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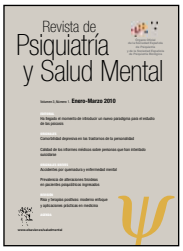

EDITORIAL

A paradigm shift in modern psychiatric diagnosis? Neural network dysfunction as a pathophysiological concept and novel diagnostic tool

¿Un cambio de paradigma en el diagnóstico psiquiátrico moderno? Anomalías en las redes neuronales como concepto fisiopatológico y nueva herramienta de diagnóstico

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During the last three decades, structural neuroimaging methods such as cranial computed tomography (cCT) and magnetic resonance imaging (MRI) have become increasingly important supportive diagnostic tools for a variety of clinically relevant neuropsychiatric disorders. Their primary use in establishing a diagnosis of exclusion as defined by traditional operationalised diagnostic criteria to elucidate an etiological basis in unspecific syndromal presentations is now ever expanding to provide a positive diagnosis based on supportive biomarker information complementary to clinical and neuropsychological information. Therefore, the exclusionary approach on neuropsychiatric disorders with primary screening for vascular pathology such as cerebral infarctions, bleedings, inflammation or space-occupying processes such as tumors are not longer center stage in psychiatric diagnostic neuroimaging. Modern computational neuroanatomy using CT and MRI allows for a precise and early assessment of more disease characteristic neurodegenerative morphological changes of the brain. Major psychiatric disorders have been increasingly associated with morpho-structural abnormalities. For example, schizophrenia has been linked with volume loss in the temporal lobes, basal ganglia and thalamus along with with white matter abnormalities, enlarged ventricles and abnormal structural asymmetry.[1] Unfortunately, despite great efforts and an exponentially increasing number of psychiatric experimental neuroimaging studies, macrostructural changes of the brain could still not be established and/or validated as sufficiently clinically useful diagnostic markers of most psychiatric diseases, mainly because of high variability and due to only moderate correlation with clinical and functional states. Some neurodegenerative and dementia disorders seem to present encouraging exceptions to these limitations as they show characteristic morphological atrophy patterns that can indeed support the detection and diagnosis of the underlying pathology. Specific brain atrophy indices can discriminate between Alzheimer's disease (AD), mild cognitive impairment (MCI) and healthy control subjects with high sensitivity and specificity.[2]

However, one of the major limitations of an isolated assessment of macrostructural changes is that structure and function do not necessarily correlate with each other. On the contrary, structural atrophy of certain brain areas can even be associated with increased functional activation and relatively unaffected functional performance.[3] Subjects at genetic risk of AD show abnormal overactivation of brain areas during cognitive tasks despite inconspicuous brain morphology and despite normal cognitive performance.[4]

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An analysis of a large body of neuroimaging studies in ageing and dementia has revealed that damaged brain areas can show a large spectrum of functional activation alterations: from underactivation through normal activation to overactivation, when compared with healthy control groups. Moreover, these changes are most likely determined by the necessity (as modulated by task difficulty) *and* by the capacity to compensate for impaired processing efficiency.[5] Because of their large variability, changes of functional brain activation may therefore not be the most useful way to detect impaired brain function or abnormal brain states.

Since neither brain structure nor brain activation can entirely explain or consistently reflect functional abnormalities that occur in various psychiatric disorders, there is great need for alternative or additional parameters which can be assessed with neuroimaging and which may further improve diagnostics.

Ideally, a neuroimaging marker or a set thereof, should fulfil one or more of the following criteria: 1.) early detection of the disease, even during preclinical stages, 2.) accurate prediction of the further course of disease (prognosis), 3.) discrimination between different diseases, 4.) prediction of therapy response to specific drugs or treatments and 5.) sensitive and accurate monitoring of (drug) therapy effects.

Currently, one of the most promising neuroimaging candidate markers are measures reflecting neuronal coordination (NC). NC denotes the coordinated work of neurons, neuronal assemblies and entire brain areas, particularly large-scale interconnectivity networks (the underlying basis of complex cognitive processing) as measured by the degree of temporal coherence of spatially distinct neuronal signals ("functional connectivity"). Moreover, sophisticated statistical analysis methods are being increasingly applied to functional as well as to structural imaging and neurophysiology data in order to account for the complexity of neuronal networks and their changes in brain diseases[6] (Bullmore and Sporns, 2009). At the moment, NC is being extensively researched in various important psychiatric disorders using different functional brain imaging methods, including functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). The results so far raise hopes that NC may have outstanding diagnostic potential and that it may substantially complement structural and functional neuroimaging markers.

