# Methodological approaches for the study of resting-state functional magnetic resonance imaging in Down syndrome

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DOCTORAL THESIS

# METHODOLOGICAL APPROACHES FOR THE STUDY OF RESTING-STATE *f*MRI IN DOWN SYNDROME

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# METHODOLOGICAL APPROACHES FOR THE STUDY OF RESTING-STATE FUNCTIONAL MAGNETIC RESONANCE IMAGING IN DOWN SYNDROME

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The current thesis comprises five studies all of them published in peer-reviewed journals, with the regulations approved by the Doctoral Committee of the University of Barcelona.

Dr. Joan Guàrdia Olmos has supervised this research and thesis.

During this research course, I did a research stay in Beijing under the supervision of Dr. Chao-Gan Yan.

*"Discovery is seeing what everybody*

*else has seen and thinking what nobody*

*else has thought"*

Albert Szeint-Györgyi, 1958

*A vosotros, Quique y Victor. Almas llenas de conocimiento. Me habéis inspirado y me habéis ayudado a crecer, me habéis acompañado siempre con vuestra sonrisa y me habéis enseñado vuestro mundo, que en definitiva, es el nuestro.*

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# Summary

Down syndrome is the most common chromosomal condition associated with intellectual disability. Although many researchers have focused on their physiological and cognitive characteristics, the underlying brain dysfunction of this syndrome is still unknown.

The present thesis has five original studies that address two principal aims. Firstly, the two first studies try to overcome some methodological issues that arise from working with the Down syndrome population: missing data and small sample sizes. The recruitment of the Down syndrome population is strenuous, and missing data is very common, especially when working with neuroimaging tools. In this sense, neuroimaging studies are usually characterized by small sample sizes, which leads to low and inconsistent effects. Both first studies have also an applied aim: operationalize the cognitive reserve concept in Down syndrome population and summarize the principal results of functional magnetic resonance imaging (*f*MRI) studies in intellectual disability population. The second aim of the present thesis is to study the state-of-art in the field of *f*MRI in Down syndrome and to use different strategies of resting-state analysis in a sample of young people with Down syndrome compared with age and gender-matched controls. All the studies were successfully published and are under the "Studies" section.

For study 1, 35 persons with Down syndrome (25.7% women, $M_{age}$=24.4; $SD_{age}$=5.42) participated. On the one hand, to solve the missing data problem, we performed multiple imputations. Confirmatory factor analysis with bayesian estimations was performed on the final database with non-informative priors, to operationalize the construct of cognitive reserve for people with Down syndrome. On the other hand, to solve the sample size problem, two additional corrections were made: first, we followed the Jiang and Yuan (2017) schema, and second, we made a Jackknife correlation correction, recommended for these cases. When there is no possibility to resample, the proposed methodologies and techniques could be useful. From an applied point of view, we resolved these challenges for operationalizing the cognitive reserve concept in Down syndrome population. This study demonstrates the feasibility of assessing the cognitive reserve in Down syndrome considering factors such as quality of life, physical activity levels, cognitive outcome, and personal conditions of the person with intellectual disability. This finding may provide a starting point in studying the individual differences in both clinical and neuropathological appearance of dementias.

Study 2 is a meta-analysis, which includes the 10 studies matching our inclusion criteria. The included papers were both qualitative and quantitative analysed. For the final quantitative results, we used *Seed-based d-Mapping* software. Results showed that small sample sizes are very typical when using populations with intellectual disability. This issue is even graver with

neuroimaging studies, as they involve more expensive costs and more complications in the registration. Meta-analyses tools can help summarize the qualitative and quantitive findings found throughout different studies. Regarding the results of the study, a clear pattern of dysconnectivity was found in participants with intellectual disability in the right temporal gyrus compared with controls. However, more task-*f*MRI studies on this field must be published by adding larger samples to address the pathophysiological questions more directly.

Study 3 is a systematic review that includes a total of 9 studies. It was a qualitative analysis performed by three independent reviewers, with a high percentage of agreement. The third study reviews the main works published concerning *f*MRI data and people with Down syndrome. Despite the scarcity of studies published in the field, *f*MRI could be a valued tool to evaluate the cognitive state of a person with Down syndrome, taking into account some difficulties found in this population, such as excessive head movement. There is evidence of functional and structural differences in this population, demonstrating the lower cerebral volume in some areas and differences in functional connectivity. However, in light of the literature, differences found are not congruent within studies and do not enable the establishment of a stable and regular pattern typical of Down syndrome people.

Regarding the sample for studies 4 and 5, it comprised 18 persons with Down syndrome (27.8% women, $M_{age}$=28.7; $SD_{age}$=4.2) and 18 controls matched by age and gender (27.8% women, $M_{age}$=28.6; $SD_{age}$=4.3). For study four, fALFF and ReHo techniques, resting-state measures of spontaneous brain activity were used to disentangle brain differences among Down syndrome participants and controls. Finally, in the fifth study, degree centrality, seed-based functional connectivity, and brain network analyses were used to find brain abnormalities in the Down syndrome sample compared with controls. With the last two studies, *Data Processing Assistant for Resting-State fMRI* software was used to perform image preprocessing and the following analyses. Both resting-state techniques allow us to affirm that Down syndrome population presents abnormal spontaneous brain activity and functional connectivity, and these abnormalities found could be related to their cognitive profile, finding alterations in the frontal and temporal lobes. These regions are engaged in language, executive functions and memory, functions highly altered in Down syndrome. The areas that displayed differences between both populations are also engaged in early amyloid deposition in young and cognitive stable adults with Down syndrome. Finally, those areas are also related to structural abnormalities already found in this population.

The results and conclusions of the present thesis highlight the use of resting-state *f*MRI analysis to disentangle the underlying brain mechanism of the Down syndrome population, and

the possibility to use this as a biomarker of cognitive function, as well as for dementia appearance detetction.

*Keywords*: Down syndrome, small sample, *f*MRI, Intellectual Disability, resting-state.

# Resumen

El síndrome de Down es la condición cromosómica más común asociada con discapacidad intelectual. A pesar de que muchos investigadores se han centrado en sus características fisiológicas y cognitivas, la disfunción cerebral subyacente de este síndrome aún se desconoce.

La presente tesis tiene cinco estudios originales que responden a dos objetivos principales. Para comenzar, los dos primeros estudios tratan de solventar algunos asuntos metodológicos que aparecen cuando se trabaja con la población con síndrome de Down: datos perdidos y muestras pequeñas. La recogida de muestra en esta población implica mucho esfuerzo, y los datos perdidos son muy comunes, especialmente cuando se trabaja con herramientas de neuroimagen. En este sentido, los estudios de neuroimagen se suelen caracterizar por muestras pequeñas. Como consecuencia, los efectos de los estudios individuales suelen ser bajos e inconsistentes. Los dos primeros estudios tienen también una orientaciçon más aplicada: operacionalizar el concepto de reserva cognitiva en la población con síndrome de Down y resumir los principales resultados de los estudios con resonancia magnética funcional (*f*MRI) y población con discapacidad intelectual. El segundo objetivo de la presente tesis es estudiar el estado del arte en el campo de *f*MRI en síndrome de Down y utilizar diferentes estrategias de análisis en estado de reposo en una muestra de jóvenes con síndrome de Down, comparados con controles emparejados por edad y género. Estos estudios fueron exitosamente publicados y están en la sección de "*Studies*".

35 personas con síndrome de Down (25.7% mujeres, $M_{edad}$=24.4; $DS_{edad}$=5.42) participaron en el primer estudio. Para solventar el problema de datos perdidos, se utilizaron técnicas de imputación múltiple. Para operacionalizar el concepto de reserva cognitiva para personas con síndrome de Down, se utilizaron técnicas bayesianas de análisis factorial confirmatorio con antecedentes no informativos. Sin embargo, para solventar la poca muestra, se realizaron dos correcciones adicionales: primero, se siguió el esquema de Jian y Yuan (2017) y segundo, realizamos correcciones de correlaciones Jackknife, recomendados para estos casos. Cuando no existe posibilidad de remuestrear, las presentes metodologías y técnicas propuestas pueden ser útiles. Desde un punto de vista aplicado, solventamos estos desafíos para operacionalizar el concepto de reserva cognitiva en la población con síndrome de Down. Este estudio demuestra la posibilidad de evaluar el concepto de reserva cognitiva en síndrome de Down, considerando factores como la calidad de vida, los niveles de actividad física, el rendimiento cognitivo y las condiciones personales de la persona con discapacidad intelectual. Este hallazgo podría proporcionar un punto de comienzo para estudiar las diferencias individuales en la aparición clínica y neuropatológica de las demencias.

El estudio 2 es un metaanálisis que incluye 10 estudios que coincidían con nuestros criterios de inclusión. Los estudios incluidos fueron analizados cualitativa y cuantitativamente. Para los resultados cuantitativos, se usó el software *Seed-based d-Mapping*. Los resultados mostraron que las muestras pequeñas son muy típicas cuando se utilizan poblaciones con discapacidad intelectual. Este hecho es aún más grave cuando son estudios de neuroimagen, ya que involucran mayores costes y mayores complicaciones de registro. Las herramientas de metaanálisis pueden ayudar a resumir de forma cualitativa y cuantitativa los resultados encontrados en los diferentes estudios. Un claro patrón de desconexión se encontró en los participantes con discapacidad intelectual en el giro temporal derecho comparado con controles. Sin embargo, más estudios de *f*MRI con tarea en este campo tienen que ser publicados, añadiendo muestras más grandes, para poder dirigir las preguntas patofisiologicas más directamente.

El estudio 3 es una revisión sistemática que incluye un total de 9 investigaciones. Fue un análisis cualitativo realizado por tres revisores independientes, con un porcentaje de acuerdo muy alto. Este estudio revisa los principales trabajos publicados con *f*MRI y la población con síndrome de Down. A pesar de los pocos estudios publicados en el campo, el *f*MRI podría ser una herramienta muy útil para evaluar el estado cognitivo de las personas con síndrome de Down. Sin embargo, algunas consideraciones deben tenerse en cuenta, como el excesivo movimiento durante el registro. Hay evidencia de diferencias estructurales y funcionales entre sujetos controles y personas con síndrome de Down, demostrando un menor volumen cerebral o diferencias en conectividad funcional. Sin embargo, a la luz de la literatura, las diferencias encontradas no son congruentes entre estudios y no permiten el establecimiento de un patrón regular y estable típico de las personas con síndrome de Down.

Con respecto a la muestra de los estudios 4 y 5, estuvo compuesta por 18 personas con síndrome de Down (27.8% mujeres, $M_{edad}$=28.7; $DS_{edad}$=4.2) y 18 controles emparejados por edad y género (27.8% mujeres, $M_{edad}$=28.6; $DS_{edad}$=4.3). Para el estudio 4, las técnicas de fALFF y ReHo, medidas en estado de reposo de la actividad espontánea del cerebro, fueron utilizadas para descubrir diferencias entre personas con síndrome de Down y controles. Finalmente, en el quinto estudio se utilizadoron medidas comoel grado de centralidad, análisis de conectividad basado en semillas y análisis de redes para encontrar anormalidades cerebrales en la muestra con síndrome de Down. Para ambos estudios, se utilizó el software *Data Processing Assistant for Resting-State fMRI* para realizar el preprocesamiento de las imágenes y los siguientes análisis. Ambos estudios nos permiten afirmar que la población con síndrome de Down presenta actividad espontánea anómala, así como diferencias importantes en conectividad funcional. Estas anormalidades podrían estar relacionadas con su perfil cognitivo, ya que encontramos alteraciones en los lóbulos temporales y frontales. Estas dos regiones parecen estar comprometidas con funciones ejecutivas, lenguaje y memoria, funciones altamente alteradas en esta población. Además de esta explicación,

existe la hipótesis de la deposición amiloide, que parece ya estar presente en jóvenes cognitivamente estables con síndrome de Down. Finalmente, las diferencias estructurales ya demostradas en esta población podrían estar relacionadas con sus alteraciones en conectividad funcional.

Los resultados y conclusiones de la presente tesis subrayan el uso de *f*MRI en reposo para descubrir los mecanismos subyacentes del cerebro en la población con síndrome de Down. También subrayan la posibilidad de utilizar estas técnicas como biomarcadores de función cognitiva, así como para la detección de la aparición de la demencia.

*Palabras clave:* síndrome de Down, muestras pequeñas, *f*MRI, discapacidad intelectual, estado de reposo.

# Resum

La síndrome de Down és la condició cromosòmica més freqüent associada amb discapacitat intel·lectual. Tot i que molts investigadors s'han centrat en les seves característiques fisiològiques i cognitives, la disfunció cerebral subjacent d'aquesta síndrome és menys coneguda.

La present tesi té cinc estudis originals que responen a dos objectius principals. Primer, els dos primers estudis intenten solucionar alguns assumptes metodològics que apareixen quan es treballa amb població amb síndrome de Down: dades perdudes i mostres petites. La recollida de mostra en aquesta població implica molt d'esforç i les dades perdudes són molt comunes, especialment quan es treballa amb eines de neuroimatge. En aquest sentit, els estudis de neuroimatge se solen caracteritzar per mostres petites. Com a conseqüència, els efectes dels estudis individuals solen ser baixos i poc consistents. A banda dels objectius més metodològics, els dos estudis tenen un objectiu de caire més aplicat: operacionalitzar el concepte de reserva cognitiva en la població amb síndrome de Down i resumir els principals resultats dels estudis amb ressonància magnètica funcional (*f*MRI) i la població amb discapacitat intel·lectual. El segon objectiu de la present tesi és estudiar l'estat de l'art en el camp del *f*MRI en síndrome de Down i utilitzar diferents estratègies d'anàlisis en estat de repòs en una mostra de joves amb síndrome de Down, comparats amb controls emparellats per edat i gènere. Tots els estudis van ser existosament publicats i estan en la secció de "*Studies".*

35 persones amb síndrome de Down (25.7% dones, $M_{edad}$=24.4; $DS_{edad}$=5.42) van participar en el primer estudi. Per a solucionar el problema de dades perdudes, es van utilitzar tècniques d'imputació múltiple. Per a operacionalitzar el concepte de reserva cognitiva per a persones amb síndrome de Down, es van usar tècniques bayesianes d'anàlisis factorial confirmatori amb antecedents no informatius. Tanmateix, per a resoldre la poca mostra, es van realitzar dues correccions addicionals: primer, es va seguir l'esquema de Jian i Yuan (2017) i segon, vam realitzar correccions de correlacions Jackknife, recomanades per aquests casos. Quan no existeix la possibilitat de remostrejar, les metodologies i tècniques proposades poden ser útils. Des d'un punt de vista aplicat, es van resoldre els desafiaments per operacionalitzar el concepte de reserva cognitiva en la població amb síndrome de Down. En aquest estudi es demostra la possibilitat d'avaluar el concepte de reserva cognitiva en aquesta mostra, considerant factors com la qualitat de vida, els nivells d'activitat física, el rendiment cognitiu i les condicions personals de la persona amb síndrome de Down. Aquesta troballa podria proporcionar un punt d'inici per a estudiar les diferències individuals en l'aparició clínica i neuropatològica de les demències.

