NeuroImage: Clinical 2 (2013) 459–468

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Reorganisation of brain networks in frontotemporal dementia and progressive supranuclear palsy

Laura E. Hughes [a,b,*], Boyd C.P. Ghosh [c], James B. Rowe [a,b,d]

[a] Department of Clinical Neurosciences, University of Cambridge, CB2 2QQ, UK
[b] Medical Research Council Cognition and Brain Sciences Unit, Cambridge, CB2 7EF, UK
[c] Wessex Neuroscience Centre, Southampton, SO16 6YD UK
[d] Behavioural and Clinical Neuroscience Institute, Cambridge, UK

ARTICLE INFO

Article history:
Received 4 December 2012
Received in revised form 15 March 2013
Accepted 15 March 2013
Available online 25 March 2013

Keywords:
Connectivity
Dementia
Dynamic causal modelling
Magnetoencephalography
MMNm

ABSTRACT

The disruption of large-scale brain networks is increasingly recognised as a consequence of neurodegenerative dementias. We assessed adults with behavioural variant frontotemporal dementia and progressive supranuclear palsy using magnetoencephalography during an auditory oddball paradigm. Network connectivity among bilateral temporal, frontal and parietal sources was examined using dynamic causal modelling. We found evidence for a systematic change in effective connectivity in both diseases. Compared with healthy subjects, who had focal modulation of intrahemispheric frontal–temporal connections, the patient groups showed abnormally extensive and inefficient networks. The changes in connectivity were accompanied by impaired responses of the auditory cortex to unexpected deviant tones (MMNm), despite normal responses to standard stimuli. Together, these results suggest that neurodegeneration in two distinct clinical syndromes with overlapping profiles of prefrontal atrophy, causes a similar pattern of reorganisation of large-scale networks. We discuss this network reorganisation in the context of other focal brain disorders and the specific vulnerability of functional brain networks to neurodegenerative disease.

1. Introduction

A key challenge to understanding the effects of neurodegeneration is to characterise the changing patterns of brain network connectivity, in response to both the disease and its treatment (Pievani et al., 2011; Seeley et al., 2009; Warren et al., 2012). The network paradigm of disease has many advantages, with the potential to elucidate selective vulnerability to a given neuropathology, explains the consequences of disease at a macroscopic level, and increases sensitivity of tools such as brain imaging that captures both integrative and segregated brain functions (Bassett and Bullmore, 2009; Mesulam, 1990). Many studies examine macroscopic networks using task-free 'resting state' paradigms, in which coactivation of distributed regions, or coherence among spontaneous neural oscillators, is thought to reflect functional networks (Corbetta, 2010). In response to task demands or experimental conditions, these networks are rapidly reconfigured to create a dynamic neuronal workspace for cognitive processing (Kitzbichler et al., 2011).

Neurodegenerative syndromes commonly disrupt such large scale networks (Rowe, 2010). For example, reductions in resting state connectivity mirror disease related changes in anatomical structure and connectivity with Alzheimer's disease, frontotemporal dementias and Parkinsonian syndromes (Greicius, 2008; Greicius et al., 2004; Seeley et al., 2009; Whitwell et al., 2011; Zhou et al., 2010). Task based network configuration can also be changed by focal degeneration and atrophy (Sonty et al., 2007). However, neurodegeneration not only weakens specific network connections, but can also lead to reorganisation of the networks by enhancing connectivity among the relatively unaffected regions (Seeley et al., 2008; Zhou et al., 2010). Moreover, recent studies have emphasized the concordance between reductions in network connectivity during resting state and the distinctive focal atrophy patterns in neurodegenerative dementias (Seeley et al., 2009; Zhou et al., 2010) or changes in white matter tracts supporting those networks (Raj et al., 2012).

Different clinical syndromes can result in specific changes to brain networks, but there may also be generic reorganisation in response to degeneration associated with diverse pathologies. In this study, we examined two distinct neurodegenerative diseases and asked whether disease specific neurodegeneration is related to particular network changes, or whether there is a 'transdiagnostic' network-level response affecting the macroscopic network dynamics.