Bokde and colleagues used functional magnetic resonance imaging (fMRI) demonstrating in subjects with mild cognitive impairment (MCI) abnormally impaired functional connectivity in visual networks during a visual face-matching task, while functional activation was still preserved.[7] This was one of the first studies to indicate that abnormal NC may reveal more sensitive (and specific) information about disease-related brain pathology than functional activation.[8]

Cognitively intact healthy elderly subjects that show increased accumulation of fibrillar Aß in the brain likely represent very early preclinical and presymptomatic stages of AD, well before first symptoms of mild cognitive impairment develop and probably many years before the onset of dementia syndrome. Such presymptomatic AD patients have significantly impaired functional connectivity[9] (a measure of neuronal coordination) within the default mode network (DMN). The DMN is a large network comprising medial frontal as well as medial and lateral parietal cortical areas and is typically characterized by high levels of resting-state activity and task-induced deactivation. Moreover, there is a close structural and functional association between the DMN and episodic memory networks, including the hippocampus. Consequently, in AD patients who show typical deterioration of episodic memory, functional network disconnection could be detected between the hippocampus and other parts of the DMN, including the posterior cingulate cortex (PCC).[10] A recent study showed that even young healthy carriers of the ApoE4 allele, harbouring increased risk for late-onset AD, have aberrant functional connectivity in the DMN,[11] a finding that can be detected as early as several decades before the typical onset time of clinical dementia.

Emerging pathophysiological concepts of neurodegeerative disorders propose that aberrant neuronal coordination may not only be a sensitive indicator of early pathophysiology but that may even represent a critical driving factor of molecular pathophysiological processes, such as increased production of neurotoxic Aß-peptides[12] (Palop & Mucke, 2010).

But NC may not only be a useful to detect neurodegenerative disorders in presymptomatic stages but also to support diagnosis in various other neuropsychiatric disorders. For example, auditory hallucinations in schizophrenia patients have been linked to structural and functional hyperconnectivity, probably reflecting abnormal backpropagation of unconscious auditory imagery to primary auditory cortex.[13] In depression, increased connectivity has been observed between the DMN, the cognitive control network and the affective network. These three distinct large-scale networks are abnormally functionally connected in patients with depression, probably contributing to typical symptoms in depressive patients such as difficulty to focus on cognitive tasks, increased self-focus and impaired emotional regulation.[14]

In summary, non-linear progressively adapting parameters of functional neural network integrity appear to be extremely promising dynamic functional neuroimaging biomarker candidates, potentially even candidates for surrogate marker status, particularly at functional presymptomatic and potentially reversible disease stages.

Currently validated biomarkers mostly reflect on a molecular target, a mechanism or an aspect of disease-related pathophysiology. These are important features making those biomarkers very useful for diagnostic purposes. Exemplary, the CSF-based "AD core biomarkers" $Aß_{1-42}$, t-tau and p-tau have been shown to distinguish with high sensitivity and specificity (80-90%) between healthy subjects and patients with AD. They can even support the prediction of conversion from MCI to AD and thus indicate prodromal AD stages.[15] However, they are not able to sensitively reflect complex changes in brain functionality and their use is not sufficient to predict

possible adverse cognitive effects of AD compounds in clinical trials. As a recent example, two phase III trials on semagacestat, a gamma-secretase inhibitor, which had been demonstrated (by the use of biomarkers) to reduce Aß production and Aß levels in CSF and plasma, have recently failed and were terminated.[16] One reason for trial abortion was an unexpected acceleration of cognitive decline in treated AD patients when compared with controls. This example impressively shows the necessity of so called surrogate markers — biomarkers that correlate with clinical outcome and that could accurately predict outcome not only on a pathophysiological but on a functional and cognitive level as well. Because of the extreme complexity and dynamics of functional brain networks that underlie cognitive functions, it is unlikely that a single molecular biomarker can be used as a surrogate endpoint. Brain functional network systems show high levels of modularity, redundancy and plasticity. These properties allow for adaptational reorganization on various levels. This is one reason why cognitive symptoms in AD occur relatively late in the course of the disease, while underlying pathophysiological processes start even several decades before the onset of clinical dementia. A surrogate marker should be able to indicate dynamic abnormalities of cognitively relevant functional brain networks. One important advantage of such surrogate biomarkers would be their ability to indicate subtle functional changes (advantageous or detrimental) independently of interposed adaptational neuroplasticity processes. By the use of such markers, effects on cognition might be predicted even after relatively short time of active drug administration and before initiation of large and expensive phase III clinical trials.

In summary, existing research suggests that NC may provide an excellent candidate surrogate marker due to the ability to directly reflect early adaptational and functional integrity states in cognitively relevant large-scale neuronal networks. An increasing body of evidence suggests that neurodegenerative diseases such as AD display a typical progression pattern starting with pure functional abnormalities in the earliest presymptomatic stages which later on switch into measureable degradation of functional integrity as indicated by reduced functional connectivity. These changes may be followed by neurodegenerative microstructural (as measured with diffusion tensor imaging, DTI) and macrostructural (as measured by e.g. volumetric MRI) degradation.

This specific sequence of abnormal changes allows to apply a multimodal battery of various functional and structural imaging methods which could tremendously improve accuracy and sensitivity of early and differential diagnosis of neurodegenerative and dementia disorders.

Since abnormalities of NC appear to be differentially altered in various psychiatric disorders NC represents a potential candidate surrogate biomarker not only in neurodegenerative but for use in a broad spectrum of other psychiatric disorders as well.[17]

At the moment, much effort is being put in national and international multicentric studies, including collaborations between academic and industry partners, with the purpose to validate NC as a surrogate marker. The development and validation of NC as a functional surrogate marker would indeed represent a true conceptual paradigm shift in modern neuro-psychiatric diagnosis and therapy development.[18]

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