefore sought to confirm these activations further by using SVC. For both post training contrasts ($MTO > NTO$ and $MTO > VTO$) as well as for the general pre < post comparison, significant activations emerged with SVC based on a posterior parietal training related activation described by Weisberg and colleagues (2007) (all $p < .05$, FDR-corrected).

For VTO , the only cluster showing larger post training activity compared to NTO was found in the left middle temporal gyrus ($x = -58$, $y = -40$, $z = -8$, $Z = 3.46$, cluster size 38 voxels; see Figure 4E). This activation was also confirmed by SVC, based on a specific training related activation in the left middle temporal gyrus, which had previously been reported (Weisberg et al., 2007). Although activation differences between pre and post training were also found near this region (see above), SVC did, however, not yield significant pre-post activation increases. Importantly, none of the reported contrasts yielded significant activations at the reported locations before training.

3.3. Causal influence of manual or visual type of training with objects on fronto-parieto-temporal effective connectivity networks

Based on the activation results presented above, we used Bayesian Model Selection of Dynamic Causal Models to investigate the optimum pattern of causal effective connectivity influences determined by MTO and VTO. As this analysis focused on specific changes in effective connectivity induced by different types of training, it was based on regions showing evidence of activation increase from pre to post training, either for both VTO and MTO or for only one type of object related experience. These regions comprised a left-lateralized brain system constituted by LIPL as a common region (activated more strongly after training by both VTO and MTO), the LPPC and the LIFG as MTO-specific regions, and the LMTG as a VTO-specific region (but not activated significantly more than MTO; coordinates of group activations: LIPL: $x = -46$, $y = -52$, $z = 48$; LPPC: $x = -30$, $y = -68$, $z = 44$; LIFG: $x = -56$, $y = 14$, $z = 32$; LMTG: $x = -56$, $y = -38$, $z = -8$; see also Table 1 and the explanations in the Results section).

We generated a model space comprising 144 dynamic causal models involving the four aforementioned brain regions, with a focus on how their connections were influenced by the MTO- and VTO-parametric learning effects (p.l.e.). The model space resulted from the combination of 9 different intrinsic connection configurations (Int1-9, Figure 2A) with 4 modulatory (Mod1-4, Figure 2B), and 4 intrinsic input configurations (Dir1-4, Figure 2C).

For a clearer treatment of the relatively large model space, we grouped the 144 dynamic causal models at a higher level of hierarchy, i.e. into 16 different families, resulting from all possible combinations of the modulatory and direct input configurations, while disregarding the specific intrinsic connection configurations.

BMS at family level yielded evidence in favor of the family characterized by the combination of Mod4 and Dir1 (Figure 2B, C). This is the family in which, with respect to modulatory input configurations, MTO-p.l.e. and VTO-p.l.e. modulate “reciprocal” connections (MTO-p.l.e. modulates connections between regions activated by VTO-p.l.e., whereas VTO-p.l.e. those between regions activated by MTO-p.l.e.); with respect to direct input

configurations, the LIPL, as the sole region receiving direct inputs, allowed for signal propagation by the stimuli of all conditions. The ratio of exceedance probabilities between the winning family and the second-best family amounted to 36.7 (significance cut-off ≥ 20). A random-effects ANOVA on the posterior probabilities, with families as a main factor, showed that the winning family Mod4/Dir1 significantly differed from the second-best family and from all the other families ($F(15,2) = 22.17$, $p = .0036$; Post-hoc Tukey tests: all significant at $p < .05$).

BMS at the model level yielded evidence in favor of the model characterized by the combination of Int6, Mod4 and Dir1 (Figure 5A). The ratio of exceedance probabilities between the winning model and the second-best model was 68.1 (significance cut-off ≥ 20). A random-effects ANOVA on the posterior probabilities with models as a main factor, showed that the winning model Int6/Mod4/Dir1 significantly differed from the second-best model and from all the other models ($F(15,143) = 4.74$, $p < .0001$; Post-hoc Tukey tests: all significant at $p < .05$). The specific intrinsic connection configuration in the winning model Int6/Mod4/Dir1 includes bidirectional connections between the LIPL and the LMTG, and between the LPPC and the LIFG, and forward connections from the LIPL to the LPPC and to the LIFG. Interestingly, the average modulatory connection strengths in the winning model indicate an opposite influence of MTO-p.l.e. onto “reciprocal” VTO-connections, compared to the influence of VTO-p.l.e. onto “reciprocal” MTO-connections (Figure 5A). Manual training with objects exerts positive modulations, i.e. an increase of connection strengths between the LIPL and the LMTG, i.e. the regions activated by VTO. In turn, visual training with objects exerts negative modulations, i.e. a decrease of connection strengths between the LIPL and both the LPPC and the LIFG, i.e. the regions activated by MTO.

Insert Figure 5 about here

Given these results, we wished to clarify whether the investigated brain system, in addition to being dominated by such modulations of connectivity strengths in “reciprocal” connections,

also presented a significant modulation of “own” connections induced by manual or visual training with objects. Positive hints in support of this second type of modulatory influences was provided by the fact that the second-best family in the family exceedance probability ranking was the family characterized by the combination of Mod3 and Dir1 (Figure 2B, C). The second-best family is the mirror-reverse of the winning family, in that the modulatory inputs of MTO-p.l.e. and VTO-p.l.e. are directed toward “own” rather than toward “reciprocal” connections. Furthermore, the second-best model in the model exceedance probability ranking was a model belonging to the second-best family, characterized by the combination of Int2, Mod3 and Dir1. In this specific intrinsic connection configuration, all bidirectional connections between the brain regions in the system are present, with the exception of “extrinsic” connections between the two regions for MTO-p.l.e. and the LMTG for VTO-p.l.e. (Figure 5B).

