Cognitive Impairment and EEG Background Activity in Adults With Down's Syndrome: A Topographic Study

Svetla Velikova,¹ Giuseppe Magnani,¹ Claudia Arcari,¹ Monica Falautano,¹ Massimo Franceschi,² Giancarlo Comi,¹ and Letizia Leocani^{1*}

¹Department of Neurology, Clinical Neurophysiology, Neurorehabilitation, Institute of Experimental Neurology-INSPE, IRCCS University Hospital, San Raffaele, Milan 20132, Italy

²Department of Neurology, IRCCS Multimedica, Santa Maria, Castellanza (VA) 21053, Italy

Abstract: *Objective:* Studies correlating electroencephalographic (EEG) data and cognitive performance in Down's syndrome (DS) showed conflicting results. The aims of this study were to investigate the sources of EEG rhythms in adults with DS at three dimensional representation of current source density (CSD) using exact/standard Low Resolution Electromagnetic Tomography (e/sLORETA), and their correlation with cognitive performance. *Methods:* Twenty-five adults with DS underwent a neuropsychological battery and 5 min of resting, eye-closed 29-channel EEG were recorded. After e/sLORETA analysis, data were compared with those from age and gender-matching control subjects as following: absolute and relative power in delta (1–3 Hz), theta (4–7 Hz), alpha1 (8–9 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (19–21 Hz), beta3 (22–30 Hz); alpha and theta bands adjusted to individual alpha peak frequency (IAF). Current source activities in DS group in regions showing significant differences compared with controls underwent correlation analysis with psychometric scores. *Results:* In DS, IAF was shifted to lower frequencies and correlated positively with Wechsler Adult Intelligence Scale and Mini-Mental State examination. Compared with controls, DS showed increased CSD in: theta, alpha-1, and beta1 classical bands and in IAF-adjusted bands, while relative alpha2 was decreased. A negative correlation between cognitive performance and theta/alpha CSD in the right frontal lobe and right posterior cingulate cortex was found. The relative alpha2 correlated positively with cognitive tests. *Conclusions:* Increased CSD in DS, correlating with cognitive performance, for both slow and fast rhythms suggests involving of cortical and subcortical mechanisms. LORETA might be useful for objective measure of cognitive decline in DS. *Hum Brain Mapp* 32:716–729, 2011. © 2010 Wiley-Liss, Inc.

Key words: Down's syndrome; QEEG; e/sLORETA; EEG rhythms

INTRODUCTION

The pathophysiology of cognitive impairment in Down's syndrome (DS), caused by trisomy of chromosome 21, is not completely understood, although converging evidence suggests a strong parallelism with Alzheimer's Dementia (AD). Virtually all subjects with DS develop neuropathological changes similar to those of AD by the age of 40 years [Mann and Esiri, 1989]. Moreover, the prevalence of dementia increases from 11% between ages 40 and 49% to 77% between 60 and 69 [Visser et al., 1997].

*Correspondence to: Letizia Leocani, Department of Clinical Neurophysiology, Hospital of San Raffaele, Via Olgettina 60, Milan 20132, Italy. E-mail: letizia.leocani@hsr.it

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Establishing neurophysiological correlates of cognitive performance in adults with DS might contribute to understand the pathophysiology and an early detection of cognitive decline in these subjects.

The leading EEG abnormalities in DS, according to the literature, have been attributed to alpha oscillations [Devinsky et al., 1990; Kaneko et al., 1996; Katada et al., 2000; Ono, 1993; Ono et al., 1992; Partanen et al., 1996; Politoff et al., 1996; Schmid et al., 1985]. Some authors, however, found parallel with alpha changes in theta [Ono, 1993; Schmid et al., 1985], or in all bands [Politoff et al., 1996], whereas others describe (mainly in demented patients) abnormalities restricted in lower delta and theta frequencies [Medaglini et al., 1997].

Regarding the changes in alpha peak frequency, the existent data are consistent, reporting a marked alpha slowing in DS in comparison with controls [Katada et al., 2000; Ono, 1993; Ono et al., 1992; Partanen et al., 1996; Politoff et al., 1996]. Further, analysis on chronological changes of alpha waves in DS has shown that the slowing in DS starts in the central and frontal regions and later extends to the occipital, in contrast to healthy subjects where the slowing starts in occipital regions while in the central and frontal areas it seems to occur at a higher age [Katada et al., 2000]. These changes seem different from those observed in other forms of mental retardation, with a later onset of alpha rhythm slowing and a slower progression rate [Katada et al., 2000].

Concerning the changes in alpha power, the literature data show ambiguity in results, especially regarding the absolute power. A slight increased absolute alpha in adults with DS in comparison with controls has been reported, in parallel with significant increase in the other frequencies [Politoff et al., 1996]. In contrast, in DS children, a decrease of absolute alpha alone [Kaneko et al., 1996] or in parallel with its relative value [Schmid et al., 1985] has been found. In the latter study, the reduced alpha has been associated with increased absolute power, especially in the theta band. Regarding the relative/normalized alpha in adults DS subjects, no differences have been reported [Politoff et al., 1996].

