# Down syndrome as a model of preclinical Alzheimer's disease: preliminary findings using MEG

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## Introduction

Alzheimer's disease (AD) is the most common form of dementia characterized by gradual onset and progressive deterioration of cognitive function. A major challenge in AD is to find biomarkers that can predict the development of this disease. There is growing evidence that AD is not only associated with localized structural changes, but involves large-scale changes across distributed cortical regions at the earliest stage of the disease (Buckner et al, 2005; Fotenos et al 2005, 2008; Dickerson et al, 2009). We propose to use Down syndrome (DS) as a model for predicting preclinical AD since these individuals have a known high risk of developing AD (Haier et al, 2008). The objective of our research is to determine which MEG-based measures are most sensitive to the spatio-temporal signatures associated with changes in functional connectivity, as well as the structural and dynamical character of the brain during the early phases of AD.

## Methods

Participants:

- 8 adults with Down syndrome (DS) (mean age = 49 years, range: 35-63 years) and 8 healthy adults (mean age= 35 years, range: 19-50 years).

MEG Recording:

Two to ten minutes of data recorded on a 151 channel MEG system (VSM MedTech) at a sample rate of 600 samples/s while subjects were seated in a magnetically shielded room with their eyes closed. Continuous head localization was used to monitor each subject's head motion.

Data analysis:

Data was filtered to 0.5 – 150 Hz frequency range and inspected for the head motion and other artifacts. Corresponding segments were excluded from further analysis. The 151 physical sensor array was divided into 30 regions of ~5 adjacent sensors in each region (Fig 1).

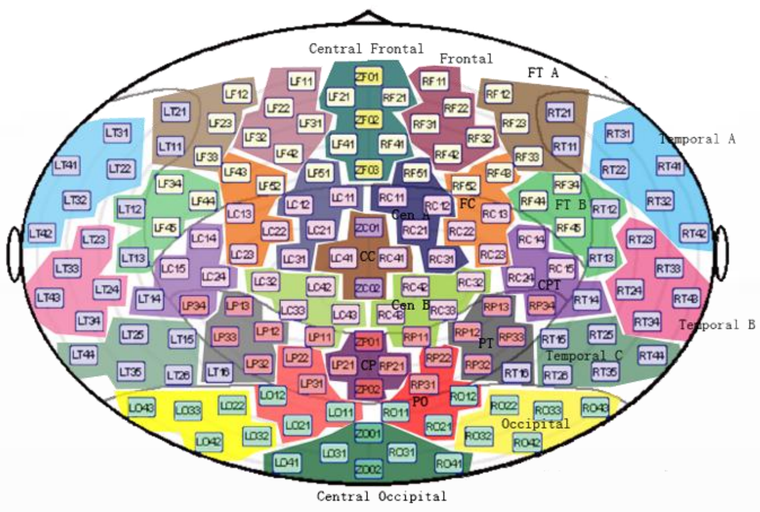


Figure 1: Sensor groupings

Results were averaged over the sensors in the region to account for variability in subjects head position relative to the array. Power spectra were estimated using Bartlett's method with 10 sec Hamming window. Mean frequencies of the spectra were calculated (Posa et al, 2007) in 3 – 150 Hz band. Lower frequencies were excluded to eliminate possible head motion artifacts.

Time-frequency spectrograms were obtained using 0.5 s sliding window with 50% overlap. For each window position, the amplitudes (i.e. absolute values) of frequency components of the MEG sensor signals were recorded. This way the "time courses" of the frequency amplitudes were obtained. Covariance and correlation matrices of the frequency amplitudes for each sensor were averaged over the sliding window positions, assuming stationarity of the resting state activity. These matrices characterize linear dependence of the fluctuations of the amplitudes of various frequency components. Single-channel matrices were averaged over the sensors in each region and group-averaged.

## Results

Spectral analysis revealed that the DS group had significant spectral slowing averaged over all sensors, with a mean frequency of 12.2 Hz compared to 14.4 Hz for the control group ($p < 0.002$). (Fig 2).