In order to provide formal support to these positive hints, we used the BMS calculated in the first step and we reduced the model space by excluding all models with the modulatory input configuration Mod4 (i.e. “reciprocal” modulations). We then submitted this reduced model space to family and model level inferences.

At the family level, a random-effects ANOVA on posterior probabilities with families as a main factor, showed that the second-best family Mod3/Dir1 significantly differed from all the other families in the reduced model space ($F(15,1) = 23.07$, $p = .0610$; Post-hoc Tukey test: significant at $p < .05$).

At the model level, a random-effects ANOVA on posterior probabilities with models as a main factor, showed that model Int4/Mod3/Dir1 (Figure 5C) belonging to the second-best family Mod3/Dir1 significantly differed from all the other models in the reduced model space ($F(15,107) = 5.23$, $p = .0001$; Post-hoc Tukey tests: all significant at $p < .05$). The configuration of model Int4/Mod3/Dir1 is equivalent to the second-best model Int2/Mod3/Dir1, except for the missing backward intrinsic connection from the LIFG to the LIPL. Interestingly, both models Int2/Mod3/Dir1 and Int4/Mod3/Dir1 show an almost completely opposite modulatory pattern with respect to the winning model Int6/Mod4/Dir1. In Int2/Mod3/Dir1 and

Int4/Mod3/Dir1, MTO-p.l.e. exerts predominantly positive modulations in “own” connections, i.e. an increase of connection strengths between the LIPL, the LPPC, and the LIFG. In turn, VTO-p.l.e. exerts negative modulations in “own” connections, i.e. a decrease of connection strengths between the LIPL and the LMTG (Figure 5B, C).

Thus, taken altogether, the resulting best and second-best dynamic causal models in the BMS analysis suggest a much greater involvement of fronto-parieto-temporal inter-regional interactions induced by manual training with objects, as opposed to decrement of causal interactions in the same system in the visual training condition.

4. Discussion

The aim of the present study was to elucidate the impact of the modalities involved in object-related sensorimotor experience on the neural representations of objects in semantic memory. As the history of sensorimotor experience is highly individual and cannot be controlled in the case of existing representations of familiar objects, novel manipulable tools were used to address this issue. Applying a method similar to Weisberg et al., 2007, object-related brain activity was assessed during an object matching task before and after subjects received object-specific trainings. In contrast to the previous study, however, the modalities of object-related experience were varied. Subjects manually manipulated one set of objects during training, whereas another set of objects was explored only visually, while information about object function was given for both sets. Furthermore, the effective connectivity interactions between brain regions showing higher post training activity were examined by means of DCM.

After training, images of the objects elicited larger activity compared to pre training in a bilateral fronto-parietal network, which was most pronounced in the left hemisphere for MTO and extended into the left middle temporal gyrus for VTO. Direct comparisons between object sets after training revealed larger activations for MTO compared to both VTO and NTO in small parts of the left inferior/middle frontal gyrus and the left posterior inferior parietal

lobule. For VTO, a region in the left middle temporal gyrus was more activated than for NTO after training. A modulation of the activity pattern by the type of object presentation – with or without hands indicating an ongoing manipulation – was not observed. As discussed in a recent review, mirror-like activity may be induced only if an entire person performing an action is observed, but not if only a hand is visible (Turella et al., 2009).

The pattern of results in the left fronto-parietal cortex confirms the findings of other studies examining training-induced representations of novel tools (Creem-Regehr et al., 2007; Weisberg et al., 2007). The present study extends these findings indicating that specific regions within the fronto-parietal network are more strongly involved in tool representations, if subjects have had sensorimotor experience with the tools compared to mere visual exploration, providing evidence for a significant influence of object-related sensorimotor experience on object representations.

The strongest effect of manipulation training was found in the left inferior/middle frontal gyrus (a right hemisphere cluster emerged only for the comparison of MTO and VTO, but not MTO and NTO). Studies requiring simple viewing or naming of familiar tools or the access of specific tool related knowledge consistently report activations in this region, as well as in slightly more posterior regions in the ventral premotor cortex (Canessa et al., 2008; Chao et al., 1999; Chao and Martin, 2000; Creem-Regehr and Lee, 2005; Lewis, 2006; Perani et al., 1999). Different functions for the left premotor and inferior/middle frontal cortex were described in a recent investigation on the role of object information in action observation (Bach et al., 2010). The left premotor cortex was shown to be mostly involved in the basic spatial aspects of tool use. In contrast, the middle frontal gyrus showed evidence of a more abstract coding of actions, linking object information to both action goals and spatio-motor properties. In accordance with this finding, inferior frontal gyrus activations were found for the observation and verbal description of object-directed hand actions (Baumgaertner et al., 2007) and for understanding the concept of the use of previously unfamiliar tools in action observation (Menz et al., 2010). Tettamanti et al. (2005) showed that listening to action-related sentences activates a region in the inferior frontal gyrus

independent of the effector referred to in the sentence (mouth, arm or leg). Both the left ventral premotor cortex and inferior frontal gyrus pars triangularis and opercularis have been implicated in a neural system representing semantic knowledge of tools and the associated actions (Johnson-Frey, 2004; Lewis, 2006), possibly reflecting a continuum of semantic knowledge related to tools from more concrete aspects represented near the premotor cortex to more abstract aspects linked to regions further anterior (Lewis, 2006).

