Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Do Short-Term Changes in White Matter Structure Indicate Learning-Induced Myelin Plasticity?

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Review of Hofstetter et al.

Learning and memory formation are largely thought to result from structural and molecular plasticity in neurons. However, white matter, which is composed of bundles of axons, all major types of glia, and blood vessels, is rarely thought to play a principal role in learning processes. Depending on the developmental stage, axon diameter, and specific tract, axons within white matter may be myelinated to different degrees or not at all. Myelin is a fundamental component in many mature neuronal circuits and alters connectivity between different brain regions through modulation of action potential conduction velocity (Fields, 2008). There is growing interest in understanding if and how changes in myelination occur during learning and whether or not myelin plasticity is an active player in these processes (Zatorre et al., 2012).

Diffusion tensor imaging (DTI) is a powerful magnetic resonance imaging technique that noninvasively measures the preferential diffusion of protons of water molecules in tissue (Beaulieu, 2002; Mori and Zhang, 2006). Because of the highly ordered orientation of fibers in white matter regions, water primarily diffuses parallel to axonal bundles, enabling DTI to provide details about the regional microstructure and how this diffusion changes during development, learning, and disease. DTI data are primarily reported as mean diffusivity (MD), a value representing water diffusion in multiple directions; fractional anisotropy (FA), a fraction representing diffusion restricted to a single direction; and radial diffusivity (RD), diffusion perpendicular to barriers such as cell membranes. Using these types of measurements, multiple reports have demonstrated long-term changes (from weeks to years) in the volume of the extracellular space (MD) and the linear diffusion of water (FA) during human development (Lebel et al., 2008) and in conjunction with behaviors such as practicing piano and learning to juggle (for review, see Zatorre et al., 2012). What cellular phenomena these changes in water diffusivity represent is not entirely clear, and how quickly these changes can occur in white matter had not been investigated in detail.

A recent study by Hofstetter et al. (2013) used DTI to investigate whether learning-induced structural changes in white matter regions can be detected in a timeframe of hours in humans and rats. Detection of such changes could represent a form of underappreciated short-term white matter plasticity that may contribute to cellular mechanisms underlying learning and memory. In the human study, 70 young adults were split into three experimental groups all receiving MRI scans with DTI acquisition before and after a 2 h testing period. Between the scans, the learning group (LG) was required to navigate and learn a specific racetrack within a computer driving simulation game. LG participants' goals were to learn the track and improve individual lap times over the training session. The first control group, termed the active control (AC), played the same game for the same amount of time but the track for each lap was different so spatial and navigational learning did not occur. The second control group, termed passive control (PC), simply received two DTI scans at an interval of 2 h. The authors of the study compared the MD and FA changes that occurred between the two scans specifically in the fornix, a white matter tract that connects the hippocampus to the medial diencephalon and is thought to transmit memory related information.

The authors found that, unlike in the two control groups, there were significant changes in the MD values in the LG participants, indicating that water diffusion within the fornix was more spatially restricted after only 2 h of learning in the driving task. In addition, they found a correlation between changes in MD in the hippocampal gray matter and MD in the fornix, suggesting a relationship between short-term structural plasticity in gray and white matter. Finally, Hofstetter et al. (2013) demonstrated a correlation between behavioral performance (measured by improvement in lap times and ability to identify specific parts of the tracks) and

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the differences in the DTI parameters FA or MD. Importantly, these results suggest that the restriction of water diffusion to a more singular direction within individual voxels is connected to behavioral performance and could possibly represent a cellular change that facilitates enhanced behavior.

To complement the human findings, the authors performed a similar experiment with rats, measuring the same DTI parameters in the fornix 1 d after training in a water maze task. Similar to the human findings, the authors reported that MD values were changed in LG but not control groups. Furthermore, they found a correlation between changes in MD in the hippocampal gray matter and MD and radial diffusivity in the fornix. Finally, they demonstrated a correlation between improvement in water maze performance and changes in RD, once again suggesting that the magnitude of change in certain DTI indices positively relates in some way to behavioral performance.

While these data provide convincing evidence that learning induces structural changes in both human and rat white matter over short time periods, they raise several important questions. First and foremost: which cellular mechanisms contribute to changes that are detected with DTI specifically in this context? As mentioned above, white matter is composed of both myelinated and unmyelinated axons, blood vessels, and all major types of glia. While Hofstetter et al. (2013) were careful and correct not to conclude that the changes they observe are myelin-specific, a likely first interpretation is that the changes result from activity-dependent changes to myelination, particularly because DTI in white matter is generally considered a measure of myelination. Even in white matter, however, several other cellular phenomena may contribute to the changes observed with DTI and other similar MRI modalities. One way to infer which of these phenomena result in changes to DTI indices in the experiments described here is to consider the temporal window in which various cellular events have been reported to occur after changes in neuronal activity and learning.

