NeuroImage 190 (2019) 1–3

Contents lists available at ScienceDirect

NeuroImage

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

Editorial

Disease-informed brain mapping teaches important lessons about the human brain

Technological progress continues to advance the potential of neuroimaging to detect brain pathology *in vivo* and trace its impact on human brain function. Both, magnetic resonance imaging (MRI) and positron emission tomography (PET) have pushed the frontiers of diagnostics of brain diseases in recent years, enhancing the level of detail at which one can detect metabolic, functional and structural abnormalities in individual patients. Neuroimaging has also proven highly effective as an investigative tool to unravel the pathogenesis and pathophysiology of disease states in the human brain. Hence, it is not surprising that the use of neuroimaging to study brain diseases mainly focusses on its diagnostic accuracy and precision, with parallels between its use in clinical practice and clinical neuroscience. Yet, neuroimaging of brain diseases merits a broader perspective that extends well beyond its clinical impact. We propose that insights from neuroimaging the diseased brain can also be leveraged to understand human brain development and function.

In this special issue, a series of scientific contributions describe how the study of diseased brains can teach important lessons about the normal brain. Comparing individuals affected by a brain disease with healthy individuals can yield important mechanistic insights into brain function, organization, and structure in general. Such disease-informed brain mapping studies fully match the scope of Neuroimage, where they advance the understanding of structure-function or brain-behaviour relationships. We bring together a set of Invited Review Articles to give a comprehensive and balanced account on how neuroimaging of a wide range of brain diseases can teach about the brain in general. The issue also includes Original Research Articles which "showcase" the potential of neuroimaging of brain disease as a means of understanding human brain function.

Many neurological brain diseases present with substantial changes in brain structure, with diffuse or focal loss of neural tissue due to acute events (e.g., trauma or stroke) or more protracted processes, involving neurodegeneration or neuroinflammation. In contrast, structural abnormalities are lacking or often subtler in patients presenting with psychiatric disorders or patients with neurological disorders such as essential tremor, Tourette syndrome, migraine, even when functional alterations are severe. In this special issue, we wish to make the point that neuroimaging of disease state is a valuable source for understanding the normal brain regardless of whether a given brain disorder is accompanied by substantial structural damage or not. We acknowledge that it was not possible to cover all relevant diseases. For instance, epilepsy, traumatic brain injury, depressive disorders are not covered in this issue. But, the concept that neuroimaging of disease states provides key mechanistic insights into normal human brain function, is applicable to any brain disorder.

Overview of special issue

In the following, we provide a brief overview of the topics covered in this Special Issue.

The section of the special issue covering neurological disorders starts with a review on how to map the functional consequences of focal brain lesions. Focal brain lesions can tell us a great deal about how the damaged brain region contributes to human brain function. Karnath et al. (2019) reviews the portfolio of complementary brain mapping approaches that link lesion location to specific brain functions. Focusing on the language network, Hartwigsen and Saur (2019) show that longitudinal brain mapping after stroke can reveal the brain's capacity to undergo reorganization in response to a focal lesion, revealing important properties in terms of the functional architecture of language related networks in the human brain. Filippi et al. (2019) review how the application of multimodal MRI in multiple sclerosis provide relevant information on the human brain, for instance by pinpointing strategically important white-matter tracts that can cause symptoms due to disconnection. Turner et al. (2019) used multiple sclerosis as a model to study the relationship between regional neuronal-glial-vascular coupling and optimal cognitive performance.

In neurodegenerative brain diseases, the transition from a normal "compensated" to a symptomatic state is gradual. Large-scale structural MRI data sets can capture the temporal and spatial dynamics of neurodegeneration (Lorenzi et al., 2019; Zeighami et al., 2019). In their contribution, Lorenzi et al. (2019) discuss the potential of neuroimaging-based disease progression modelling in Alzheimer's disease to derive dynamic MRI-based patterns that mark the transition from normal to pathological stages along the disease time axis. Understanding the transition from covert to overt (symptomatic) disease states provide key insights into which brain properties help to maintain sufficient levels of brain function. Zeighami et al. (2019) make a similar point, showing that structural MRI of the spatial atrophy patterns can reveal clinical-anatomical signatures of Parkinson's disease already at an early stage of the disease. Brain diseases may also affect the function of modulatory neurotransmitter systems. In these instances, functional MRI in conjunction with pharmacological manipulations can give important clues about the functional relevance of the neurotransmitter system of interest. This line of research has been particularly applied in Parkinson's disease because neurodegeneration affects a range of key brain nuclei that are critical to dopaminergic, cholinergic, adrenergic and serotonergic neurotransmission. Focusing on the dopaminergic system and functional MRI, Meder et al. (2019) summarize these lines of research, while Kim et al. (2019a, 2019b) applied PET to elucidate the role of cholinergic neuromodulation and its interaction with the dopaminergic

https://doi.org/10.1016/j.neuroimage.2019.02.040

Available online 21 February 2019

system in executive control. Another study by Nettersheim et al. (2019) took advantage of the exquisite temporal resolution of electroencephalography (EEG) to tap into dopaminergic modulation of interhemispheric coupling between motor cortical areas during bimanual movements.

