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Neuropsychological and neurophysiological characterization of mild cognitive impairment and Alzheimer's disease in Down syndrome

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ABSTRACT

Down syndrome (DS) has been considered a unique model for the investigation of Alzheimer's disease (AD) but intermediate stages in the continuum are poorly defined. Considering this, we investigated the neurophysiological (i.e., magnetoencephalography [MEG]) and neuropsychological patterns of mild cognitive impairment (MCI) and AD in middle-aged adults with DS. The sample was composed of four groups: Control-DS (n = 14, mean age 44.64 ± 3.30 years), MCI-DS (n = 14, 51.64 ± 3.95 years), AD-DS (n = 13, 53.54 ± 6.58 years), and Control-no-DS (healthy controls, n = 14, 45.21 ± 4.39 years). DS individuals were studied with neuropsychological tests and MEG, whereas the Control-no-DS group completed only the MEG session. Our results showed that the AD-DS group exhibited a significantly poorer performance as compared with the Control-DS group in all tests. Furthermore, this effect was crucially evident in AD-DS individuals when compared with the MCI-DS group in verbal and working memory abilities. In the neurophysiological domain, the Control-DS group showed a widespread increase of theta activity when compared with the Control-no-DS group. With disease progression, this increased theta was substituted by an augmented delta, accompanied with a reduction of alpha activity. Such spectral pattern—specifically observed in occipital, posterior temporal, cuneus, and precuneus regions—correlated with the performance in cognitive tests. This is the first MEG study in the field incorporating both neuropsychological and neurophysiological information, and demonstrating that this combination of markers is sensitive enough to characterize different stages along the AD continuum in DS.

1. Introduction

Owing to the overexpression of chromosome 21, virtually all Down syndrome (DS) adults would exhibit signs of Alzheimer's disease (AD) neuropathology by the age of 40 years (Ballard et al., 2016), although not all cases would develop clinical symptoms of dementia (Mullins et al., 2013). Hence, DS has been considered a unique model for the investigation of the AD spectrum (Hartley et al., 2015). Notwithstanding, the number of publications devoted to the characterization of predementia stages such as mild cognitive impairment (MCI) in DS is not very extensive (Mak et al., 2017) and, thus, the symptomatology of MCI in DS is not yet clearly defined. Nonetheless, longitudinal studies showed that some neuropsychological tests are sensitive to small changes, not only in

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memory but also in other cognitive functions that are affected in MCI-DS cases (Devenny et al., 2002; Esteba-Castillo et al., 2013). For example, a decrease in episodic memory was found 20 months before the diagnosis of dementia in a DS sample (with mean age 47 years) (Devenny et al., 2002). In addition, DS cases in which MCI is suspected can present subtle losses in other cognitive domains such as visuospatial organization (Devenny et al., 2002), ability to generate new learning (Devenny et al., 2000), visuospatial working memory (Krinsky-McHale and Silverman, 2013), executive problems, as well as changes in personality or behavior (Ball et al., 2008). Regarding the latter, interestingly, symptoms related to prefrontal structures (apathy, lack of cooperation, challenging behavior, etc.) have been also suggested to be the first to appear (Key and Dykens, 2014; Nieuwenhuis-Mark, 2009). Therefore, some discrepancies are observed with regard to the first symptoms that might be considered as indicative of the early stages of dementia in DS.

Neurophysiological techniques (EEG or magnetoencephalography [MEG]) are suitable methods for the investigation in population with intellectual disabilities (IDs) because of their direct measurement of primary neural activity accompanied by a minimal invasiveness (Neale et al., 2018). DS and AD share some basic neurophysiological characteristics, such as the general slowing of EEG oscillations (Politoff et al., 1992), particularly in the alpha peak frequency, which has been consistently reported in EEG studies (Katada et al., 2000; Ono, 1993). For example, DS adults without dementia exhibited an age-related decline in alpha rhythm that appeared at an earlier age compared with healthy adults (Menendez, 2005; Murata et al., 1994). In addition, a reduced alpha power within occipital regions correlated with global cognitive deterioration, decreased attention span, as well as with cerebral atrophy in nondemented adults with DS (Visser et al., 1996). Furthermore, a recent work searching for a link between alpha activity and general cognitive ability, showed an association between high cognitive performance, higher frontal alpha peak amplitude, and higher alpha band power distributed across several brain regions (Hamburg et al., 2019). This pattern seems to be slightly different in DS patients with dementia. For instance, Medaglini et al. (1997) reported an increased power in delta and theta bands, and Salem et al. (2015) confirmed an increased theta band power in DS cases with AD. These results supported the notion, broadly accepted within the field of AD investigation, that a slowing of brain activity correlates with the level of cognitive deterioration and, therefore, might predict the onset of dementia (Prichep, 2007).

Actually, several previous studies have observed a slowing of brain activity correlating with the level of cognitive impairment (Katada et al., 2000; Medaglini et al., 1997; Ono, 1993; Salem et al., 2015; Visser et al., 1996) and that might indeed predict the onset of dementia (Prichep, 2007). Previous reports have successfully used MEG to investigate neurophysiological features in AD and MCI (Nakamura et al., 2018), offering results that are consistent with the EEG findings presented previously (Baillet, 2017; Hari et al., 2000). For instance, a slowing of the background activity in posterior parietal and occipital cortices was associated with the progression from MCI to AD, and allowed the detection of those individuals at risk of conversion (Fernandez et al., 2006; Garces and Lopez-Sanz, 2017; Lopez et al., 2014). Despite its well-demonstrated utility, MEG studies assessing spectral variations in adults with DS are really scarce (Virji-Babul et al., 2007), and no previous investigation has addressed the characterization of MCI or AD in DS population. The aim of the present study was thus to define the neurophysiological (i.e., MEG) and neuropsychological profiles of MCI and AD in adults with DS, to help characterize the different phases of the AD continuum in this population by using this combination of techniques.