Also studies searching for correlates between EEG parameters and cognitive performance in DS reported contrasting results. Cognition-related alpha reactivity abnormalities have been reported to eyes opening [Partanen et al., 1996] or to 12 Hz flash stimulations [Politoff et al., 1996]. In young subjects with DS, no correlation between resting EEG and cognitive tests has been reported, whereas in older DS decreased alpha has been associated with dementia and parietal hypometabolism [Devinsky et al., 1990]. Other investigators found a negative correlation between cognitive performance and increased power at 4.5- and 8.8-Hz bins, but not with the total and band-based power [Politoff et al., 1996]. The basis of such uncertainty regarding EEG power and its correlations with cognitive functions is unclear. As mentioned above, alpha slowing in DS has been consistently reported. According to the literature, the application of fixed bands,

ignoring possible peak frequency differences, might contribute to variability of results. Therefore, analysis of alpha subbands on the basis of individual alpha peak frequency (IAF) has been recommended [Doppelmayr et al., 1998; Klimesch, 1999; Moretti et al., 2004]. This issue points to the question as to whether some discrepancies regarding EEG power findings in DS might be a result of application of fixed band, without consideration of the parallel changes in alpha peak frequency. Another possible source of confusion regarding the interpretation of previous literature on EEG power in DS is that in most of the studies absolute or relative power data only have been provided. Therefore, a second question that has to be answered is whether increased absolute alpha power reported in DS would parallel or not corresponding changes in relative/normalized power. Finally, a third question is whether discrepancies in findings concerning correlation with cognition arise from application of classical or narrow frequency bands. In fact, studies concerning alpha on healthy subjects have established that only upper alpha (10–12 Hz) is related to memory performance [Klimesch et al., 1997; Vogt et al., 1998], while the previously reported lack of correlation in DS has been based on a whole alpha band analysis [Politoff et al., 1996].

Summarizing, the abnormalities in alpha oscillations in subjects with DS seems to have a complex character, considering frequency, power, reactivity changes, as well as their topography and temporal evolution. To limit uncertainty, a complex approach for analysis of the data is required. The present EEG study in DS adults is aimed at clarifying these questions by combining different approaches in the analysis of resting EEG: absolute, relative and adjusted to IAF power. In the search for correlation between EEG parameters with psychometric tests, in order to avoid ambiguity, parallel with classical and adjusted to IAF bands, narrow bands were also applied.

This study is based on 3-D analysis of resting EEG activity, which according to our knowledge, has not been applied yet in DS. The link between spatial distribution of brain generators of EEG rhythms and cognitive abilities has been object of several studies [Babiloni et al., 2004, 2006, 2009; Gianotti et al., 2007; Thatcher et al., 2007] mainly using Low Resolution Electromagnetic Tomography (LORETA) method [Pascual-Marqui et al., 1994].

In this EEG investigation, exact/standardized Low Resolution Electromagnetic Tomography (e/sLORETA) method of analysis [Pascual-Marqui, 2002] was applied. The advantages of this newer software version are linked with its higher localizing precision [Greenblatt et al., 2005; Sekihara et al., 2005] and possibility for obtaining the current source density (CSD) in selected regions of interests, providing the option for correlation analysis.

The aims of this study were, using e/sLORETA, to search for: (i) differences in EEG background activity between adults with DS and control subjects; (ii) correlates between EEG background activity and cognitive performance in adults with DS.

SUBJECTS AND METHODS

Twenty-five adults with DS followed in our Institute (19 females; mean age 38, range 30–69 years), all fully right handed as measured by the Edinburgh inventory [Oldfield, 1971] were participated in the study. They were referred to our Memory Centre from patients' association "Vivi Down," Milan. After complete description of the study, written informed consent from patients and their legal representatives was obtained. Additionally, 25 cognitively normal subjects age (mean age 36, range 28–65 years) and gender matched, all right handed, were enrolled to form a control group. All control subjects underwent physical and neurological examinations as well as cognitive screening. Excluding criteria were chronic systemic illness, previous neurological and psychiatric disturbances, and treatment with psychoactive drugs.

Subjects with DS underwent a complete neurological and neuropsychological examination besides neurophysiological testing.

Neuropsychological Examination

Neuropsychological examination was based on a neuropsychological battery of standardized tests including: *Intelligence and deterioration scales*: Mini Mental State examination (MMSE) [Folstein et al., 1975], Wechsler Adult Intelligence Scale (WAIS)-revised, Italian version [Orsini and Laicardi, 1997; Wechsler, 1981]; *Attention and information processing*: Attentive Matrices test [Spinnler and Tognoni, 1987]; *Memory*: Digit Span test [Spinnler and Tognoni, 1987], Rivermead Behavioural Memory (RBM) test [Della Sala, 1990; Wilson et al., 1985], Short story recall [Carlesimo et al., 2002]; *Abstract reasoning*: Raven's Coloured Progressive Matrices [Raven et al., 2003]; *Executive functions*: Token test [De Renzi and Vignolo, 1962; Spinnler and Tognoni, 1987], Semantic Verbal Fluency test [Novelli and Papagno, 1986], *Constructive Praxis*: Geometric shape copy with or without program elements [Caltagirone et al., 1995].