* Corresponding author at: Cambridge University Department of Clinical Neurosciences, Herchel-Smith Building, Forvie Site, Robinson Way, Addenbrooke's Hospital, Cambridge, CB2 0SZ, UK. Tel.: +44 1223 355 294; fax: +44 1223 359 062.
E-mail address: laura.hughes@mrc-cbu.cam.ac.uk (L.E. Hughes).

2213-1582
http://dx.doi.org/10.1016/j.nicl.2013.03.009

We examined behavioural variant frontotemporal dementia (bvFTD) and progressive supranuclear palsy (PSP); two rapidly progressive neurodegenerative diseases that have key differences in clinical phenotypes. bvFTD is characterised by changes in behaviour, cognition and personality (Rascovsky et al., 2011). In contrast, PSP is defined by a vertical supranuclear gaze palsy, akinetic rigidity and falls (Litvan et al., 2003; Richardson et al., 1963), with typically milder cognitive impairment including apathy. The two syndromes have distinct and overlapping macroscopic anatomy of tissue loss. bvFTD is associated with marked atrophy of prefrontal cortex (orbital, ventral and/or medial), anterior insula, anterior cingulate and anterior temporal lobes including cortex and the amygdala (Schroeter et al., 2007, 2008; Seelaar et al., 2011; Seeley, 2010; Seeley et al., 2009), although other atrophy patterns with temporoparietal atrophy have been reported (Whitwell et al., 2009). In PSP atrophy is severe in the upper brain stem and superior cerebellar peduncle, with moderate atrophy of medial prefrontal cortex, insula/frontal operculum, cingulate cortex, precentral gyrus and superior parietal lobule (Brenneis et al., 2004; Chiu et al., 2012; Ghosh et al., 2012; Nicoletti et al., 2008).

To compare the impact of bvFTD and PSP on macroscopic *functional* brain networks, we used an auditory oddball paradigm, providing a physiological measure of automatic change detection. Such paradigms include a stream of 'standard' stimuli, interspersed with 'deviant' stimuli (e.g. differing from the standard by pitch or duration). This unpredictable change elicits a robust electrophysiological mismatch negativity signal (MMN, or MMNm in the context of MEG studies), detectable by electro- or magneto-encephalography in auditory cortex between 100 ms and 200 ms after the onset of the deviant tone. This signal has been proposed as a marker of psychiatric and degenerative conditions such as Alzheimer's disease, Parkinson's disease and schizophrenia (Naatanen et al., 2011, 2012). Moreover, from a basic science perspective, change detection is an important element of higher order cognitive functions, such as attention and memory (cf. Naatanen et al., 2007).

In addition to the auditory cortex, other brain regions contribute to the generation of the MMN response. These include prefrontal cortex (Boly et al., 2011; Doeller et al., 2003; Liasis et al., 2001; Rosburg et al., 2005; Schall et al., 2003), which is necessary for early change detection through frontal to temporal feedback connections (Alain et al., 1998; Alho et al., 1994; Garrido et al., 2009a). Parietal cortex is also associated with the MMN, in both electrophysiological (Hsiao et al., 2010; Marco-Pallares et al., 2005) and fMRI studies (Molholm et al., 2005).

To measure the network connectivity among these frontal, temporal and parietal cortical sources, we adopted dynamic causal modelling for magnetoencephalography data. Magnetoencephalography is sensitive to the spatiotemporal effects of bvFTD during cognitive tasks (Hughes et al., 2011), proportional to clinical deficits, and well tolerated by patients as a functional brain imaging modality. Dynamic causal modelling has several advantages over other methods to test our hypotheses, including (1) empirical priors that introduce biophysical constraints on the network models; (2) the use of generative (predictive) models that can be tested against the observed data, and evaluated and compared using objective measures of the model evidences; and (3) embodying different hypotheses about the impact of disease on network structures and connectivity in explicit and directional spatiotemporal network models. Dynamic causal modelling also incorporates the modulatory effects of experimental manipulations on connections, such as the difference between standard and deviant stimuli, providing evidence of the critical connections for change detection (Kiebel et al., 2006, 2007, 2008, 2009).