Regions of the (dorsal) premotor cortex, belonging to the tool use network, were not activated in the present study. This is not surprising, as the task used during fMRI acquisition in the present study did not aim to access specific types of object-related knowledge. Rather, the pattern of brain responses observed reflects the “automatic” activation of object representations by the mere observation of the objects. Three training sessions were apparently not enough to induce object representations as strong as those of familiar everyday objects, which entail well-defined and overlearned finger and hand movements.

Neural representations of manipulable tools have consistently been reported to involve both frontal and parietal cortex (Johnson-Frey, 2004; Lewis, 2006). Accordingly, post training activity was also found to be stronger for MTO than VTO (and NTO) in the left posterior inferior parietal cortex in the present study, albeit with a difference less pronounced than in the case of the left frontal cortex. Similar activations have been described in studies examining the representation of familiar tools and their associated actions or functions (Boronat et al., 2005; Canessa et al., 2008; Chao and Martin, 2000; Creem-Regehr and Lee, 2005; Grezes and Decety, 2002; Kellenbach et al., 2003), as well as for imagination and planning of tool use (Creem-Regehr and Lee, 2005; Johnson-Frey et al., 2005). It thus seems that, as for the inferior frontal cortex, parts of the posterior parietal regions involved in tool representations are specifically recruited for tools with which the subject has had active manipulation experience. Compared to the findings reported by Weisberg et al. (2007), specific parietal activations for MTO were, however, observed in a more posterior part of the inferior parietal lobule. This discrepancy may be related to the more prominent role of verbally mediated information in the present study. Interestingly, previous studies on neural

tool representations found activations in the posterior inferior parietal lobule for silent verb generation in response to tool pictures (Grezes and Decety, 2002) or for sentences describing tool actions (Baumgaertner et al., 2007), which might suggest that an integration of verbally mediated information (function naming) and manipulation information led to the relative activation increase for MTO.

Lesions in the fronto-parietal cortex are often associated with ideomotor apraxia, a neuropsychological syndrome characterized by deficits in carrying out learned movements in the absence of elementary motor disturbances, including but not restricted to impairments of tool-related actions (Heilman and Rothi, 2003). Deficient use of objects in apraxia has frequently been interpreted in terms of a loss of knowledge about the typical manipulation of objects (see Buxbaum and Kalenine, 2010). In contrast, knowledge about object function is often preserved (Buxbaum and Saffran, 2002). While the neural networks coding manipulation and functional knowledge overlap, specific regions for manipulation knowledge have been described in the left frontal and parietal cortex (Boronat et al., 2005; Canessa et al., 2008; Kellenbach et al., 2003), in locations similar to the activations specific for MTO seen in the present study. Within a dual route account for the imitation of familiar gestures (Rothi et al., 1991), it has been proposed that the proper use of familiar objects does not necessarily require access to stored information in semantic memory, but can also rely on the extraction of function, and thus potential manipulation, from the object structure based on its “affordance for action” (Buxbaum and Kalenine, 2010). The most severe impairments in the use of familiar tools have in fact been described in patients showing both deficient access to stored manipulation information for tools and reduced ability to detect and use object affordance (Goldenberg and Hagmann, 1998; Goldenberg and Spatt, 2009). It is thus unlikely that lesions restricted to the manipulation-specific regions described in this study would lead to severe apraxia.

The stronger frontal and parietal activations for MTO than VTO observed in the present study may also be interpreted in terms of planned object grasping. The frontal region at the transition between the inferior and middle frontal gyrus has been shown to contain

canonical neurons which are activated when graspable objects are presented (Buccino et al., 2004b; Buccino et al., 2004a; Gazzola and Keysers, 2009; Murata et al., 1997; see Rizzolatti and Craighero, 2004). This explanation, however, appears to be unlikely, as VTO and NTO also represented graspable objects, but did not elicit as strong activations as MTO.

The results of the BMS of Dynamic Causal Models also speak against an interpretation in terms of (planned) object grasping, again due to evidence of limited involvement of the fronto-parietal network for VTO. The highest level in a model ranking based on exceedance and posterior Bayesian probabilities was represented by the winning model Int6/Mod4/Dir1. Surprisingly, the configuration of modulatory influences in the winning model suggests that the strongest effect in terms of effective connectivity changes induced by object training is a decrease of connection strength in left fronto-parietal circuits for VTO. As outlined above, objects may by themselves have an “affordance for action”, and patients with lesions in the left fronto-parietal cortex are impaired in detecting this affordance, as revealed by a test involving the selection and use of novel tools (Goldenberg and Hagmann, 1998; Goldenberg and Spatt, 2009). Given the finding that the processing of pictures of simple unknown shapes recruits fronto-parietal brain regions during imagined grasping (Creem-Regehr and Lee, 2005), it is likely that the mere observation of unfamiliar tools with stronger affordances such as those used in the present study already elicits some activation in the fronto-parietal network, even if the exact way of tool manipulation is unknown. Representations of known objects in the fronto-parietal cortex go, however, beyond simple object affordances (Creem-Regehr and Lee, 2005). It is conceivable that one mechanism contributing to our DCM effect is a down regulation of a tool related network in response to familiar objects for which no information on manipulation is available. Affordance-induced processing may be reduced when during experience with the tools other modalities than the sensory-motor domain predominate, as is the case for the VTO in the present study. As a result, seeing the never “used” objects appears to induce a functional decoupling of manipulation related brain regions.

