

## Mapping the functional connectome traits of levels of consciousness

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### ABSTRACT

Examining task-free functional connectivity (FC) in the human brain offers insights on how spontaneous integration and segregation of information relate to human cognition, and how this organization may be altered in different conditions, and neurological disorders. This is particularly relevant for patients in disorders of consciousness (DOC) following severe acquired brain damage and coma, one of the most devastating conditions in modern medical care.

We present a novel data-driven methodology, *connICA*, which implements Independent Component Analysis (ICA) for the extraction of robust independent FC patterns (FC-traits) from a set of individual functional connectomes, without imposing any a priori data stratification into groups.

We here apply *connICA* to investigate associations between network traits derived from task-free FC and cognitive/clinical features that define levels of consciousness. Three main independent FC-traits were identified and linked to consciousness-related clinical features. The first one represents the functional configuration of a “resting” human brain, and it is associated to a sedative (sevoflurane), the overall effect of the pathology and the level of arousal. The second FC-trait reflects the disconnection of the visual and sensory-motor connectivity patterns. It also relates to the time since the insult and to the ability of communicating with the external environment. The third FC-trait isolates the connectivity pattern encompassing the fronto-parietal and the default-mode network areas as well as the interaction between left and right hemispheres, which are also associated to the awareness of the self and its surroundings.

Each FC-trait represents a distinct functional process with a role in the degradation of conscious states of functional brain networks, shedding further light on the functional sub-circuits that get disrupted in severe brain-damage.

### Introduction

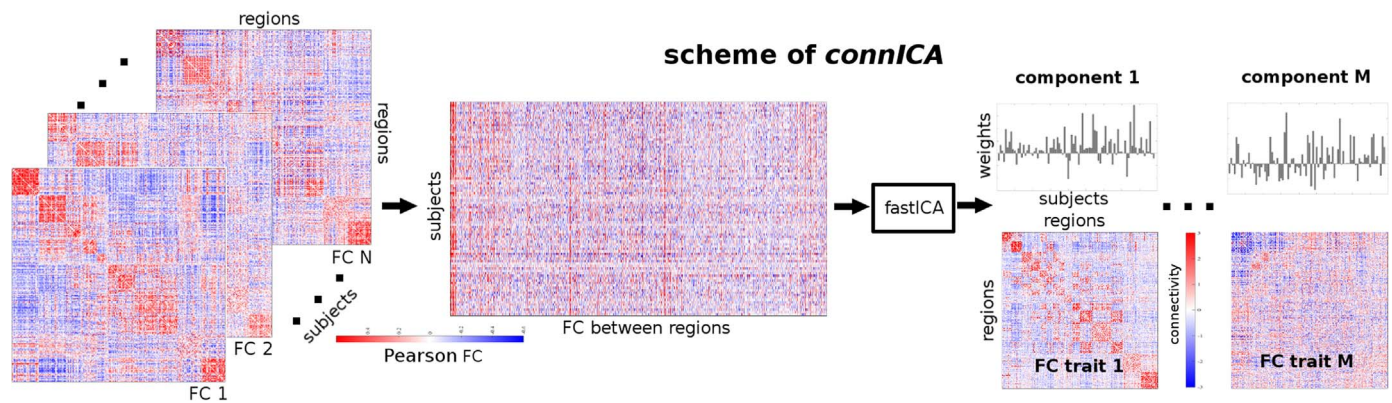
Disorders of consciousness (DOC) remain among the most challenging and poorly understood conditions in modern medical care. The term spreads over several pathological states qualified by dissociation between awareness and arousal (Bernat, 2009; Laureys, 2005). Among these, patients in coma show no signs of awareness nor arousal; patients with unresponsive wakefulness syndrome/vegetative state (UWS) show no signs of awareness but do have an altered sleep and

wake cycle; patients in a minimally conscious state (MCS) retain minimal non-reflexive and highly fluctuating signs of awareness. When patients regain functional object use and/or reliable communication they are referred to as emerging from MCS (EMCS) (Giacino et al., 2014; Laureys et al., 2004). A particular outcome is represented by patients with a locked-in syndrome (LIS), who have no means of producing speech, limb or facial movements (except mostly for eye movement and/or blinking) but are still awake and fully conscious (Giacino et al., 1995; Laureys et al., 2005). To date, the most validated

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**Fig. 1.** Workflow scheme of the Connectivity Independent Component Analysis (*connICA*). The upper triangular of each individual functional connectivity (FC) matrix (left) is added to a matrix where rows are the subjects and columns are their vectorized functional connectivity patterns. The ICA algorithm extracts the  $M$  independent components (i.e. functional traits) associated to the whole population and their relative weights across subjects. Colorbars indicate positive (red) and negative (blue) connectivity values, being Pearson's correlation coefficient values in the case of individual FC matrices (left side of scheme), and unitless connectivity weights in the case of FC-traits (right side of the scheme). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

diagnosis of these patients is based on the behavioral presentation of the patient. The distinction between these pathological levels of consciousness can be very challenging, as the boundaries between these states are often uncertain and ambiguous (Giacino et al., 2014).

