DEFAULT MODE NETWORK AND COGNITIVE OUTCOME IN DOWN SYNDROME

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INTRODUCTION

Down syndrome (DS) is the most common genetic intellectual disability (ID) disorder seen in clinical practice (Elliott-King et al., 2016). The appearance of different types of dementia, mainly Alzheimer Disease (AD), is very common in Down Syndrome (Fleming et al., 2020). Some studies have reported a huge variability in the appearance and in the age of onset of AD in DS.

In the last few years, neuroimaging techniques, concretely, the analysis of functional connectivity, have become popular (Friston, 1994). These neuroimaging techniques usually produce large datasets of functional connection patterns and there has been an increased interest in characterizing these networks (Rubinov & Sporns, 2010).

The Default Mode Network (DMN) is a set of brain regions that collaborate while a person is at rest (Wilson et al., 2019). However, reduced or abnormal DMN functional connectivity has found to be implicated in some psychiatric, neurological and neurodevelopmental disorders (Anterapaer et al., 2017; Grasjski, Bressler & Alzheimer's Disease Initiative, 2019; Dutta et al., 2019; Kottaram et al., 2019).

The aim of this research is to estimate network complexity indicators in 24 regions belonging to the Default Mode Network (DMN) through fMRI signal with a resting state paradigm in DS. In addition, we intend to study their possible relationship with adapted neuropsychological test scores to assess IQ and cognitive performance.

METHODS

Sample: . The sample was composed of 35 people with DS between the ages of 16 and 35. However, due to excessive movement, 13 of the 35 subjects were not considered, so our final sample was composed of 22 (M = 25.55 and SD = 5.12; 23.8% of women.).

Instruments: A post-hoc battery was administered to each person with DS.

- Ad hoc questionnaire to assess clinical and educational history.
- Dementia Screening Questionnaire for individuals with Intellectual Disability
- Kaufman Brief Test of Intelligence (KBIT) (Kaufman and Kaufman, 1990): measure of verbal (vocabulary subtest) and non-verbal (matrices subtest) intelligence. In the case of the study, we will only use the nonverbal outcome, because DS population has demonstrated to have a consistent pattern of weaknesses in the processing of verbal information (Greigo et al., 2015)

Image acquisition: A 3 Tesla system was used for the acquisition of resonance images with usual parameters. A high resolution T2 and T1-weighted structural image and also a 6 minutes resting-state fMRI dataset were acquired.

Data Analysis: The structural image data were analysed using a FSL (FMRIB Software Library v5.0), with pre-processing pipeline adapted under authorization from Diez et al. (2015). The automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002) was used to define the regions of interest (ROIs). In this study, only DMN region was included, and therefore only 24 ROI's were identified.

The analysis of the 24 ROI's described was made by indicators of non-directed connectivity networks, using the ROI's as free. Even though there are millions of indicators to describe complex networks (Rubinov & Sporns, 2010), we choose the indicators basically for the purpose of the study and of course, considering the limitations of our sample. Basically, we considered number of triangles (ti, segregation indicator), Characteristic path length (L) and it's mean and standard deviation (integration indicators), modularity (Q) and complexity (that is the summary of the alternative paths within a network).

$$t_i = \frac{1}{2}\sum_{j,h\epsilon N} a_{ij}a_{ih}a_{jh};\ L = \frac{1}{n}\sum_{i\in N}\frac{\sum_{j\in N j\neq i} d_{ij}}{n-1};\ Q = \sum_{u\in M}\left[e_{uu} - \left(\sum_{v\in M} e_{uv}\right)^2\right]$$

Where a_{ij} is the connection status between nodes i and j, *dij* is the shortest path length between nodes *i* and *j*, where the network is fully subdivided into a set of nonoverlapping modules M, and e_{uv} is the proportion of all links that connect nodes in module u with nodes in module *v*.

Three multiple regression linear models were made. In first place, we used a full model with other complexity indicators (as smallworldness, centric degree and other known complex network indicators, Rubinov and Spirnov, 2010).