2. Methods and materials

2.1. Participants

The DS sample consisted of 41 participants (16 males and 25 females, mean age 49.93 ± 0.60 years) with genetically confirmed karyotype, excluding cases of mosaicism and translocations. Candidates were recruited from the Adult Down Syndrome Unit (La Princesa University Hospital, Madrid, Spain). The DS sample was divided into three groups: (1) DS subjects who did not match the criteria for MCI or AD diagnosis, henceforth called CN-DS group; (2) DS subjects who matched the criteria for MCI (MCI-DS group); and (3) DS subjects who matched the criteria for AD (AD-DS group). In addition, a group of healthy control subjects (CN—no-DS) matched in age and gender with the CN-DS group (4 males and 10 females, mean age 45.21 ± 4.38), and who were free of any significant medical, neurologic, and/or psychiatric disease, was included in the investigation. All DS subjects were aged above 40 years, and presented a mild or moderate level of ID according to DSM-5 criteria (American Psychiatric Association, 2013). To establish the baseline status of intellectual and developmental disabilities, and according to the definition of ID level, all participants were evaluated by means of an IQ test (K-BIT 2) and the Adaptive Behavior Scale (Vineland II) (Sparrow et al., 2008). Participants were not receiving any drug treatment that could interfere with MEG or neuropsychological assessments at the moment of the evaluation, including any antidementia drugs (cholinesterase inhibitors or NMDA antagonists). Individuals showing clinical hypo/hyperthyroidism, uncontrolled B9/B12 vitamin deficiency, delirium, disorders that may show some symptoms that can be confused with cognitive impairment (e.g., depression), and severe uncorrected sensory impairment (auditory or visual), were excluded. The demographic characteristics of the sample are displayed in Table 1.

2.2. Standard protocol approvals, registration, and patient consents

The study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and the protocol was approved by the Clinical Research Ethical Committee of La Princesa University Hospital. Written informed consent was obtained from parents or legal guardians. Verbal or written assent was additionally obtained from DS participants.

2.3. Clinical assessment

An exhaustive clinical and neuropsychological assessment protocol was applied to all DS subjects (see the following). Tests used for cognitive evaluation were especially sensitive to cognitive

Table 1
Demographic characteristics and neuropsychological performance of each group

	Mean ± SD/ #not completed			
	CN—no-DS (n = 14)	CN-DS (n = 14)	MCI-DS (n = 14)	AD-DS (n = 13)
Age	45.21 ± 4.39	44.64 ± 3.30	51.64 ± 3.95	53.54 ± 6.58
Gender	4 M - 10 F	4 M - 10 F	8 M - 6 F	4 M - 9 F
CAMCOG-DS	-	76.64 ± 17.86/0	59.08 ± 15.37/1	56.92 ± 15.91/1
ADVM	-	23.29 ± 10.56/0	18.31 ± 10.73/1	10.00 ± 6.46/0
WM	-	15.58 ± 3.09/2	18.33 ± 4.31/2	21.09 ± 5.07/2
DVM	-	0.86 ± 1.10/0	4.36 ± 4.20/3	7.58 ± 4.32/1
TO	-	47.31 ± 28.35/1	31.62 ± 20.71/1	20.00 ± 23.51/0

Regarding the performance of each group in each test, the number of participants who did not complete a certain test is also presented.
Key: AD, Alzheimer's disease; DS, Down syndrome; CN, control; MCI, mild cognitive impairment; M, male; F, female; WM, working memory; ADVM, auditory delayed verbal memory; DVM, delayed visual memory; TO, temporal orientation.

deterioration in DS (Esteba-Castillo et al., 2013, 2017), and adapted to Spanish-speaking population. All DS participants were evaluated with the Cambridge Cognitive Examination for older adults with Down's Syndrome (CAMCOG-DS) Spanish version (Esteba-Castillo et al., 2013); the temporal orientation (TO), delayed visual memory (DVM), and auditory delayed verbal memory (ADVM) subtests of the Barcelona Test-Intellectual Disability (Esteba-Castillo et al., 2017); the working memory (WM) subtest of the Behavior Rating Inventory of Executive Function-Parents (BRIEF-P) (Gioia et al., 2000); and the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities (CAMDEX-DS-Spanish version) (Ball et al., 2006; Esteba-Castillo et al., 2013). CAMDEX-DS was only utilized as a diagnostic tool. At this point it is important to point that the aforementioned cognitive measures used in the study, with the exception of the CAMDEX-DS, were not used as part of the diagnostic classification (see below for further information on clinical diagnosis), avoiding thus a potential circularity problem.

The diagnosis of MCI and AD was based on expert clinical judgment, as it is recommended in the standard practice for DS (Fenoll et al., 2017; Pujol et al., 2018; Sheehan et al., 2015). To obtain an MCI diagnosis, (1) a report of cognitive impairment by the patient (confirmed by a reliable informant), or a report of cognitive impairment by a reliable informant implying a change from previous capacities; paired with (2) no clinically relevant deterioration in adaptive skills according to CAMDEX-DS informant section, were required. The diagnosis of AD, on the other hand, was established when a patient previously meeting the MCI criteria showed a perceptible deterioration in adaptive skills and presented memory impairment and at least one of the following disorders: aphasia, apraxia, agnosia, or disexecutive syndrome (Fenoll et al., 2017; Pujol et al., 2018). All participants were clinically assessed three times over a 3-year follow-up period. On each assessment, CAMDEX-DS was applied for follow-up diagnosis purposes.