L'estudi 2 és un metaanàlisis que inclou 10 investigacions que coincidien amb els nostres criteris d'inclusió. Els estudis inclosos van ser analitzats qualitativament i qualitativament. Per

als resultats quantitatius, es va utilitzar el software *Seed-based d-Mapping.* Els resultats van demostrar que les mostres petites són molt típiques quan s'usen poblacions amb discapacitat intel·lectual. Aquest fet encara és més greu quan són estudis de neuroimatge, ja que involucren majors costos i majors complicacions de registre. Les eines de metaanàlisi poden ajudar a resumir de forma qualitativa i quantitativa els resultats trobats en els diferents estudis. Es va trobar, en aquest estudi, un clar patró de desconnexió en els participants amb discapacitat intel·lectual en el gir temporal dret comparat amb controls. Tanmateix, més estudis amb *f*MRI amb tasca s'han de publicar, afegint mostres més grans, per a poder dirigir les preguntes patofisiològiques més directament.

L'estudi 3 és una revisió sistemàtica que inclou un total de 9 estudis. Va ser un anàlisis qualitatiu realitzat per tres revisors independents, amb un percentatge d'acord molt alt. Aquest estudi revisa els principals treballs publicats amb *f*MRI i la població amb síndrome de Down. Tot i que hi ha pocs estudis publicats en aquest àmbit, l'*f*MRI podria ser una eina molt útil per avaluar l'estat cognitiu de les persones amb síndrome de Down. Tanmateix, s'han de tenir en compte algunes consideracions, com el moviment excessiu durant el registre. Existeix evidència de diferències estructurals i funcionals entre subjectes controls i persones amb síndrome de Down. Malgrat això, a la llum de la literatura, les diferències trobades no són congruents entre estudis i no permeten l'establiment d'un patró regular i estable típic de les persones amb síndrome de Down.

Respecte a la mostra dels estudis 4 i 5, va ser composta per 18 persones amb síndrome de Down (27.8% dones, $M_{edat}$=28.7; $DS_{edat}$=4.2) i 18 controls emparellats per edat i gènere (27.8% dones, $M_{edat}$=28.6; $DS_{edad}$=4.3). Per a l'estudi 4, les tècniques de fALFF i ReHo, mesures en estat de repòs de l'activitat espontània del cervell, van ser utilitzades per a descobrir diferències entre persones amb síndrome de Down i controls. Finalment, en el cinquè estudi, el grau de centralitat, anàlisis de connectivitat basat en llavors i anàlisis de xarxes cerebrals van ser fets servir per a trobar anormalitats cerebrals entre les dues mostres. Per als dos estudis, es va usar el software *Data Processing Assistant for Resting-State fMRI* per a preprocessar les imatges i per als següents anàlisis. Les dues tècniques de repòs ens permeten afirmar que la població amb síndrome de Down presenta una activitat espontània anòmala, així com diferències importants en connectivitat funcional. Aquestes anormalitats podrien estar relacionades amb el seu perfil cognitiu, ja que trobem alteracions en els lòbuls frontals i temporals. Aquestes dues regions semblen estar compromeses amb funcions executives, llenguatge i memòria, funcions que estan altament afectades en síndrome de Down. Més a més d'aquesta explicació, existeix la hipòtesi de la deposició amiloide, que sembla estar present en joves cognitivament estables amb síndrome de Down. Finalment, les diferències estructurals ja demostrades en aquesta població podrien estar relacionades amb les seves alteracions en connectivitat funcional.

Els resultats i conclusions de la present tesi subratllen l'ús de *f*MRI en repòs per a descobrir mecanismes subjacents del cervell en la població amb síndrome de Down. També recalquen la possibilitat d'utilitzar aquestes tècniques com a biomarcadors de funció cognitiva això com per a la detecció de l'aparició de la demència.

*Paraules clau:* síndrome de Down, mostres petites, *f*MRI, discapacitat intel·lectual, estat de repòs.

# 1. Introduction

## 1.1 Neuroimaging techniques

In the last few years, the number of neuroimaging studies has grown exponentially (Zhang et al., 2020), leading to advancements in research methods and understanding of the brain (Banedettini, 2009). New technologies and methodologies developed in this field have increased our knowledge of the healthy brain and the study of clinical populations. Among all neuroimaging techniques, it is crucial to highlight some useful tools used in clinical diagnostic and in research.

The study of gray and white matter imaging has been very popular in recent years. Two techniques must be highlighted at this stage: Voxel based morphometry (VBM) and Diffusion tensor imaging (DTI). VBM allows the comparison of local gray matter concentration between groups of subjects (Ashburner & Friston, 2000). DTI allows the characterization of white matter, specifically, the directionality of white matter tracks (Tournier et al., 2011).

Electroencephalogram (EEG) measures electrical activity in the brain using small electrodes attached to the scalp (Thakor & Tong, 2004). Magnetoencephalography (MEG) measures neuronal activity by recording magnetic fields produced by electrical currents occurring naturally in the brain (Bénar et al., 2021). Both EEG and MEG suffer from poor spatial resolution (Matthews & Jezzard, 2004)

Magnetic Resonance Imaging (MRI) is a neuroimaging technique widely used for noninvasive studies such as anatomy, physiology, and function in a single setting (Zhou et al., 2019). Structural MRI provides detailed anatomical images in vivo. Functional MRI (*f*MRI), which studies the blood-oxygen-level-dependent (BOLD) signal, has transformed brain mapping. This technique provides a noninvasive, real-time visualization of brain function. *f*MRI has become the recently used tool for the cognitive neuroscience community. It is essential for those interested in understanding the functional correlates of behavior and disease in populations (Matthews et al., 1999).

### *1.1.1 fMRI*

*f*MRI has grown exponentially because of the noninvasiveness, relative ease of implementation, high spatial and temporal resolution, and to greater extent, the signal fidelity (Matthews et al., 1999). As with all neuroimaging techniques, in recent years, the immense advancements in *f*MRI have led to a higher resolution in time and space, a better understanding of the signal and more robust or sensitive processing methods. Consequently, new applications, and new neuroscience or clinical findings have appeared (Platt et al., 2021).

#### *1.1.1.1 Obtaining fMRI data*

Basically, the signal BOLD *f*MRI is extracted from an MRI scanner, which is able to detect functional and structural imaging.

The functioning of the MRI scanner is quite simple for detecting structural changes. The nucleus of hydrogen atoms behaves like a small magnet, and the MRI scanner generates a strong magnetic field. In the MRI scanner, all the hydrogen nuclei of the body tend to align with the magnet field generated by the scanner. When the ratio frequency (RF) magnetic pulse is applied to the right frequency, these hydrogen nuclei absorb energy and then create a brief signal, which can be mapped and turned into an image.

However, the MRI signal for mapping brain function the MRI signal is not directly sensitive to the neural activity. At a microscopic level, the post-synaptic activity of neurons generates a localized increase in blood flow that far exceeds the oxygen demands of the neural activity, leading to a local increase in blood flow oxygenation level. Oxygen-rich blood and oxygen-poor blood have different magnetic properties related to the hemoglobin that binds oxygen in blood. When the blood-flow is more oxygenated the signal is slightly stronger, meaning an increase in the neuronal activity. Figure 1 summarizes this process. So, basically, BOLD *f*MRI detects local increases in relative blood oxygenation that are most probably a direct consequence of neurotransmitter action, and thus reflect local neuronal signaling. Therefore, the MR signal change is an indirect effect related to the changes in blood flow that follow the changes in neural activity (Matthews et al., 1999).


*Figure 1. Neuronal processes to obtain BOLD signal.*

Note: Adapted from Bijsterbosch et al. (2017).

*f*MRI measures this increase in blood oxygenation called a hemodynamic response. This process is relatively slow and only reaches its peak approximately 5-6 seconds after the start of neural activity, as shown in figure 2. The hemodynamic response function represents the transfer function linking neural activity with the *f*MRI signal (Blamire et al., 1992).

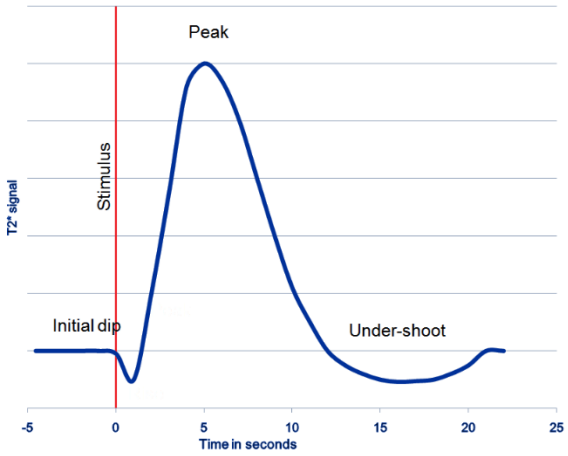


*Figure 2. The standard form of the hemodynamic response function.*

Note: Extracted from http://miykael.github.io/nipype-beginner-sguide/

Contrary to EEG and MEG methods, BOLD *f*MRI allows the spatial image resolution of a few millimeters, with a temporal resolution of a few seconds (limited by the hemodynamic response itself (Matthews & Jezzard, 2004)).

#### *1.1.1.2 Task and resting-state analyses*

There are two paradigms in *f*MRI. First, task-related *f*MRI studies require subjects to perform a task during the registration and assign functions to a specific brain region. Second, the resting-state measures indirect brain activity when there is no presentation of stimuli to the subjects. Both approaches can be mixed into design blocks or an event-related design, combining task and resting-state procedures within a single design.

In the restig-state approach, as there is no task derived from this paradigm, this widely used technique measures patterns of synchronous and spontaneous activation (Yang et al., 2020). It tries to elucidate how different brain regions communicate with each other. It also shows how information is passed from one brain area to the next. These types of designs measure the similarity of the BOLD signals from different brain regions. If the signals are similar, the regions are passing on information from one region to the other. When studying connectivity in the brain, the acquired *f*MRI data from a subject lying "at rest" in the scanner is used, and in this process, the spontaneous timeseries from functionally related brain regions are correlated (Biswal et al., 1995, Greicius et al., 2003). Given the sufficient quantity and quality of resting-state *f*MRI data, one can generate maps of all major functional networks in the brain, as each spontaneously fluctuates in its activation levels (Smith et al., 2009). The registration of the resting-state can be done with the eyes closed, or open. Commonly the open-eyes is more used to avoid the person falling asleep. Some studies register the signal fixing the eyes in a cross, which usually has more reliable findings (Bijsterbosch et al., 2017).

### *1.1.1.3 Data acquisition*

With the acquired data from the *f*MRI, it is essential to consider some characteristics of the MRI scanner and the signal register.

- Repetition time (TR): the amount of time it takes to acquire a single whole-brain volume (temporal resolution)
- Voxels size: three-dimensional pixels
- Coverture field of view (FOV)
- Number of slices: number of slices that are needed to generate a brain volume (directly related to the voxel size)
- EPI multiband or no multiband: in the multiband registry, the acquirement of different brain slices happens spontaneously.

It is crucial to register an anatomical image (or T1) that will help correct the distortion produced during the registration of the scanner.

### *1.1.1.4 The preprocessing steps*

One of the main challenges of *f*MRI is the amount of structured noise it produces. Therefore, once the resting-state *f*MRI data has been acquired and has undergone some form of quality control, the next step would be the preprocessing steps to reduce the influence of artifacts and other types of structured noise. Among all the sources of structured noise, it is essential to highlight the hardware noise, head motion and physiological noise. Moreover, to perform a group analysis, it is also crucial to ensure that we are comparing the same brain regions, and therefore it is vital to bring the images to a standard space. The most common standard spaces used are the Tailarach Atlas (Tailarach & Tournoux, 1988) and the Montreal Neurological Institute (MNI) space (Evans et al., 1993). Figure 3 summarizes the most common preprocessing steps.


*Figure 3. The usual application preprocessing steps for fMRI.*

It is important to note that the procedure doesn't require all the steps. It is also essential to mention that all the steps do not need to follow the order.

- Motion correction or realignment: This step aims to correct the effect of subject head motion in the scanner. In this step, a reference volume is chosen (the first one or the middle ones). This reference volume aligns all the volumes registered. In addition, this step also provides outputs of head motion estimates throughout the scan (motion parameters). There are six motion parameters that can be used in later preprocessing stages.
- Slice timing correction: this step aims to correct the slight difference in time from each acquired slice. As the *f*MRI register is a bidimensional space and the usual register time is immense, it is adequate to correct the time between images (Poldrack et al., 2011).
- Corregister: similar to the realignment, this step consists of the movements created by the anatomical registers and functional registers are corrected.
- Segmentation: In this step, the grey matter is linked with the standard space of grey matter to preserve the signal in the gray matter of the normalized positions.
- Normalization: This step places the cerebral volumes in standard space (Talairach or MNI). This step is crucial for the comparison between individuals.
- Smoothing: this step aims to make the images uniform by applying a spatial filter.
- Scrubbing regression: when working with populations with excessive movement, this step is useful to reduce head movements. Basically, it is a process in which TRs with excessive motion or signal deviation are identified and then removed from the data (Power et al., 2012; Power et al., 2013; Yan et al., 2013). It is usual to control the movement exceeding 0.2 mm in Jenkisnon's Framewise Displacement (FD) (Jenkinson et al., 2002).

