Myelination: An Overlooked Mechanism of Synaptic Plasticity?

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Myelination of the brain continues through childhood into adolescence and early adulthood—the question is, Why? Two new articles provide intriguing evidence that myelination may be an underappreciated mechanism of activity-dependent nervous system plasticity: one study reported increased myelination associated with extensive piano playing, another indicated that rats have increased myelination of the corpus callosum when raised in environments providing increased social interaction and cognitive stimulation. These articles make it clear that activity-dependent effects on myelination cannot be considered strictly a developmental event. They raise the question of whether myelination is an overlooked mechanism of activity-dependent plasticity, extending in humans until at least age 30. It has been argued that regulating the speed of conduction across long fiber tracts would have a major influence on synaptic response, by coordinating the timing of afferent input to maximize temporal summation. The increase in synaptic amplitude could be as large as neurotransmitter-based mechanisms of plasticity, such as LTP. These new findings raise a larger question: How did the oligodendrocytes know they were practicing the piano or that their environment was socially complex? NEUROSCIENTIST 11(6):528–531, 2005. DOI: 10.1177/1073858405282304

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Consider the following aspects of myelination, which hint at something more than a developmental process. 1) There is substantial evidence that neural impulse activity can affect myelination (for review, see Zalc and Fields 2000). The evidence is particularly well documented in the visual system, but this can also be reproduced in cell cultures of central (Demerens and others 1996; Stevens and others 2002) and peripheral neurons (Stevens and others 1998; Stevens and Fields 2000). 2) Myelination begins in late fetal development and early postnatal period, but it continues in the forebrain regions of humans through adolescence and into early adult life (Giedd 2004). 3) Development of white matter structure in children correlates with increased development of motor skills and reading ability and increased cognitive function (Paus and others 1999; Casey and others 2000; Yurgelun-Todd and others 2002; Schmithorst and others 2005). Conversely, weaker decision-making skill and increased risk taking in adolescents has been associated with incomplete white matter development in the forebrain of adolescents (Beckman 2004). A recent study using diffusion-tensor MRI shows a correlation between development of white matter fiber tracts with cognitive ability (specifically, IQ) in children between the ages of 5 and 18 years (Schmithorst and others 2005). The imaging method cannot distinguish how much of this increase in white matter structure results from increased fiber organization or greater myelination, but further research will be necessary to analyze this interesting finding.

Much like synaptic plasticity, these aspects of myelination are suggestive of a process influenced by functional interaction with the environment. Changes in brain structure through experience are well documented (Bennett and others 1964), and this remodeling includes not only neuronal and vascular changes but also robust glial responses (astrocyte and oligodendrocyte) (Sirevaag and Greenough 1987). It has been known for 30 years that the number of oligodendrocytes increases 27% to 33% in the occipital cortex of young rats raised in an enriched environment (Szeligo and Leblond 1977), and this effect has been confirmed by Greenough and colleagues (see Sirevaag and Greenough 1987). The influence of environment on oligodendrocytes is not limited to the visual cortex; raising rats in enriched environments increases the number of myelinated axons in the corpus callosum (Juraska and Kopcik 1988). It is not limited to rats: rhesus monkeys reared in enriched environments develop greater white matter volume in the corpus callosum, and these differences correlate with improved cognitive performance on tests of learning and memory (Sanchez and others 1998). The evidence extends beyond animal studies: MRI scans show that childhood neglect is associated with a 17% decrease in the corpus callosum area

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(Teicher and others 2004). Similarly, several mental disorders are associated with reduced white matter volume, including schizophrenia (Kubicki and others 2005) and depression (Steingard and others 2002).

Such facts have stimulated the Greenough laboratory to begin testing whether myelination remains sensitive to experience during adulthood. Their preliminary findings suggest that activity-dependent effects on myelination may not be limited to the visual system or early postnatal development (Markham and Greenough 2005), but further research will be necessary to draw firm conclusions.