2.4. MEG recordings

All healthy and DS participants adequately tolerated MEG recordings, which consisted in four minutes of eyes-closed resting-state activity. Only one DS subject did not cooperate during his/her first MEG session, and was rescheduled for another day, completing the recording uneventfully. DS patients' MEG recordings were performed by an expert on IDs (JGA). The measurements were acquired at the Center for Biomedical Technology (Madrid, Spain) with an Elekta Vectorview 306-sensor system (102 magnetometers and 204 planar gradiometers). Four coils were used to continuously determine the head position with respect to the MEG helmet, and two electrodes were used to record the ocular activity. The coil position and the subject's head shape were digitalized using a Fastrak Polhemus system. During the recordings, subjects sat inside a shielded room and were instructed to keep still and relax.

Data were anti-alias-filtered (0.1–330 Hz) and digitalized with a sampling frequency of 1000 Hz. The spatiotemporal signal space separation method (Taulu and Simola, 2006), implemented by Neuromag Software (MaxFilter version 2.2, correlation 0.90, time window 10s), was used to remove external noise and to compensate for head movements inside the MEG scanner.

2.5. MEG preprocessing

The recordings were inspected automatically for artifacts using the FieldTrip toolbox (Oostenveld et al., 2011), and the result was confirmed by an MEG expert (RB). Data were segmented in 4-second epochs of continuous artifact-free data, and only subjects with at least 20 segments were kept for further analysis. Finally, considering that after spatiotemporal signal space separation the information contained in the MEG data is highly redundant (Garces and Lopez-Sanz, 2017), only magnetometers' information was selected for analysis.

2.6. Source reconstruction

Source reconstruction was performed over the Montreal Neurological Institute (MNI) template. A homogeneous grid with a spacing of 1 cm was defined over the template. Only sources placed in the cortex were selected from the grid using the Harvard-Oxford probabilistic atlas (Desikan et al., 2006), resulting in 1485 cortical sources clustered in 64 regions of interest. The MNI T1 was segmented using SPM12 algorithm (Ashburner and Friston, 2005) and a realistic single shell surface was defined from brain segmentation. The scalp from the MNI template was linearly transformed to fit the subject's head shape, and volume conductor and grid were transformed accordingly. The forward model was solved with a realistic single-shell model (Nolte, 2003).

Time series of each source location were obtained using linearly constrained minimum variance beamformers (Van Veen et al., 1997). The beamformers were calculated using the covariance matrix of the data filtered from 2 to 45 Hz (Lopez-Sanz et al., 2016) using a finite impulse response filter of order 1800 designed with Hamming window, adding two seconds of real data at each side as padding.

2.7. Spectral analysis

For each source position, a spectral power density map with a spectral resolution of 0.25 Hz was obtained using the method of averaged periodograms. The measured spectrum was divided into the classical bands: delta (2–4 Hz); theta (4–8 Hz); alpha (8–12 Hz); low beta (12–20 Hz); high beta (20–30 Hz); and gamma (30–45 Hz). The relative power was calculated as the ratio of the power in a given band and the total power within the six defined bands, thus ranging from 0 to 1.

2.8. Statistical analysis

The statistical analysis was structured in three phases. First, demographic characteristics and neuropsychological performance were assessed. Gender distribution among groups was compared with a χ^2 test, whereas age distribution was compared with a one-way ANOVA. A nonparametric Kruskal-Wallis statistic was performed for each cognitive test.

Second, the spectral variations in MEG source space were compared using a nonparametric cluster-based permutation test (CBPT) (Bullmore et al., 1999). In the comparison between the CN-DS and the CN–no-DS groups, we used an independent sample *t*-test as basis for CBPT. The differences among DS groups were analyzed by means of an ANCOVA test using age as a covariate. The CBPT addresses the multiple comparison problem for the multiplicity of sources, but not for the multiplicity of frequency bands. Therefore, we also applied a false discovery rate (FDR) correction (Benjamini and Hochberg, 1995) to the cluster significance level, taking into account the six frequency bands and the four between-group comparisons.

Finally, the correlation between significant frequency bands and significant neuropsychological tests was also checked using the CBPT. To avoid that the division in diagnostic groups may lead to a spurious statistical significance, the correlation analyses were performed considering the sample as a whole. The Pearson's linear correlation coefficient and its associated *t*-statistic were used as source-level statistic test. An FDR correction was applied to the

cluster significance level taking into account the two frequency bands and the five cognitive tests.

For all comparisons, we set the number of permutations to 100.000, the source-level significance to 0.05 and the cluster-level significance to 0.05. The FDR was set to 10% (q = 0.1). Statistical analysis was accomplished using FieldTrip software (Oostenveld et al., 2011) and our own MATLAB scripts.

3. Results

3.1. Demographics

The diagnostic groups did not differ in gender (see Table 2). However, a one-way ANOVA indicated that the effect of age was significant; Fisher's least significant difference test was used as post hoc analysis, and all the *p*-values are shown in Table 2. Considering these results, age was included as a control covariate in the subsequent ANCOVA models.

3.2. Between-group comparison of cognitive performance

Table 2 contains the statistical information regarding the between-group comparisons concerning the neuropsychological testing. The AD-DS performance was significantly poorer as compared with the CN-DS group for all tests, as expected. The AD-DS group also showed poorer performance as compared with the MCI-DS group in the WM and ADVM tests. Finally, the MCI-DS group exhibited poorer performance than the CN-DS group in the CAMCOG-DS and DVM evaluations. It is important to note that high standard deviations were observed in some variables (CAMCOG, ADVM, and TO). In addition, a reduced number of subjects did not complete some tests, a fact that should be taken into consideration as a potential contributor to the important variance in some tests as well as for interpretation of results (see Table 1).