The section on neuroimaging in psychiatric diseases focuses on schizophrenia and autism spectrum disorder. Sterzer et al. (2019) address the question how neuroimaging in schizophrenia has provided evidence for hierarchical predictive coding in brain networks during decision making. Mikanmaa et al. (2019) review how investigations of oscillatory and event-related brain activity with EEG and magnetoencephalography (MEG) in individuals at high-risk for the development of schizophrenia, can establish functional relationships between dysfunctional neural circuits and emerging psychopathology. Larsen et al. (2019) address a related issue reviewing similarities regarding abnormal brain activity patterns during a range of tasks in individuals with a 22q11.2 deletion syndrome or schizophrenia and their implications in terms of increased risk for psychosis in the general population. Jiang et al. (2019) report how resting-state functional MRI can reveal abnormal functional brain connectivity patterns in schizophrenia, which can indicate normal features of functional interactions when comparing these patterns to healthy controls.

Three contributions to this special issue focus on various aspects of resting-state functional brain connectivity in individuals with autism spectrum disorder, describing abnormal connectivity patterns that scale with clinical features of the disorder. Nunes et al. (2019) report a more idiosyncratic organization of intrinsic cortical networks in autism spectrum disorder, while Fu et al. (2019) identified altered dynamics of resting-state functional connectivity. Jung et al. (2019) report converging evidence for altered functional and structural connectivity of the occipital cortex in boys with autism spectrum disorders, which correlate with impaired social communication skills. In patients with social anxiety disorders, Yang et al. (2019) applied graph theoretical analyses to derive alterations in functional brain network organization from resting-state functional MRI data. Again, connectivity changes scaled with anxiety symptoms. Together, the studies indicate the potential of connectivity-centered neuroimaging approaches to delineate network features that are associated with behaviors or experiences that cause mental illness or psychological impairment. At the same time, these studies can identify network features that confer resilience, and thus pinpoint beneficial network properties of the healthy brain.

The last section of the special issue illustrates the diversity of neuroscientific questions that can be addressed by neuroimaging of brain disorders. Four MRI studies share a common focus on the visual system. Ahmadi et al. (2019) used 7T MRI to trace visual cortical reorganization associated with a novel congenital visual pathway disorder. Farivar et al. (2019) employed functional MRI to map altered cortical processing caused by amblyopia, and Urgen et al. (2019) adopted an imaging genetics approach to identify structural and functional changes of visual attention networks in homozygous carriers of a LAMC3 mutation, causing complex bilateral occipital cortical gyration abnormalities. Papanikolaou et al. (2019) applied functional MRI to study the organization of area hV5/MT+ in five patients with dense homonymous defects in a quadrant of the visual field due to partial V1+ or optic radiation lesions.

Two contributions illustrate the potential of single-patient neuroimaging studies to reveal sensorimotor brain function and plasticity: Dogonowski et al. (2019) performed sequential functional MRI examinations to show dynamic changes in task-related functional connectivity during recovery from motor conversion disorder, shedding light into volitional control of actions. Valyear et al. (2019) employed functional MRI in a patient who had undergone surgical hand transplantation. In this patient, increasingly normal grasp kinematics were paralleled by increasingly robust grasp-selective fMRI responses within the anterior intraparietal, premotor and cerebellar cortices.

Bulthé et al. (2019) applied multi-modal brain imaging in adults with dyscalculia to demonstrate deficient cortical representations of numeric magnitudes along with a hyper-connectivity in visual brain regions in adults with dyscalculia. Finally, Chung et al. (2019) employed PET in a rat model of neuropathic pain to show a correlation between pain sensing and the levels of metabotropic glutamate receptor 5 in brain regions involved in sensory, cognitive, and affective aspects of pain processing.

In his classic monograph "*The functions of the brain*", the neurologist David Ferrier (1886) showed clearly how the study of focal brain lesions could help us understand the normal functional architecture of the brain, in humans and animals. The integration of studies of brain structure and function in both heath and disease was facilitated by the advent of brain imaging. However, the holistic approach has been undermined by later professional boundaries between clinical and cognitive neuroscience, and by hard boundaries between the publication and media accessed by different readers. We hope that this special issue will remind all of us interested in brain function to look beyond the categorisation of research as 'clinical' or 'non-clinical'. Instead, we should ask what we can learn from imaging studies of neurological and psychiatric disorders: both about the disorder itself, but also about the vital connections between normal brain structure, function and behaviour.

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