If the ability of oligodendrocytes and myelination to respond to features of the animal's environment extends beyond the developmental time frame into the adult brain, Markham and Greenough (2005) suggest that this form of plasticity could increase synaptic efficacy by regulating the speed of conduction. Considering the long length of these axons, the timing of spike arrival among individual fibers could vary widely (Swadlow and others 1978; Swadlow and others 1980). Poo has emphasized the importance of spike timing on synaptic plasticity (Dan and Poo 2004), and the degree of temporal summation of convergent inputs through incoming axons will have a significant effect on the amplitude and duration of the postsynaptic response. Indeed, in an electric fish, the synchronous arrival of action potentials to electrocytes from axons of widely different lengths is determined by differences in myelination (Bennett 1971). In another electric fish, the structure of the nodes of Ranvier differ to vary the series capacitance to regulate the time course of current flow rather than simply propagating the action potential at maximal velocity (Waxman and others 1972). Also, conduction velocity is regulated among axons to synchronize arrival of inputs from axons of different length in the retina (Stanford 1987) and cerebellum (Sugihara and others 1993). Coordinating conduction time between different cortical regions is critical for higher level cognitive function. Timing deficits in information processing are associated with dyslexia (Kaminsky and others 2002) and deficits in learning language (Merzenich and others 1996).

In their recent studies, Ullén and colleagues compared white matter structure in professional concert pianists to age-matched controls by using magnetic resonance diffusion-tensor imaging (Bengtsson and others 2005). Professional pianists had more heavily myelinated white matter tracts than controls in one specific region, the posterior limb of the internal capsule, as judged by this imaging technique. This is not a direct measure of myelination, but rather a measure of anisotropy in water diffusion, which increases with myelination. Within the group of professional musicians, a positive correlation between white matter development and number of hours of piano practice was found. Comparing the effects of practice at different ages (based on the pianist's recollection of the number of hours he or she practiced as a child, adolescent, and adult), the investigators found significant increases in myelination as practice time increased for all ages, but these changes were evident in different fiber tracts, depending upon what age the piano practice occurred.

Practicing piano as a child increased myelination in the posterior limbs of the internal capsule bilaterally (Fig. 1), the corpus callosum, and the fiber tracts in the frontal lobe in proportion to the number of hours at the piano. These regions carry sensory motor information for independent finger movement and cross-connections between auditory regions and premotor cortex coordinating bimanual movement, respectively. In adolescence, increased myelin was seen in interhemispheric fibers from superior temporal and occipital cortical areas, which include auditory and visual processing regions, respectively. Practicing the piano as an adult increased myelination in the arcuate fasciculus, which connects the temporal and frontal regions. The long association fibers of the forebrain, which are increased by adult practicing, continue maturation into at least the third decade of life (Yakovlev and Lecours 1967).

If impulse activity increases myelination in the brain, how do myelinating glia detect neural impulses? Interest in activity-dependent interactions between neurons and glia is increasing, but this has focused primarily on perisynaptic glia (Fields and Stevens-Graham 2002; Fields 2004). This is because neurotransmitter receptors on glia provide an obvious mechanism for glia to detect nervous activity via the spillover of neurotransmitter from the synaptic cleft. In recent years, it has been found that premyelinated axons release ATP when they fire a burst of action potentials, but the release mechanisms are not fully understood (Fields and Stevens 2000; Stevens and Fields 2000). Membrane receptors for ATP or its breakdown products, notably adenosine, on Schwann cells (Stevens and others 1998; Stevens and others 2004) and oligodendrocytes (Stevens and others 2002), enable premyelinating glia to detect and respond to neural impulse activity. Through the activity-dependent activation of purinergic receptors, action potentials can regulate development, proliferation, and myelination of Schwann cells (Stevens and others 1998; Stevens and Fields 2000) and oligodendrocytes (Stevens and others 2002). The effects differ in the CNS and PNS and operate through different cell-cell signaling molecules (Fields 2004b).

The field of activity-dependent plasticity, historically divided between those favoring a pre- or postsynaptic mechanism as preeminent, is expanding its scope to consider the role of perisynaptic glia in synaptic function and modulation. Now a further expansion may be required to consider a possible role for myelinating glia. A number of questions need to be addressed. The specific aspects of neural impulse activity that influence myelination are not well defined. However, there is some evidence that the effects on myelination can depend on specific frequencies of action potential firing, rather than the overall level of impulse activity (Stevens and others 1998). Although myelinating glia can sense and respond to impulse activity, the type of functional feedback that would orchestrate the proper changes in myelination to optimize function is unknown. Purinergic signaling molecules (Stevens and others 1998, 2002, 2004; Stevens

