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Interregional compensatory mechanisms of motor functioning in progressing preclinical neurodegeneration

Elisa Scheller [a,b,c,*], Ahmed Abdulkadir [a,b,d], Jessica Peter [b,c,e], Sarah J. Tabrizi [f], Richard S.J. Frackowiak [g], Stefan Klöppel [a,b,e]

[a] Department of Psychiatry and Psychotherapy, University Medical Center Freiburg, Hauptstrasse 5, 79104 Freiburg, Germany
[b] Freiburg Brain Imaging Center, University Medical Center, University of Freiburg, Breisacher Str. 64, 79106 Freiburg, Germany
[c] Department of Psychology, Laboratory for Biological and Personality Psychology, University of Freiburg, Stefan-Meier-Str. 8, D-79104 Freiburg, Germany
[d] Department of Computer Science, University of Freiburg, Georges-Koehler-Allee, 79110 Freiburg, Germany
[e] Department of Neurology, University Medical Center Freiburg, Breisacher Str. 64, 79106 Freiburg, Germany
[f] UCL Institute of Neurology, University College London, Queen Square, London WC1N3BG, UK
[g] Département des Neurosciences Cliniques, CHUV, University of Lausanne, 1011 Lausanne, Switzerland

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ABSTRACT

Understanding brain reserve in preclinical stages of neurodegenerative disorders allows determination of which brain regions contribute to normal functioning despite accelerated neuronal loss. Besides the recruitment of additional regions, a reorganisation and shift of relevance between normally engaged regions are a suggested key mechanism. Thus, network analysis methods seem critical for investigation of changes in directed causal interactions between such candidate brain regions. To identify core compensatory regions, fifteen preclinical patients carrying the genetic mutation leading to Huntington's disease and twelve controls underwent fMRI scanning. They accomplished an auditory paced finger sequence tapping task, which challenged cognitive as well as executive aspects of motor functioning by varying speed and complexity of movements. To investigate causal interactions among brain regions a single Dynamic Causal Model (DCM) was constructed and fitted to the data from each subject. The DCM parameters were analysed using statistical methods to assess group differences in connectivity, and the relationship between connectivity patterns and predicted years to clinical onset was assessed in gene carriers. In preclinical patients, we found indications for neural reserve mechanisms predominantly driven by bilateral dorsal premotor cortex, which increasingly activated superior parietal cortices the closer individuals were to estimated clinical onset. This compensatory mechanism was restricted to complex movements characterised by high cognitive demand. Additionally, we identified task-induced connectivity changes in both groups of subjects towards pre- and caudal supplementary motor areas, which were linked to either faster or more complex task conditions. Interestingly, coupling of dorsal premotor cortex and supplementary motor area was more negative in controls compared to gene mutation carriers. Furthermore, changes in the connectivity pattern of gene carriers allowed prediction of the years to estimated disease onset in individuals.

Our study characterises the connectivity pattern of core cortical regions maintaining motor function in relation to varying task demand. We identified connections of bilateral dorsal premotor cortex as critical for compensation as well as task-dependent recruitment of pre- and caudal supplementary motor area. The latter finding nicely mirrors a previously published general linear model-based analysis of the same data. Such knowledge about disease specific inter-regional effective connectivity may help identify foci for interventions based on transcranial magnetic stimulation designed to stimulate functioning and also to predict their impact on other regions in motor-associated networks.

Introduction

Cognitive reserve (CR; Katzman, 1993; Stern, 2002; for a review see Valenzuela, 2008) is a concept to explain relatively preserved cognition in the face of neurodegeneration (Bartrés-Faz and Arenaza-Urquijo, 2011; Murray et al., 2011; Steffener et al., 2011). Passive CR is characterised in terms of brain size or number of neurons (e.g. Satz, 1993), whilst active CR refers to spontaneously variable reactions of the brain when faced with cognitive challenges. Neuroimaging can

Abbreviations: BOLD, Blood Oxygen Level Dependent; cSMA, caudal supplementary motor area; DCM, Dynamic Causal Modelling; fMRI, functional Magnetic Resonance Imaging; GLM, General Linear Model; HC, healthy controls; lM1, left primary motor cortex; lPMd, left dorsal premotor cortex; lSPC, left superior parietal cortex; PET, positron emission tomography; preHD, preclinical Huntington's disease; rPMd, right dorsal premotor cortex; rSPC, right superior parietal cortex; TMS, Transcranial Magnetic Stimulation; VBM, Voxel-based Morphometry.

