



## Commentary

## Neural Compensation in Huntington's Disease: Teaching Mental Disorders New Tricks?



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The brain's ability to maintain function in the presence of an incipient or ongoing detrimental neural condition is well-recognized (Grady, 2008). In neurodegenerative diseases, such neural mechanisms may be able to counteract progressive pathology, at least until the minimum capacity which is needed until cognitive and sensorimotor performance falls below a critical threshold. Such mechanisms have been often referred to as “compensatory” and may involve neural activity increases in brain regions normally recruited during a task, reconfiguration of functional coupling or recruitment of alternative neural pathways. In neuropsychiatric diseases, identifying neural mechanisms as “compensatory” – and not just as aberrant patterns of brain function – is of outstanding relevance. If neuroimaging should be used as a technique for identifying, validating and implementing biological markers, then any measurable deviation of brain activity will need to be classified not only as “abnormal” but also with respect to its functional consequences, i.e. whether they may be detrimental or beneficial for thought and behavior. If compensatory mechanisms are at play then in an interventional trial designed to delay the onset or progression of a disease, a specific intervention may not want to disrupt neural compensation. In such a case, promoting compensation is one of the primary goals.

Huntington's disease (HD) in many ways is a neuropsychiatric “model disease” (Ross and Tabrizi, 2011). The availability of genetic testing allows an identification of persons who carry the HTT-gene mutation but who will remain presymptomatic for several decades (preHD). In these individuals functional magnetic resonance imaging (MRI) has been shown to be sensitive to neural dysfunction in situations where atrophy can be hardly detected by standard structural neuroimaging. Klöppel and colleagues for the first time explicitly investigate potential compensatory mechanisms in preHD (Klöppel et al., 2015). The essential advance for future research is that compensation was not addressed post-hoc or discussed among other plausible explanations. The authors employ a specific statistical model which takes into account task performance, structural disease load and neural activity. The assumption is that higher structural disease burden is accompanied

by linear effects at the level of regional activity and functional coupling, and compensation of neural activity is by definition associated with maintaining task performance. In our view, there is a strong teleological component underlying this assumption, but at the same time this is a prerequisite if one wants to avoid speculations on what activity change actually reflects. An important point of results is the biological plausibility of their findings: the role of the parietal and dorsolateral prefrontal cortices in working memory neurobiology is well established (Gazzaley and Nobre, 2012). But this is just the tip of the iceberg, since the Track-On HD data set yields additional and invaluable information potential. Further analysis strategies may shed light on more complex (e.g. nonlinear) interactions between resting-state and task-based functional connectivity, brain volume and cognitive/motor requirements.

The study by Klöppel and colleagues can decisively shape future functional neuroimaging research in HD and other neurodegenerative conditions, but we believe that there is much more to learn from this study. The rationale and design should also motivate psychiatric research, where there is still an urgent need of valid and reliable biological markers. In depression or schizophrenia, for example, where cognitive deficits are prominent and deleterious for clinical outcome, there has been substantial effort to map neural correlates of cognitive dysfunction and to define neural predictors of treatment response (Fu et al., 2013; Ramsay and MacDonald, 2015). In both depression and schizophrenia, there is a long-standing debate if regionally increased activity is reflective of neural compensation, whether this may be efficient or not (Callicott et al., 2003). Surprisingly, there have been only a few attempts to integrate structural data into the functional data analyses (Sui et al., 2012; Vasic et al., 2015). At multiple levels of biology and symptom expression there are clear differences between depression/schizophrenia and HD. But there is a loss of brain volume over time in both depression and schizophrenia, as much as there is evidence for compensatory neural activity which is so far unexplained in terms of its underlying neurobiology. Functional changes could be primary in the sense that they are intrinsic to the disorder and not secondary to structural alterations. Alternatively, functional compensation for structural damage is a possible explanation (as much as other explanations may be plausible as well, such as compensation for aberrant neural transmission), yet this possibility has not been addressed so far in a theoretically convincing

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and explicitly model-driven approach. In this regard, the work provided by Klöppel and colleagues may foster integrative neuroimaging approaches using explicit models of neural compensation at various levels of model complexity. Clearly, in depression and schizophrenia genetic and environmental influences need to be considered (although recent data suggest that the very same applies to HD; Mo et al., 2015), and any “close-to-real-world” compensation model in these disorders will seek to account for these variables in advanced stages of research. But before doing so, why not start with the obvious, especially when the available neuroimaging data invites and justifies such an approach. In this sense, this paper paves the way for an innovative path that opens up novel avenues of research not only for neurodegeneration but also for several other mental disorders.

### Disclosure

The authors declare no conflicts of interest.  
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