**How Might Training Improve Cognition?[[1]](#footnote-1)**

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 **Abstract**

Why does training on a task improve reaction time for performing it? New research points in the direction of changes in white matter pathways as one likely mechanism. These pathways connect remote brain areas involved in performing the task. Genetic variations may be involved in individual differences in the extent of this improvement. If this mechanism is involved in improved reaction time with training, it may point the way

toward understanding where and how generalization occurs. We examine the hypothesis that brain pathways shared by different tasks may result in improved performance of cognitive tasks remote from the training

**Introduction**

 There has been substantial debate over how training might improve an array of cognitive processes remote from training on a specific task. As an example, researchers at Stanford University and Max Planck Institute posted a letter rejecting claims of remote transfer from training in a cognitive task ([http://longevity3.stanford.edu/blog/2014/10/15/](http://longevity3.stanford.edu/blog/2014/10/15/%22%20%5Ct%20%22_blank)). This letter brought a reply from Michael Merzenich and a large number of other researchers ([http://www.cognitivetrainingdata.org/](http://www.cognitivetrainingdata.org/%22%20%5Ct%20%22_blank)) citing empirical evidence for transfer in human and animal studies, although little is yet known about how this improvement in performance takes place. It is the hope of this paper that understanding what we know or might learn about improved task performance during training can enhance our understanding of transfer.

 Most people agree that training improves the task being trained. Reaction time is a particularly important measure of performance in many skills and it is generally thought that over a wide range of conditions there is a monotonic relationship between number of practice trials and reaction time to perform the task (Anderson, Ficham & Douglass, 1999; Fitts & Posner, 1967; Heathcote, Brown & Mewhort, 2000; Newell & Rosenbloom, 1981). The shape of the function has been disputed, with some arguing for a power function (Anderson et al 1999; Fitts & Posner, 1967; Newell & Rosenbloom, 1981) and others an exponential function (Heathcote et al., 2000), but both agree there is a monotonic improvement in reaction time with training.

 A deeper understanding of how training improves performance on the trained task may help us gain perspective on the issues of how far such training may assist general cognition. Thus this paper is designed to put a somewhat broader perspective on transfer by considering what is known or might be learned about the cellular and molecular mechanisms influencing improvement in reaction time with training. We hope this approach might also illuminate the issue of the relationship between training effects and transfer to new tasks.

**Forms of training**

 We have suggested that network and state training are two different methods for training the brain (Tang & Posner, 2014). These two methods fit with two types of MRI studies. The older imaging approach involves scanning the brain during performance of a task (Posner & Raichle, 1994). Generally two conditions are compared, one while performing the complete task and a second in which the person performs some part of the task (control condition). Subtraction of control condition from the complete task condition is designed to isolate operations involved in the first condition that are not present in the second condition. A different MRI method is to examine brain areas whose activation is correlated when the person is not performing any task (Raichle, 2009). These reflect the ongoing state of the brain (default state) without instruction to perform a task.

 The first method of training involves using a specific cognitive task (Tang & Posner, 2014). Two of the most studied are training in working memory (Buschkuehl, Hernandez-Garcia, Jaeggi, Bernard, & Jonides; 2014) and attention (Rueda, Checa & Combita, 2012), but specific networks related to visual perception (Zatorre, Fields, Johansen-Berg, 2012), reading (Schlaggar & McCandliss, 2007) and arithmetic (Ansari, 2008) are also well studied. The second method involves training to produce a brain state that might lead to improved performance on many specific networks. The most explored forms of state training have been physical training (Hillman, Erickson, & Kramer, 2008) and meditation (Tang & Posner, 2014).

**Brain Changes**

 Most of us have learned to think about white matter changes as occurring in child

development but not in adults. However, in recent years this view has been altered by

findings that dormant oligodendroctyes can be activated when people suffer from a demyelinating disease (Beirowski, 2013). In addition, many forms of training in adults have been shown to result in changes in the efficiency of white matter connections as measured by Diffusion Tensor Imaging with MRI (Wang & Young, 2014; Zatorre et al., 2012).

 There is also evidence from a study of mice learning to run on a wheel with irregular

spokes, requiring acquisition of a new and complex motor skill. This learning has also been shown to activate dormant oligodendrocytes. (McKenzie, et al., 2014). When activation of the dormant oligodendrocytes was blocked, the animals did not learn, showing the importance of cells producing myelin for acquiring a motor skill.

 The mechanism for white matter change seems to be a general one requiring repeated activation of the pathways associated with training (Gibson et al., 2014). Similar effects of learning on white matter have been reported in human subjects (for a review see Wang & Young, 2014) using a variety of network and state training methods. These include meditation (Tang & Posner, 2014), juggling (Scholz, Klein, Behrens, & Johansen-Berg, 2009) and working memory training (Takeuch et al., 2010). Most of these tasks show change in a statistic called Fractional Anisotropy (FA) measured by Diffusion Tensor Imaging (DTI). This statistic measures the directionality of water molecules and is thought to reflect the efficiency of the white matter tracts along which the molecules move. In some studies changes are measured in axial diffusivity (AD) which is thought to relate mainly to the density of axons within the pathway. Measures of radial diffusivity (RD) have been related in animal studies to changes in myelination (Fields, 2008, 2015; Zatorre et al., 2012).