Table 2
Statistics, *p* values, and size effects associated with the demographic characteristics and the neuropsychological tests

	General	AD-DS versus CN-DS	MCI-DS versus CN-DS	AD-DS versus MCI-DS
Age				
F	13.2318			
p-value	<.0001	<.0001	.0011	NS
η^2	0.4105			
Gender				
χ^2	2.9466	-	-	-
p-value	.2292	-	-	-
Cramer's V	0.2681	-	-	-
CAMCOG-DS				
K	9.2439			
p-value	.0098	.0069	.0121	NS
η^2	0.2012			
WM				
K	7.1763			
p-value	.0276	.0075	NS	.02127
η^2	0.1618			
ADVM				
K	11,3784			
p-value	.0034	.0008	NS	.0358
η^2	0.2535			
DVM				
K	16.1946			
p-value	.0003	<.0001	.0480	NS
η^2	0.4175			
TO				
K	7.8776			
p-value	.0194	.0050	NS	NS
η^2	0.1633			

In the post hoc comparison, *p* values lower than .05 are presented. Otherwise, the result is marked as Not Significant (NS).
Key: AD, Alzheimer's disease; DS, Down syndrome; CN, control; MCI, mild cognitive impairment; WM, working memory; ADVM, auditory delayed verbal memory; DVM, delayed visual memory; TO, temporal orientation.

3.3. Between-group comparison of relative power values

Overall, an intuitive view of Fig. 1 indicates that DS individuals, particularly in the MCI-DS and AD-DS groups, are characterized by a slowing of the spectra and a power increase in the low-frequency bands. The detailed *p*-values and other statistical information of the between-group comparison are displayed in Table 3.

3.3.1. Control–Down syndrome versus control–no-Down syndrome

Results showed a statistically significant increase in theta band power within the CN-DS group when compared with the CN–no-DS group. These differences were found widespread, but they appeared as especially significant in the superior parietal cortex, the superior occipital cortex and the superior temporal gyrus (see Fig. 2A).

3.3.2. Alzheimer's disease–Down syndrome versus control–Down syndrome

Results indicated a statistically significant increase in delta band power within the AD-DS group in comparison with the CN-DS participants. These differences were found widespread, but with a clearer pattern in the left middle temporal gyrus, the left postcentral gyrus and the inferior part of the precuneus. In addition, a statistically significant decrease in alpha band power was observed within the AD-DS group. Such differences were of particular significance in the right temporal cortex and left middle occipital cortex (see Fig. 2B).

3.3.3. Alzheimer's disease–Down syndrome versus mild cognitive impairment–Down syndrome

The AD-DS group was characterized by a significant decrease of alpha power when compared with the MCI-DS group. These differences were of particular significance in the cuneus and the entire occipital cortex (see Fig. 2C).

3.3.4. Mild cognitive impairment–Down syndrome versus control–Down syndrome

Results showed a statistically significant increase in delta band power within the MCI-DS in comparison with the CN-DS group. Such differences were found widespread, but the significance level was higher in both anterior temporal cortices and in the medial superior frontal cortex (Fig. 2D).

3.4. Linear correlations between cognitive performance and relative power values

The detailed information on linear correlations (including coefficients and *p*-values) is displayed in Table 4. As it was partly expected, an increased delta accompanied by a decreased alpha power correlated with poorer cognitive performance. Such association was statistically significant in WM and DVM tests (Fig. 3A and Fig. 3B). The positive correlation with delta band and the negative correlation with alpha band are explained by the fact that higher scores in these two tests indicate an impaired performance. On the contrary, because higher scores of the ADVM test indicate better cognitive status, the sign of the correlation with delta power was negative (Fig. 3C). Similarly, a positive correlation was found between alpha power, CAMCOG-DS, and TO scores, indicating that an increased power within this band was associated with better performance in both tests (Fig. 3D and E). Crucially (see Table 4 and Fig. 3), the

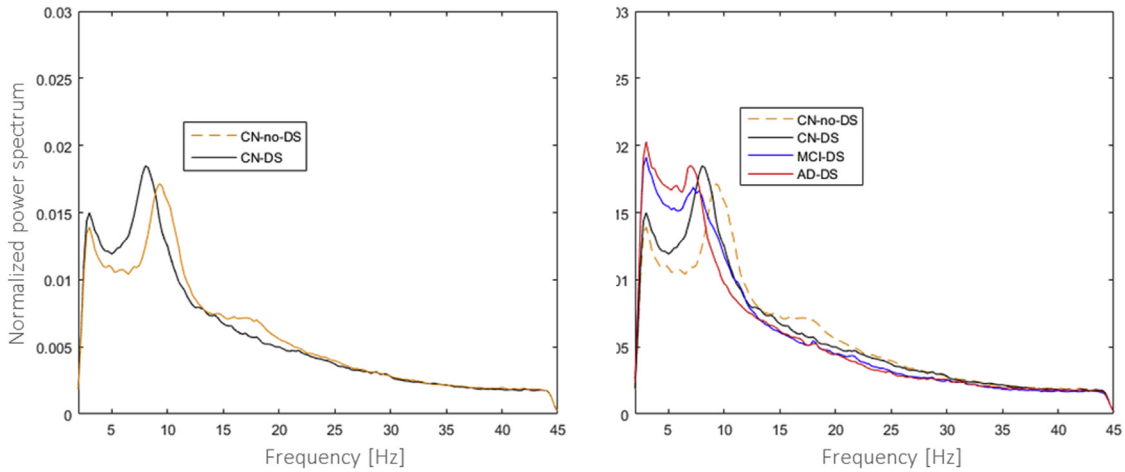

Fig. 1. Power spectrum of each diagnostic group. On the left, the mean power spectrums of the CN-DS and CN—no-DS groups. On the right, the mean power spectrums of all groups. Abbreviations: DS, Down syndrome; CN, control; MCI, mild cognitive impairment.

regional distribution of the previously described correlations showed a quite stable pattern. In summary, an increase of delta accompanied by a reduction of alpha power in occipital, posterior temporal, cuneus, and precuneus was associated with impaired performance in WM, ADVM, DVM, and TO tests. On the contrary, CAMCOG-DS exhibited a particular behavior because its positive correlation with alpha power showed a more anterior distribution.