EEG Recording

The EEG (5 min rest with the eyes closed) was recorded with 29 scalp electrodes mounted on an elastic cap (Electro-cap International, Eaton, OH) according to the 10–20 international system plus additional electrodes placed along the longitudinal axis, with binaural reference. The EEG signal was amplified (Synamps amplifiers, Neuroscan Inc., Herndon, VA), filtered (DC to 50 Hz), and digitized (250 Hz sampling frequency). Bipolar recordings of the electrooculogram and of bilateral EMG from the right extensor pollicis brevis (EPB) muscle were obtained to detect eye movement or failure to relax respectively.

EEG Spectral Analysis

During off-line EEG analysis, segments with artifacts were removed by visual inspection of the raw data. The artifact-free 2 sec epochs (at least 70 per subject) underwent Fast Fourier Transform (FFT) analysis and average absolute power (μV^2) for each of the 29 derivations was computed in the 1–30 Hz interval, with 1 Hz steps.

IAF was measured as the frequency displaying the maximum power within alpha band over occipital electrodes (O1 and O2).

Analysis of absolute and relative power based on classical fixed frequency bands has been performed: delta (1–3 Hz), theta (4–7 Hz), alpha1 (8–9 Hz), alpha2 (10–12 Hz), beta1 (13–18 Hz), beta2 (19–21 Hz) and beta3 (22–30 Hz). Percent power [Politoff et al., 1996; Vogt et al., 1998] was calculated as percent value of a segment of 1 Hz, referred to the total power spectrum (1–30 Hz) for each electrode, then, averaged values from all electrodes were obtained.

According to previous literature [Doppelmayr et al., 1998; Klimesch, 1999], additional analysis of the absolute power in theta and alpha bands was performed using frequency bands adjusted to IAF: theta (IAF-6 Hz to IAF-4 Hz); lower alpha1 (IAF-4 Hz to IAF-2 Hz); lower alpha2 (IAF-2 Hz to IAF); and upper alpha (IAF to IAF +2 Hz). Group effects on IAF was searched using nonparametric Mann-Whitney test, while for correlation analysis between EEG data and psychometric tests in DS Spearman's rank correlation was applied.

e/sLORETA

For source localization analysis, e/sLORETA software package (R. D. Pascual-Marqui, The KEY Institute for Brain-Mind Research, Zurich, Switzerland) was used. The e/sLORETA is a method [Pascual-Marqui, 2002] for estimating the localization of cortical generators, performing source localization in 6,239 cortical gray matter voxels sized 5 mm^3 rather than 7 mm^3 offered by the previous LORETA version [Pascual-Marqui et al., 1994]. The solution space of e/sLORETA is defined via a reference brain from the Brain Imaging Center at the Montreal Neurological Institute (MNI). Computations were made in a realistic head model using for inverse solution the electric potential lead field computed with boundary element method [Fuchs et al., 2002], applied to the MNI152 template [Mazziotta et al., 2001]. The cortical surface used by e/sLORETA is based on Van Essen average cortex [Van Essen, 2005]. The software reports MNI coordinates [Jurcak et al., 2007]. Anatomical labels as Brodmann areas are reported using an appropriate correction from MNI to Talairach space [Brett et al., 2002]. Therefore, e/sLORETA images represent the electric activity at each voxel in neuroanatomic Talairach space [Talairach and Tournoux, 1988] as the squared standardized magnitude of the estimated current density. Using e/sLORETA, source localization was provided on the basis of fixed (for absolute and relative

TABLE I. Correlation values (Spearman's rank r) between qEEG data and psychometric scores in DS subjects

qEEG measures		WAIS_T	MMSE	RBM
IAF		0.437 (0.029)	0.444 (0.026)	
Maximal alpha power		-0.427 (0.033)		-0.438 (0.028)
Adjusted frequency bands	BA 9-R theta	-0.432 (0.031)		
	BA 6-R theta			-0.414 (0.039)
Fixed frequency bands	BA 9-R theta	-0.418 (0.038)		
	BA 9-R alpha1			-0.406 (0.041)
	BA 10-R theta	-0.431 (0.032)		
	BA 31-R theta	-0.462 (0.020)		
	BA 31-R alpha1	-0.421 (0.035)		
Relative power	alpha2-averaged	0.438 (0.028)		
	alpha2-occipital	0.399 (0.048)	0.401 (0.047)	

The data obtained by e/sLORETA are presented according to Brodmann area (BA) and side (R: right) for different EEG bands only significant values ($P < 0.05$) are shown. P values are in parentheses. WAIS_T, Wechsler adult intelligence scale (total score); MMSE, mini mental state examination; RBM, Rivermead behavioural memory test.

power) and adjusted to IAF frequency bands. To evaluate the general quality of e/sLORETA solution, initially a grand average of cortical sources of fixed and adjusted bands has been obtained. The software was then used to perform voxel-by-voxel between-group comparisons of the current density distribution applying nonparametric statistical analyses [statistical nonparametric mapping (SnPM)] employing a log- F -ratio statistic for independent groups. The results correspond to maps of log- F -ratio statistics for each voxel for corrected $P < 0.05$. The SnPM methodology corrects for multiple comparisons and does not require gaussianity assumptions [Nichols and Holmes, 2002].

Brodmann areas showing significant differences between DS and controls were selected. CSD in each selected BA was measured applying ROI analysis option. The obtained values were used for correlation analysis (Spearman's correlation test) with data from cognitive test performance.