 Meditation training has been shown to change white matter (Tang et al., 2012). With respect to the practice of meditation, a current puzzle is how a purely mental activity like control of attention through mindfulness training could influence white matter axonal and myelination changes. We previously developed a working hypothesis (Posner, Tang & Lynch, 2014) that views frontal theta as releasing a protease to influence the activity of dormant oligodendrocytes or precursor cells.

 To test these ideas we are using transgenic mice expressing light-sensitive receptors that allow for temporally precise activation of neurons in the anterior cingulate cortex, a method known as optogenetics (Fenno, Yizar & Deisseroth, 2011). We targeted this structure based on our human data showing white matter changes in a number of pathways surrounding the anterior cingulate following one month of meditation training (Tang et al., 2010).

 There is considerable evidence that meditation training produces a frontal theta rhythm (Xue, Tang, Tang , & Posner, 2014). Frontal theta is also produced during tasks involving cognitive control (Jiang, Zhang & van Gaal, 2015; Wolmelsdorf, Johnson, Vinck, & Everling, 2010) and is associated with plastic changes in learning and memory. Based on these findings we are examining the effects of inducing theta and other rhythmicities on mouse behavior and myelination. We use optogenetics to stimulate excitatory activity phase-locked to 1, 8 or 40 Hz rhythms for half an hour each day for 30 days. We expect changes due to theta stimulation. The changes may relate to the finding that Long Term Potentiation (LTP), a major brain mechanism related to learning, can be induced in hippocampal cells following theta stimulation ([Larson, Wong, & Lynch, 1986](#_ENREF_28)). In accord with recent evidence for activity dependent myelination (Fields, 2015), repeated stimulation of a broad population of cells via theta might influence overall connectivity.

 Although we hypothesized a unique place for theta rhythm, recent studies suggest that even direct current (DC) stimulation can induce or improve a frontal theta rhythm (Miller, Berger & Sauseng, 2015; Reinhart, Zhu, Park, & Woodman, 2015). There have also been findings that DC stimulation over frontal electrodes can improve learning (Cohen Kadosh, Soskic, Iuculano, Kanai, Walsh, 2010; Rhinehart et al. 2015). However, there is still as much dispute over the efficacy of DC stimulation as there is for the general proposition that some forms of network specific learning can transfer to a wide range of subsequent tasks (Horvath, Forte, Carter, 2015). We believe that the lack of specific mechanistic explanations, either for producing the far transfer sometimes found in network training or for producing the facilitatory effect of frontal DC stimulation on learning, has made it difficult to establish their links to plasticity. We hope the direction of work described in this paper might help to provide the needed mechanisms.

**Individual Differences**

 While almost all persons improve on a trained task, the rate of training can vary among persons. How does this occur? Most of the quantitative accounts of how reaction time improves are strictly at the psychological level. They propose priming of specific subroutines (Anderson et al., 1999) or the elimination of inefficient strategies of performing the task (Fitts & Posner, 1967). However, it has been argued that the development of myelination is regulated by environmental influences on expression of DNA through epigenetics (Emory & Liu, 2015).

 Although various strategies, backgrounds, motivation etc. are clearly involved in the improvement of RT with training, our paper in this special issue (Voelker, Sheese, Rothbart & Posner, 2015) argues that epigenetic differences in the efficiency of methylation may also be important in the rate of improvement. We report that an allelic variation in a gene related to improved methylation of DNA can influence the rate of learning in 7 year old children when practicing the Attention Network Test. We found that those children with the higher efficiency allele of the methylenetetrahydrofolate reductase gene (MTHFR) showed greater improvement in reaction time over three sessions of practice on the Attention Network Test (ANT).

 The Voelker et al (2015) paper is limited to 7 year old children, but we have subsequently found that adults with higher efficiency methylation show significantly faster RTs for resolution of conflict in the ANT than those with the lower efficiency alleles of MTHFR (Voelker, Rothbart & Posner, submitted). This finding extends to implicit and explicit performance in a quite different serial reaction time task (Curran & Keele, 1993) but MTHFR alleles are not related to learning of an unspeeded paired associate learning task. We believe that the improved performance in both development and in learning results from the effects of methylation on neural networks through changing dopamine release or increasing the efficiency of white matter tracts. The effect of development between age 7 and adulthood produces 10 times greater effect on RT (400 millisec) than the effect of learning at each age (40 millisec). We believe this reflects the lack of myelination in childhood as well as the many years of development between ages 7 and adulthood compared to the brief learning period we studied in children and adults.

