International Journal of Psychophysiology 78 (2010) 89–99

Contents lists available at ScienceDirect

International Journal of Psychophysiology

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

Group independent component analysis of resting state EEG in large normative samples

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ARTICLE INFO

Article history:
Received 15 December 2009
Received in revised form 3 June 2010
Accepted 4 June 2010
Available online 18 June 2010

Keywords:
Electroencephalography (EEG)
Resting state
Default mode
Blind source separation (BSS)
Independent component analysis (ICA)
Norms
Inverse solution
Source localization

ABSTRACT

EEG (Electroencephalography) resting state was studied by means of group blind source separation (gBSS), employing a test–retest strategy in two large-sample normative databases (N = 57 and N = 84). Using a BSS method in the complex Fourier domain and a model-driven distributed inverse solution we closely replicate both the spatial distribution and spectral pattern of seven source components. Norms were then constructed for their spectral power so as to allow testing patients against the norms. As compared to existing normative databases based on scalp spectral measures, the resulting tool defines a smaller number of features with very little inter-correlation. Furthermore, these features are physiologically meaningful as they relate the activity of several brain regions, forming a total of seven patterns, each with a peculiar spatial distribution and spectral profile. This new tool, that we name normative independent component analysis (NICA), may serve as an adjunct to diagnosis and assessment of abnormal brain functioning and aid in research on normal resting state networks.

1. Introduction

Over two decades ago it was demonstrated that the resting state of the brain in normal individuals is characterized by spectral features that could be reliably described by a series of mathematical equations as a function of age across the human life span (6–90 years). Patients with psychiatric and neurological conditions show significant deviations from such spectral patterns (Ahn et al., 1980; John et al., 1977, 1980a,b, 1987, 1988). These norms have been shown to be culture-fair and replicable, with high sensitivity and specificity to neuropsychiatric disorders (Kondacs and Szabo, 1999; Prichep, 2005; Hughes and John, 1999; Coburn 2006). It has been theorized that this baseline or "ground state" of the brain results from a complex homeostatic system regulated by neurotransmitters and exists as a property of the resonant systems of the brain (John and Prichep, 2009).

For several reasons EEG is a suitable tool for building and using large-sample normative databases. First, modern EEG equipment is small, light and economical; EEG can be safely recorded on individuals of any age (including premature newborns), in any condition (even if extremely disabling such as profound states of unconsciousness), and virtually anywhere (e.g., at the bed of an intensive care unit, in the incubator, on top of a mountain, etc.). Second, given enough data are averaged, EEG spectral measures of the same individual are highly reliable over months and even years (Fein et al., 1984; Kondacs and Szabo, 1999). EEG spectral features stabilize after a few handfuls of seconds, with as few as 1 min of artifact-free EEG yielding reliable spectral measures (Nunez and Srinivasan, 2006; Oken and Chiappa, 1988). Such reliability is better verified in EEG continuously recorded during a resting state with the eyes closed and for relative power measures (John et al., 1987). Such stability is now also reported with PET (although norms still do not exist), but not with fMRI (Raichle and Snyder, 2007). Third, consistent EEG norms have been found across cultures and ethnicities, as verified comparing independent studies from a multitude of countries (Hughes and John, 1999; Prichep, 2005). It is accepted that the independence of the EEG spectrum from cultural and ethnic factors reflects the common genetic heritage of the mankind. For example, a study on a large sample of 16-year-old twins found that the variance of EEG power is mostly (76% to 89% depending on the frequency band) explained by heritability (van Beijsterveldt et al., 1996). In summary, intra-subject reliability, inter-subject consistence and the ease of recording procedures can be considered the fundamental properties of EEG enabling quantitative assessment of brain integrity in persons of any age, origin or background through comparison to normative values.

The interest for brain function in resting state has recently re-gained considerable interest with the advent of PET (positron emission

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doi:10.1016/j.ijpsycho.2010.06.003

tomography) and fMRI (functional magnetic resonance imaging). We now know that on average the human brain extracts about 40% of available oxygen in the blood and disposes about 20% of the energy for the whole body. Still, it amounts to only 2% of the total body weight. A considerable amount of this energy is consumed when the brain is at rest. On the other hand, it is has been estimated that the local task-related increase of energy consumption relative to the baseline is less than 5% (Fox and Raichle, 2007; Raichle and Mintum, 2006). It is still unclear why the brain requires such an important supply of energy in the absence of targeted goals, but these observations have prompted a new wave of investigation on the "baseline" (ground level) brain functions. The functional organization of the brain at rest is currently conceived in terms of resting state networks (RSN), clusters of brain regions, mostly cortical, inter-connected anatomically and functionally. The study of RSNs has shifted the focus in neuroimaging from the exact localization of specialized brain functions (looking for "things in a place") to the understanding of the interplay of widespread brain structures (identifying networks). A consistent finding is that regions in the brain with similar functionality tend to be correlated in their spontaneous activity (Fox and Raichle, 2007). Several of such RSNs have been identified by PET and fMRI, relating to the motor, auditory and visual system, language, memory, dorsal and ventral attention and the default mode (Auer, 2008; Beckmann et al., 2005; Damoiseaux et al., 2006; Fox et al., 2005, 2006; Fox and Raichle, 2007; Fransson, 2005; Mantini et al., 2007; van den Heuvel et al., 2008). The default mode network (DMN), appears the most active RSN at rest (for a review see Auer, 2008; Broyd et al., 2008; Buckner et al., 2008; Fox and Raichle, 2007), thus it is putatively the most energy-demanding brain function of all. As for EEG spectral measures, the DMN appears to have a counterpart in primates (Rilling et al., 2007; Vincent et al., 2007) and to develop with age (Bluhm et al., 2008; Fair et al., 2007), while clinical studies accumulate evidence on the alteration of the DMN in Attention Deficit Disorder (Castellanos et al., 2008; Uddin et al., 2008), Alzheimer's disease (Greicius et al., 2004; Rombouts et al., 2005; Sorg et al., 2007), autism (Kennedy et al., 2006), chronic pain (Baliki et al., 2008), epilepsy (Laufs et al., 2007) and schizophrenia (Garrity et al., 2007). That is to say, as for EEG spectral norms discussed above, the DMN is not a mere epiphenomenon, but an essential ingredient of the healthy brain functioning, peculiar to the phylogenetic and ontogenetic evolution of the mankind.