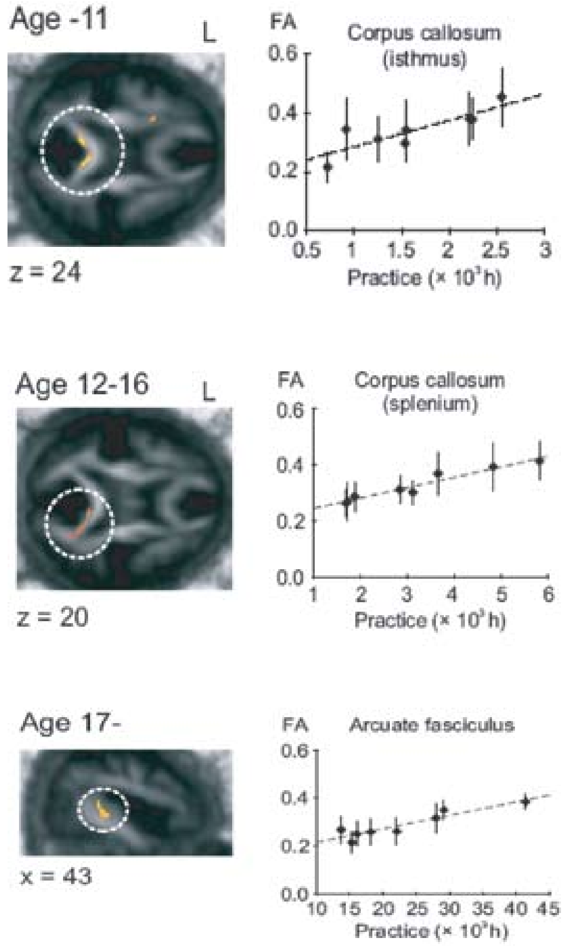

Fig. 1. Childhood piano practicing increases fractional anisotropy (FA), a measure of white matter development, in proportion to the number of hours played. MRI diffusion-tensor imaging of adult professional musicians was used to correlate development of white matter tracts with the age pianists started playing and the total number of hours practiced in childhood, adolescence, and adulthood. Different white matter tracts in the brain are developed by piano practice at different ages, and the increase is proportional to the number of hours practiced. (Modified from Bengtsson and others 2005. Used with permission.)

and Fields 2000) and activity-dependent changes in cell adhesion molecules on axons (Itoh and others 1995; Stevens and others 1998) regulate myelination according to functional activity in axons, but what other cell-cell mechanisms of communication may be involved? The detailed anatomical changes in myelin thickness, internodal distance, or nodal structure, which could influence conduction, are not well studied in the context of activity-dependent plasticity. Further research is required to determine the degree to which brain imaging techniques reflect changes in axonal organization or glial structure (astrocytes and myelination by oligodendrocytes).

Considering the difficult history of correlating structural changes in synapses with functional plasticity, it is not surprising that activity-dependent plasticity in myelination has become apparent only relatively recently, but collectively these studies suggest that conduction properties of axons should not be excluded as a mechanism of modifying the nervous system in accordance with function.

References

Beckman M. 2004. Crime, culpability, and the adolescent brain. Science 305:596–9.

Bengtsson SL, Nagy Z, Skare, S, Forsman L, Forssberg H, Ullén F. 2005. Extensive piano practicing has regionally specific effects on white matter development. Nat Neurosci 8:1148–50.

Bennett EL, Diamond MC, Krech D, Rosenzweig MR. 1964. Chemical and anatomical plasticity of brain. Science 146:610–19.

Bennett MVL. 1971. Electric organs. In: Hoar WS, Randall DJ, editors. Fish physiology. Vol. 5. New York: Academic Press. p 347–491.

Casey BJ, Giedd JN, Thomas KM. 2000. Structural and functional brain development and its relation to cognitive development. Biol Psychol 54:241–57.

Dan Y, Poo M-M. 2004. Spike timing-dependent plasticity of neural circuits. Neuron 44:23–30.

Demerens C, Stankoff B, Logak M, Anglade P, Allinquant B, Couraud F, and others. 1996. Induction of myelination in the central nervous system by electrical activity. Proc Natl Acad Sci U S A 93:9887–92.

Fields RD. 2004b. Volume transmission in activity-dependent regulation of myelinating glia. Neurochem Int 45:503–9.

Fields RD. 2004. The other half of the brain. Sci Am 290(4):54–61.

Fields RD, Stevens B. 2000. ATP in signaling between neurons and glia. Trends Neurosci 23:625–33.

Fields RD, Stevens-Graham B. 2002. New views of neuron-glia communication. Science 298:483–90.

Giedd JN. 2004. Structural magnetic resonance imaging of the adolescent brain. Ann N Y Acad Sci 1021:77–85.

Itoh K, Stevens B, Schachner M, Fields RD. 1995. Regulation of the neural cell adhesion molecule L1 by specific patterns of neural impulses. Science 270:1369–72.

Juraska JM, Kopcik JR. 1988. Sex and environmental influences on the size and ultrastructure of the rat corpus callosum. Brain Res 450:1–8.

