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The subcortical connectome: Hubs, spokes and the space between – a vision for further research in neurodegenerative disease

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The neural circuit basis of neurodegenerative disease: characterising endophenotypes

The neurodegenerative diseases of ageing, such as Alzheimer disease (AD), neurocognitive disorders/dementias, movement disorders and cerebrovascular disease, have widespread impact on the neuropsychiatric domains of cognition, emotion, behaviour and movement. Therapeutic interventions are based on understanding the *in vivo* neurobiology of these diseases, as a basis for disease modifying, symptomatic and palliative treatments. Thus, there has been much interest in understanding the neurobiology of these diseases and, accordingly, the neural circuit basis of the neuropsychiatric dysfunction that characterises these disorders. A related challenge is to identify the spatio-temporal course of disease. Neuropathologic studies yield important information post mortem, but neuroimaging potentially provides the detail needed to map disease progression *in vivo*. Accordingly, a framework for conceptualising and planning neuroimaging analyses towards this end is needed.

Clinical research studies are focused on the phenotype of the disease (i.e. the manifestation of dysfunction arising from the underlying genetic, epigenetic and environmental factors contributing to the disease). The concept of an intermediate phenotype, or 'endophenotype', is useful to help understand

the pathophysiological basis of manifestations of neurodegenerative disease, such as neuropsychological dysfunction, motor dysfunction, and changes in emotion and behaviour. Delimited subsets of neuropsychiatric dysfunction may share a common neural circuit basis and spatio-temporal course of disruption. This is characteristic of the frontostriatal circuits in frontotemporal lobar degeneration (FTLD) (Looi et al., 2012), and more broadly the cortico-striatal-thalamic circuits, including the striatum, a crucial hub in such circuits (Looi and Walterfang, 2012). Neuroimaging can help quantify neuroanatomical change in psychiatric and degenerative disease, towards establishing endophenotypes, and we sketch briefly here an outline of the conceptual basis for a research program to meet these aims. Our vision is that neuroanatomical changes in neurodegenerative disease may be quantitatively mapped, specifically with respect to subcortical structures, and that the topography of such maps corresponds to the contours of the circuits affected by disease, and accordingly relates to dysfunction. Thus, we propose a vision to investigate a subcortical connectome, as follows.

Neural networks: hubs and spokes

To understand the neural circuit basis of neurodegenerative disease (Seeley et al., 2009), there has been much

research modelling the spread of disease using intrinsic connectivity patterns (comprising network hubs and spokes) discovered by resting state functional magnetic resonance imaging (rs-fMRI) (Zhou et al., 2012). These studies support a model of trans-neuronal spread of network-based vulnerability to disease such as a protein-misfolding aggregation (e.g.

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amyloid beta or tau proteins), propagated through particular hubs identified by rs-fMRI (Zhou et al., 2012). Using these methods, it is possible to identify when and where functional hubs and spokes of the networks are affected by disease, and to show that altered functional connectivity has mappable structural correlates. Most studies to date focus on cortical network hubs such as specific cortical loci associated with cognitive functions, but subcortical structures are also involved in network breakdown, such as the caudate in behavioural variant frontotemporal dementia (FTD) (Seeley et al., 2009) and in progressive nonfluent aphasia (PNFA) (Zhou et al., 2012); these models have also been supported by our structural MRI findings in the striatum in these disorders (Looi and Walterfang, 2012). Thus, aside from attempting to map entire trajectories of disease spread, we can attempt to measure disease-related structural change in individual network components, and especially subcortical regions, which have been less investigated. We begin with discussing primarily subcortical hubs, as potential core features of a subcortical connectome.