In the last decade, advances in neuroimaging techniques have allowed the medical community to gain important insights into the pathophysiology of DOC and to observe that altered states of consciousness are related to complex disruptions in the functional and structural organization of the brain (Boly et al., 2012; Di Perri et al., 2014; Fernández-Espejo et al., 2012; Koch et al., 2016; Owen et al., 2009).

At the same time, quantitative analysis based on complex networks have become more commonly used to study the brain as a network (Bullmore and Sporns, 2009), giving rise to the area of research so called Brain Connectomics (Fornito et al., 2016; Sporns, 2011). In brain network models, nodes correspond to grey-matter regions (based on brain atlases or parcellations) while links or edges correspond to connections. Structural connections are modeled using white matter fiber-tracts and functional connections represent coupling between brain regions while subjects are either at rest or performing a task (van den Heuvel and Hulshoff Pol, 2010). Recent advances in functional neuroimaging have provided new tools to measure and examine *in vivo* whole-brain temporal dependence of the dynamics of anatomically separated brain regions, defined as functional connectivity (FC) (Fox and Raichle, 2007; Fox et al., 2005; Friston et al., 1993).

In parallel to the development of methods and network features in Brain Connectomics, analyses of functional magnetic resonance imaging (fMRI) data based on independent component analysis (ICA) have become an increasingly popular voxel-level approach (Calhoun et al., 2009). ICA, by relying upon a general assumption of the independence of the mixed signals, is a powerful and versatile data-driven approach for studying the brain, at both temporal and spatial scales (Erhardt et al., 2011).

Examining functional connectivity in the human brain offers unique insights on how integration and segregation of information relates to human behavior and how this organization may be altered in diseases (Boly et al., 2012; Greicius, 2008). In the case of disorders of consciousness, voxel-level ICA-based fMRI studies of levels of consciousness in DOC patients have mainly shown alterations in the functional connectivity of the default mode network (DMN) (Heine et al., 2012; Soddu et al., 2012; Vanhaudenhuyse et al., 2010). Recent studies have also shown disrupted functional connectivity in resting state networks other than DMN (Demertzi et al., 2014) and possibility to correctly classify patients based on the level of connectivity of the “auditory” network (Demertzi et al., 2015). Furthermore, analyses of the functional networks of comatose brains have also evidenced a

radical reorganization of high degree “hub” regions (Achard et al., 2012) and also showing that most of the affected regions in patients belonged to highly interconnected central nodes (Crone et al., 2014; Koch et al., 2016).

The potential of functional connectivity (FC) in particular and of Brain Connectomics in general in exploring the diseased human brain as a network going through systemic changes is undisputed. However, there is still no clear way to accomplish two critical steps of great clinical importance. First, to separate underlying FC patterns representing different functional mechanisms and, second, to relate those FC patterns or subsequent network features to individual cognitive performance or clinical evaluations. This is specially the case when studying a continuum of states, where the stratification of the cohort-subjects into categories or groups is inappropriate and/or poorly defined. Furthermore, standard FC techniques are not able to model and disentangle common underlying forces or competing processes arising from different functional patterns of healthy and diseased human brains in a data-driven fashion, as for instance ICA does in the case of fMRI voxel time series (Calhoun et al., 2009; Erhardt et al., 2011). This was indeed our motivation for the approach presented here.

In this study we bridge this gap by presenting a novel data-driven methodology, *connICA*, which consists of the extraction of robust independent patterns (traits) from a set of individual functional connectomes (see scheme in Fig. 1). In this sense, *connICA* is a multiplex network framework both in the input (i.e., layers are individual FC connectomes) and in the output (i.e., layers are independent patterns or FC-traits). Here we apply *connICA* to investigate the link between cognitive/clinical features that define states of consciousness and resting-state functional connectivity (FC) data. This method allows the assessment of individual FC patterns (or FC layers) in a joint data-driven fashion providing as outputs multivariate independent FC-traits, which model independent sources or phenomena present in the input (i.e. the aforementioned individual FC patterns). In a final step, we assess the predictability of the weights (fingerprints) of each FC-trait on each subject from demographic and consciousness related variables, allowing for a continuous mapping of levels of consciousness within functional connectomes.

## Materials and methods

### Subjects

The cohort studied here consists of 88 subjects with different levels of consciousness. From those, 31 were healthy controls (mean age 44 years  $\pm$  15 years, 20 males, 11 females). We included 57 patients from

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