4. Discussion

By using both neuropsychological and neurophysiological methods, the present investigation was able to shed light on the characteristics of the different stages of AD in adults with DS, with important findings and conclusions to add to this field. First, we found that the source analysis of spontaneous brain activity was sensitive not only to differentiate CN-DS cases from healthy controls, but also to identify the progression of cognitive deterioration in the MCI and AD stages of DS. Second, the utilized neuropsychological protocol was also sensitive to determine cognitive features at different stages of the AD spectrum in DS. Moreover, neurophysiological and neuropsychological measures showed significant correlations that allowed a better understanding of the disease. To the best of our knowledge, this is the first study addressing these issues with the simultaneous use of these techniques in the research field of DS.

Table 3
Spectral analysis results

Bands	Relative power		
	Value (mean ± SD)	Cluster size (#sources)	*p* value
Delta		1238	.0001*
AD-DS	0.1207 ± 0.0082		
CN-DS	0.0872 ± 0.0118		
MCI-DS	0.1184 ± 0.0132	1223	.0010*
CN-DS	0.911 ± 0.0124		
Theta		1066	.0008*
CN-DS	0.2244 ± 0.0147		
CN—no-DS	0.1715 ± 0.0102		
Alpha		794	.0106*
AD-DS	0.1810 ± 0.0311		
CN-DS	0.2340 ± 0.0567		
AD-DS	0.2087 ± 0.0204	328	.0481
MCI-DS	0.2615 ± 0.0302		

Key: FDR, false discovery rate; AD, Alzheimer's disease; DS, Down syndrome; CN, control; MCI, mild cognitive impairment.
The relative power results are grouped with respect to the frequency band and the comparison group. For each result, the value of the relative power in the significant cluster, the number of cortical sources in the significant cluster, and the cluster significance level is presented. For the sake of clarity, only the (uncorrected) significant results are presented. An asterisk (*) indicates that the comparison survived FDR correction.

4.1. Neuropsychological characterization

As briefly described in the introduction section, there are few neuropsychological studies that characterized MCI in DS (Jenkins et al., 2012). According to our results, the MCI-DS group showed an intermediate performance in all neuropsychological tests, with poorer scores when compared with the CN-DS group, but reaching statistical significance only for the CAMCOG-DS and DVM tests. Thus, a significant deterioration in CAMCOG-DS and DVM scores, along with a slight impairment in domains such as TO, WM, and ADVM, might be considered a potential cognitive marker of MCI in DS. On the other hand, the AD-DS group showed a significantly poorer performance in ADVM and WM when compared with the MCI-DS group. CAMCOG-DS, DVM, and TO scores also evidenced a poorer—but not significant—impaired performance in this group. Consequently, our findings suggest that the transition from MCI to AD in individuals with DS is characterized by a worsening in global cognition, an increase in temporal disorientation and, especially, by a marked amnesic deficit. The AD-DS group exhibited a loss of the ability to consolidate verbal and visual information, with difficulties not only in the codification but also in the retrieval of the given material. In addition, they displayed a deterioration of complex memory processes involved in executive functions. These findings are in line with a recent study that characterized the clinical onset of AD in DS by means of its cognitive semiology (Firth and Startin, 2018), in which its authors claimed that changes in memory and orientation may be crucial to detect the progression to AD but could be masked by the inherent cognitive profile of the DS phenotype. Thus, as previously proposed, these changes could only be detected by highly sensitive tests in exhaustive neuropsychological evaluations (Dekker et al., 2018; Esteba-Castillo et al., 2013, 2017; Garcia-Alba et al., 2017).

Notably, although the sample was balanced at the baseline in terms of cognitive performance to avoid a high intragroup variability, we found elevated standard deviations in some variables. Such pattern was in line with the typical high cognitive variability of the DS phenotype observed in several previous studies, although the cause of this variability is still unknown (Rosser et al., 2018; Tsao and