* Corresponding author at: Department of Psychiatry and Psychotherapy, University Medical Center Freiburg, Freiburg Brain Imaging, Breisacher Str. 84, D-79110 Freiburg, Germany. Fax: +49 761 270 54160.
E-mail address: elisa.scheller@uniklinik-freiburg.de (E. Scheller).

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help to examine neural compensation (NC) as well as neural reserve (NR), which are subcomponents of active CR (Stern, 2009). NC describes the recruitment of additional brain areas to maintain performance, whilst NR reflects that impaired and non-impaired individuals use the same areas to maintain functioning, though to different levels of efficiency and capacity (Stern, 2009). NR is presumably instantiated by differential regional interactions (Seghier et al., 2010) shifting control from one set of regions to another (see below). Thus, one approach to investigate compensatory mechanisms in neurodegenerative diseases is to look at between-group as well as individual differences in NR (see e.g. Holtzer et al., 2009; Steffener et al., 2011). The assessment of compensatory mechanisms should preferably be undertaken in pre- or early clinical stages when therapeutic interventions are most likely to be effective. As such preclinical stages cannot easily be identified in the majority of neurodegenerative disorders, we chose to investigate Huntington's disease (HD), where preclinical stages can be identified with certainty and graded according to estimated proximity to symptom onset.

HD is a genetically caused hereditary neurodegenerative disease. As the exact location and nature of the genetic mutation are known (The Huntington's Disease Collaborative Research Group, 1993), it is possible to identify HD gene carriers decades before actual symptom onset. This clinical onset is defined by the presence of unequivocal motor symptoms (Beglinger et al., 2010; Walker, 2007). Therefore, patients without overt motor symptoms are described as 'pre-manifest' or 'preHD'. Using a pre-manifest patient's current age and the degree of genetic mutation (i.e. the number of CAG trinucleotide repeats in the Huntingtin gene on chromosome four), the years to clinical onset (yto) can be estimated with a parametric survival model (Langbehn et al., 2004; Langbehn et al., 2010). The diagnostic status as well as the yto are used in neuroimaging studies to determine relationships with potential structural or functional imaging markers of the pre-manifest stage of disease (Feigin et al., 2006; Klöppel et al., 2008; Klöppel et al., 2009; Mühlau et al., 2007; Novak et al., 2012; Rosas et al., 2005; Scahill et al., 2013; Tabrizi et al., 2009; Tabrizi et al., 2011; Tabrizi et al., 2012; Wolf et al., 2007).

Previous studies focusing on compensatory mechanisms in motor functioning were conducted in the context of, among others, stroke (Grefkes et al., 2008b), preclinical Parkinson's disease (Buhmann et al., 2005) as well as mild to moderate HD and preHD (Bartenstein et al., 1997; Klöppel et al., 2009). Regarding HD, a supporting role of parietal motor related regions was first discussed in a PET experiment reported by Bartenstein et al. (1997). These parietal regions were more activated in HD patients than controls.

Nevertheless, Klöppel et al. (2009) stated that a simple shift in activation towards parietal regions might be too simplistic a view of the compensating mechanism and emphasised an additional role for the supplementary motor area (SMA), in which activations correlated with gene status, a finding well in line with those in patients with manifest HD (Gavazzi et al., 2007): Compared to healthy controls (HC), preHD activated caudal SMA during a finger tapping task to a greater extent in all movement conditions, and this activation increased with approaching clinical onset estimations. More complex finger movements led to even higher activations in pSMA in subjects further from predicted disease onset. Outside the SMA, the left superior parietal cortex (lSPC) showed reduced activation with increased movement complexity in preHD compared to HC, and in right SPC (rSPC), the preHD group showed greater activations in all but the most demanding conditions (Klöppel et al., 2009).