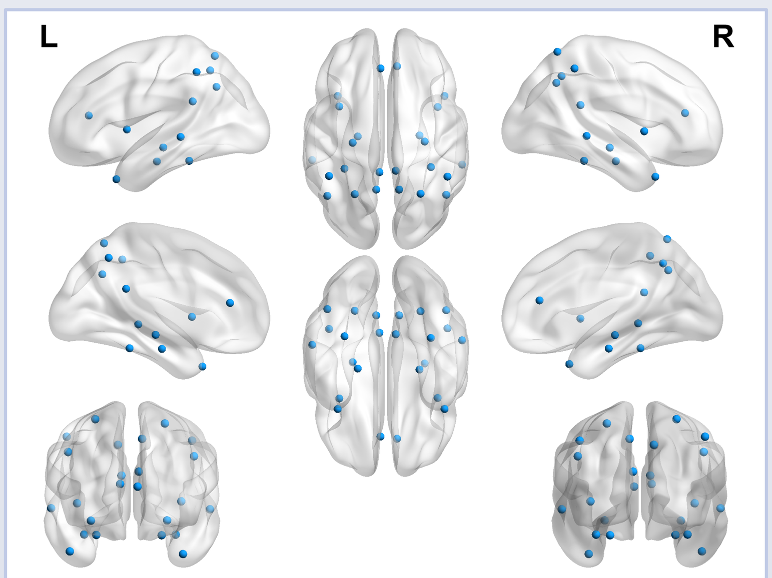
In second place, a stepwise regression model was estimated using as an inclusion criterion the significance of the change in the coefficient of determination (R^2) and the adjustment value of the Akaike Information Criteria (AIC). Finally, a third model was tested: the negative binomial regression model. This model is recommended when high variability is found in the exogenous variables (Ver Hoef & Boveng, 2007). This three models were compared between them and using as a point of reference the null model. The higher value of multiple and adjusted R^2 was found in the step-wise model and the R^2 was significantly higher and a 10% of reduction in the AIC value was found.

RESULTS

Complexity Indicators	Mean	SE(Mean)	SD	Symmetry	Kurtosis
T_i	878.81	155.502	712.599	1.337	1.292
Q	0.376	0.061	0.278	-4.388	19.752
L	-1.0220	1.409	6.458	-1.855	4.380
$\bar{x}$ integration	0.5830	0.0356	0.1634	-1.202	1.460
SD integration	0.2892	0.0383	0.1756	0.763	-0.105
Complexity	0.5821	0.0120	0.0553	0.517	-1.259
Standardized non-verbal KBIT score	47.476	3,000	13,757	-0,063	0,879

Parameter	p	Akaike Criteria	Multiple R^2	Adjusted R^2
8.171	<.001	91.94	0.779	0.682

	Coefficients
B_0 (intercept)	49.59
Triangles (B_1)	-0.007
Q (B_2)	19.78
ASPL (B_3)	2.35
Mean integration (B_4)	-231.8
Deviation Integration (B_5)	-92.91
Complexity (B_6)	277.8



CONCLUSIONS

- High variability is found in DMN complexity indicators through individuals with DS. Moreover, high variability is also found in neuropsychological outcomes.
- Both issues complicate the estimation of the parameters by conventional statistical regression models.
- Three regression models were tested, two classical multiple regression models and one binomial negative regression model, specified for high variability of the exogenous variables.
- However, the best results were found in the step wise regression model with the exogenous variables of triangles, modularity, characteristic path length, mean integration, deviation integration and complexity.
- These variables explain the 77.9% of the variability found in the endogenous variable: Standardized non-verbal KBIT score.
- Triangles coefficient is very low. Mean integration and Deviation integration seem to have negative and high coefficients, and therefore they could be inversely related to cognitive performance. However, complexity indicator and modularity have a positive coefficient, and therefore could have a direct relation with cognitive performance.
- Further investigations: chronological and mental age controls to study the possible effects in healthy population.

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