The hippocampus is a hub for which topographically distinct shape and volume changes on MRI reflect cell loss corresponding to cytoarchitectonic regions, and help to predict the development of mild cognitive impairment and AD (Apostolova et al., 2010). Similarly, altered hippocampal morphology may differentiate FTLD subtypes, as well as AD (Lindberg et al., 2012). Another hub is the cerebellum, whose extensive connectivity mediates its role in action selection in subcortical loops, as well as cognition and behavioural functions and thus may be a potentially quantifiable hub, given its highly specific topographic organisation of interconnections to cognitive, motor and behavioural cortical-subcortical circuits (Sherman and Guillery, 2006). The prototypic disorders in which cerebellar atrophy occurs are the spinocerebellar ataxias,

which manifest dysfunction in all domains the cerebellum subserves. The thalamus, or 'inner chamber' of the mammalian brain, is a hub worthy of further exploration. Considered classically as a simple relay station of sensory information, not only is much of the thalamus concerned with cortico-cortical communication (Sherman and Guillery, 2006), but given its substantial subcortical interconnectivity, the thalamus can integrate information from multiple neural networks. In the paradigm of the subcortical connectome proposed herein (a key feature of thalamic organisation is the topographical relationship of thalamus to cortex), one would predict that the thalamus could serve as a map of structural change in the cortical afferent pathways in various neurodegenerative conditions. Whilst the thalamus has received little attention in the neurodegenerative disorders, preliminary data suggest that thalamic atrophy is associated with cognitive deterioration in Alzheimer's and other dementias (de Jong et al., 2008). Our understanding of neurodegenerative diseases and their impact on motivation, cognition and motor control will benefit greatly from studying this paired subcortical structure.

Mapping brain hubs, spokes and the space between

A key step in relating functional disturbances to structure is to quantify disease effects on brain morphology – that is, to map the topography of structural changes in the subcortical connectome. The morphology of hubs and spokes can be correlated with the functions served by the circuits they are in. Structural MRI can visualise neurodegenerative disease in vivo, with higher spatial resolution than functional imaging methods. Structural morphology of hubs in particular can be quantified using computational image analysis methods to measure the shape and volume of neural structures. Basically, these

methods measure the surfaces of neural structures using mathematical meshes (or 3D models) to parcellate each surface into regions that are grouped for analysis and compared across diagnostic groups. The methods we have used in our collaborative studies include: spherical harmonic point distribution method (SPHARM-PDM) (Styner et al., 2006); radial distance mapping (Madsen et al., 2010); and more straightforward measures such as mid-sagittal callosal thickness and contour measurement (Adamson et al., 2011). Within the closed space of the cranial vault, atrophy of brain structures results in an expansion of the volume of the negative spaces – the sulci, fissures and ventricles that contour the brain's inner and outer surfaces. Therefore, measuring the negative space between the hubs and spokes yields additional quantitative information about neurodegeneration in vivo.

Now we come to white matter as part of the spokes along which neurodegenerative structural change may be detectable. The major interhemispheric white matter connection of the corpus callosum is also a collection of topographically organised 'spokes', enabling efficient interhemispheric transfer of information for a range of sensory, motor and cognitive functions. Diffusion tensor imaging (DTI) and tractography has been widely used during the last decade to visualise discrete white matter neural tracts (i.e. pathways that were not possible to delineate using traditional structural imaging). These pathways are the spokes of the connectome, described above. Diffusion parameters measured by DTI correlate with cognitive measures and neurological function in both health and disease (Salat et al., 2009). Combined with subsequent probabilistic tractography, DTI can map networks (Daianu et al., 2013), and can better define functional domains of putative hubs, such as subdividing the thalamus into thalamocortical domains (Jakab et al., 2012).

White matter lesions such as age-related white matter change may also bear upon mapping of white matter tracts. Apart from visualising the morphology of the tracts themselves, primarily via tractography, we and others have developed methods for quantification of diffusion changes along specific tracts (Mårtensson et al., 2013). These methods, in addition to automated methods for quantification of white matter lesions (van der Lijn et al., 2012), can be used to perform correlations with subcortical morphologic data. Presently, these methods are still in development/being improved, and the gold standard remains manual segmentation and/or visual rating.