#### *1.1.1.5 Statistical analysis*

After preprocessing, the *f*MRI resting-state data are ready for functional connectivity (FC) analyses. The methods used to study resting-state FC aim to detect the similarities among the brain regions. However, there are a wide variety of different connectivity methods that can be broadly divided into voxel-based and node-based methods. In this sense, voxel-based methods estimate FC value for each voxel of the brain. As there are many methods in resting-state *f*MRI, in this section the main types of analyses included in this thesis will be explained.

##### 1.1.1.5.1 Seed-based correlation analyses

In this type of analysis, a chosen region will drive the resulting FC map. This region of interest (ROI) or seed-based region, can be a single voxel, or more commonly a functional region made

up of a group of voxels. This method aims to obtain a whole brain map that describes the strength of FC of each voxel in the brain with the ROI. This analysis requires a priori determination of the seeds, which is often based on a hypothesis or prior results. Once the ROI or seed is defined, the BOLD time-series from the ROI in each subject must be extracted. If the ROI is larger than one voxel, the mean across voxels for each time point is typically used. Once the ROI timeseries has been extracted, the next step is to calculate the seed-based connectivity map for each subject, as an estimation of the correlation coefficient between the timeseries of voxel A and the times series of the seed ROI. Several measures can used instead. This is repeated for all the voxels in the brain, resulting in a whole brain connectivity map (Lv et al., 2018). The resulting seed-based connectivity map is obtained for each subject, and these subject maps can be used in subsequent group-level analyses. However, before performing a group-level analysis, the subject-wise correlation maps are often transformed to Z-scores using Fisher's r-to-Z transformation. Table 1 summarizes the advantages and disadvantages of this approach. This approach has been used in many psychiatric diseases (Yu et al., 2020), neurodevelopmental disorders (Rubia et al., 2019) and dementias (Tang et al., 2021).

*Table 1. Advantages and disadvantages of seed-based approach.*

| Advantages | Disadvantages |
|---|---|
| It addresses a specific question | Dependence on the selection and to the spatial definition of the seed |
| Hypothesis-driven | Only considers one system |
| Relatively easy and fast to estimate, as well as easy interpretation. | Oversimplification of the true network |

Note: Adapted and actualized from Bijsterbosch et al. (2017), Lv et al. (2018) and Smitha et al. (2017).

#### 1.1.1.5.2 The amplitude of low-frequency fluctuation (voxel-based measure)

As previously stated, resting-state FC usually focuses on detecting similarities in fluctuations of the BOLD signal between two regions. However, it is also possible to measure the amplitude of low-frequency fluctuations (ALFF) for each voxel of the brain, which is proportional to regional neural activity (Zang et al., 2007). Due to the slow timescale of the hemodynamic response function, the BOLD signal is dominated by low-frequency fluctuations. For the estimation of ALFF, the Fourier transform is used to calculate the power spectrum of a timeseries, which reflects how the signal is composed of separate frequencies. ALFF can be estimated by taking the average square root power within the low-frequency range (0.01-0.1 Hz) and standardized by dividing it by the global mean ALFF. However, ALFF is sensitive to some noise fluctuations. The fractional amplitude of low-frequency fluctuations (fALFF) is more specifically sensitive to low-frequency fluctuations (Zou et al., 2008), and it's estimated as:

$$fALFF = \frac{total\ power\ in\ the\ low\ frequency\ range\ (0.01 - 0.1Hz)}{total\ power\ across\ the\ entire\ frequency\ range}$$

In many psychiatric diseases (Gao et al., 2021), neurodevelopmental disorders (Jiang et al., 2020), and dementias (Yang et al., 2020) this approach has been used. Table 2 summarizes the advantages and disadvantages of fALFF.

*Table 2. Advantages and disadvantages of fALFF.*

| Advantages | Disadvantages |
|---|---|
| Summarizes the frequency characteristics of the local BOLD data | Does not measure FC directly |
| Remarkably high temporal stability and long-term test-retest stability | More sensitive to non-neuronal noise |
| Relatively easy and fast to estimate | |
| No need to have hypothesis | |

Note: Adapted and actualized from Bijsterbosch et al. (2017), Lv et al. (2018), Smitha et al. (2017) and Zuo & Xing (2014).

#### 1.1.1.5.3 Regional homogeneity (voxel-based measure)

Most resting-state *f*MRI methods investigate FC across the entire brain and are sensitive to long-distance connections. However, Regional homogeneity (ReHo) measures the similarities between the time-series of a given voxel and its nearest neighbors, measured by the *Kendall's coefficient of concordance*. This method describes the FC at a local level between neighboring voxels. Therefore, the output of a ReHo analyses is a single whole brain map, in which higher values represent voxels that have strong temporal correlation with their immediate neighborhood of voxels, so increased coherence and centrality. Recently, this approach has been used in many psychiatric diseases (Wang et al., 2022), neurodevelopmental disorders (Li et al., 2018) and dementias (Yue et al., 2020). Table 3 summarizes the advantages and disadvantages of ReHo approach.

*Table 3. Advantages and disadvantages of ReHo.*

| Advantages | Disadvantages |
|---|---|
| Interesting marker | Highly sensitive to the amount of spatial smoothing |
| High test-retest reliability, and long-term stability | Heavily confounded by non-neuronal localized fluctuations. |
| Does not require a priori definition of the ROI | Not sensitive to potential differences in the shape of the local neighborhood |

Note: Adapted and actualized from Bijsterbosch et al. (2017), Lv et al. (2018), Smitha et al. (2017) and Zuo et al. (2014).

#### 1.1.1.5.4 Node-based Connectivity Analyses

The node-based connectivity analyses let us know how connectivity is structured between distinct functional regions. In this approach, it is useful to adopt nodes and edges approach. Nodes represent brain regions (voxels or ROIs), and edges represent the links between the nodes (the correlation between the time-series of two nodes).

Regarding this approach, the network modelling analysis is one of the most used currently.

In this approach, the network matrix is built from nodes and edges. This network is used to find which edges differ in strength between two groups. This approach has been recently used in many psychiatric diseases (Li et al., 2021) and dementias (Skidmore et al., 2011), among others. Table 4 summarizes the advantages and disadvantages of this approach.

*Table 4. Advantages and disadvantages of network modelling analyisis.*

| Advantages | Disadvantages |
|---|---|
| It is possible to perform different types of FC research<br>Enables to map the functional connectome of the brain | Nodes must be spatially defined at the start and it cannot change the shape or size |

Note: Adapted and actualized from Bijsterbosch et al. (2017), Lv et al. (2018) and Smitha et al. (2017).

#### 1.1.1.5.5 Graph analysis

*f*MRI produces enormous datasets that are difficult to manage. Regarding all the analysis techniques in *f*MRI, graph metrics are a competent tool to characterize these datasets and measure the global organization of large-scale networks (Rubinov & Sporns, 2010; Watts & Strogatz, 1998). Graphs are data structures that are composed of nodes and edges. Graph metrics have been used to compare the FC between healthy and diseased people in a variety of populations such as autism spectrum disorder (Kazeminejad et al., 2020), attention-deficit/hyperactivity disorder (ADHD; Wang et al., 2020) and Alzheimer disease (AD; Behfar et al., 2020).

A graph can be expressed as a mathematical construction that summarizes the information of the relationship between these nodes and links, the connectivity matrix (Rubinov & Sporns, 2010). Depending on the specific network characteristics, links can either be directed or undirected, and the two approaches examine the degree of relationship between nodes. On the one hand, to represent whether there is correlation or not between two nodes, binary matrices are used. Binary matrices have zeros and ones as their elements, the ones representing the existence of a connection between nodes and zeros, meaning no connection at all. On the other hand, weighted matrices are more informative, where the link between two nodes is represented by their correlation value, which ranges from zero to one when normalized.

Graph theory provides a theoretic framework for analyzing the topology of brain networks by examining both local and global organization (Rubinov & Sporns, 2010). Segregation metrics (clustering coefficient, transitivity, modularity) evaluate the brain capacity to divide itself in different interconnected groups. Integration measures (characteristic path length, efficiency) indicate the brain's ability to combine specialized information from distributed regions (Rubinov & Sporns, 2010). Finally, the small world is a global measure that combines path length and clustering coefficient. Many graph metrics inform about the segregation and integration of the networks. A complete review of the metrics can be found in Rubinov & Sporns (2010).

Regarding the node-wise summary measure, it is essential to highlight one of the most important and simplest ones, Degree centrality (DC). It is a graph metric that assesses the importance of each node in the brain network, evaluating the connectivity strength to every voxel (Buckner et al., 2009; Telesford et al., 2011; Zuo et al., 2012). It has been used in many other diseases as myopia (Hu et al., 2018), Parkinson's disease (Guo et al., 2020); ADHD (Jiang et al., 2019) among others. Table 5 summarizes the advantages and disadvantages of this approach.

*Table 5. Advantages and disadvantages of graph analysis*

| Advantages | Disadvantages |
|---|---|
| Summarizes the complex networks into a single value per subject | Includes both indirect and direct connections between nodes and can be influenced by confounding variables<br>Binary matrices simplify and lose information |

Note: Adapted and actualized from Bijsterbosch et al. (2017), Lv et al. (2018) and Smitha et al. (2017).

#### *1.1.1.6 Multiple comparisons*

In neuroimaging studies, millions of data are used from different parts of the brain to perform the group analysis, many statistical tests are used, and it exists a multiple comparison problem related to the null hypothesis testing, which is one of the most critical aspects of *f*MRI (Eklund et al., 2016). In this sense, the usual *f*MRI analysis involves more than ten to hundred voxels. Due to this fact, the possibility of encountering Type I error is likely to be significantly inflated when we use the most common *p-value* threshold ($p<.05$) (Han, 2020). Therefore, when performing an abundant number of tests, it is essential to apply some form of correction to control the number of false positives and address the multiple comparison problem. A large number of strategies can be found to correct for multiple comparison (Chen et al., 2018). However, it is still a methodological issue and a tough challenge in *f*MRI (Bennett et al., 2009). All the strategies have in common to adopt a more stringent threshold or adjust the rate of potential false positives. The main aim of this methodological issue is to find an appropriate balance between trying to minimize false positives (Type I error) while not being too stringent and omitting true effects (Type II error) (Han & Glenn, 2018). The following tests are classic methodologies and used the most in the field of *f*MRI.

- Family-wise error rate (FWER) correction (Benjamini & Hochberg, 1995): these methodologies control for the FWER, which is the probability of getting a false positive.
  - Bonferroni correction: it is one of the most traditional methods (Han & Glenn, 2018). This technique divides the nominal significance level (e.g., *p<.05)* by the number of tests being performed (Bland & Altman, 1995). Despite producing good results for controlling the Type I error, when it is applied in neuroimaging can remove both false and true positives (Han & Glenn, 2018).
  - Gaussian Random Field (GRF) theory correction (Nichols, 2012): it focuses on the maximum value (across voxels) of the test statistic, parametric approach. Unlike the traditional Bonferroni method, which only accounts for the total number of comparisons, this method assumes that the error fields can be a lattice approximation to an underlying random field usually with a Gaussian distribution (Brett et al., 2004; Eklund et al., 2016).
  - Monte Carlo simulations (AlphaSim): estimates the overall significance level of the functional images (Ward, 2000). By means of Monte Carlo simulations and combining voxel probability thresholding and minimum cluster size thresholding, the probability of a false positive is estimated.
  - Permutation test: it is a non-parametric approach.
    - Threshold-Free Cluster Enhancement (TFCE): it is a strict multiple comparison correction strategy (Winkler et al., 2016), which reaches the best balance between family-wise error rate (under 5%) and test-retest reliability and replicability (Chen et al., 2018) for voxel wise multiple comparisons. This method provides improved sensitivity, with a richer and more interpretable output than other methodologies (Smith & Nichols, 2018).
- False discovery rate (FDR) correction: This method is more sensitive and less likely to produce Type II error than FWE correction methods (Han & Glenn, 2018). Unlike the precedent methods that control for the possibility of any false positives, this method focuses on the expected proportion of false positives only among survived entities (Genovese et al., 2002). In this type of correction, 5% of all voxels would be declared to be significant in the brain. Generally, it is not used in whole-brain, but mostly in network analysis (Chen et al., 2018).

Chen et al. (2018) performed a riveting review on selecting the best multiple comparison correction strategy and the importance of the sample size to enhance reproducibility in resting-state *f*MRI studies.

These correction methods can be performed at different levels of inference. In the Voxel-wise approach, each voxel is treated as a unit for analysis, and any voxel exceeding a threshold after applying one of the precedent correction methods is considered statistically significant in the whole brain or specified region of interest (Nichols, 2012). In the case of cluster wise inference, statistically significant clusters showing activation are detected based on the number of contiguous voxels. This type of inference does not control the estimated false positive probability of each individual voxel in each region, but controls such a probability of the region as a whole (Woo et al., 2014). This cluster wise inference has been one of the most popular methods used for multiple comparison correction because it is more sensitive than voxel-wise inference (Woo et al., 2014).

## 1.2 Intellectual Disability

Intellectual disability (ID) is a lifetime condition that impacts individuals and their families. It is characterized by significant limitations both in cognitive performance and adaptative behavior. These limitations include conceptual, social and practical adaptative skills (Schalock et al., 2010). In recent years, this ID conceptualization has changed, incorporating new terminology to the concept, giving the same importance to the ID and to the adaptative behavior, and highlighting the evaluation based on the person's needs for supports rather than the individual's intelligence quotient (IQ) level (Schalock et al., 2021).

This new approach to ID offers new perspectives and intervention models linked with supports. Due to the individualized support mediation, optimal environments for the development and well-being of the person with ID can be promoted (Schalock et al., 2021). Nowadays, there is a firm conviction that with adequate support, a person with ID would have enhanced their functional abilities, and his or her results and quality of life can be improved (Schalock et al., 2021).

From this perspective of ID and considering that it answers to the environmental demands thanks to the support's mediation, we ask ourselves if the brain functioning of people with ID could present some irregularities. In other words, due to the adaptative behavior and the individualized supports, people with ID can develop and have a quality of life, despite their low intellectual functioning.

With a prevalence of 2-3% worldwide, ID represents one of the biggest medical and social challenges in our society (Iwase et al., 2017). Etiologies in ID vary, some of them arising because of environmental factors, chromosomal aberrations, and single gene mutation (Iwase et al., 2017). The brain connectivity patterns of people with ID could be different from the brain connectivity patterns of people without ID.