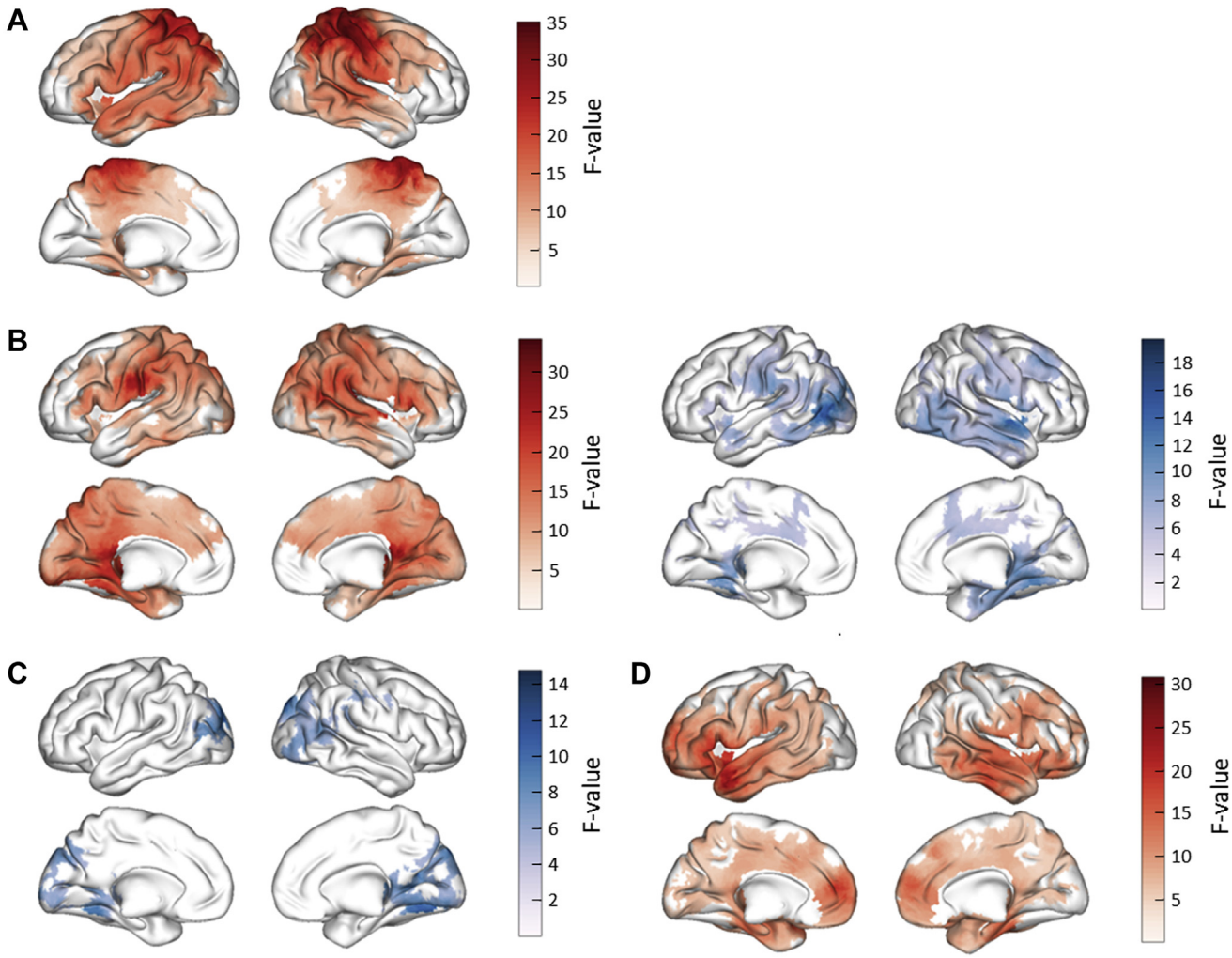

Fig. 2. Relative power statistics obtained by the CBPT. The colored brains represent the statistic value for each source in the significant clusters. Red color map indicates a significant power increase in the first group of the comparison. Blue color map indicates a significant power decrease in the first group of the comparison. For shake of clarity, the original t-values in CN-DS versus CN−no-DS comparison are transformed into F-values $\left(F = \frac{n(\bar{X}-\mu)^2}{\sigma^2} = t^2\right)$. (A) CN-DS versus CN−no-DS comparison. Increased power in the CN-DS group within theta band. (B) AD-DS versus CN-DS comparison. Increased power in the AD-DS group within delta band (left) and decreased power in AD-DS group within (right) alpha band. (C) AD-DS versus MCI-DS. Decreased power in AD-DS group within alpha band. This comparison does not survive FDR correction. (D) MCI-DS versus CN-DS. Increased power in MCI-DS group within delta band. Abbreviations: AD, Alzheimer's disease; DS, Down syndrome; CN, control; CBPT, cluster-based permutation test; FDR, false discovery rate; MCI, mild cognitive impairment. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Kindelberger, 2009). In addition, as commented in the previous sections, a small amount of the present subjects were unable to perform or complete some of the tests (see Table 1). Specifically, six subjects (14.63%) were unable to perform the WM test because of severe dysarthria; ADVM could not be completed by one subject (2.43%) because of the effect of fatigue; four subjects (9.75%) did not perform DVM because of the "acquiescence effect"; TO could not be completed by 2 subjects (4.87%) because of the use of omnibus and repetitive sentences "I don't Know", which were coded as "not completed". Despite these issues, it is important to note that the tests used to evaluate these functions were adapted and validated for the population with ID (Esteba-Castillo et al., 2017), being already prepared to avoid the "floor effect". The rest of the subjects scored within the normative values of each test for the DS population.

4.2. Neurophysiological characterization

As already commented in the introduction, the lack of investigations devoted to AD, and particularly to MCI, in DS applying neurophysiological markers is quite remarkable, and the vast majority of published studies were focused on comparing groups of young or middle-aged DS patients with age-matched controls. As previously described, DS individuals tend to exhibit a slowing of the spontaneous background activity, that in some investigations correlated with cognitive performance (Salem et al., 2015; Visser et al., 1996). The study of Katada et al. (Katada et al., 2000) is, nevertheless, an exception. These authors performed a cross-sectional investigation comparing DS cases with healthy controls and ID cases not due to DS, revealing the typical slowing of EEG activity localized in the occipital lobe. Interestingly, authors also performed a follow-up study that showed an earlier and steeper slowing in DS cases than controls. Furthermore, healthy subjects exhibited a "slow-alpha component" (i.e., 8 Hz) at ages above 50 years, whereas such component was visible in DS cases already by the age of 30 years. Hence, Katada et al. posed that such modification of the oscillatory activity might be a sign of the underlying neuropathological changes. Overall, these evidences demonstrated that the posterior dominant alpha activity is substituted by an oscillatory pattern that falls within the limits of theta band in relatively young DS individuals. Our results support that notion because we observed that the CN-DS group presented a widely distributed increase of theta band power as compared with the CN−no-DS

Table 4
Linear correlations results

	Linear correlation		
	ρ (mean ± SD)	Cluster size	*p* value
CAMCOG-DS			
Alpha rel. pow.	0.3944 ± 0.0579	636	.0147*
WM			
Delta rel. pow.	0.4422 ± 0.0688	639	.0217*
Alpha rel. pow.	−0.4320 ± 0.0557	791	.0069*
ADVM			
Delta rel. pow.	−0.3781 ± 0.0429	662	.0174*
DVM			
Delta rel. pow.	0.4226 ± 0.0664	868	.0125*
Alpha rel. pow.	−0.4127 ± 0.0562	457	.0252*
TO			
Alpha rel. pow.	0.3857 ± 0.0463	394	.0357*
	Cortical areas		
CAMCOG-DS			
Alpha rel. pow.	Right temporal cortex, inferior precentral gyrus, posterior frontal operculum, parahippocampal cortex, inferior postcentral gyrus.		
WM			
Delta rel. pow.	Occipital cortex, right posterior temporal cortex, cuneus and precuneus.		
Alpha rel. pow.	Occipital cortex, superior parietal cortex, both right and left posterior temporal cortex, cuneus and precuneus.		
ADVM			
Delta rel. pow.	Both right and left posterior temporal cortex, occipital cortex, cuneus, precuneus and hippocampus.		
DVM			
Delta rel. pow.	Occipital cortex, left temporal cortex and right posterior temporal cortex, cuneus and precuneus.		
Alpha rel. pow.	Occipital cortex, cuneus and precuneus.		
TO			
Alpha rel. pow.	Right inferior occipital cortex, cuneus and precuneus.		