 The effect of variation in MTHFR was most often associated with variation in genes regulating neurotransmitter activity. For example, individual differences in executive function involved variation in both MTHFR and catechol *O*-methyltransferase (COMT). The COMT gene product metabolizes synaptic dopamine and functional variation in COMT has been associated with differences in brain activity during an executive task (Osinsky, Hewig, Alexander & Hennig, 2012). We also identified individual differences in reaction time across sessions attributed to differences in alerting as a gene x gene effect of MTHFR and a variation in dopamine β-hydroxylase (DBH), whose product converts dopamine to norepinephrine. The change in alertness underlies the tendency of children for an upswing in reaction time late in practice (Voelker et al., 2015).

Differences in neurotransmitter activity in task-relevant pathways may differentially induce the process of myelination via activity-dependent methylation. Our observations that individual differences in learning are related to both neurotransmitter activity and methylation efficiency support this view.

 Our effort to study genetic and epigenetic influence in humans relies on an approach using functional polymorphisms within genes such as MTHFR. Unfortunately, it is impossible with this method to be sure that the influence of MTHFR on the efficiency of white matter causes the RT differences we have found since MTHFR influences other processes throughout the brain and in other places in the body. In addition, we do not know which cell types and brain areas are critical to our observations. To move further we have begun using our mouse model to better understand these mechanisms at the molecular level.

**Implication for Transfer**

 Many cognitive tasks and skills are studied through the use of reaction time. An understanding of the molecular and genetic influences on the speed of responding could be useful in explaining transfer as well as other psychological aspects of human performance . Although the changes in conduction speed due to myelination may be small they could be important because many tasks depend upon the precisely timed arrival of information at a neural area and also upon the oscillatory synchronization of remote areas (Fields, 2015). These factors could lead to increased response speed as connectivity is changed. It may be possible to get a more precise measure of speed changes due to changes in white matter using MRI to gauge white matter efficiency or by using the more fine-grained methods made possible with animal models.

 Do any of the above ideas illuminate the problem of transfer from the trained task to more general cognitive functions? The issue of transfer is rather specific to network training methods. Since state training does not relate to a specific task its range of influence does not involve transfer, but instead how brain state changes brain activity.

*Network Training*

 We have argued above that with white matter changes, improvement may be limited to speed and not to other aspects of learning. If correct, this is one restraint on the generality of the effects of training. The speed of activation requirement is not specific to the type of task, but to all tasks using the same network and for which speed or consistency of activation are critical elements of transfer. However, the use of reaction time as an indicant of task performance is very widespread in Cognitive Psychology and many tasks may show enhanced performance from more rapid or reliable conduction between neural areas even when reaction time is not explicitly measured.

 Consider training of working memory by the N back method (Buschkuehl et al., 2014). There is evidence that this training strengthens the activation and connections between lateral frontal and parietal areas. These areas are involved in orienting of attention and more generally in tactical shifts of perspective (Dosenbach et al., 2007) For this reason tasks involving orienting to external stimuli ought to improve even if they involve modalities separate from the working memory task and are improved with faster transmission speed. However, many tasks do not involve the frontal-parietal system and one would not expect transfer to tasks such as the Stroop or flanker tasks that involve primarily frontal midline rather than lateral brain areas or to unspeeded tasks like vocabulary tests.

 Evidence for far transfer from network training remains inconclusive. Change of white matter pathways would seem to be limited to the domain of the trained task in the case of working memory connections between lateral frontal and parietal areas. However, this pathway is shared by many different cognitive tasks (Duncan & Owen, 2000), and thus it may be possible to see far transfer across tasks.

*State Training*

 Although there has been a great deal of interest in different neural states since the development of resting state MRI, there is no clear definition of exactly what methods designed to change brain state such as physical training, meditation or DC stimulation might have in common.

 There have been many reports of improved learning following DC stimulation over the frontal lobe. The ability of DC stimulation to potentiate the activation of brain networks may lead to a better definition of exactly what is involved in state changes. We believe that our ideas regarding the role of the theta rhythm in improving connectivity may also relate to DC stimulation. One study found that DC stimulation induced vertically over the frontal cortex produces theta activity that can be recorded subsequently in the resting state (Miller et al., 2015). This study used only a brief period of stimulation, so we do not know whether more sustained stimulation will show a longer lasting effect.

 Despite the clear differences between state and network training at the psychological level, the two might be united and also related to the use of DC stimulation at the level of how they influence the brain. All these forms of learning may require low frequency oscillations during the course of learning to enhance white matter. The oscillations may serve to aid in producing long term potentiation and thus improve the synaptic connections between specific cells (Larson, Wong & Lynch, 1986). Repeated activation of adjacent cells over time could produce an overall improvement in white matter, perhaps first by an increase in axonal density and later in the thickness of the myelin sheath that covers the axons as reported in fMRI studies of meditation (Tang et al., 2012).

 The studies reviewed here may point the way toward a deeper understanding of how a given task improves in speed with training. The link between improved connectivity and speed of response suggests one constraint upon how training in a task may change cognition through transfer. The requirement of the transfer task to use the pathways altered by the training may provide a second constraint. We anticipate that continued efforts to connect molecular mechanisms with neural networks of cognition will provide an enlarged context for understanding transfer.

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