### *1.2.1 Down syndrome*

Among all ID, Down syndrome (DS) is the most common chromosomal condition associated with the ID (Bull, 2020), affecting 5.8 million people worldwide (Ballard et al., 2016). DS is characterized, mainly, by the third copy of the chromosome 21, which results in an extra chromosome affecting all the body cells. Therefore, different systems are affected by it, as the musculoskeletal, neurological, and cardiovascular systems (Antonarkis et al., 2020). Individuals with DS commonly present ID and developmental disabilities. They can also present short stature, atlantoaxial instability, reduced neuronal density, cerebellar hypoplasia, muscle hypotonia and congenital heart defects, among others (Antonarkis et al., 2020).

Individuals with DS are also susceptible to the development of certain health conditions, including hypothyroidism, autoimmune diseases, obstructive sleep apnoea, epilepsy, hearing and vision problems, haematological disorders, recurrent infections, anxiety disorders and early-onset AD (Antonarkis et al., 2020).

However, there is a vast variability in the symptomatology in DS. There is considerable phenotypic variation among patients, and ID is most commonly moderate but ranges from mild to severe. Moreover, social function is often linked to the cognitive impairment (Bull, 2020).

#### *1.2.1.1 Neuropsychological profile*

ID is one of the most prominent features of DS (Constestabile et al., 2010). The IQ of DS individuals ranges from 30 to 70 with an average value of 50 ranging from profound to borderline intellectual functioning (Gardiner et al., 2010). A vast variability has been found in the cognitive functioning of this population, and often changes across the lifespan and is moderated by several comorbid factors such as sensory impairments, seizures, autism, sleep disruption, and other medical and psychiatric conditions (Gasquoine, 2011).

Language, learning, and memory appear to be significantly affected in DS. Learning deficits in DS children involve both short-term and long-term memory. Both hippocampal- and prefrontal-related functions appear defective in individuals with DS (Contestabile et al., 2010).

#### *1.2.1.2 Alzheimer disease*

The prevalence of dementia in DS is much higher in the DS population than in the general population. At age 40, virtually all adults will develop neuropathology linked with AD (Lott & Head, 2019). This increased prevalence in this population can be explained, in the first place, by the overexpression of Amyloid-β (Aβ), encoded by the amyloid precursor protein (APP) due to the location of this gene on chromosome 21. Aβ accumulates in the brain across the lifespan of people with DS, it can occur in very young people with DS, but commonly it is observed after 30 years old. However, it is still very far from the age of observation in the general population. Moreover, it has been demonstrated that after age of 40 in DS population, the accumulation of brain amyloid is not linear, whereas it is exponential (Cenini et al., 2012).

Other factors such as neuroinflammation and neurocerebrovascular pathology can also explain the early age onset and prevalence of AD in DS (Lott & Head, 2019).

The diagnostic and clinical management of dementia in DS is a big challenge, because of the combination of progressive and functional decline, learning disabilities and neuropsychiatric and behavioural symptoms common in DS (Ballard et al., 2016).

Despite the high prevalence of AD in DS; the age of onset varies and there might be no development in some subjects with DS (Contestabile et al., 2010).

#### *1.2.1.3 Cognitive reserve in DS*

As mentioned, it is well described that practically all adults with DS over the age of 40 years develop neuropathology consistent with AD. It has been commonly believed that genetic factors are responsible of AD in adults with DS (Zigman & Lott, 2007). However, there are big differences in the reporting prevalence rates suggesting congenital or environmental factors may also play a significant role in determining either the age of onset or whether dementia develops at all (Temple et al., 2001).

Epidemiological studies in the non-DS population have identified several other factors believed to influence the onset of dementia. Besides non-modifiable risk factors, such as age, sex and genetics, there is good support for modifiable risk factors as contributors to the risk of developing dementia in later life (O'Donnell et al., 2015). Recent estimations suggest that one in three dementia cases may be attributable to common modifiable risk factors (Norton et al., 2014).

Moreover, several healthy living behaviours have been identified, e.g. regular physical exercise, high mental activity, adequate blood pressure control (Livingston et al., 2015), more years of education (Katzman, 1993; Stern, 1992;), more challenging employment, regular participation in social and leisure activities (Fabrigoule et al., 1995) and healthy diet (Heger et al., 2019). Protective factors in individuals from the general population may be worthwhile in understanding dementia in individuals with DS. Although individuals with DS do not have levels of cognitive ability or education equal to those in the general population, it is still the case that these variations in ability exist within the DS population.

Given this variability, it is possible that individuals with DS who have a higher level of cognitive functioning or higher intellectual ability will be less likely to develop dementia. Following the same logic, it might be hypothesized that a higher level of education, more recreational activity and more challenging employment are linked to a lower rate of dementia. Furthermore, if community living is understood to be more active and stimulating than institutional life then the number of years an individual spends in the community may also be protective (Temple et al., 2001).

Stern et al. (2018) has defined all these factors as Cognitive Reserve (CR), meaning, the adaptability of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging or pathology.

Adults with DS often have maladaptive lifestyles (low levels physical activity and leisure activities) (Snyder et al., 2020). Recently, Mihaila et al. (2019) demonstrated that adults with DS

without dementia who engaged in higher levels of cognitively stimulating and social leisure activity experienced less decline across three years in episodic memory. Moreover, leisure activity at baseline mitigated the association between an increase in Aβ assessed via PET and a decline in episodic memory across three years. This demonstrates that these behaviors could play an important role in cognition in the early stages of AD in DS.

The information described above regarding protective factors for dementia in individuals from the general population may be helpful, also, to understanding dementia in individuals with DS. Given the variability that exists in DS, the implications of CR for individuals with DS deserve special attention in order to generate a more systematic definition (McCarron et al., 2013).

#### *1.2.1.4 Neuroimaging findings in DS*

Despite the high number of publications in the last few years using neuroimaging techniques, in the DS population there is a scarcity of studies in this field. More concretely, structural and functional MRI neuroimaging techniques have demonstrated how useful tools are in understanding brain pathology and diseases. Particularly, in DS, neuroimaging tools could enhance their brain understanding and could detect biomarkers for the dementia appearance (Rodrigues et al., 2019). Therefore, before starting, a brief review of findings in neuroimaging and, more concretely, in functional MRI in DS population will be done. Table 6 summarizes neuroimaging findings in DS, the majority structural findings. Table 7 summarizes studies using functional MRI in DS and their major findings.

As we can see, sample sizes are very low in all the studies, but in accordance with neuroimaging studies in other populations (Szucs & Ioannidis, 2020). Regarding structural and other neuroimaging studies, the participants are very young, finding also fetuses' participants. The key findings include differences in cortical thickness in DS, as well as abnormalities in cerebellum and frontal and temporal lobes.

Regarding functional neuroimaging findings, it is essential to highlight the scarcity of studies in this field, specifically those using resting-state designs. Moreover, the high variability of the age of the participants can reduce the validity of the findings, because AD features can be present already.

*Table 6. Major structural findings and other neuroimaging studies in DS in the last 10 years.*

| Authors | Technique | n (DS) | Mean age DS (years) | Major findings |
|---|---|---|---|---|
| Strydom et al. (2002) (Brief report) | Structural MRI | 8 studies (Four of these included adults with DS and dementia.) | | Overall, the size of brain structures such as cerebellum, hippocampus and cortex of adults with DS without dementia was significantly smaller than in normal controls. The basal ganglia were similar in size, and ventricles were enlarged. Furthermore, the size of brain structures in adults with DS and dementia was significantly different than in DS without dementia. In particular, ventricular and hippocampal volumes were affected. |
| Guidi et al. (2011) | Different methodologies | 7 | 19,28 weeks | In fetuses with DS the cerebellum had an immature pattern, a reduced volume and notably fewer cells (-25%/-50%) in all cerebellar layers. In the cerebellum of DS fetuses there is a generalized hypocellularity and that this defect is due to proliferation impairment, rather than to an increased cell death. The reduced proliferation potency found in the DS fetal cerebellum, in conjunction with previous evidence, strengthens the idea that the trisomic brain is characterized by widespread neurogenesis disruption. |
| Neale et al. (2018) (review) | Neuroimaging studies | 11 studies (five of these included adults with DS and AD) | | Amyloid accumulation seen on PET occurs prior to dementia onset, possibly as a precursor to the atrophy and white matter changes seen in MRI studies. Future PET studies relating tau distribution to clinical symptoms will provide further insight into the role this protein plays in dementia development. Brain activity changes demonstrated by EEG and metabolic changes seen via PET may also follow predictable patterns that can help track dementia progression. Finally, newer approaches such as retinal imaging will hopefully overcome some of the limitations of neuroimaging and allow for detection of dementia at an earlier stage. |
| Levman et al. (2019) | Structural MRI | n=47 | 4 groups, mean 9,89 | Increased average cortical thickness in the postcentral gyrus and abnormalities in BA 1 and 3b in DS across all age ranges. Strong effect sizes associated with decreased cortical thickness variability in the lateral orbitofrontal gyrus, the postcentral gyrus in DS. Findings suggest regionally irregular GM development in DS. |
| Rodrigues et al. (2019) (review) | Neuroimaging studies | | | Functional and structural brain abnormalities are present in DS and may be further characterized by advanced neuroimaging techniques. |
| Baburami et al. | Neuroimaging | | | As little is known about early brain development in human Down syndrome, we review recent |

| Authors | Technique | n (DS) | Mean age DS (years) | Major findings |
|---|---|---|---|---|
| (2019) | studies | | | advances in MRI that allow non-invasive visualization of brain macro- and microstructure, even in utero. It is hoped that together these advances may enable DS to become one of the first genetic disorders to be targeted by antenatal treatments designed to 'normalize' brain development. |
| Shiohama et al. (2019) | Structural MRI | 20 | 1,6 | Decreased volumes in bilateral cerebellar GM, right cerebellar WM, brainstem, and cortical abnormalities in the right superior temporal, right rostral anterior cingulate, and left rostral middle frontal gyrus, independent of comorbid effects. Only bilateral cerebellar GM volumes and brainstem volumes showed differences between DS and healthy groups during infancy. |
| Lee et al. (2020) | DTI | 15 | 17 | Marked hypoplasia of cerebellar afferent systems in DS, including fronto-pontine (middle cerebellar peduncle) and olivo-cerebellar (inferior cerebellar peduncle) connections. Prominent GM hypoplasia was observed in medial frontal regions, the inferior olives, and the cerebellum. Very few abnormalities were detected by classical diffusion MRI metrics, such as fractional anisotropy and mean diffusivity. |
| Patke et al. (2020) | Structural MRI | 52 | Fetuses (>28 weeks) | Deviations in development and altered regional brain growth in the fetus with DS from 21 weeks 'gestation were detected, when compared to age-matched controls. Reduced cerebellar volume was apparent in the second trimester with significant alteration in cortical growth becoming evident during the third trimester. Developmental abnormalities in the cortex and cerebellum are likely substrates for later neurocognitive impairment, |

Note: BA: Broadman's area; GM: Grey matter; MRI: Magnetic Resonance Imaging; WM: white matter

*Table 7. Studies using functional MRI in DS and major findings.*

| Authors | Design | n (DS) | Mean age DS | Area | Analyisis | Major findings |
|---|---|---|---|---|---|---|
| Seyffert et al. (2002) | Block design (Task: silent naming of pictures) | 3 | - | - | | Greater activation was observed in the right inferior frontal and right superior temporal gyrus in the DS group than in the controls. |
| Reynolds Losin et al. (2009) | Block design (Task: passive story listening) | 9 | 16.5 | Whole brain | | The TD group exhibited greater activation than did the DS group in classical receptive language areas (superior and middle temporal gyri) for forward > backward speech; the DS group exhibited greater activation in cingulate gyrus, superior and inferior parietal lobules, and precuneus for both forward speech > rest and backward speech > rest. The DS group showed almost no difference in activation patterns between the language (forward speech) and nonlanguage (backward speech) conditions. |
| Jacola et al. (2011) | Block design (Task: decision based on semantic information from visual stimuli) | 13 | 18.30 | Whole brain | | Controls had 13 areas activated, whereas DS had 20 areas activated. |
| Anderson et al. (2013) | Visualizing cartoons | 15 | 20.2 | Whole brain | | DS showed higher levels of synchrony between distributed brain networks as well as between the vast majority of GM regions. They exhibited weaker correlations only for a relatively small subset of the most correlated regions, whether negatively or positively related. Regardless of the distance separating the regions, pairs of regions that showed anticorrelation in a large control sample showed increased correlation (reduced anticorrelation) in DS. |
| Jacola et al. | Block design (Task: | 11 | 18.30 | Whole brain | | Activation in the DS group differed significantly in magnitude and |

| Authors | Design | n (DS) | Mean age DS | Area | Analyisis | Major findings |
|---|---|---|---|---|---|---|
| (2014) | passive story listening) | | | | | spatial extent when compared with chronological and mental age matched TD control groups during a story listening task. Results provide additional support for an atypical pattern of functional organization for language processing in this population. |
| Anderson et al. (2015) | Visualizing cartoons | 15 | 20.2 | Dorsal attention network | | In TD individuals, the brain's dorsal attention network was most active during violent scenes in the cartoons; this was significantly and specifically reduced in DS participants. Individuals with DS exhibited significantly reduced activation in the primary sensory cortices, and such perceptual impairments may constrain their ability to respond to more complex social cues such as violence. |
| Vega et al. (2015) | Resting-state | 10 | 38.98 | Seven functional networks (Yeo et al., 2011) | Network analyses | The results showed that alterations of between-network connectivity, particularly in the DMN, are a characteristic of a number of neurodevelopmental disorders involving ID, including DS and WS. Perhaps within-network connectivity is a feature that shows more variable patterns across different neurodevelopmental disorders. |
| Pujol et al. (2015) | Resting-state | 20 | 24.4 | Whole-brain | DC and seed-based | DS showed higher connectivity degree in a region involving the ventral ACC and extending to the ventral portion of the medial frontal cortex and implicated the right amygdala.DS showed lower connectivity degree in the dorsal ACC, dorsal extent of the medial prefrontal cortex, dorsal prefrontal cortex, and posterior insula. Seed-based analyses confirmed FC alterations in DS. |
| Wan et al. (2017) | Block design | 38 | 13.17 | Whole brain | | The results showed that the DS intervention group had significant improvements in after the intervention. The *f*MRI results indicated more activation in the superior and inferior parietal lobes (spatial manipulation), as well as the precentral gyrus and dorsal premotor cortex (motor imagery) in the DS intervention group.In within |

