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Brain oscillatory complexity across the life span

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HIGHLIGHTS

- A significant quadratic (curvilinear) relationship between age and oscillatory complexity exists, with complexity maxima reached by the sixth decade of life.
- As in previous studies, females exhibit higher complexity values than males, at least in some brain regions.
- The evolution of oscillatory complexity across the life span is interpreted as a physiological rhythm which is altered by several brain pathologies.

ABSTRACT

Objective: Considering the increasing use of complexity estimates in neuropsychiatric populations, a normative study is critical to define the 'normal' behaviour of brain oscillatory complexity across the life span.
Method: This study examines changes in resting-state magnetoencephalogram (MEG) complexity – quantified with the Lempel–Ziv complexity (LZC) algorithm – due to age and gender in a large sample of 222 (100 males/122 females) healthy participants with ages ranging from 7 to 84 years.
Results: A significant quadratic (curvilinear) relationship ($p < 0.05$) between age and complexity was found, with LZC maxima being reached by the sixth decade of life. Once that peak was crossed, complexity values slowly decreased until late senescence. Females exhibited higher LZC values than males, with significant differences in the anterior, central and posterior regions ($p < 0.05$).
Conclusions: These results suggest that the evolution of brain oscillatory complexity across the life span might be considered a new illustration of a 'normal' physiological rhythm.
Significance: Previous and forthcoming clinical studies using complexity estimates might be interpreted from a more complete and dynamical perspective. Pathologies not only cause an 'abnormal' increase or decrease of complexity values but they actually 'break' the 'normal' pattern of oscillatory complexity evolution as a function of age.

1. Introduction

Neurophysiological studies of human brain have emphasised the critical role of age effects in the electroencephalograms (EEGs) or magnetoencephalograms (MEGs) of healthy individuals. As Clarke et al. (2001) pointed out, EEG maturational changes were reported even in very early investigations (Lindsley, 1939). Matousek and Petersén (1973) established some 'norms' for the developing EEG in a large sample of healthy individuals aged 1–21 years. John et al. (1980) further studied the developmental aspects of the EEG in healthy children and calculated a series of 'developmental equations' that demonstrated a linear behaviour of the conventional delta, theta, alpha and beta bands. Low-frequency bands exhibited

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a negative slope as a function of age while high-frequency bands exhibited the opposite tendency. In essence, a 'substitution process' occurs. Low-frequency bands (delta and theta) are predominant until the age of 4 years, but both show a sustained decrease. As age increases, the dominant low-frequency bands are substituted by activity in the alpha and beta frequency ranges. Thus, the mean frequency of the so-called 'central alpha' is 7 Hz by the first year of life, 9 Hz by 4 years of age and stabilises at around 10 Hz in mild adolescence (see Marshall et al., 2002). Alpha rhythm in the 8–12 Hz frequency band becomes the most prominent rhythm in the awake EEG and MEG of healthy adults.

Adolescence is a key transition point for the oscillatory activity in the brain. During adolescence, a significant tendency to reduced power in all frequency bands was observed (Gasser et al., 1988); a power reduction that correlated with a decrease of grey-matter volumes in the transition from infancy to early adolescence (Whitford et al., 2007). These observations are supported by Dustman et al. (1999); they confirmed that such decrease of absolute power continues into adulthood, although changes are not so radical when compared to the transition between infancy and adolescence. Finally, healthy ageing is defined by a new 'substitution process' in the spectral profile, characterised now by the so-called 'slowing' of EEG and MEG traces. Overall, a pronounced decrease in the amplitude of the basic alpha rhythm (8–12 Hz) has been noticed, accompanied by a power increase in the theta and delta frequency ranges. Interestingly, during this new substitution process, low-frequency bands also increase their topographic location, following a posterior-to-anterior tendency (see John et al., 1988, and the review by Rossini et al., 2007).

All the above-mentioned studies used classical spectral analysis methods to investigate developmental changes. Traditional methods have been challenged by new techniques derived from the non-linear analysis theory, since EEG and MEG signals can be regarded, at least to some extent, as generated by complex systems with non-linear dynamics (Lopes da Silva, 1991; for a critical review on this issue see also Stam, 2005). Complexity analysis is a particular form of non-linear analysis that has been applied to EEG or MEG data. Unfortunately, there is no consensus for a unique definition of the term complexity within this background, and several estimates have been proposed. For example, Tononi and coworkers' (1994) proposed a measure, called 'neural complexity (CN)', which can be defined as a balance between functional segregation and integration in the brain. The correlation dimension is a widely used method that seems to represent a non-linear estimate of the number of independent neuronal populations or oscillators which give rise to an EEG/MEG signal (Lutzenberger et al., 1995). The algorithmic complexity (Kolmogorov, 1965) is defined as the length of the shortest computer program that generates a particular bit string. Most of these complexity estimates might be interpreted as a measure of the regularity/variability of brain oscillations and/or an attempt to evaluate the number of independent oscillators or frequency components underlying the observed signal (Aboy et al., 2006; Lutzenberger et al., 1995).