We used dynamic causal modelling to measure network connectivity underlying the detection of change. We included different families of network models to test two principal hypotheses. First, we predicted that the network recruited in health for change detection would be altered by disease. Specifically, since bvFTD and PSP have prefrontal neuropathology, we predicted that network reorganisation would lead to more distributed networks with enhanced connectivity among the less affected parietal regions. Secondly, we predicted that disease would also affect the modulation of the network by the experimental context (i.e. the difference between the standard and deviant tones). Thus, we not only predict that patients will have a change in network architecture, but also a change in the dynamic modulation of connectivity from trial to trial. A corollary of this network change is reduced automatic detection of unpredictable change, and therefore a reduction in amplitudes and delayed latency of the MMNm response in the auditory cortex.

2. Methods

2.1. Subjects

Seventeen patients with bvFTD were recruited using clinical diagnostic criteria, including abnormal clinical imaging, (Rascovsky et al., 2011). We did not include patients with non-progressive mimics of bvFTD (Kipps et al., 2010). Ten patients with progressive supranuclear palsy were recruited, according to clinical diagnostic criteria (Litvan et al., 1996). Subjects underwent neuropsychological assessment including: the 100 point revised Addenbrooke's cognitive examination (ACE-r) (Mioshi et al., 2006), the mini mental state examination (MMSE), the motor section of the Unified Parkinson Disease Rating Scale (UPDRS) (Fahn, 1986) and the Progressive Supranuclear Palsy Rating Scale (PSPRS, PSP cases only) (Golbe and Ohman-Strickland, 2007). Thirty-four healthy aged-matched older adults were recruited from the volunteer panel of the MRC Cognition and Brain Sciences Unit or were relatives or spouses of the patients. No subjects in the control group had a history of significant neurological, rheumatological or psychiatric illness, or cognitive complaints. Subject details are summarised in Table 1. The study was approved by the local Research Ethics Committee and participants gave written informed consent.

2.2. MMNm paradigm

The paradigm used to study cortical function and network connectivity was the multi-feature 'Optimum-1' paradigm (Naatanen et al., 2004), a variant of the auditory oddball paradigm for identification of the mismatch negativity. The stimuli comprised a sequence of harmonic tones presented every 500 ms in three blocks of 5 min. The standard tone was 75 ms duration and contained three sinusoidal partials of 500, 1000 and 1500 Hz. The five deviant tones differed from the standard by either frequency band (550, 1100, 1650 Hz), intensity (+/−6 dB), duration (25 vs 75 ms), side of sound source (left or right rather than bilateral), and by a silent gap (silent mid 25 ms). The sequence started with fifteen standard tones, after which every other tone presented was one of the five deviant types, such that in a sequence of 10 tones, each deviant was presented once but the same deviant type was never immediately repeated. There were a total of 900 standards and 900 deviants. The tones were presented binaurally via plastic tubes and earpieces at approximately 60 dB above the hearing threshold.

2.3. Magnetoencephalography and data processing

MEG data were collected with a 306-channel Vectorview system (Elekta Neuromag, Helsinki) in a light Elekta-Neuromag magnetically-shielded room. A magnetometer and two orthogonal planar gradiometers were located at each of 102 positions. Vertical and horizontal eye movements were recorded using paired EOG electrodes. Head position was monitored using five Head-Position Indicator (HPI) coils. The three-dimensional locations of the HPI coils and approximately 80 'head points' across the scalp, and three anatomical fiducials (the nasion and left and right pre-auricular points), were recorded using a 3D digitizer (Fastrak Polhemus Inc., Colchester, VA). Data were down sampled