MTO-induced increases in effective connectivity may thus represent a second, coincidental mechanism which contributes to post experience differences in neural representations of objects. Evidence for this expected DCM effect was provided by the second-best models in the Bayesian probability hierarchy. Namely, the second-best models Int2/Mod3/Dir1 and Int4/Mod3/Dir1 were dominated by a predominant increase of connection strength in fronto-parietal circuits for MTO, particularly between the left inferior frontal and posterior parietal cortex, corroborating the relevant role of these brain regions in learning about object features through manual interactions and in representing information about manipulable objects (see above).

The interplay between the two mechanisms revealed by the DCM analysis may be determined by the dominant modality of experience. During manipulation, learning about visual features of objects is of course also important. However, this type of visual experience does not result in a down regulation of the tool use network because subjects have learned to associate the visual appearance of the object with the manipulation. If, however, no information about manipulation is provided for a tool-like object, and visual features are emphasized instead, this might result in the observed decrease in functional coupling between manipulation-related brain regions.

An analogous differentiation between inter-regional causal interactions that become stronger as a consequence of their greater functional relevance induced by learning, as opposed to inter-regional causal interactions that become weaker due to their reduced learning-associated functional relevance, has been previously demonstrated in a seminal study on artificial grammar learning (Fletcher et al., 1999). The effect was observed to take place between a left-hemispheric fronto-parietal system subserving semantic memory and a right-hemispheric fronto-parietal system subserving episodic memory. More generally, effective connectivity strength modifications, either increases or decreases, induced by learning have been interpreted as correlates of brain plasticity mechanisms (Buechel and Friston, 1999; Toni et al., 2002), possibly reflecting hebbian changes in synaptic strength (Ma et al., 2010). Learning-related increases or decreases of connection strengths therefore most

likely represent, respectively, a more pronounced and more efficient, or a reduced involvement of the associated neural systems in processing the newly acquired information.

The only region showing evidence of specific activations related to visual object exploration relative to NTO (but not MTO) was located in the left middle temporal gyrus, with a peak in or near BA 21. Given that this area was not present in our a-priori predictions, any interpretation of these findings must be tentative. Many studies have linked BA 21 to the integration of semantic information for lexical retrieval (Assaf et al., 2006b; Assaf et al., 2006a; Booth et al., 2002; Booth et al., 2006; Canessa et al., 2008; Chou et al., 2006; Creem-Regehr and Lee, 2005; DeLeon et al., 2007; Gronholm et al., 2005; Kalenine et al., 2009; Pulvermuller and Hauk, 2006; Vingerhoets, 2008). The activation in the middle temporal gyrus observed for VTO may thus reflect the learning of associations between visual object features and verbally described object function. It has to be noted, however, that there was no activation difference between VTO and MTO in this region, suggesting that this learning effect may be present also in the case of MTO. The results of the BMS of Dynamic Causal Models are also difficult to interpret. VTO did not increase the effective connectivity between the left middle temporal gyrus and the left inferior parietal cortex either in the winning or second-best models yielded by BMS, while MTO induced an increase of connectivity between the left inferior parietal lobule and the left middle temporal gyrus. Actually, the second-best models indicated that VTO induced a decrease of effective connectivity between the left inferior parietal lobule and the left middle temporal gyrus from pre to post training,

Taken together, the present study provides evidence compatible with the hypothesis that the history of sensorimotor experience related to an object significantly affects its neural representation, lending support to the sensory/functional theory of semantic memory representations (Martin, 2007; Warrington and McCarthy, 1987; Warrington and Shallice, 1984). Specific increases in object related activations in the left inferior/middle frontal cortex and – to a lesser extent – in the left posterior inferior parietal cortex observed for objects

undergoing active manipulation during training indicate that manipulation knowledge became an integral part of object representations which was automatically activated when the objects were seen. The activation differences between MTO and VTO after training were likely caused by a down regulation of tool use regions for VTO and an up regulation for MTO. It has to be noted, however, that specific activations for MTO were restricted to relatively small regions within the fronto-parietal cortex. Future studies will have to further examine the precise nature of the contribution of dorsal stream structures to object representations and object recognition, considering also recent work suggesting that the information stored in dorsal stream structures does not represent object identity (Almeida et al., 2010).

A clear limitation of the present study is that the short-term learning effects observed here in adult subjects are not directly comparable to the natural, long-term learning mechanisms taking place during development. Nevertheless, the study of the emergence of object representations for previously unfamiliar objects seems to be a promising approach in attempts to disentangle the interplay of predetermined neural circuits and the role of experience in object representations in semantic memory.

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Appendix 1

For the specification of the dynamic models of interest, we first defined for each participant two General Linear Models that were specifically designed to encompass the requirements of the intended DCM analysis. The first GLM matrix (dcm-GLM) was entered during DCM model specification and included a separate regressor representing all stimuli of all conditions (ALL) and additional regressors for the individual conditions MTO, VTO, NTO, and SCI, and for their parametric modulation regressors contrasting pre and post training for each condition. To avoid the issue of colinearity within dcm-GLM, which would interfere with the definition and extraction of volumes of interest, we also specified a second GLM matrix (voi-GLM) that only included the regressors for the MTO, VTO, NTO, and SCI conditions, but not the ALL regressor. The voi-GLM matrix was only used to extract volumes of interest and was not directly entered during DCM model specification.