Long-term learning- or behavior-induced structural changes have been reported previously in human white matter with DTI, and specifically for myelin with histological techniques in rodents (for review, see Zatorre et al., 2012). Furthermore, it is well established that neuronal activity can influence myelin formation in cell culture systems. However, all *in vitro* studies demonstrating effects of neuronal activity on oligodendrocyte differentiation and mature myelin sheath formation have shown such events to occur over days to weeks, not minutes to hours (Demerens et al., 1996; Stevens et al., 1998). This distinction is critical as the changes observed by Hofstetter et al. (2013) in the human study occurred over 2 h. It was recently reported that neuronal activity could induce local translation of myelin basic protein *in vitro* in a timeframe of minutes to hours (Wake et al., 2011). While this finding is striking and is the closest demonstration of activity-induced myelin-related changes occurring over very short time periods, production of myelin basic protein does not designate assembly of a mature myelin sheath. Furthermore, localized protein translation over 1 or 2 h does not seem likely to change water diffusivity enough to be detected using millimeter resolution DTI. Therefore, it seems unlikely that alterations in myelin sheath assembly or changes in the differentiation of oligodendrocyte progenitor cells would significantly contribute to the altered DTI signals over such short time frames. This is not to say that neuronal activity does not influence myelin production or that DTI cannot detect changes in myelination *in vivo* (Beaulieu, 2002; Mori and Zhang, 2006; Jones et al., 2013), but that these events likely take longer to occur.

In addition to changes in the number of myelinated axons or myelin thickness, other cellular mechanisms account for longer-term structural plasticity. Increases in axon diameter and even sprouting can occur in response to neuronal activity, all of which could be reflected by changes in DTI measures. Importantly however, these changes have only been detected over weeks to months, so changes in axon structure or organization are unlikely to be responsible for the relatively quick changes in diffusion measured by Hofstetter et al. (2013).

Studies investigating temporary structural changes report that on a time scale of seconds, neuronal activity results in transient alterations in axon volume (Tasaki, 1999), local blood vessel diameter, and regional blood flow (Iadecola and Nedergaard, 2007), all of which could modify MD and FA values by shrinking extracellular volume and restricting water diffusion. Because these changes occur over short time frames, however, they would not likely be maintained over the temporal window analyzed in the study by Hofstetter et al. (2013). On a time scale of minutes to hours, neuronal activity can result in the extracellular accumulation of K^+ in white matter tracts, and this can cause sustained swelling of both astrocytes and oligodendrocytes (Syková and Nicholson, 2008). Increases in cell volume could result in a decrease in extracellular space and a corresponding decrease in the MD. Whether or not these changes would result in increases in FA indices is not clear, because, given the highly ramified morphology of astrocytes, increased volume would not necessarily restrict water diffusion to a single direction. Oligodendrocyte swelling, however, might result in linear compression of the extracellular space, because oligodendrocyte processes are aligned with the axonal tracts. Direct evidence for sustained cell swelling influencing DTI parameters is not available; however, the temporal dynamics resemble those reported by Hofstetter et al. (2013) in the human study. Therefore, given the current available data present in the literature, one might propose that the short-term structural changes observed by Hofstetter et al. (2013) could result from increases in glial cell volume and not changes in oligodendrocyte differentiation or myelin production. Further study is necessary to tease apart these possibilities.

Independent of the cellular mechanisms, other important questions come from the study by Hofstetter et al. (2013). Are the structural changes that occur after 2 h of training sustained for days to weeks and do they correlate with the continued performance of the learned behavior? Are these rapid changes confined to young adults or can they occur in elderly individuals? Do specific tasks cause short-term changes in particular white matter tracts and if so can these be used to elucidate important behaviorally relevant connections between brain regions?

In summary, care must be taken when interpreting changes in white matter structure measured with DTI and similar MRI techniques. The rapid structural changes in white matter observed by Hofstetter et al. (2013) are intriguing, but they also highlight the need for detailed analysis into the cellular mechanisms detected by DTI and other noninvasive imaging techniques. More importantly, these findings emphasize the need for further cellular and molecular investigation and understanding into the correlation between short- and long-term changes in white matter regions and their relationship to learning and memory formation.

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