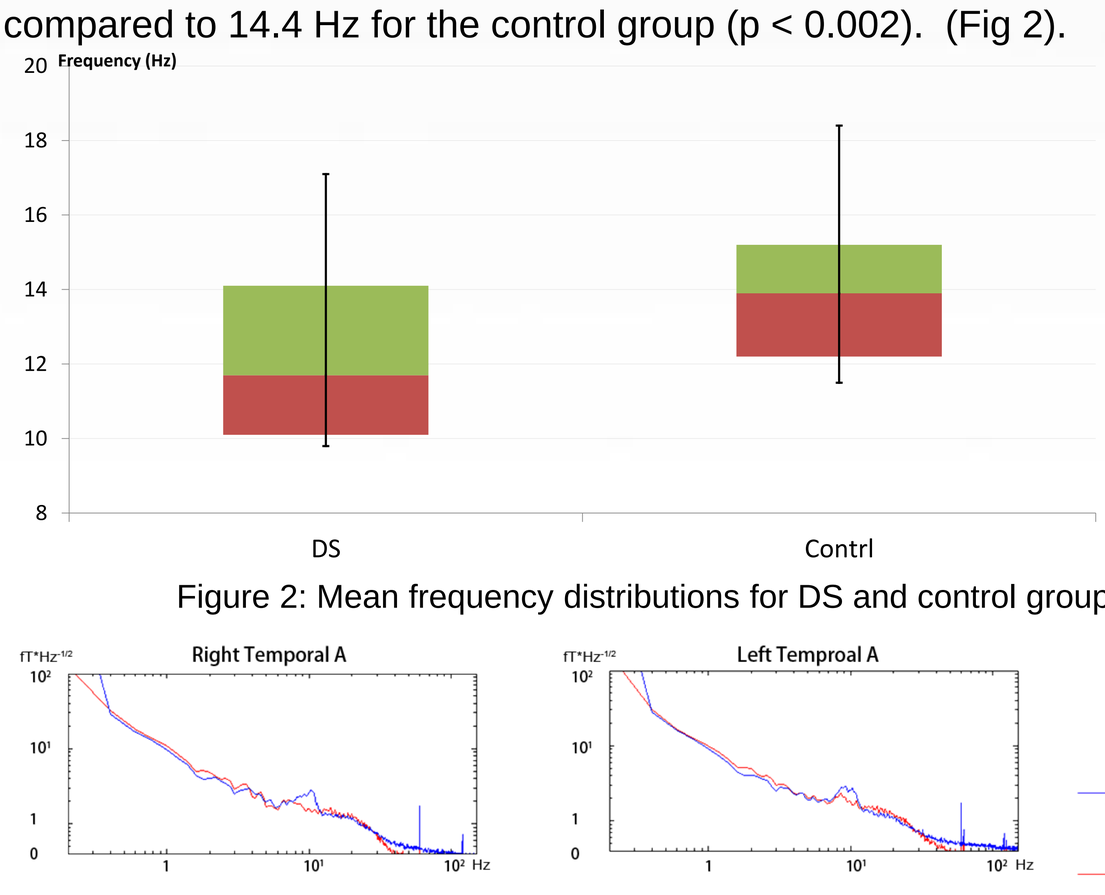


Figure 2: Mean frequency distributions for DS and control groups.