In both the voi-GLM and the dcm-GLM, the time series of each participant were high-pass filtered at 128 s and pre-whitened by means of an autoregressive model AR(1). Evoked responses were modeled with the canonical hemodynamic response function, time-locked to the onset of each trial block. We modeled the six sequences pre- and the six sequences post training as one single concatenated fMRI session, and we included $(12-1=11)$ additional constant regressors, each with values of 1 for the scans of one session and 0 for the other scans, to account for the separate functional scanning sessions.

Within the voi-GLM model of each participant, we computed one t-Student contrasts defining the main effect of learning vs. baseline $[(MTO+VTO+NTO)-SCI]$. This contrast was used to identify subject-specific volumes of interest for the four brain regions in the parieto-frontal and temporal cortex which were finally included in the dynamic causal models: LIPL, common to both MTO and VTO, LPPC and LIFG for MTO, and LMTG for VTO (see Results section for the analyses yielding these activations and for the coordinates of activation peaks).

Subject-specific volumes of interest were defined through a small volume correction procedure. After computing the main effect contrast for each subject, we defined spherical

volumes (radius = 8 mm) around the group-level coordinates of the four target brain regions (see Results section), and extracted the maximum activation peaks for each subject. We also checked that the subject-specific coordinates identified through this procedure actually corresponded to the same anatomical location represented by the group-level coordinates. We extracted spherical volumes of interest of 8-mm radius centered on the identified subject-specific coordinates. The volumes of interest were corrected for the effects of interest (mass univariate F-test), such that it was not biased toward any particular experimental conditions, but rather included the information relative to the stimuli of all conditions. Finally, we also checked that the locations of the volumes of interest for LIPL and LPPC were entirely non-overlapping in all the subjects.

The extracted volumes of interest were then used for the specification of dynamic causal models, based on the dcm-GLM matrix.

Appendix 2

Generation of model space (Figure 2):

For the intrinsic connection configurations (Figure 2A), we included: Int1) a fully connected model as a totally unconstrained reference, and we then defined 8 other configurations by progressively applying the following constraints; Int2) elimination of “extrinsic” connections, namely connections between region pairs that were not both activated by either MTO or VTO (i.e. LPPC ↔ LMTG, LIFG ↔ LMTG); Int3-5) elimination of backward connections from condition-specific regions to LIPL, one at a time (i.e. either PPC → LIPL, LIFG → LIPL, or LMTG → LIPL); Int6-8) elimination of backward connections from condition-specific regions to LIPL, two at a time; Int9) elimination of all three backward connections from condition-specific regions to the common region LIPL.

Of especial experimental interest are the 4 specified configurations of modulatory inputs (Figure 2B): Mod1) in the first configuration, MTO-p.l.e., VTO-p.l.e. and NTO-p.l.e. were all allowed to modulate all the connection strengths in the dynamic causal models; Mod2) in the second configuration, only MTO-p.l.e. and VTO-p.l.e. were allowed to modulate

the connection strengths; Mod3) in the third configuration, MTO-p.l.e. and VTO-p.l.e. were only allowed to modulate “own” connections, namely those between regions they themselves activated (i.e. for MTO-p.l.e., all specified connections between LIPL, LPCC, and LIFG; for VTO-p.l.e., all specified connections between LIPL and LMTG); Mod4) in the fourth configuration, MTO-p.l.e. and VTO-p.l.e. were only allowed to modulate “reciprocal” connections, namely, for MTO-p.l.e., those between regions activated by VTO-p.l.e. (all specified connections between LIPL and LMTG), whereas, for VTO-p.l.e., those between regions activated by MTO-p.l.e. (all specified connections between LIPL, LPCC, and LIFG).

With respect to direct inputs (Figure 2C), in all four specified configurations the ALL regressor representing all stimuli of all conditions provided input to LIPL, allowing for condition-independent signal propagation to the entire dynamic causal model. In the first direct input configuration (Dir1), no other inputs were provided to the dynamic system. In the second configuration (Dir2), MTO-p.l.e. provided additional inputs to LPCC and LIFG, whereas VTO-p.l.e. provided input to LMTG. In the third configuration (Dir3), MTO-p.l.e. provided additional input to LPCC only, whereas VTO-p.l.e. provided input to LMTG. In the fourth configuration (Dir4), MTO-p.l.e. provided additional input to LIFG only, whereas VTO-p.l.e. provided input to LMTG.

A random effects BMS analysis was performed to select the winning family among the specified 16 families and the winning model among the specified 144 models. The winning family and the winning model were chosen as those having the highest exceedance probability in the respective rankings. Post-hoc tests based on Group Bayes Factor (GBF) were used to assess the significance of the best family/model. The GBF index was calculated as the ratio of the exceedance probability of the best family/model and that of the other families/models: thus, the higher is the GBF ratio, the more is the evidence in favor of the best family/model (significance cut-off ≥ 20). Analogously, we also performed post-hoc tests based on posterior probabilities, by computing the product of the ratios between the posterior probability of the best family/model and that of the other families/models. We also

used random effects ANOVAs on posterior probabilities, with subjects as a random factor, to assess significant differences of posterior probability between models within a category.

In order to identify the second-best family and second-best model, we reduced the model space by excluding all models with the modulatory input configuration Mod4 (i.e. “reciprocal” modulations). We then again used random effects ANOVAs, with subjects as a random factor, to assess significant differences of posterior probability between models in the reduced space. Post-hoc Tukey tests were used. Finally, we calculated mean modulatory connection strengths for all the connections of the winning model and second-best models, averaged over the 16 experimental subjects.