Complexity estimates have been specifically employed to investigate developmental changes of brain oscillatory activity measured with EEG. Anokhin's group (Anokhin et al., 1996) performed dimensional complexity analysis in a large sample of healthy males with an age range from 7 to 60 years. Complexity values increased monotonously as a function of age. Gender effects on maturational changes were not investigated in these first studies. In an ulterior investigation, Anokhin's group analysed dimensional complexity values in a new sample, now including healthy females with an age range from 7 to 66 years (Anokhin et al., 2000). Age effects were identical to those observed in their previous study. However, gender emerged as an important variable, since results indicated higher complexity values in females. Girls exhibited higher complexity values when compared to boys, and gender differences increased until adolescence. The authors interpreted these findings as an evidence of faster maturation of cortical activity in females. In parallel, Meyer-Lindenberg (1996) confirmed Anokhin's results using correlation dimension (D_2) and the first Lyapunov exponent ($L1$). It is noteworthy that gender differences were also reported in some developmental EEG studies using conventional spectral measures (see, e.g., Clarke et al., 2001).

Age-related changes of brain signals have been also investigated by means of estimators such as sample entropy and multi-scale entropy. For example, multi-scale entropy values were calculated by McIntosh et al. (2008) to assess age-related trial-to-trial variability in a face-recognition visual memory task. Results indicated that brain signal variability increased with age, and showed a positive correlation with subjects' accuracy on task performance. Authors understood that brain maturation increases brain signal variability and this process is accompanied by an increase in behavioural stability. Lippe et al. (2009) calculated multi-scale entropies of visual and auditory-evoked responses in a sample of healthy infants and children aged 1 month–5 years of age. As in all previous studies, complexity increased with age, although signal complexity was higher for visual as compared to auditory stimuli. Bruce et al. (2009) accomplished an interesting study where the regularity of EEG signals during sleep was compared in samples of middle-aged and elderly individuals. Signal complexity was estimated by means of sample entropy, and results indicated that sample entropy was larger in elderly individuals in sleep stage 2.

Overall, these investigations basically support the notion of an uninterrupted, linear increase of brain oscillatory complexity during maturation and ageing. In a recent MEG study (Fernández et al., 2010), we suggested that such uninterrupted complexity increase observed in Anokhin's studies may be explained by the characteristics of the sample. Our sample was composed of subjects between the sixth and eighth decades of life, and a linear decrease of complexity scores as a function of age was observed. These apparent contradictions suggest that normative studies with larger samples and more robust complexity estimates are needed.

Previous investigations used methods derived from the chaos theory, such as D_2 and $L1$. The use of these estimates to characterise biomedical time series poses significant problems. First, to accurately compute both metrics, one needs an amount of data beyond the experimental possibilities for biomedical time series (Eckmann and Ruelle, 1992). In addition, time series need to be stationary, something that is usually not true with physiological signals. With these limitations in mind, Lempel–Ziv Complexity (LZC), a complexity estimator introduced by Lempel and Ziv (1976), has been proposed for EEG/MEG signals analysis. The LZC is a metric that, similar to the algorithmic complexity, reflects the number of distinct substrings and the rate of their recurrence along the given sequence (Radhakrishnan and Gangadhar, 1998). Larger LZC values correspond to more complex time series. One important advantage of this metric is that it can be calculated even for short data segments and in non-stationary signals (Zhang et al., 1999). Moreover, LZC is more precise than $L1$ for characterising order or disorder (Kaspar and Schuster, 1987) and is better suited for the electromagnetic brain activity analysis than D_2 (Zhang et al., 2001).

LZC has been used to analyse EEG and MEG signals in patients with Alzheimer's disease (Abásolo et al., 2006; Fernández et al., 2010; Gómez et al., 2006), attention deficit-hyperactivity disorder (ADHD) (Fernández et al., 2009), depression and schizophrenia (Li et al., 2008; Fernández et al., 2011a; Méndez et al., 2011;) as well as to measure the depth of anaesthesia (Zhang et al., 2001), or to study epileptic seizures (Radhakrishnan and Gangadhar, 1998). The increasing clinical use of LZC and other estimates of oscillatory