Kaminsky M, Eviatar Zl, Norman J. 2002. The timing deficit hypothesis of dyslexia and its implications for Hebrew reading. Brain Cognit 48:394–98.

Kubicki M, Park H, Westin CF, Nestor PG, Mulkern RV, Maier SE, and others. 2005. DTI and MTR abnormalities in schizophrenia: analysis of white matter integrity. Neuroimage 26:1109–18.

Markham J, Greenough WT. 2005. Experience-driven brain plasticity: beyond the synapse. Neuron Glia Biol. Retrieved from www.journals.cambridge.org/jid_NGB. DOI: 10.1017/S1740925X05000219. Published online July 29, 2005.

Merzenich MM, Jenkins WM, Johnston P, Schreiner C, Miller SL, Tallal P. 1996. Temporal processing deficits of language-learning impaired children ameliorated by training. Science 271:77–81.

Paus T, Zijdenbos A, Worsley K, Collins L, Blumenthal J, Giedd JN, and others. 1999. Structural maturation of neural pathways in children and adolescents: in vivo study. Science 283:1908–11.

Sanchez MM, Hearn EF, Do D, Rilling JK, Herndon JG. 1998. Differential rearing effects corpus callosum size and cognitive function of rhesus monkeys. Brain Res 812:38–49.

Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. 2005. Cognitive functions correlate with white matter architecture in normal pediatric population: a diffusion tensor MRI study. Hum Brain Mapp 26(2):139–47.

Sirevaag AM, Greenough WT. 1987. Differential rearing effects on rat visual cortex synapses: III. Neuronal and glial nuclei, boutons, dendrites, and capillaries. Brain Res 424:320–32.

Stanford LR. 1987. Conduction velocity variations minimize conduction time differences among retinal ganglion cell axons. Science 238:358–60.

Steingard RJ, Renshaw PF, Hennen J, Lenox M., Cintron CB, Yurgelun-Todd DA. 2002. Smaller frontal lobe white matter volumes in depressed adolescents. Biol Psychiatry 52:413–7.

Stevens B, Fields RD. 2000. Action potentials regulate Schwann cell proliferation and development. Science 287**:**2267–71.

Stevens B, Ishibashi T, Chen J-F, Fields RD. 2004. Adenosine: an activity-dependent axonal signal regulating MAP kinase and proliferation in developing Schwann cells. Neuron Glia Biol 1:23–34.

Stevens B, Porta S, Haak LL, Gallo V, Fields RD. 2002. Adenosine: A neuron-glial transmitter promoting myelination in the CNS in response to action potentials. Neuron 36:855–68.

Stevens B, Tanner S, Fields RD. 1998. Control of myelination by specific patterns of neural impulses. J Neurosci 15:9303–11.

Sugihara I, Lang EJ, Llinas R. 1993. Uniform olivocerebellar conduction time underlies Purkinje cell complex spike synchronicity in the rat cerebellum. J Physiol (Lond) 470:243–71.

Swadlow HA, Rosene DL, Waxman SG. 1978. Characteristics of interhemispheric impulse conduction between prelunate gyri of the rhesus monkey. Exp Brain Res 33:455–67.

Swadlow HA, Waxman SG, Geschwind N. 1980. Small-diameter nonmyelinated axons in the primate corpus callosum. Arch Neurol 37:114–15.

Szeligo F, Leblond CP. 1977. Response of the three main types of glial cells of cortex and corpus callosum in rats handled during suckling or exposed to enriched control and impoverished environments following weaning. J Comp Neurol 172:247–63.

Teicher MH, Dumont NL, Ito Y, Vaituzis C, Giedd JN, Andersen SL. 2004. Childhood neglect is associated with reduced corpus callosum area. Biol Psychiatry 56:80–5.

Waxman SG, Pappas GD, Bennett MVL. 1972. Morphological correlated functional differentiation of nodes of Ranvier along single fibers in the neurogenic electric organ of the knife fish *Stenarchus*. J Cell Biol 53:210–24.

Yakovlev PI, Lecours A-R. 1967. The myelogenetic cycles of regional maturation of the brain. In Minkowski A, editor. Regional development of the brain in early life. Oxford, UK: Blackwell Scientific. p 3–70.

Yurgelun-Todd DA, Killgore WD, Young AD. 2002. Sex differences in cerebral tissue volume and cognitive performance during adolescence. Psychol Rep 91:743–57.

Zalc B, Fields RD. 2000. Do action potentials regulate myelination? Neuroscientist 6:5–12.