



## Structural and functional neuroplasticity in human learning of spatial routes



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### ABSTRACT

Recent findings with both animals and humans suggest that decreases in microscopic movements of water in the hippocampus reflect short-term neuroplasticity resulting from learning. Here we examine whether such neuroplastic structural changes concurrently alter the functional connectivity between hippocampus and other regions involved in learning. We collected both diffusion-weighted images and fMRI data before and after humans performed a 45 min spatial route-learning task. Relative to a control group with equal practice time, there was decreased diffusivity in the posterior-dorsal dentate gyrus of the left hippocampus in the route-learning group accompanied by increased synchronization of fMRI-measured BOLD signal between this region and cortical areas, and by changes in behavioral performance. These concurrent changes characterize the multi-dimensionality of neuroplasticity as it enables human spatial learning.

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### Introduction

The ability of the central nervous system to learn from experience and adapt to the environment is undeniably the result of its remarkable capacity for structural and functional change. The term *neuroplasticity* refers to a wide range of such changes, both anatomical and physiological, and it is studied at multiple levels and units of analysis. Neuroplastic mechanisms include changes at molecular, biochemical, synaptic, dendritic, axonal, morphological, and connectomic levels. Part of the challenge of understanding neuroplasticity lies in relating its multiple facets to each other.

Although neuroplasticity has been studied in animals for over half a century by examining both anatomical (Diamond et al., 1964) and physiological (Zhang and Sejnowski, 2000) changes related to experience, only recently has neuroimaging allowed neuroplasticity to be investigated in vivo in humans. High-resolution structural images of the living human brain enabled precise measurement of changes in tissue volume longitudinally. Early correlational evidence showed that macroscopic morphological changes could be detected with MRI. For example, the posterior hippocampi of London taxi drivers with extensive navigation experience were larger than those of control participants (Maguire et al., 2000). Draganski et al. provided some of the first longitudinal evidence of learning-induced structural plasticity in humans by showing

voxel-based morphometric changes in the gray matter of bilateral temporal visual motion areas and the left intraparietal sulcus following three months of training on juggling (Draganski et al., 2004). Additional studies of gray matter have suggested neuroplastic changes resulting from intensive training or learning in domains such as medical knowledge (Draganski et al., 2006), spatial memory (Maguire et al., 2006; Woollett and Maguire, 2011), and aerobic exercise (Colcombe et al., 2006; Erickson et al., 2011).

Another MRI-based structural imaging technique, diffusion-weighted imaging, also provides evidence of neuroplasticity resulting from intensive training and/or learning. Keller & Just showed that approximately 100 h of intensive reading remediation led to increased fractional anisotropy (FA) in the left frontal lobe, and that this change was correlated with changes in reading ability among children (Keller and Just, 2009). Sholz et al. found that six weeks of juggling training in adults resulted in FA increases in the white matter beneath the right intraparietal sulcus (Scholz et al., 2009). Additional studies now suggest adult FA increases following balance training (Taubert et al., 2010), working memory training in aging participants (Lövdén et al., 2010; Engvig et al., 2011), and meditation training (Tang et al., 2010). A number of reviews and critiques of both the gray matter and white matter changes resulting from relatively long-term, intensive learning or training regimens in adults have recently appeared (Zatorre et al., 2012; Lövdén et al., 2013).

Although these human in vivo experimental studies of neuroplasticity have involved extensive training, and have examined rather macroscopic structural changes, it is clear that learning-related changes in the brain must occur over shorter intervals and at more microscopic levels (Fu and Zuo, 2011). The cellular bases of experience-based structural changes

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in both gray and white matter remain speculative, but in a pioneering study that related structural and cellular changes, Blumenfeld-Katzir et al. demonstrated that diffusion imaging can detect neuroplastic changes in gray matter (Blumenfeld-Katzir et al., 2011). Following long-term training (a week) on a spatial-learning water maze task, rats showed decreases in diffusivity of water in the hippocampus and increases in quantitative cellular-level markers for synapses and astrocytes.

These findings of neuroplasticity have been extended to humans and to shorter training episodes in a series of recent papers from the same laboratory (Sagi et al., 2012; Hofstetter et al., 2013; Tavor et al., 2013). Sagi et al. trained both rats and humans on a spatial route-learning task for 2 h, comparing diffusion-weighted imaging before and after the training. The human participants engaged in a video-game driving task where they practiced driving the same route repeatedly. Compared to a control group that practiced on many different routes, this learning group showed effects of the spatial learning and decreased diffusivity in the left hippocampus and right para-hippocampus after only 2 h of practice. Rats trained on the water maze for only 2 h showed decreased diffusivity in the hippocampi (greater decreases on the left) and increases in markers for synaptic changes, astrocyte changes, and in brain-derived neurotrophic factor (BDNF), which may be a marker for long-term potentiation. Hofstetter et al. showed that in both rats and humans, diffusivity decreased as a result of learning in the fornix connecting the hippocampus to the diencephalon. Moreover, this decrease was correlated with the changes in diffusivity in the hippocampus, although no histological measures in the rats were reported. Tavor et al. repeated this same experiment with both a standard diffusion tensor model and with a more complex diffusion sequence and model (the composite hindered and restricted model of diffusion (CHARMED) proposed by Assaf and Basser (2005)). They again found decreased diffusivity in the left hippocampus, bilateral para-hippocampal gyrus and the bilateral insula, and showed that the changes in the left hippocampus and right parahippocampal gyrus were accompanied by an increase in the volume of water in the restricted compartment of the CHARMED model.