| Authors | Design | n (DS) | Mean age DS | Area | Analyisis | Major findings |
|---|---|---|---|---|---|---|
| | | | | | | comparisons, , TD individuals showed highly significant bilateral activations in the middle occipital gyrus, middle temporal gyrus, middle frontal gyrus, and inferior frontal gyrus. |
| Wilson et al. (2019) | Resting-state eyes closed | 34 | 43.5 | DMN | Seed based FC | The results revealed widespread positive connectivity of the DMN in people with DS and a stark lack of anticorrelation. However, in contrast to typically developing controls, DS group also showed significantly weaker connections in localized frontal and posterior brain regions. |
| Carbó-Carreté et al. (2020) | Resting-state | 22 | 25.5 | DMN | Graph analyses | Significant differences were obtained in Characteristic path length, SD path length, complexity, Small Worldness and Dunn index. There is a negative correlation between the complexity of the connectivity networks and the Quality-of-Life values |
| Figueroa-Jiménez et al. (2021) | Resting-state | 22 | 25.5 | DMN | Graph analyses | A higher density of overactivation was identified in DS group in the ventral, sensorimotor, and visual DMN networks, although within a framework of a wide variability of connectivity patterns in comparison with the control group network. |
| Figueroa-Jiménez et al. (2021) | Resting-state | 22 | 25.5 | DMN | Dynamic effective connectivity | Connectivity patterns appeared to be different in both groups, and networks in people with DS showed more complexity and had more significant effects than networks in control participants. However, both groups had synchronous and dynamic effects associated with ROIs 3 and 4 related to the upper parietal areas in both brain hemispheres as axes of association and functional integration. It is evident that the correct classification of these groups, especially in cognitive competence, is a good initial step to propose a biomarker in network complexity studies. |
| Figueroa-Jiménez et al. | Resting-state | 22 | 25.5 | DMN | Graph analyses | There was a significant difference in complexity indicators between groups: the control group showed less complexity than the DS group. |

| Authors | Design | n (DS) | Mean age DS | Area | Analyisis | Major findings |
|---|---|---|---|---|---|---|
| (2021) | | | | | | Moreover, the DS group showed more variance in the complexity indicator distributions than the control group. In the DS group, significant and negative relationships were found between some of the complexity indicators in some of the DMN networks and the cognitive performance scores. |
| Rosas et al. (2021) | Resting-state | 26 | 47.5 | DMN (Yeo et al., 2011) | Seed-based FC | Analysis of intra-network connectivity of the DMN revealed anterior posterior DMN dissociation and hyper- and hypo-connectivity, suggesting "accelerated aging" in DS. Disruption of the DMN may serve as a prelude for AD in DS |
| Koenig et al. (2021) | Resting-state | 11 | 29.4 | DMN (Yeo et al., 2011) | Seed-based FC | The DS group showed increased connectivity strength from the anterior cingulate to the bilateral inferior frontal gyri and right putamen. In non-demented adults with DS, FC within the DMN may be analogous to changes reported in preclinical AD, and warrants further investigation as a measure of dementia risk. |
| Koenig et al. (2021) | Resting-state | 22 | 25.5 | Hyppocampus | Seed-based FC | In the group with DS, bilateral hippocampi showed widespread reductions in the strength of FC, predominately to frontal regions. |
| DiProspero et al. (2022) | Resting-state | 29 | 48,16 | DMN | Seed-based FC | Lower functional connectivity between long-range but not short-range DMN regions predicts AD diagnosis and cognitive decline in people with DS. Aβ accumulation in the inferior parietal cortex is associated with lower regional DMN FC. |
| Csumitta et al. (2022) | Resting-state | 19 | 16.53 | Whole-brain | Whole-brain FC and network selectivity | Whole-brain functional connectivity was significantly higher in youth with DS compared to controls in widespread regions throughout the brain. Additionally, participants with DS had significantly reduced network selectivity compared to TD peers, and selectivity was significantly related to connectivity in all participants. Exploratory |

| Authors | Design | n (DS) | Mean age DS | Area | Analyisis | Major findings |
|---|---|---|---|---|---|---|
| | | | | | | behavioral analyses revealed that regions showing increased connectivity in DS predicted Verbal IQ, suggesting differences in connectivity may be related to verbal abilities. These results indicate that network organization is disrupted in youth with DS such that disparate networks are overly connected and less selective, suggesting a potential target for clinical interventions. |

Note: AD: Alzheimer's disease; DMN: Default mode network; FC: Functional Connectivity; ID: Intellectual disability; IQ: Intelectual quotient; ROI: region of interest; TD: typically developing; GM: Grey matter; WS: Williams syndrome. Adapted from Carbo et al. (2020). New studies added.

## 1.3 Justification of the current research

As mentioned, neuroimaging tools enhance healthy brain knowledge and are successful tools that can disentangle the differences between healthy and diseased brains, with the *f*MRI being the tool of choice for researchers as it allows registration in an indirect way brain activation and activity (Zhou et al., 2019).

Resting-state paradigms are acquired in absence of a stimulus of task and registers spontaneous BOLD signal alterations (Lv et al., 2018). This lack of a task makes resting-state *f*MRI particularly attractive for persons who may have difficulty with task instructions, such as those with neurologic, neurosurgical, psychiatric conditions and for pediatric patients. Thus, there's been an exponential growth in resting-state *f*MRI application in research and clinical setting in the past two decades (Smith, 2012).

However, this increase in the number of studies using resting-state is limited when including people with ID. There are many reasons to explain this fact. First, a difficult challenge in this paradigm, and in general, when using *f*MRI, is the presence of head movements, which can decrease the validity and reliability of the results (Power et al., 2015). In this sense, some populations have more propensity to experience increased movements in head motion, for instance, people with ID. It is due to the difficulties in the scan to maintain still and without moving (Pujol et al., 2014), and sometimes, there are difficulties understanding the instructions (Carbo-Carreté et al., 2020). Nevertheless, considerable training and following the instruction from the scan (Fassbender et al., 2017) can reduce movement. Moreover, the difficulties of finding samples and the misgivings of the legal tutors to participate in these studies are reasons for the decrease in the published studies of this population.

DS population offers a unique opportunity to study the temporal progression of AD because of its high incidence (Lott & Head, 2019). In addition, this population could provide researchers with tools, biomarkers and knowledge about the presentation of AD in general population. Moreover, the difficulties in evaluating the cognitive level and cognitive profile of this population makes DS an interesting population to try to find tools to evaluate their cognitive decline (Carbo-Carreté et al., 2020) and resting-state *f*MRI could provide tools and new assessments. More importantly, given the variability found in DS with the onset of AD (Contestabile et al., 2010) the study of this population could provide insights into the protective factors for dementia, and AD.

In sum, the study of the DS population with *f*MRI techniques could provide information about biomarkers of cognitive decline linked to the age of onset of AD in DS. As shown in Table 7 the studies in this population using *f*MRI have been limited and merging the different samples, the age, and methodologies. In this case, the sample age is crucial in this research. Wilson et al. (2019)

and Rosas et al. (2021) found differences in FC using the resting-state paradigm, and they hypothesize that this could be a prelude to AD.

## 1.4 Aims and hypothesis

This thesis belongs to a larger project which aims to study the relationship between FC, physical activity, neuropsychological performance, and quality of life in a sample of DS. All these factors could be related to the concept of CR, and, at the same time, could be related to the dementia prevention. The protocol applied during the thesis can be found on Appendix 1, for participants with DS, and in Appendix 2, the differences in the control's protocol compared with the one of DS. For the first study, data of neuropsychological outcome, physical activity and quality of life were used of people with DS and controls. For the second and third study, as they were reviews, no data were used. For the forth study, data concerning neuropsychological outcome and *f*MRI was used of controls and participants with DS. Finally, for the fifth study, data concerning *f*MRI was used of participants with DS and controls.

The aim of this thesis is twofold. First, there is a need to overcome some methodological issues arising from working with the DS population, which are missing data and small sample sizes. As mentioned before, the recruitment of the DS population is strenuous, and missing data in physical assessment and neuroimaging has been very common throughout the application of the protocol. At the same time, in neuroimaging studies, sample sizes are tiny, and the effects found in the different studies are often low and inconsistent (Button et al., 2013; Radua & Mataix-Cols, 2012). Thus, there is a need to quantitatively consolidate effects across individual studies to overcome problems associated with individual neuroimaging studies. In this context, meta-analyses are helpful by combining and summarizing the data of interest and potentially offer insights that are not immediately apparent from the individual studies (Radua & Mataix-Cols, 2012).

In second place, and in front of the state of art presented in DS linked with neuroimaging studies, there is a scarcity of studies in this field. Therefore, the second aim of this thesis is to study the state of art in resting-state *f*MRI in DS and use different resting-state *f*MRI techniques in a sample of young people with DS and compare them with age and gender matched controls. The techniques were selected because they were novely approaches applied in this population and because they were data-driven approaches. Given the scarcity of studies using resting-state approach in DS population, there are few hypothesis available in the literature.

Summarizing, the main aims of the studies are, therefore, the followings:

- The first study constructs an heuristic for the treatment of missing data and small sample sizes (very typical found in the DS population) and develops a measurement model for the operational definition of CR in a DS population.

- The second study describes the state of art in ID and task-*f*MRI by using metanalytic techniques to elucidate a common pattern of altered network connectivity common for all the types of ID. Moreover, tries to overcome, another time, the problem of small sample sizes in neuroimaging studies.

- The third study is a systematic review of the main studies using *f*MRI to asses' people with DS. Basically, the main aim is to provide a reference point that allows to systematically accumulate and order the available information and the findings derived from the *f*MRI and DS binomial and provide useful insights that identify the main difficulties and findings that researchers could use and discuss different ways to solve these difficulties.

- The forth study focuses on finding whole-brain resting-state differences between controls and DS using fALFF and ReHo strategies to find differences in spontaneous brain activity. Moreover, this study also tries to link the differences between both populations using cognitive outcomes.

- The fifth study elucidates the differences among DS and controls in Degree centrality, seed-based FC and finally brain network analyses.

Table 8 shows the summary of the aims, research questions and hypotheses guiding all the studies.

*Table 8. Aims, research questions, and hypotheses guiding each study of the present thesis.*

| Study number and title | Aim | Research question | Hypotheses | Main contributions |
|---|---|---|---|---|
| 1. Confirmatory factor analysis with missing data in a small sample: cognitive reserve in people with Down Syndrome | - Establish a heuristic for the treatment of missing data and small samples sizes.<br>- Develop a measurement model for the operational definition for CR in a DS population. | - Can we find a methodology to deal with missing data and small samples?<br>- Can we find an operational definition of CR in DS? | - CR in DS will follow a similar structure than in the general population, including latent factors such as personal conditions, quality of life, cognitive outcome and physical activity. | -A new method to evaluate multiple imputations when missing data is present.<br>- Application of a Confirmatory factor Analysis with Bayesian estimations, with two corrections.<br>- Operational definition of CR in DS. |
| 2. Task-Related Brain Connectivity Activation Functional Magnetic Resonance Imaging in Intellectual Disability Population | - Study the different publications in task-*f*MRI and different ID populations to make a qualitative and quantitative analysis in this field. Previous studies sustain the reason to study task-*f*MRI designs such as the one by Vega and associates (2015), outlining this procedure's utility. | - Can we find a common pattern of altered network connectivity for all the types of ID? | - Find a pattern in different brain abnormalities with ID compared with healthy controls. | - A common pattern found within ID: decrease in the right temporal gyrus, which is involved in many cognitive domains such as semantic processing and language. |
| 3. Using *f*MRI to Assess Brain Activity in People with Down Syndrome: A Systematic Review | - Describe the state-of-the-art in *f*MRI techniques for recording brain signals in people with DS.<br>- Provide useful insights identifying the main difficulties.<br>- Discuss different ways to solve these difficulties | - Which is the state-of-art of using *f*MRI to assess people with DS?<br>- *f*MRI signal is adequate for use in DS population?<br>- Which are the main difficulties in this field? | - *f*MRI is a good tool to assess people with DS.<br>- There is a scarcity of studies using *f*MRI in DS.<br>- There are difficulties using *f*MRI in DS. | - Few works have been published in this field.<br>- *f*MRI is an appropriate tool to assess cognitive function in DS.<br>- There is a need to incorporate rigorous cognitive activity procedures in evaluations of the DS population.<br>- Several factors must be considered when designing an *f*MRI study on |

| Study number and title | Aim | Research question | Hypotheses | Main contributions |
|---|---|---|---|---|
| | | | | resting-state or task *f*MRI in DS. |
| 4. Altered spontaneous brain activity in Down syndrome and its relation with cognitive outcome | - Study whole-brain resting-state using fALFF and ReHo strategies to find differences in spontaneous brain activity among young people with DS and controls.<br>- Relate the significant differences with cognitive outcome. | - Are there differences in spontaneous brain activity between young DS and controls?<br>- Could these differences be related to cognitive outcome? | - There are significant differences between both groups, as seen in other resting- state *f*MRI studies.<br>- Differences are located in the DMN and frontal lobes as seen in other FC studies.<br>- Spontaneous brain activity in temporal and frontal lobes, and frontoparietal regions are different between both populations because they seem engaged in functions which are impaired in DS (memory, executive functions and language). | - Altered fALFF and ReHo is found in DS participants, involving increased and decreased values in this population.<br>- High relationship has been found between the brain signal of the different regions which were significantly different between both populations and the cognitive outcome, evaluated with KBIT-2 and verbal fluency tests.<br>- fALFF and ReHo could be used as biomarkers of cognitive function, which is highly important given the difficulties in cognitively evaluating this population to assess dementia. More research is needed, however, to demonstrate its utility. |
| 5. Abnormal degree centrality and Functional Connectivity in Down syndrome: a resting-state functional MRI study | - Perform DC to identify voxels that show altered FC with other voxels, comparing a young DS group with controls.<br>- Conduct seed-based FC with the areas showing differences between DS and controls to disentangle the underlying mechanism of DS. | - Is DC altered in DS population?<br>- Is FC altered in DS using the significant voxels of DC analyisis?<br>- Are the brain networks of Yeo et | - DC and seed-based FC are altered in DS group.<br>- Between and within network connectivity using Yeo et al. (2011) parcellatiions are altered in DS, involving regions as the cerebellum, frontal lobes and DMN, following other findings in this population. | - Alterations in DC are found in DS, finding increased DC in the temporal and right frontal lobe, as well as in the left caudate and rectus, and decreased DC in the in regions of the left frontal lobes.<br>- Seed-based FC is altered in this population. |

| Study number and title | Aim | Research question | Hypotheses | Main contributions |
|---|---|---|---|---|
| | - Perform network analyisis using the obtained results of the significant voxels of DC and the seed-based analyisis as regions of interest, classifying them using the Yeo et al. (2011) parcellations. | al. (2011) altered in DS population? | - An anterior-posterior dissociation in the DMN could be found following other studies. | - Within connectivity is only altered in the DMN, finding also an anterior-posterior dissociation.<br>- Between connectivity is altered involving all the networks included in the Yeo et al. (2011) parcellation. |