Statistical Analysis for Comparison With LORETA Solution

To verify the sensitivity of e/sLORETA analysis a parallel statistical analysis using EEG data was provided. The scalp electrodes were subdivided into five groups for the following regions: frontal (Fp1, Fp2, F3, F4, F7, F8, Fz, FCz, FC3, FC4, FT7, and FT8), central (C3, C4, CZ, CPz, CP3, and CP4), parietal (P3, P4, Pz), temporal (T3, T4, T5, T6, TP7, and TP8), and occipital (O1 and O2).

Repeated measures ANOVA were applied using the factors Group (DS, Controls; independent variable), Region (frontal, central, parietal, temporal, occipital) and Band. The last factor includes according to the using approach diverse bands as follow: (i) for absolute/relative power: delta, theta, alpha1, alpha2, beta1, beta2, and beta3; (ii) for testing adjusted to IAF bands: theta, lower alpha1, lower alpha2, and upper alpha. The presented " P " values are obtained after Greenhouse-Geisser correction. Subsequent two-tailed Student's t -tests for unpaired data were used as post hoc comparisons ($P < 0.05$).

RESULTS

Alpha Peak Frequency

EEG

The average value of IAF peak was significantly lower in DS (9.3 ± 1.1 Hz) compared with controls (10.24 ± 1.2 Hz) [Mann-Whitney test; $z = -2.830$ ($P = 0.005$)]. WAIS-total and MMSE correlated positively with IAF. (Table I). WAIS and RBM were negatively correlated with the absolute value of maximum occipital alpha power (Table I).

Analysis of Absolute Power in Fixed Bands

Grand-average LORETA analysis showed a maximum in alpha1 in occipital regions for both controls and DS groups (Fig. 1).

When compared with controls (LORETA statistic), individuals with DS showed significantly increased CSD in theta (4–7 Hz), alpha1 (8–9 Hz), and in beta1 (13–18 Hz) frequency bands (Fig. 2, Table II). Differences in Beta1 band were predominately in the Right hemisphere, whereas for theta and alpha1 bilateral changes were observed. The WAIS values correlated negatively with current source densities in right frontal lobe (BAs 9, 10) and right posterior cingulate cortex (PCC) (BA 31) (Table I). CSD in right BA9 additionally showed a negative correlation with RBM score (Table I).

Statistical analysis of EEG data showed statistically significant interaction among the factors Group, Band, Region [$F_{(24,1,152)} = 3.214$; ($P = 0.021$)]. Figure 3 presents the mean regional power in different bands and statistical differences between groups.

The absolute power was significantly higher in DS subjects than in Controls, with differences dispersed in different regions for the different bands.

Correlation analysis based on narrow bands of 1 Hz showed a negative correlation between absolute occipital

Figure 1.

Grand average of e/sLORETA solutions (current density at cortical voxels) modeling cortical sources of fixed bands (delta, theta, alpha1, alpha2, beta1, beta2, and beta3) in cognitive normal ($n = 25$) and Down's syndrome ($n = 25$) subjects. The power estimates were scaled based on the averaged maximum value in normal subjects (alpha1 power value in occipital region). Max = 7.86×10^{10} (LORETA units).

power at 2, 3, and 7–9 Hz and cognitive tests performance (Table III).

Analysis of the Absolute Power in Adjusted to IAF Bands

Grand average based on IAF showed an occipito-parietal distribution of alpha with maximum in upper alpha band for control group, while in DS group the maximum, with higher values that in controls, was present in the lower alpha2 band (Fig. 4).

Compared with Controls (e/sLORETA-statistic), individuals with DS showed significantly increased CSD in all studied adjusted frequency bands. While in theta and lower alpha, the differences were found over the all brain regions, in upper alpha the differences were limited more anteriorly (Fig. 5, Table IV).

A negative correlation between WAIS and CSD in right BA9 (in theta) was found (Table I).

Repeated measures ANOVA showed significant interaction on the basis of factors Group, Band, and Region [$F_{(12,576)} = 3.439$; ($P = 0.035$)]. The mean regional power (adjusted to IAF) according to band as well as the significant differences between groups are presented in Figure 3. Absolute power for theta and alpha bands adjusted to IAF was significantly increased in DS.

Analysis of Relative Power

The maximum values of relative alpha power as localized by averaged e/sLORETA maps were found in alpha1 for DS and alpha2 for Controls (Fig. 6). e/sLORETA statistics showed significant between-groups difference for relative alpha2 band, with decreased CSD in cingulate cortex

(BA 23 and 24 bilaterally and right BA31) in DS subjects (Fig. 7). No correlation was found between regions with decreased relative alpha2 (as from e/sLORETA) and psychometric tests. Repeated measures ANOVA showed significant interaction on the basis of factors Group, Band, and Region [$F_{(24,1152)} = 9.299$; ($P < 0.0001$)]. A significant difference was found for relative alpha2 [$F_{(1,48)} = 23.121$; ($P < 0.0001$)], which was decreased in DS, but not for other bands (Figs. 8 and 9).

Figure 2.