For each test, the linear correlation between test scores and power within each band is presented in the upper part of table. The mean correlation coefficient in the significant cluster, the number of cortical sources in the significant cluster and the cluster significance level are presented. For the sake of clarity, only the (uncorrected) significant results are presented. An asterisk (*) indicates that the comparison survives FDR correction. Cortical areas regarding the linear correlations are presented in the lower part of the table.
Key: DS, Down syndrome; FDR, false discovery rate; CAMCOG, Cambridge Cognitive Examination; WM, working memory; ADVM, auditory delayed verbal memory; DVM, delayed visual memory; TO, temporal orientation.

group. This finding is of particular relevance because it is broadly accepted that the EEG pattern of early AD stages consists of an increase in theta activity (Jelic et al., 1996, 2000), whereas the increase of delta power seems to appear later in the progression of the disease (Dierks et al., 1993). Therefore, and agreeing with the perspective of Katada et al, an augmented theta power might be considered the first sign of a neurodegenerative process in non-demented adults with DS.

More recent EEG studies utilized improved source analysis models and offered a more precise localization of the oscillatory patterns in DS individuals. For example, Babiloni et al. (2009) found a reduced amplitude of alpha and beta rhythms in central, parietal, occipital, and temporal cortical sources, accompanied by an increase of delta activity in occipital sources. As the authors pointed out, such patterns virtually paralleled those observed in AD, although the sample included DS cases with a mean age of 22.8 years. A subsequent research by Velikova et al. (2011) using an identical approach to source modeling, presented slightly different results. In this case, adults with DS (age range 30–69 years) showed a slowing of the alpha peak but also an increased current density in theta, low alpha, and low beta classical bands, whereas only high alpha activity was reduced. The studies of Velikova et al. and Babiloni et al. are good examples of the inconclusive (e.g., observations of increased vs. decreased alpha activity) nature of some EEG studies on DS, probably because of the variability in recording conditions, as well as of differences in the age distribution of the different samples.

Although the role of alpha activity might be ambiguous in the literature to date, previous EEG studies highlighted that an increase of delta activity was a key feature in DS cases with dementia (Medaglini et al., 1997). Our results support that idea and offer a more precise localization of cortical sources: MCI-DS and AD-DS groups were characterized by a widely spread increase of delta activity, although the statistical significance was higher in posterior brain regions. Moreover, at the neurophysiological level, the MCI-DS group showed an intermediate position between AD-DS and CN-DS groups, as expected, with both pathological samples exhibiting significantly higher delta activity than controls with DS. This finding implies that MEG measures are capable to detect the neurophysiological features of the different stages of cognitive deterioration that can be observed in DS, a result of obvious clinical relevance. Previous studies by our group in non-ID population demonstrated that delta activity in posterior brain regions plays a crucial role in the discrimination of AD and MCI cases, and also in the prediction of the progression from MCI to AD (Fernandez et al., 2002, 2006, 2013). Actually, an increase of delta activity in posterior parietal cortex and precuneus was previously associated with the transition from MCI to a full-blown dementia, whereas an augment in frontal regions was associated with the transition from mild dementia to a more severe stage (Fernandez et al., 2013). Notably, a very recent study opened a new window to the interpretation of MEG spectral changes within the AD spectrum: Nakamura et al. (2018) demonstrated that the typically observed increase of theta activity is a sign of cognitive deterioration that correlates both with hippocampal atrophy and with impaired neuropsychological performance. Although such theta increase is not specific to the AD spectrum because it appeared in amyloid-positive and amyloid-negative MCI cases, an increase of delta activity in occipital and especially medial frontal regions was associated with the transition from a cognitively healthy condition to MCI within the AD spectrum (because this sign only emerged in amyloid-positive cases). Importantly, such delta increase correlated not only with cognitive performance but also with entorhinal atrophy and posterior cingulate-precuneus hypometabolism, two crucial markers of AD pathology (Nakamura et al., 2018).

Our results in this sample of DS individuals represent a further confirmation to the previously described findings. An increase of delta activity in the occipital, posterior temporal, parietal, and precuneus cortices correlated with a reduced performance in the memory domain, whereas an increase of alpha power correlated with an improved overall cognitive status seem to be crucial characteristics of the normal-cognition to MCI to AD progression in adults with DS. This evidence is of particular relevance because it represents a link between biological and cognitive markers. Cognitively, episodic memory tests such as ADVM and DVM were significantly affected both in MCI-DS and AD-DS groups, whereas WM was only significantly affected in our AD-DS group. More importantly, scores on the episodic memory tests were strongly correlated with delta activity located in key brain regions, previously highlighted as surrogate markers of amyloid deposition and cognitive deterioration within the AD spectrum (Nakamura et al., 2018). Such evidence might indicate that, agreeing with Hartley et al. (2017), the episodic memory impairment might represent a cognitive marker of the progression of AD neuropathology in DS patients.

Finally, our results demonstrated that, even considering the intrinsic difficulties for the assessment of AD and MCI in DS, a combination of sensitive cognitive testing and functional brain measurements may permit the detection of those clinical conditions.

