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CLINICAL PERSPECTIVES

A window into the molecular basis of human brain plasticity

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Cortical plasticity can be defined as the process whereby brain cortex changes in response to experience or environment. This can be described at the anatomical, physiological or behavioural level. It is a topic of major importance to humans, being critical to normal development and learning. Clinically, cortical plasticity is part of how patients with CNS disease show behavioural recovery, respond to therapy or learn to compensate.

The underlying basis of cortical plasticity has been extensively investigated. Animal studies have provided insights into the cellular and molecular events essential for these processes. For example, acquisition of a new motor skill is accompanied by changes in gene expression, growth factor levels, neuronal morphology and more. In humans, insights into underlying events have largely been at the systems level, via functional neuroimaging.

It is in this context that the report of Cheeran *et al*. (2008) in this issue of *The Journal of Physiology* provides welcomed new insights into molecular correlates of cortical plasticity in the human brain. These authors used non-invasive methods in healthy human subjects to characterize the effects that a single nucleotide polymorphism in the gene for brain-derived neurotrophic factor (BDNF) has on three neurophysiological measures related to cortical plasticity. For all three probes, results converged on the finding that plasticity is abnormal in the presence of this polymorphism.

BDNF is the most abundant growth factor in the human brain. A single nucleotide change at codon 66, present in one or both alleles in approximately 30% of people, results in the switch of a single amino acid, from valine to methionine. Significant changes in human brain structure, function and behaviour have been described in the presence of this polymorphism, whether it occurs in one or both of a subject's BDNF alleles. A landmark human study on this topic came from Egan *et al.* (2003), who found that the presence of the Val^{66}Met polymorphism was associated with poorer memory, abnormal hippocampal activation with functional MRI (fMRI) and neurochemical deficiencies with MRI spectroscopy. Indeed, a later study from this group (Hariri *et al.* 2003) found that 25% of the variance in memory performance among healthy human subjects could be explained by the interaction between *BDNF* Val^{66}Met polymorphism status and hippocampal response during a memory fMRI task. Our group (Kleim *et al.* 2006) examined motor maps in healthy subjects before and after 30 min of training. Subjects lacking the *BDNF* Val^{66}Met polymorphism showed the expected motor map expansion with training, but subjects with the polymorphism in one or both alleles showed little such plasticity. Cheeran *et al*. used three separate protocols to provide further insights into the effects of the *BDNF* Val^{66}Met polymorphism on cortical neurophysiology and plasticity in healthy human subjects. These authors interpreted their results as reflecting a BDNF effect on long-term potentiation, a process of direct relevance to numerous neurological and psychiatric conditions.

Why might we care about the molecular basis of cortical plasticity in humans? Several possible reasons might be advanced. First, greater insight into the molecular basis of human cortical plasticity might provide better insight into the pathophysiology of human disease. This then sets the table for improved prognosis and therapeutics (Floel & Cohen, 2006). Two general examples of this principle are the advances in amyotrophic lateral sclerosis research upon identification of a mutation of the free radical metabolism enzyme CuZn-SOD in selected families, and the improved prognostic ability upon identification of the *BRCA1*/*BRCA2* gene in breast cancer. Second, such studies might also provide more precise means to identify biologically distinct patient subgroups or to sharpen entry criteria in order to reduce variance in clinical trials. Third, molecular studies in humans provide a means to validate molecular findings from animal studies. That is, we rely heavily on animal models to develop new human therapeutics, and in many conditions we draw conclusions that push the limits of animal models. Molecular measures have the potential to increase the fidelity of comparisons between human subjects and related animal models. Fourth, molecular studies in humans have the potential to provide insight into genetic influences on brain function and behaviour, a topic of increasing interest to fields from neuropsychology of the healthy to clinical pharmacogenomics.

Cortical plasticity subserves much of human behaviour, and it is a key player in the brain repair that underlies recovery, or in some cases maintenance, of function with neurological and psychiatric disease. Molecular insights into the basis of cortical plasticity in humans have the potential to support advances of broad value, in health and in sickness. For example, such measures might have prognostic value (Siironen *et al.* 2007), might be used to guide features of therapy, or might even be the target of a gene-based therapeutic intervention. In addition, note that many growth factors have endogenous biological activity in multiple organ systems, and so insights into the molecular science of growth factor effects in the brain could have broad utility in clinical medicine. By focusing on a common polymorphism in a major brain molecule, Cheeran *et al*. have moved us closer towards these goals.

There are no conflicts of interest with this work.

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