Significant differences in current density between DS ($n = 25$) and control ($n = 25$) groups analyzed for absolute power in fixed bands. Images from e/sLORETA applying statistical non-parametric mapping (log-F-ratio statistic for independent groups) represented only for bands showing significant group differences. Maps indicate significant absolute power increase in DS vs. controls; red: $0.05 > P > 0.01$; yellow: $P < 0.01$.

TABLE II. Regions with significant absolute power increase in DS ($n = 25$) vs. control ($n = 25$) subjects at e/sLORETA analysis on fixed EEG bands

Lobe	Region	Theta	Alpha 1	Beta 1
Frontal	Anterior cingulate	24(R)		24(B), 32(B)
	Inferior frontal gyrus	9(B), 44(B), 45(R), 46(R), 47(R)	9(B), 44(R), 45(R), 46(R), 47(R)	9(R), 46(R), 47(R)
	Medial frontal gyrus	10(B)	10(B)	10(B), 25(B)
	Middle frontal gyrus	6(B), 11(R)	6(B), 8(R), 11(R)	6(B), 11(R)
	Paracentral lobule	5(B)	5(L)	
	Precentral gyrus	4(B)	4(R)	4(B)
Temporal	Inferior temporal gyrus	20(R)		
	Insula	13(B)	13(R)	13(R)
	Middle temporal gyrus		21(B), 37(L)	
	Parahippocampal gyrus	34(B)		34(R)
	Superior temporal gyrus	22(B), 38 (R), 42(R)	22(L), 38(R), 42(R)	38(R)
	Uncus	28(R)		28(R), 36(R)
Parietal	Cingulate gyrus	23(R), 31(B)		
	Postcentral gyrus	1(B), 2(B), 3(B), 40(B)	1(R), 2(R), 3(R), 40(R), 43(R)	1(R), 2(R), 3(R)
	Precuneus	7(L)	7(R)	

For each band, significant different ($P < 0.05$) Brodmann areas are indicated according to region and side (R, right; L, left; B, bilateral).

Figure 3.

Average absolute EEG power in μV^2 (mean + SE) for adjusted and fixed bands in DS and control groups in different bands and regions. Controls: squares, continuous line; DS: circles, dotted line. Rectangles indicate significant differences (post hoc unpaired Student's t test: $P < 0.05$) between controls and DS.

TABLE III. Correlation values (Spearman's rank r) between absolute and relative (percent) power in narrow frequency bands (1 Hz) and cognitive tests performance in DS subjects

Hz	Absolute occipital power		Percent power				
			Averaged		Occipital		
	RBM	WAIS_T	MMSE	WAIS_T	RBM	MMSE	WAIS_T
2 Hz	−0.411 (0.041)						
3 Hz	−0.429 (0.033)						
7 Hz	−0.411 (0.041)	−0.479 (0.015)		−0.412 (0.041)			
8 Hz	−0.423 (0.035)	−0.477 (0.016)		−0.427 (0.033)			
9 Hz	−0.407 (0.044)	−0.423 (0.031)					
11 Hz				0.529 (0.007)		0.408 (0.043)	0.459 (0.021)
12 Hz			0.500 (0.011)	0.728 ($P < 0.0001$)	0.435 (0.030)		0.465 (0.019)

Only significant values ($P < 0.05$) are presented. P values are in parentheses. WAIS_T, Wechsler adult intelligence scale (total score); MMSE, mini mental state examination; RBM: Rivermead behavioural memory test.

The average values of relative alpha2 (obtained by averaging of all channels) and its occipital values correlated positively with cognitive performance (Table I). Correlation analysis provided on the basis of percent power established a negative correlation between power at 7 and 8 Hz and positive one at 11 and 12 Hz with cognitive tests. The most significant values were found for 12 Hz (Table III).

DISCUSSION

Alpha Peak Frequency

Slowing of alpha background frequency in DS, as found in this study, has been consistently reported in DS [Devinsky et al., 1990; Katada et al., 2000; Ono, 1993; Ono et al., 1992; Partanen et al., 1996; Politoff et al., 1996] and found in parallel with enlarged third ventricles [Devinsky et al., 1990]. Results regarding alpha changes have been attributed to possible thalamic atrophy, leading to loss of normal alpha background, while enlargement of the ventricles has been hypothesized to be related to thalamic degeneration [Devinsky et al., 1990]. Additionally, here a link between alpha slowing and cognitive performance was found. The shifting of the alpha peak to lower frequencies in DS, together with increased power source density for the same frequency range, is in agreement with previously reported inverse relationship between IAF and amplitude of alpha rhythm at rest [Koch et al., 2008].

Absolute Power

Absolute power was significantly increased for theta, alpha1, and beta1 bands. Similar findings increased absolute power in all band has been reported by other authors also [Politoff et al., 1996], although the increased alpha was not significant. Difference concerning alpha results may partially be ascribed to subdivision of alpha, since in the present study increased alpha was found only in alpha1, effect

that could be masked if alpha is studied as a whole band as in the study by Politoff et al. [1996]. In the latter study, no correlation with increased power was found when considering the whole bands, but in very narrow bands a correlation at 4.5- and 8.8-Hz bins has been found (the last value falls in the range of our alpha1, where we also found correlation). Moreover, results from the latter study are in line with our findings based on narrow bands as well.