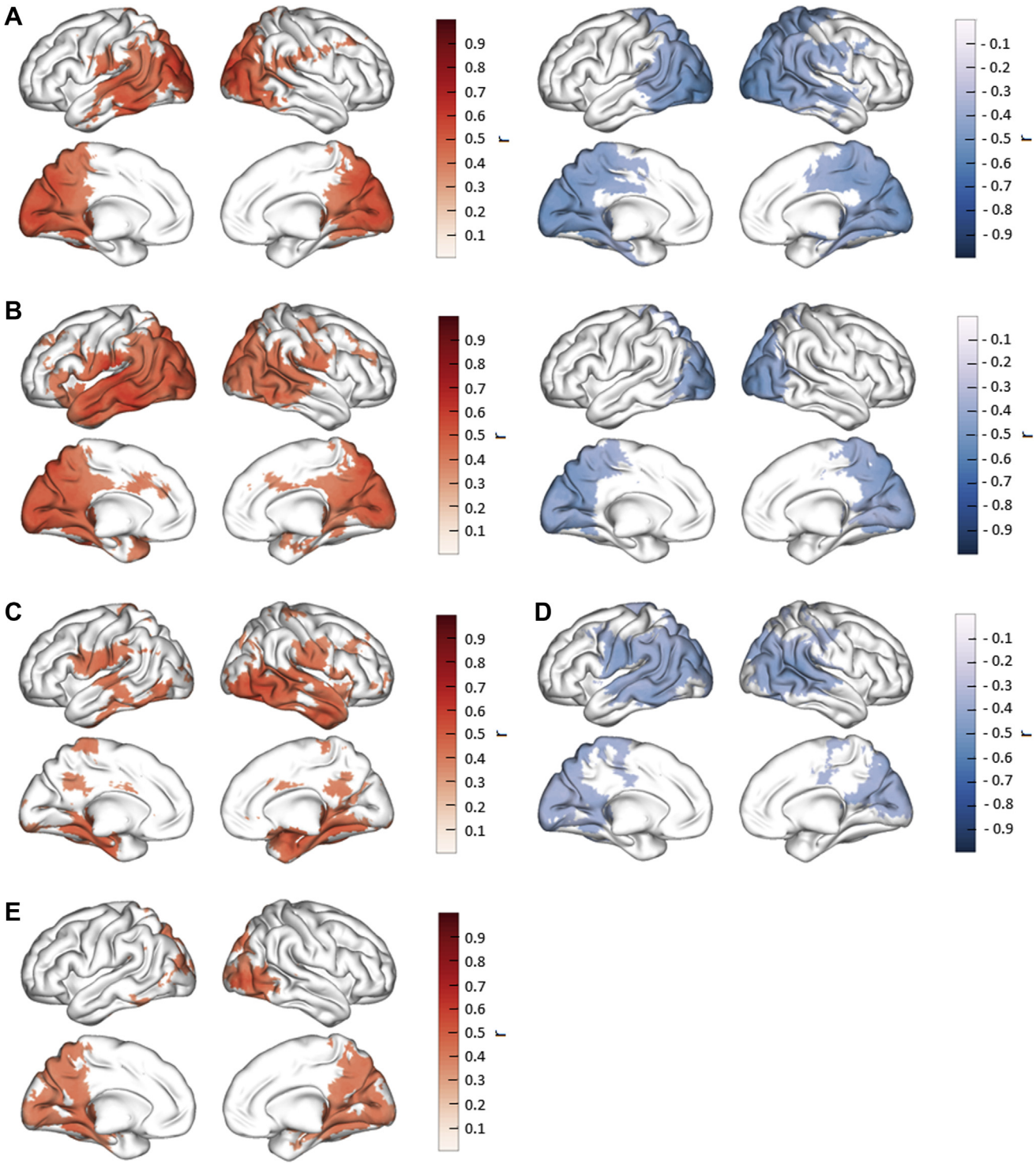

Fig. 3. Pearson correlation coefficient obtained by the CBPT. The colored brains represent the correlation coefficient between power values and cognitive test for each source position in the significant clusters. Red color map indicates positive correlation. Blue color map indicates negative correlation. (A) Linear correlation between the WM test and delta (left) and alpha bands relative power (right). (B) Linear correlation between the DVM test and delta (left) and alpha bands relative power (right). (C) Linear correlation between the CAMCOG-DS test and alpha band relative power. (D) Linear correlation between the ADVM test and delta band relative power. (E) Linear correlation between the TO test and alpha band relative power. Abbreviations: CAMCOG-DS, Cambridge Cognitive Examination for older adults with Down's Syndrome; CBPT, cluster-based permutation test; WM, working memory; ADVM, auditory delayed verbal memory; DVM, delayed visual memory; TO, temporal orientation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4.3. Limitations

This study was limited by the relatively small sample size and by the impossibility to obtain the individual MRI of every DS patient because of the particular characteristics of the DS sample. Some of the participants were not able to "resist" the noise produced by the MRI machine and found the situation too claustrophobic and stressful. As we did not obtain a structural MRI scanner for these participants, and to homogenize the data across the whole sample, we decided to use the MNI template for all the individuals. Notwithstanding, this is the first investigation that combined the neuropsychological and neurophysiological profiles of MCI and AD in DS by means of MEG. This offers an improved localization of the cortical sources and allows a better understanding of the relationship between cognition and neurophysiological patterns in DS.

Disclosure

The study was approved by the Research Ethics Committee of La Princesa University Hospital, Madrid, Spain.

No conflicts of interest exist for any of the authors.

Also, this work has been conducted according to the guidelines for ethical conduct and report of research.

Informed consent for all participants was obtained and the rights of the participants were protected.

The authors report no disclosures and no biomedical financial interests or potential conflicts of interest.

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