



## Commentary

## Compensation in the course of Huntington's disease – More than just a hypothesis?



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The discrepancy between progressive structural decline of the brain e.g. generalized or focal atrophy including neuronal loss and the observation of persistent stable performance in clinical tasks has led to the hypothesis of functional compensation. Although characterization and detailed understanding of the underlying mechanisms are of fundamental interest and may eventually lead to novel symptomatic therapeutic strategies in neurodegenerative diseases, only a few systematic studies have addressed this topic so far (Scheller et al., 2014). This probably originates from the fact that brain reserve capacity or compensation mechanisms are difficult to measure. These take place on a functional level for example by activation of neuronal networks or as transient task-dependent phenomena based on both individual as well as disease specific structural prerequisites.

Klöppel and colleagues have addressed this fascinating topic and present a new approach to visualize and characterize compensation in preclinical HD gene carriers (preHD) (Klöppel et al., 2015). For this purpose preHD subjects serve as ideal candidates since they have been shown to remain asymptomatic for years even when using sophisticated cognitive tests or motor tasks. Volumetric brain imaging indicates progressive neurodegeneration in these patients. The exact time point of preHD converting into the clinical stage of the disease however is poorly characterized and currently discussed (Bilgan et al., 2009; Tabrizi et al., 2013).

Based on the assumption that compensation requires an enhanced neuronal activation (Cabeza and Dennis, 2013; Quiroz et al., 2010) accompanied by an increased metabolism and blood flow, Klöppel and colleagues used resting state (rs-fMRI) and task related functional MRI (fMRI) to investigate a comparatively large group of preHD gene carriers. To depict brain activity suspicious for compensation, they have searched for positive correlations between brain areas showing a high disease load as defined by volumetric measures and significant increase in brain activity while detailed motor and cognitive tasks had to be performed. Functional connectivity of certain brain areas in neuronal networks was investigated under resting state conditions.

Since no alternative method to reliably investigate compensation in respect to area specific disease load has been established up to now, the presented results will need further validation. In addition methodical

aspects (e.g. sensitivity of rs-fMRI to motion generated artifacts, choice of kernels and significance thresholds, definition of seeds for assigning the area specific disease load and choice of cognitive and motor tasks especially for longitudinal investigations) will have to be discussed to further optimize this proposed model of compensation. It has to be emphasized that Klöppel et al. critically review these issues.

When discussing potential compensational mechanisms it has to be considered that downregulation of neuronal activity or disengagement of certain neuronal networks may as well reflect compensational processes (Cox et al., 2015). Thus, results revealing negative correlations between brain areas showing high disease load should not be ignored but discussed with the same emphasis as results showing positive correlations. Compensational remodeling takes place on a functional level and is partly induced as a transient task dependent activation. It represents a comparably unstable situation with changing pathways and potential coexisting strategies. This particular aspect has to be respected in the discussion of investigational results and should be analyzed in longitudinal studies, although a group analysis using rs-fMRI did not show significant changes in functional connectivity in preHD gene carriers over a period of 3 years (Odish et al., 2015).

Assuming that compensation in HD exists and that we soon will be able to reliably monitor compensational processes a multitude of questions arise for further investigations. Compensation is discussed as a substantial mechanism to prolong the preclinical phase not only in HD mutant gene carriers but also in preclinical subjects at risk for other neurodegenerative diseases as well. Thus, it would be of great interest to study whether drugs or therapeutic interventions can initiate compensational processes in order to delay symptom onset. Disease modulating effects like environmental enrichment or cognitive interventions, which have been shown to delay onset of symptoms in HD in this context, have to be discussed as influencing factors (Kotloski and Sutula, 2015; Andrews et al., 2015). Furthermore it would be important to understand whether compensation is restricted to the preclinical state in HD or if it also can be observed and used therapeutically during the clinical course of the disease as well. What are the essential structural and cellular prerequisites that must be preserved so that neuronal networks can be activated for functional remodeling? Can we identify the factors that lead to the breakdown of compensational processes? Is it really true that compensation is restricted to certain cognitive skills exclusively but is not found to stabilize other important systems like motor function? Is it really a characteristic of the right hemisphere as the results of

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Klöppel and colleagues suggest? – The list of exciting questions could be extended a lot.

Taken together, Klöppel and colleagues present an elaborate diagnostic tool to depict compensational processes in relation to area specific disease load. This model may well be suited as a fundamental resource in characterizing and monitoring compensation mechanisms in neurodegenerative diseases. This in turn may lead to novel symptomatic therapies delaying onset of symptoms and decelerating disease progression.

### Disclosure

The author declared no conflicts of interest.

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