Developing endophenotypes from topography

Endophenotypes are biological measures that correlate with, or predict, clinical features of brain dysfunction; one means to discover them is to correlate brain dysfunction with the morphometry (quantified topography) of the anatomical structures in the neural circuits involved. Our initial focus has been on hubs crucial to smaller scale neural networks. In Alzheimer disease, for example, differential morphology of the hippocampus is associated with progression from mild cognitive impairment to Alzheimer disease (Apostolova et al., 2010). Similarly, altered striatal morphology – in subregions effecting executive, emotional, and motor dysfunction – is evident in cerebrovascular disease, FTLN (and subtypes), progressive supranuclear palsy (PSP), choreoacanthocytosis (ChAc) and Huntington disease (HD) (Looi and Walterfang, 2012). Similarly, corpus callosum morphology, comprising a major interhemispheric spoke, is altered in cerebrovascular disease of ageing and is associated with executive cognitive dysfunction, slowed cognition and

movement (Jokinen et al., 2012), and is altered in multiple system atrophy (MSA) and PSP, and may represent disease-specific patterns of altered connectivity and associated cerebral atrophy (Minnerop et al., 2010).

As to other spokes, the present resolution of tractography limits its use to tracking major neural tracts. Even so, there are demonstrated diffusional and structural changes in white matter tracts with patterns specific to different neurodegenerative conditions and correlating with neurological symptoms and disease severity (Kvickström et al., 2011).

As for the spaces between the hubs and spokes, enlargement and altered morphology of the ventricles has been correlated with cognitive, depression, ischaemic and language scores, and with future clinical decline, as well as with cerebrospinal fluid measures of A β 1-42 and ApoE4 genotype (Chou et al., 2010). Therefore, measurements of these hubs, spokes and spaces offer suitable structural and topographic bases for endophenotypes of neurodegenerative disease. Given their extensive interconnectivity in subcortical circuits, other structures could also be considered as hubs in addition to the hippocampus, striatum and corpus callosum, such as the highly complex and segregated amygdala. Fourth ventricle morphology may also be a suitable target for investigation in cerebellar disorders such as spinocerebellar ataxias.

To what end?

Large-scale network studies are challenging conceptually, computationally and practically, whereas simple volumetric studies of individual structures yield little detail, so both ends of the spectrum may struggle to demonstrate functional specificity. One possible solution is to study a delimited structural connectome comprising quantified morphology of topographically specific subcortical structures and spaces. This represents an intermediate

step between mapping large-scale networks, and studying very small networks or individual structures. In so doing, our methods focus on individual brain structures, with an emphasis on the strategic network vulnerability of these structures, on the basis of their roles as hubs or spokes, or spaces within networks. We can thus derive a strategic map of the subcortical connectome in neurodegenerative disease, which will be further improved iteratively with advances in rs-fMRI mapping of networks. Such a connectome may be a useful series of biomeasures, quantifiable characteristics associated with neurobiology, or indeed biomarkers for preclinical diagnosis, monitoring progression and as a surrogate outcome for treatment trials. In addition, we can analyse the morphology of hubs, spokes and the spaces between to generate composite profiles of biomeasures/biomarkers characteristic of a discrete neurodegenerative process. These can be combined with cortical and other markers to map the morphology of brain disease. Such methods can be used to map the spatio-temporal course in which neurodegenerative disease impacts neural form, how form impacts function, and thus derive spatio-temporal signatures for disease monitoring and, ultimately, treatment.

Challenges in implementing the research program

As sketched here, we have an ambitious vision for mapping a subcortical connectome, which will require synergistic collaboration outside our existing groups, which, in a sense, is why we have come together to advance this proposal and challenge. Each group represented here has begun to collaborate in studies of this nature. However, we will need flexible large-scale group collaborative funding for international collaboration towards development and to facilitate integration as potential biomarkers in disease-modifying treatment trials.

Correlative measures will need to be developed, such as quantification of tractography that we can relate to mid-sagittal corpus callosum profiles, mapping of tractography to the surface of hubs such as the striatum, correlating ventricular contours with the contiguous surfaces of the caudate nucleus and deep white matter tracts amongst others. This will require collaborative interdisciplinary computational and clinical neuroscience. The challenge is to map hubs, spokes and spaces towards a comprehensive subcortical connectome. Such a connectome may then be a suitable integrated biomarker for monitoring disease progression and treatment trials.

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Neurodegenerative, MRI, subcortical, connectome

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