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Figure Captions

Figure 1: Example trials of the object matching task administered during fMRI acquisition with A) two conventional pictures of objects, b) two pictures showing objects being manipulated and C) two scrambled object pictures (baseline condition).

Figure 2: Model space for Bayesian Model Selection of Dynamic Causal Models. The model space was constituted by 144 models per subjects, generated by the combination of: A) 9 different intrinsic connection configurations (Int1-9); B) 4 modulatory input configurations (Mod1-4); C) 4 direct input configurations (Dir1-4). The combination of modulatory and direct input configurations of the winning family (Mod4/Dir1) is indicated by grey boxes. Four regions which showed pre-post activation increases, were used for the DCM analysis: left inferior parietal lobule (LIPL), left posterior parietal cortex (LPPC), left inferior frontal gyrus (LIFG), left middle temporal gyrus (LMTG); MTO: manual training with objects; VTO: visual training with objects; NTO: no training with objects; p.l.e.: parametric learning effects (post vs pre training); ALL: model regressor representing all stimuli of all conditions.

Figure 3: Behavioural data: A) mean accuracy and B) mean RTs during the object matching task. Error bars indicate standard deviations.

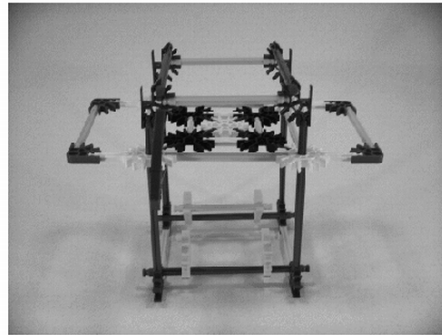
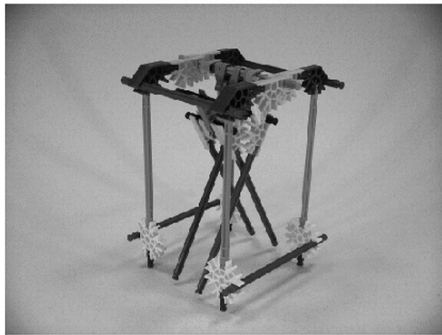
Figure 4: A) Areas of activation increase from the pre to the post training fMRI acquisition for VTO, MTO and NTO. Shown are only those regions with significant activation increase on the cluster level ($p < .05$ corrected, see also Table 1). In direct comparisons of activity between the object sets after training, higher activity for MTO was observed B) relative to VTO and NTO in the left inferior/middle frontal gyrus, C) relative to VTO in the right inferior/middle frontal gyrus and D) relative to VTO and NTO in the left inferior parietal lobule. E) VTO-related activity was higher than MTO-activity in the left middle temporal cortex. See text for coordinates of peak activations. Bar graphs above the brain images in B-E show pre

and post training percent signal change data for the different object sets in the specified regions (in B and C for the region in which activity was higher for MTO than VTO or NTO)

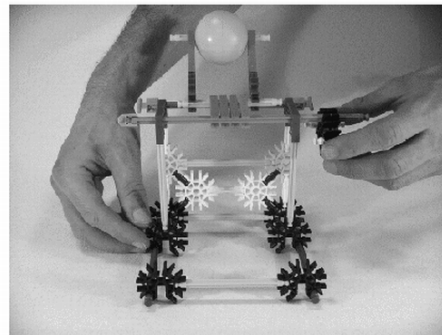
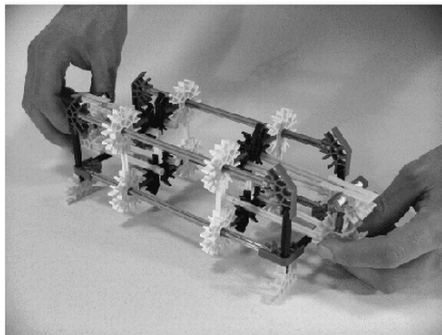
Figure 5: Winning and second-best models yielded by Bayesian Model Selection. A) The winning model Int6/Mod4/Dir1. B) The second-best model Int2/Mod3/Dir1. C) The model (Int4/Mod3/Dir1) with highest posterior probability in a reduced model space excluding all models of family Mod4. Average modulatory influences (Hz) are indicated close to the corresponding modulatory input symbols and connection arrows. A positive value indicates an increase of connection strength induced by the specific type of training from pre to post. A negative value indicates a decrease of connection strength. Figure conventions are the same as in Figure2.