Increased absolute alpha and theta in DS are likely to have multifactor nature with anatomical-, biochemical-, hemodynamical-, and oscillatory-based contribution. Increased absolute power is unlikely to be explained with Alzheimer-type neuropathology changes, since in AD subjects it has been consistently reported as decreased [Knott et al., 2001; Schreiter-Gasser et al., 1994; Strik et al., 1997], as well as alpha amplitude in demented subjects with DS [Devinsky et al., 1990].

It is difficult to ascribe our finding of increased absolute power in DS to possible augmented conductivity as result of atrophy and enlarged third ventricles, found in some subjects with DS [Devinsky et al., 1990], as enlarged third ventricles have been associated with decreased alpha in older subjects and no significant alpha amplitude changes in young subjects [Devinsky et al., 1990]. Another explanation for increased absolute power is that this phenomenon may result from increased oscillatory brain activity. The precise anatomical distribution of neuronal generators of alpha rhythm is not clear, but thalamo-cortical and cortico-cortical systems interact in generation of cortical alpha [Steriade et al., 1990]. Concerning the generation of theta, thalamic mechanism have been supposed, although other structures such as hippocampus and other limbic structures could also contribute to theta activity [Steriade et al., 1990].

On the basis of noninvasive EEG recording techniques, it has been supposed that frontal alpha and theta are generated almost exclusively by superficial radial dipole layers mainly in the gyral crowns of frontal cortex [Srinivasan et al., 2006]. The latter study also reported that frontal alpha and theta receive control from nonlocal source activity. On the other hand, it has been suggested that the

Figure 4.

Grand average of e/sLORETA solutions (current density at cortical voxels) modeling LORETA sources of adjusted bands according to individual alpha frequency (theta, lower alpha1, lower alpha2, and upper alpha) in cognitive normal ($n = 25$) and DS ($n = 25$) subjects. The power estimates were scaled based on the averaged maximum value in normal subjects (upper alpha power in occipital region). Max = 6.98×10^2 (LORETA units).

thalamus has an important role not only in cortico-subcortical circuits, but also in cortico-cortical communications and might play a role of “driver” on cortico-cortical signals with capacity to reinforce them [Guillery, 1995; Guillery and Sherman, 2002; Sherman and Guillery, 1998]. Taking into consideration that changes in thalamus in DS have been reported [Haier et al., 2008; White et al., 2003], it seems reasonable to expect a contribution of thalamo-cortical mechanisms leading to increasing synchronization of dipoles in lower alpha and theta.

Another possible explanation for increased alpha in DS might be linked with a metabolic hypothesis. An inverse relationship between alpha power and cortical perfusion or metabolism has been demonstrated using co-registration methods of EEG with measures of blood flow and metabolism [Feige et al., 2005; Goldman et al., 2002; Goncalves et al., 2006; Moosmann et al., 2003; Ritter et al., 2009]. Observations on brain metabolism in DS are not univocal, having been reported as decreased [Dani et al., 1996; Pietrini et al., 1997] and increased [Haier et al., 2003]. Nevertheless, it has been suggested that this apparent discrepancy may be related to the degree of cognitive involvement in the subjects included and to corresponding compensation mechanisms [Haier et al., 2008].

Recently combined EEG/PET studies established positive correlations between current density of theta and glucose metabolism in the ACC and in the right fronto-temporal regions [Pizzagalli et al., 2003]. Furthermore, simultaneous EEG-fMRI recordings provided evidence that theta from surface recordings is associated not only with activity of the cingulate cortex, but also in frontal, insular, superior temporal and parietal areas and hippocampus [Sammer et al., 2007]. The importance of hippocampal pathology in DS has been recognized. Morphological studies reported reduced grey matter volume of hippocampus

Figure 5.

Significant differences in current density between DS ($n = 25$) and control ($n = 25$) groups analyzed for bands adjusted to IAF (theta, lower alpha1, lower alpha2, and upper alpha). Images from e/sLORETA statistical nonparametric mapping (log-F-ratio statistic for independent groups). Maps indicate significant absolute power increase in DS vs. controls; red: $0.05 > P > 0.01$; yellow: $P < 0.01$.

TABLE IV. Absolute power analysis on the basis of adjusted bands using e/sLORETA

Lobe	Region	Theta	Lower alpha 1	Lower alpha 2	Upper alpha
Frontal	Anterior cingulate	24(B), 32(R)		24(B)	24(B), 32(B)
	Inferior frontal gyrus	9(B), 44(B), 45(B), 47(R)	9(B), 44(B), 45(R), 47(R)	9(B), 44(R), 45(R), 46(R), 47(R)	9(B), 44(R), 46(R), 47(R)
	Medial frontal gyrus	10(B)	10(R)	10(B)	10(B)
	Middle frontal gyrus	8(B), 11(B)		8(B)	8(R)
	Paracentral lobule	5(R)			
	Precentral gyrus	4(B), 6(B)	4(B), 6(B)	4(R), 6(B)	6(B)
Temporal	Inferior temporal gyrus	20(R)			
	Insula	13(B)	13(B)	13(B)	
	Middle temporal gyrus	21(R)	21(R), 39(R)	21(R)	
	Parahippocampal gyrus	34(R)	34(B), 35(R)	34(R)	
	Superior Temporal gyrus	22(B), 38(B), 42(B)	22(B), 38 (B)	22(B)	
	Uncus	28(R)		28(B), 36(R)	
Parietal	Cingulate gyrus	23(B), 31(B)	31(B)	23(R)	
	Postcentral gyrus	1(B), 2(B), 3(B), 40(B), 43(B)	1(R), 2(B), 3(R), 40(R)	1(R), 2(B), 3(B)	
	Precuneus	7(L)	7(B)		
Occipital	Cuneus	18(L), 19(L)	18(L), 19(L)		

Regions with significant power increase in DS ($n = 25$) vs. control ($n = 25$) subjects. For each EEG band, significant different Brodmann areas are indicated according to region and side (R, right; L, left; B, bilateral).