Two main data analysis approaches have been used to study functional connectivity in resting state networks by fMRI (Buckner et al., 2008, for a comparison see Bluhm et al., 2008): a seed-based connectivity analysis and independent component analysis (ICA). The latter is currently enjoying increasing popularity thanks to its complete data-driven nature (Beckmann et al., 2005; Bluhm et al., 2008; Greicius et al., 2004; Eichele et al., 2008; Mantini et al., 2007; Scheeringa et al., 2008). Regarding EEG, biophysical and neurophysiological studies suggest that each resting state pattern may exhibit complex dynamics unfolding over time with multiple frequencies (Jann et al., 2009; Mantini et al., 2007). The mass of recent literature suggests that checking univariate power measurements (at each electrode separately) may not be the best methodology for studying the resting brain (see concerns expressed by Jann et al., 2009). Studying the distribution of scalp EEG power at rest, as in the aforementioned studies on EEG normative database or more recently in Chen et al. (2008), does not allow the study of baseline patterns because scalp voltage is a mixing of underlying source activity (volume conduction: see Nunez and Srinivasan, 2006) and because scalp power is an appropriate measure of local neuronal synchronization, not of widespread coherent synchronization. Instead, we aim at extracting spatial maps of widespread synchronizations over the cortex, which can be treated as a single phenomenon and can be tested altogether (the whole cohort) along the frequency dimension. Besides allowing the study of co-activation of several brain areas, such approach allows the standardization of the spatial extent of the activations across individuals and also a smaller number of features (data compression) with lower inter-correlation (reduction of volume conduction effects). With fMRI such investigation in large samples of individuals has been performed by group ICA (Calhoun et al., 2001; Schmithorst and Holland, 2004), an approach that we introduce here in the context of EEG. This approach is essentially different from the seed-based approach in that we do not need to define explicitly measures of synchronization between different brain areas. This is particularly advantageous in the context of EEG, since many of such measures are influenced by the effect of volume conduction (Nunez and Srinivasan, 2006).

In this paper we describe the normative independent component analysis (NICA). Using this method we describe the extraction of eyes-closed resting EEG patterns using group ICA and the norming of the components thus extracted. ICA extracts scalp spatial maps and associated EEG time courses, referred together as components (Makeig et al., 2004). Since there is no way to establish a-priori how many of such components should be extracted nor if they are reliable, we employ a test–retest strategy using two independent large-sample normative databases (N = 57 and N = 84) and retain only replicable components; such strategy has been previously employed by Damoiseaux et al. (2006) in an fMRI study. Once robust ICA normative components are extracted, we characterize the cortical structures involved in each component using source localization, sLORETA (Pascual-Marqui, 2002), a model-driven distributed inverse solution of the components spatial maps (Greenblatt et al., 2005; Lopes da Silva, 2004) and their associated spectral profile. In the two databases, we describe seven replicable components with nearly identical spatial distribution and spectral profile. These components are then normed and patients tested against the normative values for each component.

2. Method and results

2.1. Subjects and EEG recording procedures

In order to avoid age effects we consider in this study only adult individuals between 17 and 30 years of age. Two independent normative databases previously acquired were used for this study. One is a subset of the normative database of the Brain Research Laboratory (BRL), New York University School of Medicine (N = 57; age range 17–30) and the other the normative database of Nova Tech EEG (NTE), Inc., Mesa, AZ (N = 84; age range 18–30). Exclusion criteria for the BRL database were known psychiatric or neurological illness, history of drug/alcohol abuse, current psychotropic/CNS active medications, history of head injury (with loss of consciousness) or seizure disorder. Exclusion criteria for the NTE database were a psychiatric history in any relative and participant of drug/alcohol abuse, head injury (at any age, even very mild), headache, physical disability and epilepsy.

Recording procedures and settings were very similar for the two databases. In both cases 3–20 min of EEG data was continuously recorded while the participant sat with the eyes closed on a comfortable chair in a quiet and dimly lit room. EEG data were acquired from the 19 standard locations prescribed by the 10–20 International System (Jasper, 1958: FP1, FP2, F7, F3, FZ, F4, F8, T3, C3, CZ, C4, T4, T5, P3, PZ, P4, T6, O1, and O2) using linked ear reference and enabling a 60 Hz notch filter to suppress power line contamination. The impedance of all electrodes was kept below 5000 Ω. Data of the NTE database were acquired using the 12-bit A/D NeuroSearch-24 acquisition system (Lexicor Medical technology, Inc., Boulder, CO) and sampled at 128 Hz, whereas data of the BRL database were acquired using the 12-bit A/D BSA acquisition system (Neurometrics, Inc., New York, NY) and sampled at 100 Hz. For consistency, we subsequently up-sampled the BRL database to 128 Hz using a natural cubic spline interpolation routine (Congedo et al., 2002). In order to minimize inter-subject variability we removed from all data any biological, instrumental and environmental artifacts, paying particular attention