Note: CR: Cognitive reserve; DC: Degree centrality; DMN: Default mode Network; FC: Functional Connectivity; KBIT: Kauffman Brief Intelligence test

## 1.5 Construction of the protocol for the recollection of the data

As it has been aforementioned, this thesis belongs to a larger project which aims to study the relationship between FC, physical activity, neuropsychological performance and quality of life in a sample of DS. Therefore, a protocol was constructed for the participants with DS and for the control participants. The Bioethical Committee of the Universitat de Barcelona approved the project (03/16/2017) The protocol applied during the thesis can be found on Appendix 1, for participants with DS. As there are very few changes between both protocols, the changes for control participants are summarized in Appendix 2. For minors and the participants with DS, informed consent of the guardians in legal charge of every person with DS was obtained. Informed consent was also acquired from all DS and control participants. For control participants also informed consent was acquired, and in case the participants were minors, the guardians in legal charge also signed the informed consent. Sample description and recruitment can be found in the studies. In this sense, the measures that were collected for both participants are summarized in table 9. All the instruments used throughout the present thesis are described briefly in the studies that have been used. It is important to highlight that data from DS subjects was recollected from January 2018 until December 2021. In the case of control subjects, the data was recollected from January 2019 until December 2021. This long period of recruitment was due to the COVID pandemic situation, which made unable to recollect data during February 2019 until September 2021.

Finally, it is important to highlight that for the first study of the present thesis, the data used was from Mexico (54,3%) and from Spain (45,7%). The same protocol was applied in Mexico as in Spain. However, data from MRI was also acquired in both countries, but the Mexican sample was not used in the rest of the studies because the scan characteristics were slightly different. Therefore, for the forth and fifth study the Spanish sample was used in order to conserve scanning procedures.

*Table 9. Instruments used to assess DS participants and control participants.*

| | DS participants | Control participants |
|---|---|---|
| Sociodemographic information | Sociodemographic questionnaire<br>DSQIID (Deb et al., 2007) | Sociodemographic questionnaire |
| *f*MRI in Spain | Philips Ingenia 3 MRI scanner T<br>fMRI recording sequence: T1, T2, Flair, and resting state (6 minutes with their eyes opened and fixed on a cross symbol on the screen). | Philips Ingenia 3 MRI scanner T<br>fMRI recording sequence: T1, T2, Flair, and resting state (10 minutes with their eyes opened and fixed on a cross symbol on the screen). |
| Cognitive evaluation | FAB (Dubois et al., 2000)*<br>KBIT verbal and nonverbal evaluation. IQ total measure | KBIT verbal and nonverbal evaluation. IQ total measure |

| | DS participants | Control participants |
|---|---|---|
| | (Kaufman, 1990) | (Kaufman, 1990) |
| | Semantic fluency | Semantic fluency |
| | Phonological fluency | Phonological fluency |
| Physical Activity | Level of Physical Activity Scale (Carbó-Carreté et al., 2016). | Sedentary level using GT3x |
| | Total Physical Activity GT3x | Total Physical Activity GT3x |
| | Sedentary level using GT3x | |
| Quality of Life evaluation | Spanish version of the Personal Outcomes Scale (Carbó-Carreté, Guàrdia-Olmos & Ginñe, 2015) | WHOQOL-BREF(Whoqol group, 1998) |
| Nutrition | ENKID (Serra-Majem et al., 2001) | ENKID (Serra-Majem et al., 2001) |

Note: *:Only administered to n=10 DS participants. The *f*MRI protocol for Mexican subjects was different fron the one presented here. As no *f*MRI Mexican data has been used for the present thesis, it will not be described. DSQIID: Dementia Screening Questionnaire for Individuals with Intellectual Disability; FAB: Frontal Assessment Battery; KBIT: Kauffman Brief Intelligence test; WHOQOL-BREF: The World Health Organization Quality of Life Scale Brief Version.

A sociodemographic questionnaire created was used to get simple information of the participants, as well as the consent for the participation. For participants with DS, the DSQUID (Deb et al., 2007) was used in order to assess the presence of other comorbid diagnoses implying cognitive dysfunction.

As it can be seen, for cognitive evaluation of the participants, in first place the FAB was used (Dubois et al., 2000). However, due to the lack of information given regarding Intelligence Quotient (IQ) assessment, the KBIT-2 (Kaufman Brief Intelligence Test; Kaufman, 1990) was used instead for all the subjects. Despite cognitive assessment of people with DS is challenging (Carbó-Carreté et al., 2020), the KBIT was chosen, in first place, to guarantee possible comparisons between DS and controls in the cognitive outcome. Moreover, this test has been used to assess neuropsychological performance in DS in multiple occasions (Anderson et al., 2013; Hamburg et al., 2019; Csumitta et al., 2022) and was chosen because of its ability to ensure items were age appropriate as the age rank for the administration is sufficiently large. In addition to the KBIT-2 evaluation, the semantic verbal fluency was also evaluated (by the number of words produced during 1 min in two conditions and the things to buy in a supermarket and names of colors), as well as the phonological verbal fluency (by the number of words produced beginning with the letter “p” during 1 min).

Physical activity was evaluated in Bellvitge using GT3x Actigraph accelerometers (ActiGraph, Fort Walton Beach, FL, USA) (Oviedo et al., 2017) for both groups. However, for people with DS the Level of Physical Activity Scale (Carbó-Carreté et al., 2016) was also used.

Moreover, ENKID (Serra-Majem et al., 2003) was used to evaluate the adherence to the Mediterranean diet, despite this test hasn’t been used in the present thesis. In a systematic review

performed recently (Idelson et al., 2017) they conclude that ENKID was one of the most used questionnaires for evaluating the adherence to the Mediterranean diet.

Finally, regarding Quality of Life, two different evaluations were done for both groups. In DS group, the Spanish version of the Personal Outcomes Scale was used (Carbo-Carreté et al., 2015). In control group, the WHOQOL-BREF Quality of life assessment (Whoqol group, 1998) was used instead.

Figure 4 is a photography recollected from the sampling of DS in Fundació Pasqual Maragall.

*Figure 4. Photo of Fundació Pasqual Maragall of the recollection of the data.*

## 1.6 Timeline

In table 10 the timeline of the present thesis can be found.

*Table 10. Timeline of the present thesis.*

| Tasks | 2017* | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|
| Literature search | | | | | | |
| Design of the protocol with the team | | | | | | |
| Data collection sample DS (team) | | | | | | |
| Data collection of control sample | | | | | | |
| Analysis study 1 | | | | | | |
| Analysis study 2 | | | | | | |
| Analysis study 3 | | | | | | |
| Publication study 3 | | | | | | |
| Publication study 1 | | | | | | |
| Publication study 2 | | | | | | |
| Data collection control samples (team) | | | | | | |
| Research stays in China (November 2021-July 2022) | | | | | | |
| Analysis study 4 | | | | | | |
| Analysis study 5 | | | | | | |
| Publication study 4 | | | | | | |
| Publication study 5 | | | | | | |
| Thesis presentation | | | | | | |

Notes: *From October when this project started. Team: Dr. Guàrdia-Olmos, Dra. Peró-Cebollero, Dra. Carbó-Carreté. Data collection was interrupted because of COVID from March 2020 until November 2021. Some tasks, like literature search, update and congresses presentations took place at several points, according to the project's progress.

# 2. Studies

## 2.1 Study 1: Confirmatory factor analysis with missing data in a small sample: cognitive reserve in people with Down Syndrome

### *2.1.1 Identifying data*

Quality & Quantity
https://doi.org/10.1007/s11135-021-01264-x

Check for updates

# Confirmatory factor analysis with missing data in a small sample: cognitive reserve in people with Down Syndrome

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### *2.1.2 Abstract*

The presence of missing data and small sample sizes are very common in social and health sciences. Concurrently to present a methodology to solve the small sample size and missing data, we aim to present a definition of Cognitive Reserve for people with Down Syndrome. This population has become an appealing focus to study this concept because of the high incidence of dementia. The accidental sample comprised 35 persons with DS (16– 35years). A total of 12 variables were acquired, four of them had missing data. Two types of multiple imputation were made. Confirmatory factor analysis with Bayesian estimations was performed on the final database with non-informative priors. However, to solve the sample size problem, two additional corrections were made: first, we followed the Jiang and Yuan (2017) schema, and second, we made a Jackknife correlation correction. The estimations of the confirmatory factor analysis, as well as the global fit, are adequate. As an applied perspective, the acceptable fit of our model suggests the possibility of operationalizing the latent factor Cognitive Reserve in a simple way to measure it in the Down Syndrome population.

**Keywords:** Missing data, Small sample, Bayesian structural equation models, Down syndrome, Cognitive reserve

### *2.1.3 Introduction*

In the field of social and health sciences the presence of sample anomalies is very common, specifically, samples are usually characterized by reduced sample size and missing data (Cohen 1990; Silvia et al. 2014). Obviously, these types of samples directly affect the validity of the data, the generalizing possibility of the results and the investigation quality. Moreover, most data analysis procedures are not designed for these abnormalities (Schafer and Graham 2002). However, in recent years Bayesian estimations have become popular in many scientifc fields (Muthén and Asparouhov 2012; McNeish 2016; König and van der Schoot 2018, Smid et al. 2020), mainly because of the availability of popular softwares and because it adds some advantages over frequentists estimations. Regarding these advantages, one of the most interesting features is it's flexibility to work with small samples sizes (MacNab et al. 2011; Smid et al. 2020).

In relation to missing data, multiple imputation (MI) techniques have become popular to replace the lost values with simulated data that allow the full cases analysis. These techniques are not exempt from controversy since they assume an arbitrary alteration of the original distributions and can modify some of their statistics (He 2010). There are a multitude of imputation possibilities and easy access, which implies an evident risk of erroneous selection of these techniques (Graham et al. 2006; Rhemtulla and Little 2012; Little et al. 2014; Smid et al. 2020).

Missing data is very frequent in studies with persons who have limitations to participate directly from themselves. Concurrently to present a methodology process to solve the small sample size and missing data, we aim to present a definition of Cognitive Reserve (CR) for people with Down Syndrome (DS). CR is the brain's ability to handle brain damage or disease, maintaining a stable level of function (Stern 2002, 2006, 2011, 2018). From our point of view, the study of CR concept in DS population would be of great advance to make a step forward in the dementia field. The prevalence and risk for dementia in this population is significantly different from general population or from people with Intellectual Disability (ID) of other aetiologies (Lott and Head 2019). In this population, as in general population, individual trajectories of cognitive changes are highly heterogenous, with some declining dramatically rapidly and others declining very slowly or even improving (Bull 2020; Temple et al. 2001). Given the variability that exists in DS, the implications of CR for individuals with DS deserve special attention to generate a more systematic definition (McGlinchey et al. 2014).

CR is considered to offer neuroprotective benefits against brain injury and disease by facilitating greater neural efficiency and/or enhanced capacity to develop compensatory cognitive mechanisms subsequent to the neuropathology onset (Jones et al. 2011; Stern 2002, 2006, 2011, 2018). Although this concept has been deeply studied, there are still measurement problems in order to operationalize CR by using different proxies. For instance, years of formal education is the most widely studied variable, and it is commonly used as the single proxy for the CR concept

(Valenzuela and Sachdev 2006). However, CR could be also conceived as an hypothetical factor, not directly quantified by a unique measure, but as a latent construct. Therefore, nowadays CR is studied from a latent variable data analysis approach with more proxies as leisure activities (Ruiz-Contreras et al. 2012; Suchy et al., 2011), early family environment and genetic factors (Lee 2007), intelligence quotient (IQ; Stern 2006; Tucker-Drob et al. 2009; Tuokko et al. 2003); parent socioeconomic status (Richards and Sacker 2003); education attainment (Foubert-Samier et al. 2012) and physical activities (Gow et al. 2012).

To address the CR concept, we have found some challenges related to the sample size and missing data, that we have had to solve through a suitable methodological procedure. The goal to define a concept of CR in DS population are included in a broadly study which the techniques used (e.g. aerobic capacity test) are difficult to administer in people with DS. Due to the complexity of the register techniques used, the sample obtained has been small and with enough missing data that could hinder the main study objectives.

Thus, the purposes of this paper are twofold; on the one hand, establish an heuristic for the treatment of missing data and small samples sizes, on the other, develop a measurement model for the operational definition for CR in a DS population. As far as we know, there have been no published works in which a chained heuristic is proposed to solve both issues.

### *2.1.4 Method*

#### *Participants*

The sample was composed of 35 persons with DS between 16 and 35 years old (M=24.4 and SD=5.42); 25.7% were women. The sampling was accidental, and recruitment was performed through several DS care institutions in Mexico (54.3%) and Spain (45.7%). The following inclusion criteria were applied: (a) age between 16 and 35 years old and (b) formal diagnosis of DS through karyotyping. Regarding the exclusion criteria: (a) evidence of other comorbid diagnoses implying cognitive dysfunction; (b) impossibility of obtaining consent from legal tutors; and (c) presence of medication affecting cognitive functions. In order to assess the presence of other comorbid diagnoses implying cognitive dysfunction, the Dementia Screening Questionnaire for Individuals with Intellectual Disability (DSQIID) was used. It has a high internal consistency ($\alpha$=0.91; Deb et al., 2007). Thus, based on the mentioned criteria the final sample was composed of 31 participants.