[Haier et al., 2008; Krasuski et al., 2002; Raz et al., 1995; Teipel et al., 2003; White et al., 2003] and dysfunction in its region has been linked with long term memory deficit in DS [Krasuski et al., 2002; Pennington et al., 2003].

The present data are in line with a combined MRI-SPECT-EEG study in pediatric DS [Aydin et al., 2007], reporting hypoperfusion, in cases with lower IQ, mainly in the right fronto-parieto-temporal regions and following by delta and theta paroxysms in EEG. An analogy could be made with the present study, with: (i) increased alpha could be an equivalent of hypoperfusion; (ii) heaviest involvement of the right hemisphere; (iii) similar topographic distribution of changes.

Increased beta1 activity in DS compared with controls could be interpreted in terms of “neurotransmitter hypothesis,” since cortical oscillations in beta frequencies (13–35 Hz) seem to be modulated by GABA [Jensen et al., 2005]. It has been reported that GABA-ergic agonists such as benzodiazepines increase the expression of beta oscillations over rolandic areas [Jensen et al., 2005]. In this view, the present finding of increased beta over the sensorimotor cortex may be consistent with reported motor slowing in DS subjects [Palisano et al., 2001]. The contribution of metabolic changes could also be considered, since an inverse relationship between metabolic rate and beta rhythms -along with α -in primary somatosensory and motor cortex in healthy subjects has been reported [Ritter et al., 2009].

Adjusted to IAF Theta and Alpha Absolute Power

LORETA findings on the basis of adjusted to IAF bands showed in theta and lower alpha (1 and 2) diffuse

changes (increased source density), similar to findings in fixed theta band, while changes in upper alpha were close to the fixed alpha1 band. These results could elucidate the apparent ambiguity between increased absolute alpha power found here and the reported decrease in some studies on children with DS [Kaneko et al., 1996; Schmid et al., 1985]. Decreased absolute alpha has been reported in association with alpha slowing and increased power in other bands [Kaneko et al., 1996]. A parallel increase of theta and decrease of relative alpha has also been found, possibly in relation to alpha slowing [Schmid et al., 1985]. However, a direct comparison between the above mentioned studies and our findings is

Figure 6.

Grand average of e/sLORETA solutions (current density at cortical voxels) modeling cortical sources of relative power in DS ($n = 25$) and control ($n = 25$) subjects. The power estimates were scaled based on the averaged alpha1 relative power value in control subjects. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Figure 7.

e/sLORETA statistical nonparametric mapping (log-F-ratio statistic for independent groups) of significant group differences in relative alpha2 current density between DS ($n = 25$) and control ($n = 25$) subjects. Maps indicate significant ($P < 0.05$) power decrease in DS vs. controls represented in blue. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

not possible, considering that both these studies were on children and that EEG analysis was based upon fixed frequency bands.

The present power analysis based on IAF in controls demonstrated occipital maximum in upper alpha, while in DS subjects it was in the low alpha2, showing that alpha changes could not be explained only with changes in peak frequency. As previously shown, several alpha rhythms differing in frequency components may coexist in the occipital cortex [Steriade et al., 1990]. On the other hand, a drop of posterior alpha 2 power has been described in AD [Chiaramonti et al., 1997]. All this considered, a process similar to AD, with drop of posterior high frequency alpha generators, might be hypothesized in DS, contributing to alpha changes found here.

Relative Power

This study found decreased relative alpha2 in DS. As previously discussed, the apparent discrepancy with the lack of such finding in the study by Politoff et al. [1996] could be explained by methodological differences in subdivision of alpha. The decreased alpha2 in DS found here could be the result of slowing of alpha peak frequency, as possibly suggested also by an increase, although nonsignificant, of alpha1. This points again to possible thalamocortical (TC) mechanisms underlying power changes in DS. One of the cellular thalamic mechanisms implicated in the generation of locally synchronised alpha activity is high-threshold (HT) bursting, occurring in a specialized subset of TC neurons [Hughes and Crunelli, 2005]. It has been determined that repetitive HT bursting in TC neurons

Figure 8.

Relative power distribution (mean $\pm$ SE) in different bands for DS subjects ($n = 25$; black columns) and control ($n = 25$; gray columns) subjects. Asterisk indicates significantly decreased relative alpha2 in DS vs. controls (post hoc unpaired Student's t test: $P < 0.05$).

Figure 9.

