Guest Editorial

A DMN-based functional taxonomy of the resting human brain: Is essential really invisible to the eye?

Keywords:
Default Mode Network
Functional neuroimaging
Resting state
Predictive potential
Functional taxonomy
Connectivity
Brain networks

Once upon a time, the Little Prince came across a planet inhabited by an old geographer who wrote voluminous books. Nevertheless, he was not able to answer to the Little Prince, who was wondering for the presence of oceans, mountains, towns or rivers on the planet. As a matter of fact, the geographer usually asked questions to explorers without ever leaving his desk: he first noted down what they recalled from their travels with a pencil, and only after they had provided cogent proofs, he put them down in ink.

Making exciting and clinically relevant discoveries, and possibly putting them down in ink, is still a fundamental scientific requisite for worldwide ‘explorers’. In 2001, a group of neuroscientists reported that when an individual is alert but not actively engaged in cognitive tasks, a spontaneously organized neural activity occurs in a unique constellation of brain regions called the Default Mode Network (DMN), which mainly involves the posterior cingulate cortex, the precuneus and regions of the ventromedial prefrontal cortex (Raichle et al., 2001). Since then, DMN structure and functions have been investigated across the whole human lifespan, from its emergence in 48-hour-old newborns (Gao et al., 2009) to its disappearance in dead brains (Boly et al., 2009). DMN-based research provided insights into the intrinsic functional architecture of human brain, as well as inter-individual differences in structural connectivity and neural activations. In addition, abnormalities and disruptions between healthy and pathological conditions were discovered (Fig. 1).

Notably, in the very last couple of months a new perspective has been emerging, since scattered interdisciplinary pieces of evidence are accounting for what we can define the ‘predictive potential’ of DMN. As a matter of fact, peculiar patterns of DMN activity and connectivity seem to anticipate future behavioral phenotypes and clinical impairment. In other words, DMN structure and function not only constitute the behavioral and neurophysiological correlates of potential and in feto neurological and psychiatric diseases (Fox and Raichle, 2007; Sandrone, 2012), but they can also offer informative predictive markers that might anticipate the overt onset of physiological and pathological phenotypes.

More in details, cerebral connectivity during resting state, along with functional modifications following working memory tasks, predicts the behavioral performance (Sala-Llonch et al., 2012), and the connections of motor-planning regions, while DMN may predict the predisposition to impulsive behavior in juvenile offenders (Shannon et al., 2011, but for perspective neuroprediction based on another potential biomarker see Aharoni et al., 2013). DMN connectivity dysfunction and resting state modifications are also associated to sustained attention deficits in traumatic brain injury patients and have been specifically linked to cognitive outcomes (Bonneille et al., 2011; Sandrone and Bacigaluppi, 2012; Palacios et al., 2013; Zhou and Lui, 2013). Moreover, DMN results altered in preclinical Huntington’s disease subjects (Wolf et al., 2012), as well as in individuals with amnestic mild cognitive impairment at risk for Alzheimer’s disease (AD) (Wang et al., 2012, 2013). Early DMN functional connectivity (FC) disruption of the inferior parietal cortex and medial temporal lobe occurs in patients with Parkinson disease before any clinical evidence of cognitive impairment shows up (Tessitore et al., 2012, but see also Niethammer and Eidelberg, 2012). As a consequence, DMN FC abnormalities can support early discrimination between dementias, such as AD and dementia with Lewy bodies (Galvin et al., 2011; but see also Sheline and Raichle, 2013; Hahn et al., 2013; Cha et al., 2013), and may constitute robust diagnostic or prognostic criteria in individual patients with autism (Anderson et al., 2011).

Failure to deactivate the DMN has been pointed as a possible endophenotype of autism (Spencer et al., 2012), where a dysmaturation of the same network seems to occur (Washington et al., 2012). Furthermore, healthy siblings of schizophrenia patients show abnormal intrinsic connectivity within the midline DMN (van Buuren et al., 2012), whole-brain FC analyses can identify major depressive individuals from healthy controls, with the most discriminating connections located across and within the DMN (Zeng et al., 2012). Specific DMN-connections might also be candidate psychosis endophenotypes discriminating between schizophrenia and psychotic bipolar probands and unaffected relatives (Meda et al., 2012; Khadka et al., 2013). The application of machine learning techniques to resting state fMRI network activity seems promising in assisting the diagnosis of major depression (Lord et al., 2012), but a proper validation of this approach in independent data sets is required.