Figure 1

A



B



C

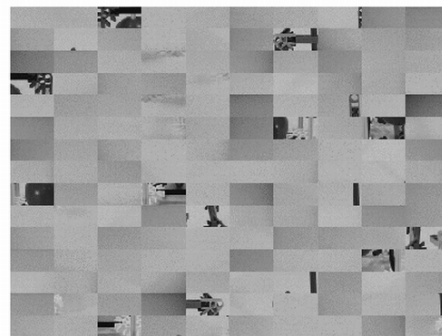
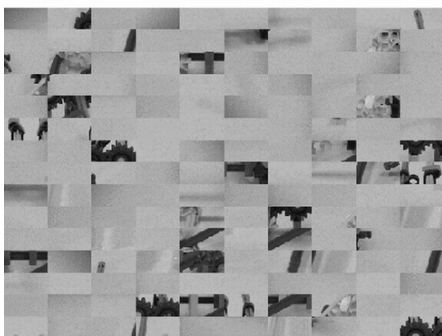


Figure 2

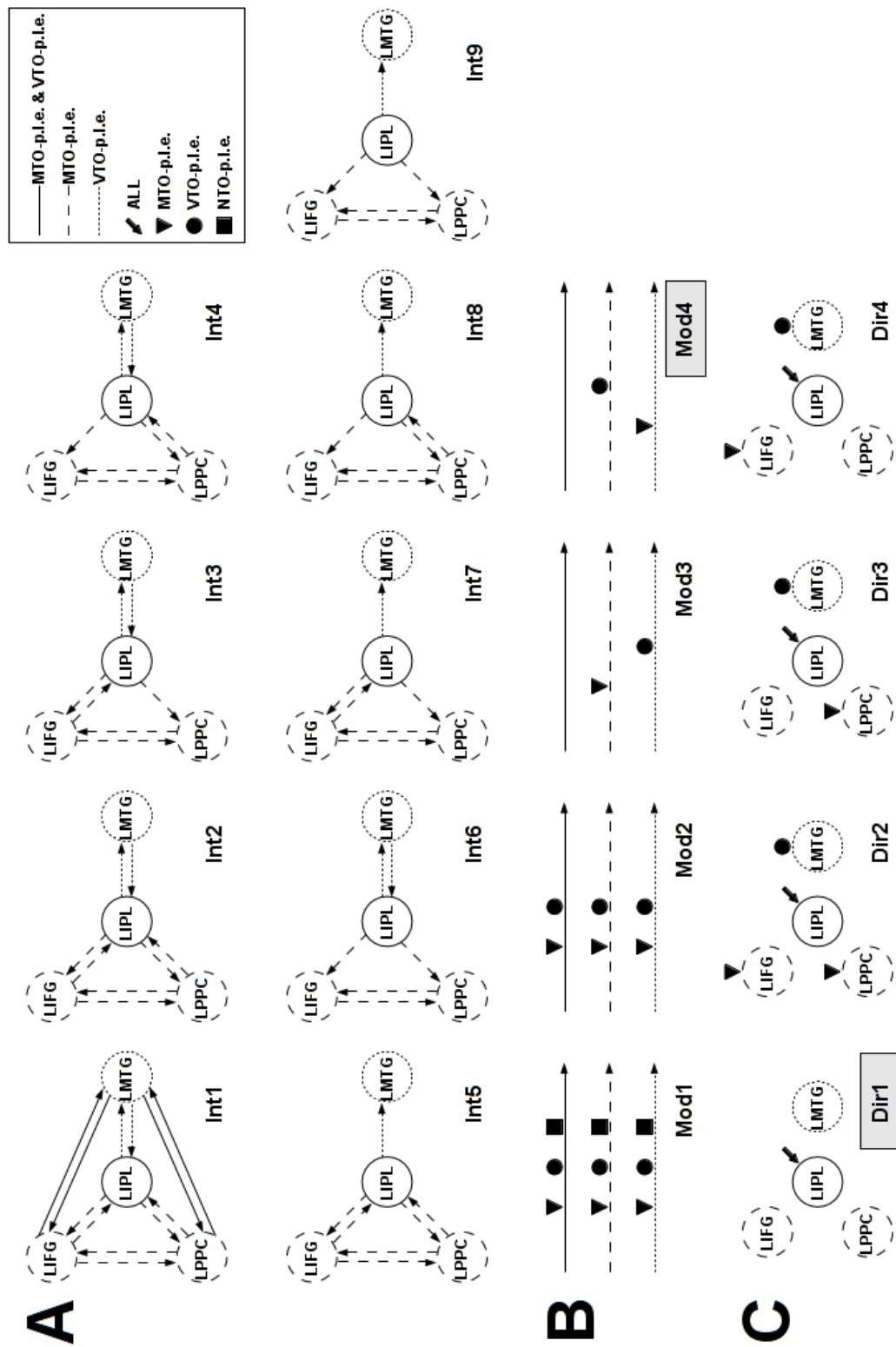