Amount of relative alpha2 in DS $n = 25$ and control $n = 25$ subjects over selected regions. Controls: squares, continuous line; DS: circles, dotted line. Rectangles indicate significant differences (post hoc unpaired Student's t test: $P < 0.05$) between controls and DS.

occurs in the range of 2 to 13 Hz and that there is a precise link between increasing depolarization and the generated frequency. In this way, a lower depolarization in the same cellular components might lead to generation of theta frequencies. It might be speculated that a similar mechanism, more evident in the right hemisphere where most changes in absolute power were found, could underline both the slowing of alpha (together with decreased relative alpha2 and increase relative alpha1) and the excess theta found in the present study, (which occur approximately over the same regions).

The analysis based on narrow frequencies showed a positive correlation between percent power at 11 Hz and, more prominently, 12 Hz and cognitive performance, consistently with findings in healthy subjects [Vogt et al., 1998]. This may favor the hypothesis about possible insufficiency of high frequency occipital alpha oscillatory systems in DS. A possible dysfunction in 12 Hz oscillations system has been supposed in adults with DS [Politoff et al., 1996] and in AD [Politoff et al., 1992], where response to 12 Hz flash has been reduced and correlated with cognition. It has been hypothesized that 12 Hz oscillatory system insufficiency is linked to Alzheimer-type neuropathological changes [Politoff et al., 1992] and this could possibly represent a link between DS and AD. On the other hand, subjects with DS have neuropathological predisposition for AD [Wisniewski and Rabe, 1986] leading to a possible earlier dysfunction of high α -oscillation system with respect to the slower alpha, which may in contrast be enhanced.

Taking together, on the basis of the present findings, two different mechanisms of oscillatory-based regulation of cognitive functions in adults with DS may be hypothesized. The first, linked with thalamo-cortical dysfunction and leading to increased absolute power, parallels with alpha slowing. The second involves high frequency (around 12 Hz) alpha oscillations, or more precisely the resulting "quota" of 12 Hz among other frequencies. Finally, cognitive performance could be supposed as influenced by the interaction between both mechanisms.

An indirect evidence that in young age and before onset of dementia the oscillatory changes are not linked only with neuropathological changes of Alzheimer type, is the known discrepancy between age of onset of Alzheimer-type neuropathology changes and the onset of dementia in DS. It has been shown that the severity of dementia correlates with that of pathological changes, but correlations have been imperfect, suggesting only contributory, but not causal relationship to dementia [Wisniewski and Rabe, 1986]. Assuming the influence of both oscillatory-based mechanisms on cognitive functions in DS may help explaining a sequential pattern of peak-frequency changes with age, which in DS differs from normal aging [Katada et al., 2000]. The initial slowing in central and frontal regions in adults with DS [Katada et al., 2000], could be hypothesized as linked mainly with thalamo-cortical mechanisms, while later changes involving the occipital

regions would relate with dysfunction of fast alpha oscillation system.

LORETA Findings

Most of the structures, where e/sLORETA detected significant differences between DS and controls in the present study, have been reported as dysfunctional [Haier et al., 2008; Krasuski et al., 2002; Raz et al., 1995; Teipel et al., 2004; Wetter and Murphy, 1999; White et al., 2003; Zucco and Negrin, 1994]. The functional implications of such differences may be interpreted considering the different meaning of increased expression of EEG rhythms.

Together with a positive correlation between alpha peak frequency and cognitive performance, a negative correlation between cognitive abilities and CSD of theta and alpha1 in the right frontal lobe (BA9, 10) and in right PCC-BA31 was also found. Brodmann areas 9 and 10 are parts of the prefrontal cortex, playing role in executive functions, which are known to be impaired in DS [Rowe et al., 2006]. In hemispheric specialization of prefrontal cortex has been established that right prefrontal cortex (BA9) is preferentially associated with coordination of visual spatial memory [Slotnick and Moo, 2006], disturbance in which is an early element of cognitive decline in Alzheimer-type dementia [Liu et al., 1991].

Increasing CSD in BA31 and its negative correlation with WAIS might be viewed in line with findings about metabolic reduction [Minoshima et al., 1997] and structural changes [Zhang et al., 2007] in PCC in a very early stage of AD. The obtained data supports the hypothesis about a possible important role of PCC in learning and memory [Minoshima et al., 1997].

In this study, a moderate dominance of right hemisphere pathology was found, moreover the cognitive performance correlated only with CSD of the structures in the right. Developing of an asymmetric (more prominent in the right) decline in the functions of the hemispheres with aging have been previously reported [Dolcos et al., 2002]. It might be assumed that in DS an accelerated decline of functioning of the right hemisphere occurs.

While the assessment of cognitive performance based on WAIS could provide information only for intelligence as such, providing no information about the presence of cognitive decline, the RBM include prospective memory items and is a sensitive instrument to detect mild memory deficit. Further follow-up studies are needed in order to test such hypothesis.

All the above considered, the correlation between EEG abnormalities and cognitive involvement in this study could be explained in two ways: (i) linked with AD histopathology; (ii) based on disruption of brain bioelectrical activity [Politoff et al., 1996]. Our findings are consistent with this view and provide a possible explanation on how the final result on cognition may be based on the interaction between both factors.

In conclusion, results from this study are in line with the clinical features and findings from structural and biochemical studies in DS, suggesting that e/sLORETA might be a useful tool for the study of DS pathology. Further studies are needed in order to assess its value in predicting future development of cognitive decline and dementia in DS.

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