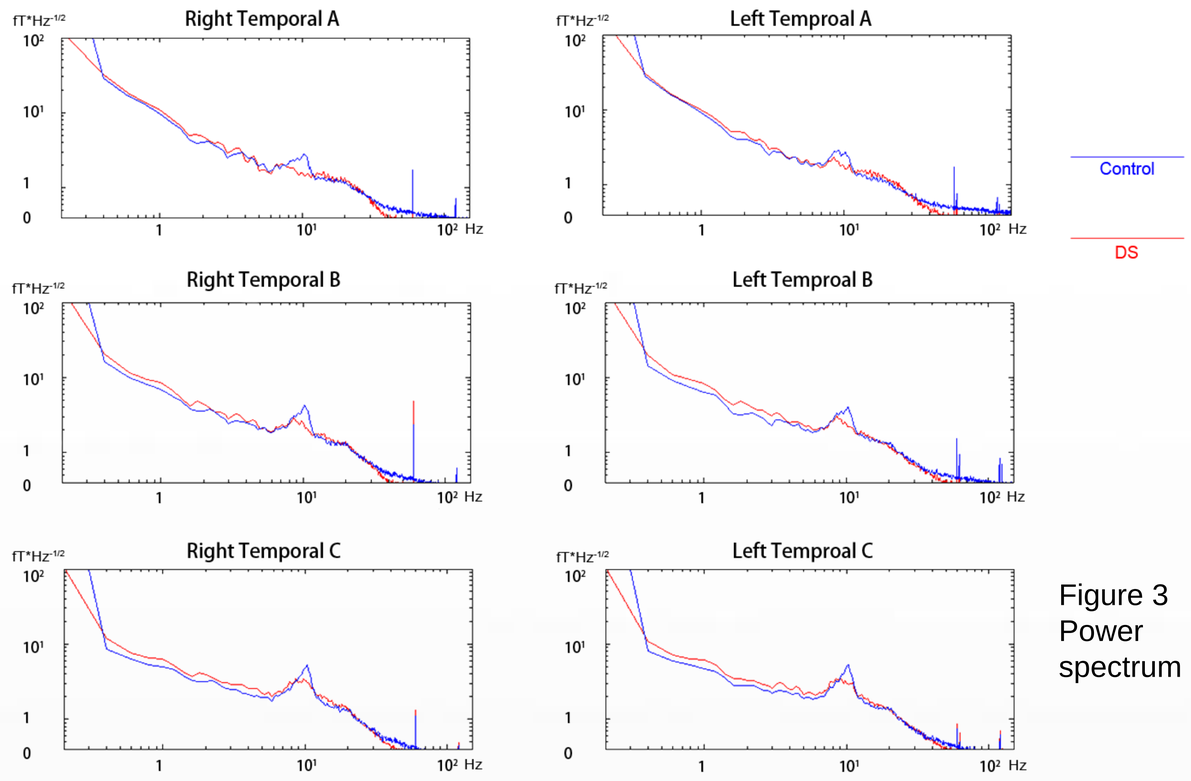


Figure 3 Power spectrum

Analysis of the frequency covariance and correlation matrices showed that the control group was characterized by synchronous activations of distinct narrow bands in many regions of the brain. In contrast, the DS group was characterized by a more diffuse correlation structure with broader bands of correlated frequencies (see Fig. 4). In addition, the DS group showed the shortest correlation times over the right temporal, bilateral frontal and central occipital regions. There differences were statistically significant using Hotelling's T-square test ($p<.00002$).

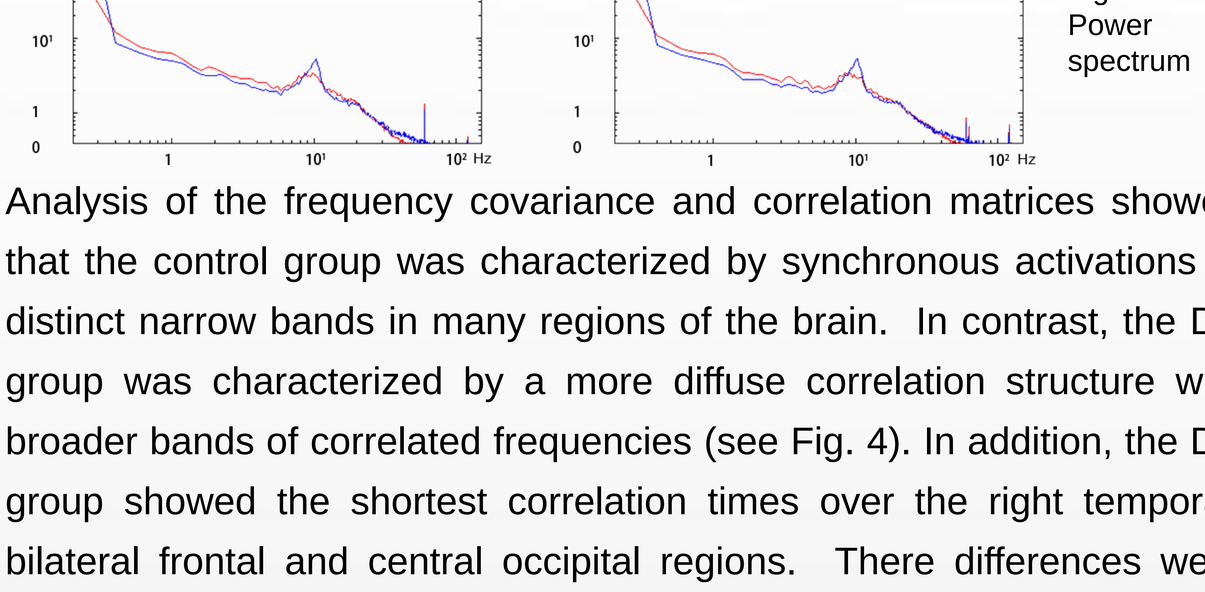


Figure 4: Frequency correlations in three representative regions

## Discussion

Our results show that at the level of physical sensors, spectral based measures from resting state data can reveal some fundamental differences associated with cognitive impairments. The slowing of resting signals with the diffuse correlation structure particularly in the temporal and frontal regions of the brain are consistent with previous results in early stage Alzheimer's disease (Stam et al, 2006). These changes may reflect loss of functional connections in areas related to memory and thalamocortical dysrhythmia (Llinas, Ribary et al, 1999). The DS model may therefore be a promising model of preclinical Alzheimer's disease.

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