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Cortical sources of EEG rhythms are abnormal in down syndrome

Claudio Babiloni [a,b], Giorgio Albertini [c], Paolo Onorati [b,d,*], Chiara Muratori [c], Paola Buffo [d], Claudia Condoluci [c], Marco Sarà [b], Francesca Pistoia [b,e], Fabrizio Vecchio [f,g], Paolo M. Rossini [b,h]

[a] Department of Biomedical Sciences, University of Foggia, Italy
[b] Department of Imaging, San Raffaele Cassino, Italy
[c] IRCCS San Raffaele Pisana, Rome, Italy
[d] Dip. Fisiologia e Farmacologia, University "Sapienza", Rome, Italy
[e] Department of Internal Medicine and Public Health, University of L'Aquila, L'Aquila, Italy
[f] A.Fa.R., Dip. Neurosci. Osp. FBF; Isola Tiberina, Rome, Italy
[g] IRCCS "S. Giovanni di Dio-F.B.F.", Brescia, Italy
[h] Clin. Neurol. University "Campus Biomedico" Rome, Italy

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ABSTRACT

Objective: Previous studies have been inconclusive whether dominant resting state alpha rhythms are greater or lower in amplitude in subjects with Down syndrome (DS) when compared to control subjects, ample resting alpha rhythms being considered as a reflection of good mechanisms of cortical neural synchronization. Here we tested the hypothesis that when the effects of head volume conduction are taken into account by the normalization of the cortical sources of resting alpha rhythms, these sources are lower in amplitude in DS subjects than in controls in line with typical findings in Alzheimer's disease patients.

Methods: Eyes-closed resting electroencephalographic (EEG) data were recorded in 45 DS subjects (25 males; mean age of 22.8 years ± 0.7 standard error of mean (SEM)) and in 45 age-matched cognitively normal subjects (25 males; mean age of 22.4 years ± 0.5 SEM). EEG rhythms of interest were delta (2–4 Hz), theta (4–8 Hz), alpha 1 (8–10.5 Hz), alpha 2 (10.5–13 Hz), beta 1 (13–20 Hz), beta 2 (20–30 Hz), and gamma (30–40 Hz). Cortical EEG sources were estimated by low resolution electromagnetic tomography (LORETA) and normalized across all voxels and frequencies.

Results: Central, parietal, occipital, and temporal cortical sources of resting alpha and beta rhythms were lower in amplitude in the DS than control subjects, whereas the opposite was true for occipital delta cortical sources. A control analysis on absolute source values showed that they were globally larger in amplitude across several frequency bands in DS than control subjects.

Conclusions: These results suggest that normalized cortical sources of alpha rhythms are lower in amplitude in DS than control subjects, as it is typically found in Alzheimer's disease.

Significance: DS is accompanied by a functional impairment of cortical neuronal synchronization mechanisms in the resting state condition.

1. Introduction

Down's syndrome (DS) or trisomy 21 is the most common genetic, non-heritable cause of developmental sensory-motor and cognitive disabilities occurring in about 1 out of 800 live births throughout the world (Nadel, 2003). It is characterized by neurodegenerative lesions similar to those recognizable in Alzheimer disease (AD): this makes DS an interesting model for exploring AD pathophysiology (Lott et al., 2006). The main neuropathological hallmarks of both AD and DS are intracellular neurofibrillary tangles, due to accumulation of phosphorylated tau protein, and extracellular neuritic plaque, due to B amyloid (Aβ) protein deposition (Moreira et al., 2006). Neurofibrillary tangles and amyloid plaques, nevertheless, are not hallmarks of Down's syndrome per se but are supposed to develop during aging in DS subjects, reaching a high prevalence at the age of 40 years and above. Another relationship between the two pathological conditions is that most of DS subjects progressively develop AD over middle age; in these subjects, clinical signs of AD are supposed to be delayed by about 10 years after the beginning of disease (Wisniewski et al., 1985; Oliver and Holland, 1986; Lott and Head, 2001). In DS subjects, clinical onset of AD can be predicted by structural or metabolic brain changes, especially in temporal and/or

* Corresponding author. Address: Dip. Fisiologia e Farmacologia, University "Sapienza", I-00185 Rome, Italy. Tel.: +39 06 49910896; fax: +39 06 49690301.
E-mail address: paolo.onorati@uniroma1.it (P. Onorati).

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posterior cingulate areas (Schapiro et al., 1988; Haier et al., 1995; Dani et al., 1996; Pietrini et al., 1997). Furthermore, gray matter loss in DS subjects is typically related to aging, pre-clinical stages of AD, and overt dementia (Pearlson et al., 1998; Aylward et al., 1999; Prasher et al., 2003; Hirata et al., 2005; Teipel et al., 2006; Teipel and Hampel, 2006).

An important target for DS research is the development of instrumental and low-cost procedures for neurophysiological assessment and therapy monitoring, in order to rationalize and optimize the rehabilitative or pharmacological intervention and to prepare social and family environment. To this aim, recording of eyes-closed resting electroencephalography (EEG) rhythms seems to be a promising tool. It allows evaluating the back-ground of brain neural synchronization in DS subjects at all degrees of severity, even those unable to fixate a visual target or to follow instructions during typical sensory-motor and cognitive tasks of neuroimaging studies.