The diagnostic of ID is based in the Spain government law about disability, which assigns a “handicap” percentage to every person with a disability to represent the condition severity. The disability percentage is assigned administratively based on all types of impairments (e.g., intellectual, physical, sensorial). In the present study, 58% of the sample had mild ID, 38.7% had

moderate ID, 3.2% had severe ID. None of the participants had sever or profound ID. IQ was assessed using the Kaufman Brief Test of Intelligence (KBIT, Kaufman and Kaufman 1990). However, due to the no adaptation of the test for people with ID, it wasn't included in the CFA model. However, IQ had a mean in our sample (n=21) of 46.21(SD: 10.91); with a minimum of 40 and a maximum of 80.

***Instruments***

These data are part of a larger protocol in which the relation between cerebral signal (*f*MRI) and variables connected with cognitive outcome, quality of life and physical activity is studied. In the current study, in addition of the age and ID diagnosis (Personal Conditions) described above, the variables assessed through the next scales and tests were included. For the Quality of Life assessment, the Spanish version of Personal Outcomes Scale was used (Carbó-Carreté et al. 2015). This scale aims to assess quality of life in people with ID on the basis of the eight domain quality of life model (Schalock and Verdugo 2002), which was arranged into three higher-order factors: Independence (personal development, self determination, interpersonal relations); Social participation (social inclusion, rights); Wellbeing (emotional wellbeing, physical wellbeing, material wellbeing) (Wang et al. 2010). The reliability is appropriate for the domains and, particularly, for the factors, with α values higher than 0.82.

The Cognitive Outcomes were assessed by three measurements tools: (a) the semantic fluency (number of words produced during 1 min in two conditions, things to buy in a supermarket and names of colors); (b) the phonological fluency (number of words produced beginning with the letter "p" during 1 min) and (c) administration of the Frontal Assessment Battery (FAB) with an internal consistency of α=0.78 (Dubois et al. 2000).

In relation the Physical Activity there were four assessments: (a) the first was related to the level of practice of physical activity, through the Level of Physical Activity Scale (LPAS) (Carbó-Carreté et al. 2016). The internal consistency of this scale is α=0.79. The next two measurements were about physical activity and sedentary level by using GT3x Actigraph accelerometers (ActiGraph, Fort Walton Beach, FL, USA) (Oviedo et al. 2017). Specifcally, (b) the Total Physical Activity (Total PA) were calculated by assessing the accelerations of the device on the longitudinal axis 1 (counts/min) and (c) the Vector Magnitude (counts/min), understood as the device accelerations on the longitudinal, sagittal and frontal axis, was calculated by the square root of the sum of the squares of the three axes. Finally, (d) the Cardiorespiratory Fitness was determined by obtaining the peak oxygen consumption relative to body weight (relative VO2 peak; ml/kg/min).

***Procedure***

The applied protocol was approved by the Bioethical Committee of the Universitat de Barcelona (16/03/2017) and the data was registered between March 2018 and July 2019. Informed consent of parents or tutors in legal charge of every person with DS was obtained. Moreover, informed consent from the participants with DS was obtained. All the participants were evaluated in two register sessions by previously trained investigators. The administration sequence was the same for all the participants, and the scales referenced above were administered first to avoid fatigue bias.

For the quality of life and for the Level of Physical Scale parent's participation was accepted. For the Cognitive Outcomes and the rest of Physical Activity it was required the direct participation of the person with DS. The researchers who administered the scales and the physical tests were specific professionals trained to do these assessments. In the Mexican and Spanish administration, the same instruments were used in all the registers to guarantee the comparability of the data and avoid measurement biases.

***Statistical analysis and heuristics***

First, the observed distribution of the variables was studied to evaluate the impact of the missing data in every variable. Of the twelve variables studied, only 4 presented missings: ID level (11.4% of missings), Cardiorespiratory fitness (22.9% of missings), Total PA (25.7% of missings) and finally Vector Magnitude (25.7% of missings). Second, the acceptable maximum percentage for missing imputation was studied. To do so, the Little's $\chi^2$ test was applied to evaluate whether the missings followed a MCAR, which would be the more desirable pattern.

In the case of the categorical variable ID diagnostic, the prediction models based on multinomial logistic models and linear discriminant analyses were studied to identify a predictor variable combination that allowed the relevance probability to be applied to one of the four categories of ID diagnostic prediction. None of the models tested offered statistically significant results. This forced us to discard the prediction models with auxiliary variable prediction. Therefore, it was decided to use simple imputation based on linear interpolation.

For the quantitative variables, the imputations derived from the linear regression (LR) and predictive mean matching (PMM) models were obtained. In the case of LR models, the linearity between pairs of variables and the possible effects of collinearity were previously analyzed, and stepwise estimation models were chosen. For both cases, LR and PMM, a total of 10 simulated samples were obtained iterating from the initial solution, following Montenegro and Chesnut (2015), and each was analyzed to identify the best adjusted iteration.

With the aim of achieving a more exhaustive study of the imputation results, the mean SE of all imputed means was obtained from the Rubin (1976) estimation. This is a standard error (SE) estimation of the parameter mean of interest (a).

$$SE(\overline{a}) = \sqrt{\frac{1}{M}\sum_{K=1}^{M} S_k^2 + \left(1+\frac{1}{M}\right)\left(\frac{1}{M-1}\right)\sum_{K=1}^{M}(a_k - \overline{a})^2},$$

where $M$ is the number of generated databases, $s_k$ is the SE on the $K$ database, $a_k$ is the parameter estimation on the $k$ database, and $\overline{a}$ is the estimated parameter mean and uses the factor (1+1/$M$) that corrects the equation because the number of databases is finite.

However, the adjustment estimation proposed by Rubin (1976), does not make a direct comparison of the mean's SE obtained in the original distribution and in the solution after the imputation mechanism. To overcome these limitations, an adjustment index associated with the SE of the original and imputed distributions was defined. The basic expressions for calculating this index, called the imputation fit index (IFI), are shown below.

$$IFI_{mk} = |EE(\bar{x}_{m(o)}) - EE(\bar{x}'_{m(k)})| \cong 0$$

$$\overline{IFI}_m = \frac{1}{k}\left(\sum_{i=1}^{k} IFI_k\right)$$

$$S^2_{IFI_m} = \frac{\sum_{i=1}^{k}(IFI_{mk} - \overline{IFI}_m)^2}{k-1}$$

$$Z_{IFIk} = \frac{IFI_{mk} - \overline{IFI_m}}{\sqrt{S^2_{IFIm}}}$$

$$\begin{bmatrix} Z_{IFI} \leq -1{,}65 \\ \alpha = 0{,}05 \end{bmatrix},$$

where $m$ are the different variables and $k$ are the different iterations, $EE(\bar{x}_{m(o)})$ is the mean SE of the initial variable (observed) and $EE(\bar{x}'_{m(k)})$ is the mean SE of the variable in the $k$ imputation. By means of this index, the difference between the mean SE of an observed variable and the mean SE of the imputed variable is estimated. Obviously, depending on whether the result of this difference tends to 0, the two distributions are closer. However, when standardizing the IFI distribution, the fit values will be placed in the bottom tail of the distribution. In this way,

$Z_{IFI} \leq -1{,}65$ was set as the reference value for the acceptance of $H_0$, that is, the observed and imputed equality of distributions.

As the final part of the present work, the resulting database was submitted to CFA. Given the small sample size, Bayesian parameter estimations were made using Bayesian structural equation models (BSEM) with non-informative priors (Muthén and Asparouhov 2012; Asparouhov et al. 2015; Hoijtink and Van de Schoot 2017).

Obviously, it would be preferable to have informative priors (Smid et al. 2020), but we do not have solid empirical data to use them as informative priors as is the first time to our knowledge that CR in DS is studied. The correlation matrix used as the input was imputed using Jackknife correlation. This procedure consists of estimating Pearson's correlations for each pair of variables, using as many samples as are obtained from removing one subject from the sample at a time. From the distribution of correlations thus obtained, the average correlation and its 95% confidence interval were estimated. To integrate the correlation matrix, the lower limit value was used for all cases to obtain correlations that were as attenuated as possible and, at the same time, that had the least possible bias. Parameter estimations were made using MPlus version 8.4 and *ad hoc* programming in R version 3.6.3.

Given the reduced sample size, it was not feasible to study the measurement adjustment model by the usual indicators. Therefore, Jiang and Yuan's (2017) strategy was used. These authors, based on the proposals of Satorra and Bentler (1988) and Jung (2013), developed a fitting index design that is effective for multivariable normal distribution violation assumption and suitable for very small samples. Jing and Yuan's proposal (2017) is based on four fitting index extractions: $T_{COR1}$, $T_{COR2}$, $T_{COR3}$ and $P_{COR4}$. All of them oscillate between [0,1], and the right settings must be assumed in values of $T_{CORi} > .90$ and $P_{COR4} > .10$. They are defined as follows:

$$T_{COR1} = \frac{T_{ML}}{C_1}$$

where $c_1 = tr(\hat{U}\hat{\Gamma})/rank(\hat{U}\hat{\Gamma})$ is fulfilled by *rank* < *df*. This condition indicates that it is impossible to estimate more parameters in the CFA than those determined by the sample size, *n* should be lower than the number of non-duplicated units in the variances-covariances matrix ($\hat{U}$). Finally, ($\hat{\Gamma}$) is the reproduced matrix from the usual estimated parameters in the adjustment of $\chi^2$. Moreover, $T_{ML} = nF_{ML}(\hat{\theta})$, where $F_{ML}(\hat{\theta})$ is the usual discrepancy function $F_{ML}(\theta) = tr(S\Sigma^{-1}(\theta)) - log\ |S\Sigma^{-1}(\theta)| - p$.

From the previous expressions, Satorra and Bentler (1988) defined $T_{ML}$ as follows:

$$T_{ML} = \sum_{j=1}^{df} \tau_j \chi_{1j}^2$$

in which every parameter ($\tau_j$) considers the statistical adjustment of $\chi^2_{1j}$. From this expression, two more indicators are proposed. The first is the $T_{RML}$ indicator in a rescaled measure:

$$T_{RML} = \frac{T_{ML}}{r}$$

$$\text{being } r = \frac{tr(\hat{U}\hat{\Gamma})}{(p^*-q)},$$

where $p^*$ is the number of different units in R and $q$ is the number of parameters to estimate. A second indicator adjusted to the variable called $T_{AML}$ is defined as follows:

$$T_{AML} = \frac{T_{ML}}{\alpha}$$

$$\text{being } \alpha = \frac{tr[(\hat{U}\hat{\Gamma})^2]}{tr(\hat{U}\hat{\Gamma})}$$

$$T_{COR2} = \frac{T_{ML}}{C_2}$$

where $c_2 = \frac{r+c_1}{2}$ with the condition that $c_2$ should be between $r$ and $c_1$ and the value of $T_{COR2}$ should be between the values of $T_{COR1}$ and $T_{RM}$

$$T_{COR3} = \frac{\frac{T_{ML}}{r} + \frac{T_{ML}}{c_1}}{2}$$

$$p_{COR4} = \frac{(p_{RML} + p_{AML})}{2},$$

where $p_{RML}$ and $p_{AML}$ correspond to the significance levels associated with the statistics of the $\chi^2$ distribution and with the degrees of freedom of the measurement model.

### *2.1.5 Results*

***Imputation estimation***

The lost percentage effect was studied from the statistical estimation of Little's $\chi^2$ test to obtain a MCAR pattern. Little's test indicates a reasonable adjustment to a characteristic MCAR pattern (Little's $\chi^2$ test=34.024, df=27, p>.05).

In the case of the categorical variable ID diagnostic, the prediction models based on multinomial logistic models and linear discriminant analyses were studied but none of the models

tested offered statistically significant results (for instance, in the case of discriminant analysis, the Wilks' $\lambda$ values ranged from 0.750 to 0.964).

In view of the impossibility of using multiple imputations in this variable, it was decided to use simple imputation based on linear interpolation. The results after applying simple imputation shown that the median, mode and absolute deviations median for both variables were the same.

In relation to the quantitative variables, the mean SE of all imputed means were calculated through Rubin (1976) estimation. Table 11 shows the SE results for every variable and for every imputation technique.

*Table 11. Imputed variables with multiple imputation techniques and SE calculated with Rubin's technique (1976).*

| Imputed variables | LR $SE(\overline{a})$ | PMM $SE(\overline{a})$ |
|---|---|---|
| Total PA | 1618.889 | 703.483 |
| Vector Magnitude | 4263.350 | 46.121 |
| Cardiorespiratory fitness | 2.263 | 1.487 |

In all cases, the Rubin (1976) estimates are higher in the LR solution. Likewise, the distribution of Rubin's proposal does not present a standardized solution that facilitates interpretation, nor does it fix or recommend reference values from which a suitable solution is considered in a given imputation. Therefore, the imputation fit index (IFI) were calculated. An iteration process was generated by fixing a maximum of iterations (k=10) with the PMM method. It is important to remember that, given the small sample, the number of iterations recommended (Schafer and Graham 2002) was doubled to guarantee that an adequate solution was obtained. After performing the different IFI estimations for each variable, values lower than or equal to−1.65 were found for the 3 variables. Table 12 shows the IFI results in the 10 iterations performed. In this first step, an adequate value of IFI ($Z_{IFI} \leq -1{,}65$) was obtained from the imputations performed with 3 variables (Total PA, Vector Magnitude and cardiorespiratory fitness). In the third column of Table 12, the iterations number for an adequate solution are shown.

*Table 12. Variables to impute, better result in ZIFI and iteration in which the better result was found.*

| Variables ($m$) | $Z_{IFI}$ | Iteration ($k$) |
|---|---|---|
| Step 1: Iteration's start (max k = 10) | | |
| Total PA | -2.07 | 2 |
| Vector Magnitude | -2.06 | 2 |
| Cardiorespiratory fitness | -2.37 | 5 |

Note: Step 1 indicates the first iteration round.