Notably, FC within this network is also reduced in patients with disorders of consciousness to a different extent depending...
on the clinical severity of the manifestations, thus underlining the pivotal role of DMN in the genesis of awareness and of the cerebral bases of these disorders (Fernández-Espejo et al., 2012; Guldenmund et al., 2012). Among others, very recent evidence claims that DMN holds valuable diagnostic and prognostic information also in attention deficit–hyperactivity disorder (Sun et al., 2012), amyotrophic lateral sclerosis (Agosta et al., 2013), borderline personality disorder (Klütsch et al., 2012), epilepsy (McCormick et al., 2013), multiple sclerosis (Sumowski et al., 2013; Rocca et al., 2012) and obsessive–compulsive disorder (Stern et al., 2012). All of these promising biomarkers are particularly interesting in the context of early diagnosis, which avoids performance-related confounds that are commonly present in patients with cognitive or sensorimotor defects (Zhang and Raichle, 2012). Resting state is a powerful paradigm, but we should carefully keep in mind that resting state acquisition can be performed differently by different subjects, and can be performed differently in a systematic way in patient groups. Resting-state fMRI data coherences still need to be further characterized and quantified across subjects and sessions (Damoiseaux et al., 2006), and technical optimization, experimental refinement and a balanced comparison among the different methods are required to deal with such data ‘explosion’ (Cole et al., 2010; Birn, 2012; Lee et al., 2012). In addition, an integrative systematic exploration of the functional connectome and the related aberrant intrinsic networks (Menon, 2011; Calhoun et al., 2011) as well as guidelines for performing research on clinical populations (Fox and Greicius, 2010) are needed to bridge the gap between basic research studies and translational application.

When left unconstrained, brain activity does not vary unpredictably (Raichle et al., 2001), and using DMN as a clinical predictive tool is a great challenge for clinicians and physician scientists. Future investigations will have to shed light on DMN ability of (i) discriminating single patients from single healthy controls with increasing sensitivity and high specificity and (ii) assisting in adequate diagnosis and prognosis processes, therefore allowing clinicians (iii) to plan the appropriate therapeutic strategy and (iv) follow clinical changes during disease progression.

When DMN was first discovered serendipitously (Buckner, 2012), it was given not much importance. They thought it was a useless (Morcom and Fletcher, 2007), or ephemeral, as the geographer would have said, background noise. Now we know that DMN-based research is emerging as a mainstream medical research avenue. A comprehensive characterization of DMN in the context of wider cerebral networks, the use of more-homogeneous experimental designs, a systematic replication of DMN experiments on larger samples and the medical open access to datasets will help improving and testing the accuracy rate of every prediction.

From an epistemological point of view, the DMN predictive potential potential blurs and jolts the boundaries of medical sciences, with its cross-disciplinary impact ranging from neurology to psychiatry and beyond, since these predictions do not a priori belong to any academic domain.

Time will tell if we would have been able to obtain a DMN-based ‘functional taxonomy’ of the resting human brain, and thus to identify population subtypes on the basis of nature and extent of the symptoms, as well as the medications used. A tight cooperation among and between explorers doing research and geographers transcribing data into a broader perspective is thus urgently needed.

What we should learn is the simple secret of the Little Prince: what is essential is invisible to the eye, or at least at the moment. It cannot be known whether functional magnetic resonance imaging will ultimately allow us to see, and possibly to make the right diagnosis and predict what is still invisible. However, we hope at least that we will get as close to that as possible, in order to catch for a moment a glimpse of the invisible with our own eyes, allowing the interpretation of cogent neuroimaging data and solid neurological and psychiatric DMN-based predictions to be carried out.

References


Stefano Sandrone a,b,*

a NATBRAINLAB - Neuroanatomy and Tractography Brain Laboratory, Department of Forensic and Neurodevelopmental Sciences, Institute of Psychiatry, King’s College, SES 8AF London, UK

b Institute of Neuroinformatics, University of Zurich and ETH Zurich, CH-8057 Zurich, Switzerland

* Correspondence address: Institute of Neuroinformatics, University of Zurich and ETH Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland.

E-mail address: sandronestefano@ini.ethz.ch

16 February 2013

Available online 6 July 2013