Figure 3

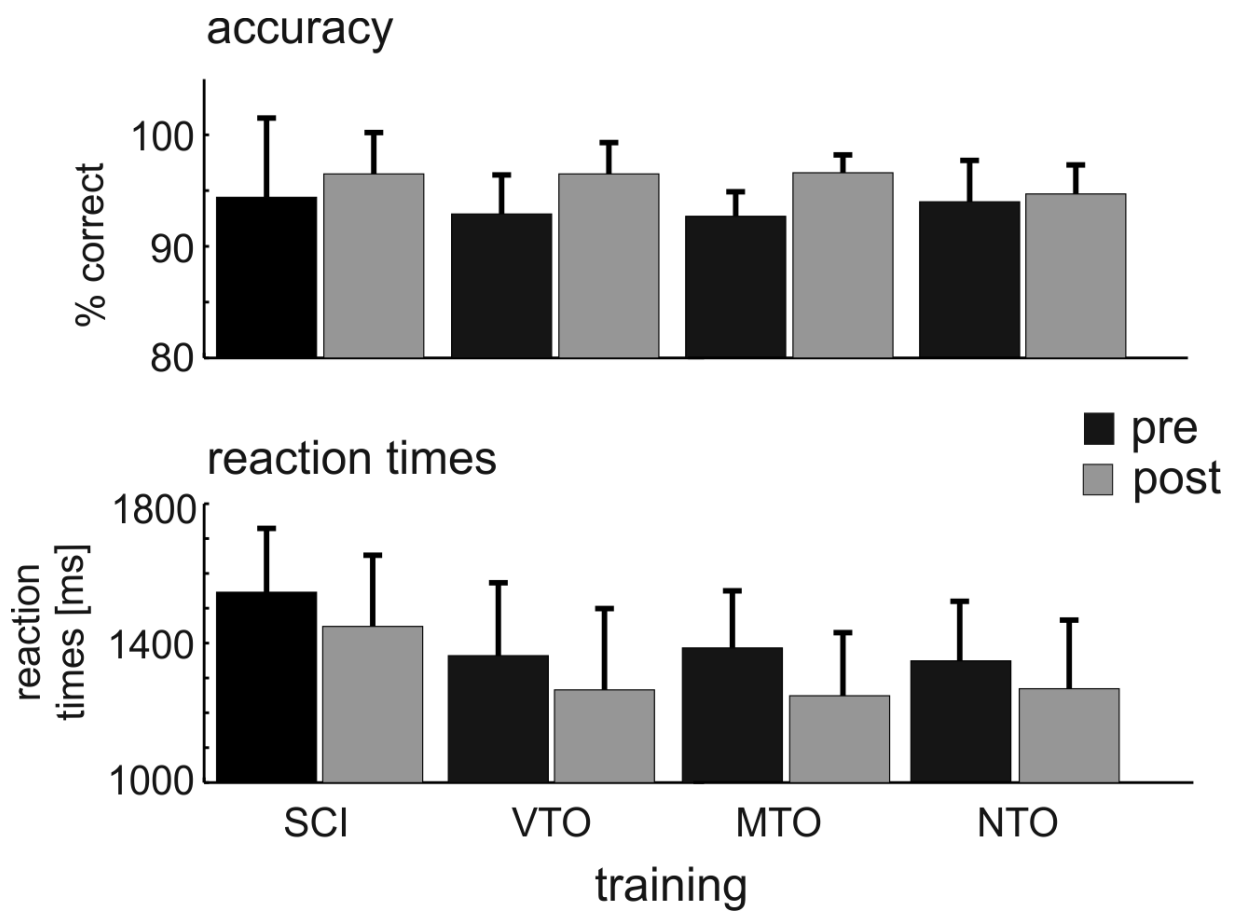


Figure 4

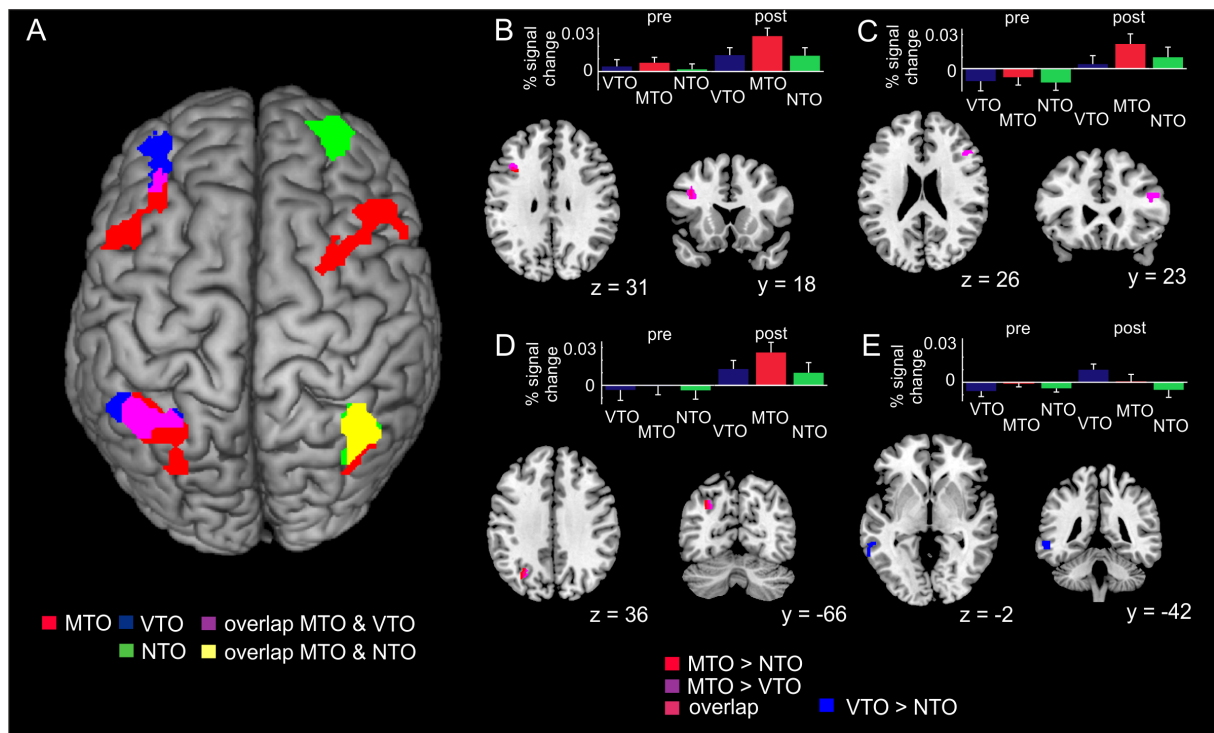


Figure 5