Neuroplasticity resulting from short-term learning has also been explored by comparing fMRI-measured functional connectivity (FC) in within-subject training experiments. Functional connectivity is a measure of the correlation or covariance across time of changes in the levels of activation among spatially separated brain regions. One of the earliest studies using the technique was in fact a learning study (Büchel et al., 1999). Participants learned spatial locations of presented objects, and despite decreases in activation with repeated presentations of the item (repetition suppression), the correlation of the activation time series between ventral object processing cortex and dorsal spatial processing cortex increased with learning. This task-related FC is thought to capture the dynamic functional changes in regional communication across networks of areas involved in the learning task, and it could be a manifestation of a number of relatively low-level short-term neuroplastic processes (e.g., LTP, synaptogenesis, astrocyte signaling). In addition, a number of studies have also used *intrinsic* FC, (sometimes referred to as resting state FC (rsFC) because it is often measured without the participant performing a specific task) to look at the effect of learning (reviewed by Kelly and Castellanos (2014)). Such intrinsic connectivity increases are found in humans for simple motor learning (Albert et al., 2009) and for learning to navigate in a virtual environment (Woolley et al., 2015). There is ample evidence this measure of functional connectivity, involving very slow low-frequency correlations between regions while the participant is unoccupied with an experimenter-imposed task, increases following many types of learning, although whether such changes should be considered functional or structural remains controversial.

Here we investigate how a diffusion-based measure of spatial learning, presumably reflecting structural changes in the brain, is related to changes in brain function. We attempt for the first time to relate the learning-related changes in diffusivity in the spatial encoding network to fMRI-measured changes in both intrinsic FC and task-related FC across the network. The much slower, intrinsic synchronized fluctuations in

BOLD signal intensity among regions are thought to reveal the networks of connectivity resulting from a history of co-activation (see Buckner et al. (2013) and Raichle (2011), for recent reviews), whereas task-related FC is thought to reveal online changes in communication among regions necessitated by performance of the cognitive task. We ask whether very recent history (over the course of the previous hour) can effect changes in these networks that can be related to the learning that has occurred during that time. We examine whether a period as short as 45 min of practice in traversing the same virtual route is sufficient to produce the changes seen in the previous studies.

The methodology explores whether the learning changes can be detected with a much shorter diffusion scan that nevertheless provides higher angular resolution. This speed-up benefits from the simultaneous multi-band stimulation (SMS) imaging (Sotiropoulos et al., 2013) used in the Human Connectome Project, but with significant improvements. The design of the experiment is shown in Fig. 1.

## Materials and methods

### Participants

Twenty-nine right-handed adults (26 females, 3 males, between the ages of 19 and 31 years,  $Mean = 22$  years,  $SD = 2.9$  years) from the Carnegie Mellon University community participated. All participants gave signed informed consent approved by the Carnegie Mellon Institutional Review Boards. All participants had less than 5 h of “action” video game experience (i.e., games played from the first-person perspective and requiring navigation in a virtual environment) during the two years prior to the experiment. These participants could therefore be considered novices who were not familiar with playing action video games. This inclusion criterion is more stringent than that used by other researchers (Bavelier et al., 2011) for considering a participant as a non-video game player. It did, however, result in a much higher proportion of female volunteers who met the criteria.

The participants were assigned to either the Route-Learning or the Control group with the restriction that the groups be as closely matched as possible on age, gender, and ethnicity. The Route-Learning group consisted of 14 participants ( $Mean$  age = 22.4 years,  $SEM = 0.91$ , 11 female and three male, two Asian, one African American, nine Caucasian, one Hispanic). The control group consisted of 14 participants ( $Mean$  age = 22.1 years,  $SEM = 0.6$ , 13 female and one male, four Asian, 10 Caucasian). An additional participant was removed from the Control group due to excessive motion (see Analyses below) during one of the scans.

### Experimental paradigm

To measure functional and structural changes resulting from practice on the driving task, two separate 30-min scanning sessions were conducted for all participants, with a one-hour interval between them. During the interval between the scanning sessions, participants in the Route-Learning group practiced driving the same route 20 times. During this same time the Control group practiced driving 19 different routes (one route being the same one practiced by the Route-Learning group, and repeated at the beginning and end of the intersession practice session).

### Driving simulation

For the virtual driving environment, we adapted code from the open source motorsport simulator *Speed Dreams 2.0* (<http://www.speed-dreams.org>). This software provides high-quality graphics and very realistic visual and physics simulation of driving. We carefully selected the simulated automobile and the virtual routes driven, and adjusted visual and physics simulation parameters such that the driving task would not be difficult to for our sample of very novice players of

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