In the past years, eyes-closed resting EEG rhythms in DS patients have shown peculiar features when compared to those of control subjects. With the increase of age, DS patients have presented a general slowing of EEG oscillations (Politoff et al., 1996; Katada et al., 2000). However, there have been some inconsistencies in the features of the dominant EEG rhythms in the resting state condition, namely the alpha rhythms (about 8–12 Hz). On one hand, parieto-occipital alpha waves have been found to be quite low in amplitude and stereotyped in shape in DS subjects (Schlack and Schmidt-Schuh, 1977). Quantitative spectral analysis has pointed to higher power of delta (about 1–4 Hz) or theta (about 4–8 Hz) rhythms and lower power of alpha rhythms in DS subjects compared with matched control subjects (Schmid et al., 1985; Kaneko et al., 1996; Partanen et al., 1996), especially in occipital areas (Ono et al., 1992; Ono, 1993; Babiloni et al., 2009). In DS subjects, a specific power reduction of occipital alpha rhythms has been also associated with cognitive deterioration, visuospatial deficits, decreased attention span, larger third ventricles, and a global decrease in cerebral glucose utilization especially in posterior cortical areas (Visser et al., 1996). On the other hand, it has been reported an increased absolute power in delta and theta (Medaglini et al., 1996) or in all bands in DS subjects compared with control subjects (Politoff et al., 1996). Furthermore, there was a correlation between cognitive performance and the power of theta and alpha rhythms in some cases (Politoff et al., 1996), and no correlation in other cases (Devinsky et al., 1990).

The above inconsistent findings may be due to some differences in the applied EEG methodologies, namely the amount of electrodes, mathematics, and normalization procedures to take into account inter-subjects' variance and head volume conductor effects. To shed light on this issue, here we applied a well-standardized procedure to evaluate the cortical sources of resting state EEG rhythms in patients with cognitive decline, namely the use of low-resolution brain electromagnetic tomography (LORETA; Pascual-Marqui and Michel, 1994). Indeed, this procedure has been successfully used to model cortical sources of resting EEG rhythms in subjects with mild cognitive impairment (MCI) and AD, showing that posterior cortical sources of resting alpha rhythms were lower in amplitude in AD and MCI than healthy subjects (Babiloni et al., 2004, 2006a,b,c,d). In this line, we tested the hypothesis that cortical sources of resting alpha rhythms are lower in amplitude in DS than control subjects.

2. Materials and methods

2.1. Subjects

We recruited 45 DS subjects (25 males, mean age of 22.8 years ± 0.7 standard error of mean, SEM) and 45 age-matched normal control subjects (25 males, mean age of 22.4 years ± 0.5 SEM). All subjects were right-handed. The DS subjects were selected on the basis of the following inclusion criteria: (i) karyotype examination showing trisomy of chromosome 21; (ii) age ranging within 15–34 years; (iii) magnetic resonance imaging (MRI) for suspect of atlo-occipital joint malformation. The exclusion criteria for both DS and control subjects were the following: (i) previous treated medical or psychiatric conditions that might have affected cognition (e.g., hypothyroidism), (ii) history of severe head trauma requiring medical attention, (iii) any neurological disability, psychiatric symptoms or history of epilepsy as revealed by clinical and instrumental routine at the Child Developmental Department of the San Raffaele Pisana Scientific Institute (Rome, Italy). No subject received psychoactive medications at the time of EEG recordings. All participants were classified following diagnostic guidelines recommended by the AAMR-IASSID Working Group for the Establishment of the Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability (Aylward et al., 1997; Burt and Aylward, 2000). These guidelines were based upon current ICD-10 criteria (WHO, 1992). Each case was classified as: (a) non-demented, indicating with reasonable certainty that significant age-associated impairment was absent; (b) MCI-DS status, indicating that there was substantial uncertainty regarding dementia status, with some indication of mild cognitive and/or functional decline but not overt dementia (Jenkins et al., 2008). We discarded DS patients categorized as status uncertain due to complications, indicating that the criteria for possible dementia had been met, but symptoms might be caused by some other substantial concern, usually a medical condition unrelated to a dementing disorder (e.g., severe sensory loss, poorly resolved hip fracture, psychiatric diagnosis). We also discarded DS patients categorized as "indeterminable", indicating that the pre-existing disability was of such severity that detection of decline indicative of dementia was not possible (i.e., multiple handicaps). All the subjects recruited for the present study proved to be non-demented.

The neuropsychological evaluation of Intelligence Quotient (IQ) was performed by means of Wechsler Intelligence Scale for Children-revised (WISC-R; Wechsler, 1982) in a sub-group of 24 DS subjects (the other refused to do it). The Full-scale, Verbal and Performance Intelligent Quotient (FIQ; VIQ; PIQ) scores for the 20 DS subjects who completed the WISC-R were 52.4 ± 2.6 SEM, 52.2 ± 2.1 SEM and 51 ± 3.1 SEM, respectively.

Local institutional ethics committees approved the study. The use of the EEG data for research purposes was performed on the basis of the written informed consent signed by each participant or caregiver before the routine EEG recording, in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the Author's Institutional Review Board. The subjects and caregivers were informed that they could require the interruption of the above clinical and instrumental procedures at any moment. None of them did it.

2.2. EEG recordings

EEG data were recorded (cephalic reference; 0.3–70 Hz bandpass; 256 Hz sampling rate; 5 min) in subjects at wakening resting state (eyes-closed) from 19 electrodes positioned according to the International 10–20 system (i.e., Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). To monitor eye movements, electrooculogram (0.3–70 Hz bandpass) was also collected. The EEG recordings were performed in the late morning in all subjects. The control subjects were requested to be relaxed and to be engaged in no specific mental activity during EEG recording. A special attention was devoted to obtain maximal relaxation and cooperation of the subjects, to obtain high-quality EEG recordings and to avoid well-known effects of stress and anxiety on theta and alpha rhythms. Before EEG recordings, clinical personnel tests if the DS subjects