However, it is difficult to directly compare the studies of Bartenstein et al. (1997) and Klöppel et al. (2009), as the former authors investigated a sample of seven HD patients already exhibiting mild to moderate motor symptoms as opposed to the preHD group in Klöppel et al. (2009). The atrophy and loss of function were probably more severe in the mild to moderate HD group. Taken together the results suggest that the superior parietal cortices and pre- and caudal SMAs could contribute to compensatory motor mechanisms in preHD. An understanding of the interactions between cortical areas subtending compensation for the effects of neurodegeneration might help to shape therapeutic interventions (see e.g. Wang et al., 2011 for pharmacologically enhanced connectivity in the motor system). As an example, region specific interventions such as transcranial magnetic stimulation (TMS) can be applied most successfully to regions that are increasingly activated closer to disease onset. However, application to regions that exert an excitatory or inhibitory influence may also prove most useful (see e.g. Grefkes et al., 2010 for rTMS over M1) in the context of network function (see McIntyre and Hahn, 2010 for a review on deep brain stimulation).

A range of network analysis methods, such as Granger causality (Goebel et al., 2003; Granger, 1980) or Dynamic Causal Modelling (DCM; Friston et al., 2003) can be used to study effective connectivity (the influence one group of neurons has on another). Causal interactions between brain areas of interest can be studied and quantified; e.g. how does one region cause a change of activity in another, or how does a particular experimental manipulation influence the connectivity between two other regions. DCM has been successfully used to characterise motor function in healthy subjects and patients other than those suffering from HD (see e.g. Boudrias et al., 2012; Grefkes et al., 2008a; Grefkes et al., 2008b; Kasess et al., 2008; Rowe et al., 2010). In HD, classical functional connectivity analyses have been used in different cognitive domains (Wolf et al., 2008a, 2008b, 2012a, 2012b), but these correlational analyses do not allow inferences about causality to be made as correlated activity in two areas may be driven by a common third area (Stephan, 2004).

Therefore, DCM was chosen as our method to build on previous studies of motor function in preHD whilst overcoming the interpretational constraints of standard functional (as opposed to effective) connectivity analyses. The same data have been published before with a standard GLM analysis (Klöppel et al., 2009). We used DCM and a finger tapping task which leads to robust activations and probe functions that are specifically affected by HD (Bartenstein et al., 1997; Gavazzi et al., 2007; Lehéricy et al., 2006; Witt et al., 2008). The task does this by manipulating movement rate and complexity.

We analysed the nature of interactions between cortical regions of the motor system on the basis of DCM parameters, which constitute measures of connectivity, with two aims: First, as an increasing number of studies indicate the existence of neurodevelopmental and trait specific markers in HD (Lee et al., 2012; Marder and Mehler, 2012; Nopoulos et al., 2011), we compared such interactions in preHD with those of healthy controls (HC). Specifically, we expected to find more differences between preHD and HC with increasing task demands. Our second and key aim was to elucidate the development of NR as the time of expected symptom onset approached. Thus, we examined the relationship of inter-regional connectivity and yto in the preHD sample. As these subjects were in the pre-manifest stage, we considered reorganisation correlated with increasing neurodegeneration to be compensatory in nature. We expected to find alterations in connectivity between parietal and premotor and supplementary motor regions based on previous motor activation results.

Materials and methods

Participants

Fifteen pre-symptomatic gene mutation carriers (7 females, mean age 36.9 years, range 26–49) and twelve healthy controls (4 females, mean age 36.5 years, range 23–60), all right handed and matched according to age and sex were examined. A trained neurologist assessed all carriers with the Unified Huntington's Disease Rating Scale (UHDRS) to stage them. Pre-symptomatic participants covered a wide range of yto; these were computed as the number of years at which the predicted probability of clinical onset exceeds 0.6 (Langbehn et al., 2004); see Table 1 for demographic and clinical data. The local Ethics Committee approved the study and all participants gave written informed consent according to the Declaration of Helsinki. The current study is a reanalysis of the data that was published by Klöppel et al. (2009) as a standard GLM analysis. We extended on these previous findings by applying DCM.