***Confirmatory factor analysis***

Once the initial data database was reconstructed, a measurement model was established to define the CR latent factor for people with DS. This model was based on the works mentioned in the introduction with some adaptations because it is addressed to a specific population. The model proposed is composed of four latent factors (personal conditions, quality of life, cognitive outcome and physical activity). Figure 5 shows these factors with their correspondent direct indicators.

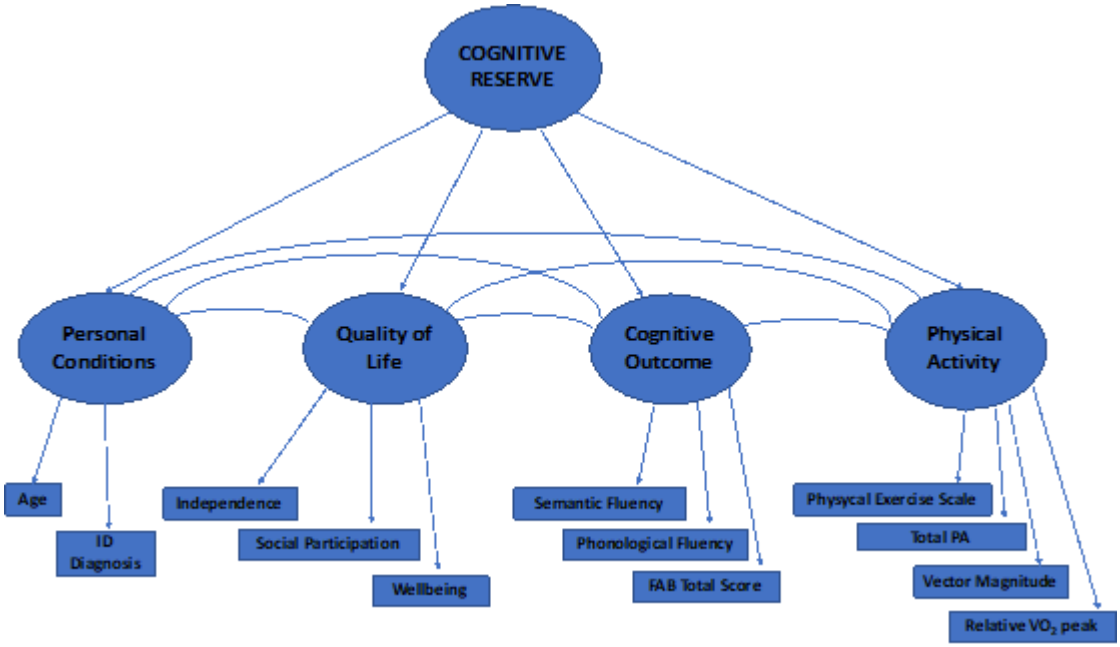


*Figure 5. Model Measurement of the Path Diagram Analysis.*

As shown in the previous figure, we have four first order latent factors, each defined by the indicators in Figure 5 and only one second-order factor. To guarantee the range condition described above, the maximum number of variables possible must be a number that allows the degrees of freedom to be equal or greater than 0. For this, the number of possible free parameters to be estimated must be known. In this case, using all the variables in Figure 5, the free parameters would be the following: Matrix $\Lambda x$ = 12 factor saturations; Matrix $\Phi$ = 6 correlation coefficients (as many as correlations other than 1 among the first-order factors); Matrix $\Theta_\delta$ = 12 estimates of the variance of the measurement error. There are no other parameters to estimate since no correlations have been established between the variances of the measurement residuals [E ($\theta_{\delta ij}$, $\theta_{\delta km}$) = 0)]. Therefore, the number of free parameters to estimate is 30. Given this value, the minimum number of possible variables is derived from the expression df = ½ [(p · p + 1)] - q, where p is the possible number of variables and q is the number of parameters. In these terms, the number of variables (p) must be greater than 8 to guarantee that $df > 0$.

In our case, the condition is confirmed; therefore, the estimates are feasible using Bayesian estimation in accordance with what is proposed by Lee and Song (2004), Muthén and Asparouhov (2012) and Smid et al. (2020). Figure 6 shows the parameter estimation, and all loading factors are statistically significant.

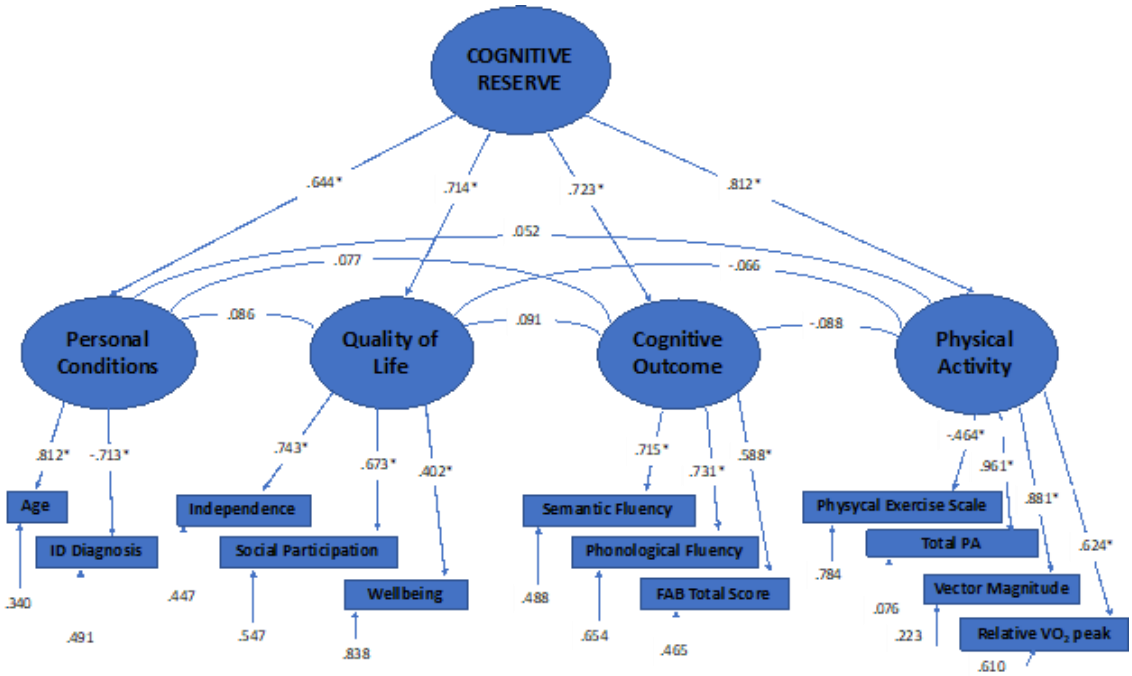


*Figure 6. Bayesian estimations of the free parameters (factor loading and correlation between factors) of the CFA with the model in Figure 5.*

Note: correlations between factors are found in the first line, factor loadings ($\lambda_i$) in the second line and finally measurement error variance $(\theta\delta_{ii})^2$ is found in the third line; * : p < .001.

Regarding the correlations between factors, they are very low in all the cases. The higher value is between factor 2 and factor 3, that are, quality of life and cognitive outcome.

Finally, Table 13 shows the adjustment values of the proposed CFA model, showing both the usual indices and those proposed in the Jiang and Yuan's work (2017) as an alternative to the adjustments for small samples. The $T_{CORR1}$, $T_{CORR2}$ and $T_{CORR3}$ values are greater than .9, and $P_{CORR4}$ is greater than .10. For all of these, we could say that the four corrections made by Jiang and Yuan (2017) demonstrate a good fit to the model. In the case of BIC values, a lower value is preferable (Asparouhov et al. 2015).

*Table 13. Statistical significance and values of the parameters of the model of measurement in Figure 6. .*

| 95% Confidence Interval for the Difference Between the Observed and the Replicated Chi-Square Values | *BIC* | $T_{COR1}$ | $T_{COR2}$ | $T_{COR3}$ | $P_{COR4}$ |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| 19.12 to 58.12 | 156.71 | .971 | .962 | .933 | .312 |

Note: BIC: Bayesian Information Criteria.

### *2.1.6 Discussion*

This study had two main objectives. The first aim of the present study was to propose a solution to overcome the problems of missing data and small sample size. MI was performed in the database, and two corrections for the small sample size were also done. The second aim of the paper was to estimate a CR model for DS people. A confirmatory factor analysis was developed and, as an applied point of view, the global fit of the model suggests the possibility of operationalizing the latent factor CR in a simple way to measure it in the Down Syndrome population.

More concretely, regarding the first aim of the study, all the variables followed MCAR distribution, and two types of MI were made, LR and PMM. Once all variables used were completed, CFA with Bayesian estimations was performed. However, to solve the sample size problem, two additional corrections were made prior to the final analysis: Jiang and Yuan (2017) schema, and a Jackknife correlation correction. The estimations of the CFA, as well as the global fit, are adequate.

Obviously, we must assume that working with missing data and small sample size is not a good scenario. Even if we add some recommendations, it is not a perfect stage to work with. Therefore, what we aim to present in this paper is only valid when resampling is not viable, and the population of interest is reduced. In the case of DS and considering the variables involved, this is the perfect situation to apply these techniques.

Past research on missing imputation has focused on which technique is the best or what point is acceptable to impute missing data (Rhetmulla and Little 2012; Little 2014). However, there is an important issue that directly affects these questions, the sample size. Our results focus on this aspect that affects all the decisions made from the first step. Our results illustrate several concerns about multiple imputation. Although the evaluation of imputations can be made by traditional estimations (Rubin 1976) and is widely used, this technique seems slightly weak because it does not directly compare the SE obtained in the original distribution and in the solution after multiple imputation. Moreover, the estimation does not evaluate which iteration works better. Therefore, to address these limitations, the use of our index (IFI) seems to be a good solution. This indicator allows us to know the point at which imputation generates a variable that behaves in a very similar way to the original one. Regarding the number of iterations made in the multiple imputations, it is important to note that although some authors argue that 5 iterations are sufficient to obtain good results (Montenegro and Chesnut 2015) and that the last iteration is normally the best, in the present paper we find that in many cases the best iteration is the second

one. As mentioned above, the proposed IFI indicator has demonstrated to be a good tool to evaluate the quality of missing imputation.

In reference to the posterior analysis, a Bayesian CFA was conducted with non-informative priors. As noted, this analysis attempted to operationalize the concept of CR in DS.

Regarding the present analysis, two specific points should be highlighted. First, we do not recommend the use of frequentist inferential techniques because of the limited sample size. Second, the use of Bayesian estimation could generate the problem of using informative or noninformative priors (Smid et al. 2020). These authors also note that the analysis with informative priors would be much stronger and much more potent in the case of small sample size, but many times, as in our case, this information is not available. The corrections that we proposed, based on Jiang and Yuan's (2017) seem to be a good approximation to study the global fit of BSEM. In the same line, our results show the capacity of conservative strategies such as the Jackknife correlation (in particular, the use of the low confidence interval value) to estimate the R matrix as an input to BSEM. The combination of both strategies makes it possible to generate a statistical framework that is more adequate to solve the small sample problem and limitations.

As an applied point of view, and regarding the second aim of this paper, the acceptable fit of the CFA model suggests the possibility of operationalizing the latent factors of CR to measure it in the DS population. The results of the individual Bayesian parameter estimation, as well the global fit, are evidence of this possibility. As proven above, Quality of Life, Cognitive Outcome, and Physical Activity can influence and mediate the concept of CR. Moreover, although years of formal education have been the principal variable studied to operationalize this concept (Valenzuela and Sachdev 2006), it is tough to measure in ID population. As mentioned above, the perspective of conceptualizing CR as a latent construct defined with different measures seems the clearer one. Obviously, according to the real properties of the sampling, this model does not allow any extrapolation for the general population and must be used strictly as an operational definition by our sample. However, it is an empirical confirmation and therefore an optimal measure for the operationalization of CR in persons with DS, at least in our sample. As it has been mentioned above, the prevalence of dementia in this population is much higher than in other ID populations and general population, this could be an initial phase in order to study the big differences encountered in DS population regarding the appearance of dementia.

These results are not exempt from some limitations. We did not study the statistical properties of the IFI to achieve a more adjusted significance or use simulations to estimate it's sensitivity specificity. Another important limitation of this study is the use of noninformative priors in the Bayesian estimation of the CFA. Clearly, more efforts are needed to develop better-performing statistics with small sample sizes and missing data in the sample. However, in relation to the CR study, this paper provides the first approximation of this concept to the DS population

and may provide a starting point to study the individual differences in the clinical and neuropathological appearance of dementias.

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## 2.2 Study 2: Task-Related Brain Connectivity Activation Functional Magnetic Resonance Imaging in Intellectual Disability Population: A Meta-Analytic Study

### *2.2.1 Identifying data*

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**REVIEW ARTICLES**

# Task-Related Brain Connectivity Activation Functional Magnetic Resonance Imaging in Intellectual Disability Population: A Meta-Analytic Study

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Authors: Cristina Cañete-Massé, Maria Carbó-Carreté, Maribel Peró-Cebollero & Joan Guàrdia-Olmos

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### *2.2.2 Abstract*

***Introduction:*** Neuroimaging studies of intellectual disability (ID) have been published over the last three decades, but the findings are often inconsistent, and therefore the neural correlates of ID remain elusive. This article aims to study the different publications in task-functional magnetic resonance imaging (*f*MRI) and different ID populations to make a qualitative and quantitative analysis on this field. ***Methods:*** After duplicates were removed, only 10 studies matching our inclusion criteria were incorporated. Moreover, a quality assessment of the included studies was done. Qualitative results of the different papers were analyzed, separated by type of task and type of ID. Seed-based d Mapping (SDM) software was used. ***Results:*** The right temporal gyrus was more activated in control subjects than in ID. Concretely, the right temporal gyrus is implicated in many cognitive domains as semantic memory processing and language. Moreover, it can be highly influenced by the type of task used in every study. Heterogeneity was not detected. A jackknife sensitivity analysis was also estimated to improve the analysis reliability, and both results were confirmed. ***Conclusions:*** More task-*f*MRI studies on ID must be published to add larger samples to address the pathophysiological questions more directly.

**Keywords:** Metanalysis, *f*MRI, Intellectual Disability, Cognitive Task

### *2.2.3 Introduction*

Intellectual disability (ID) is a common lifetime condition that significantly impacts the individuals and their family. Important limitations in cognitive performance and adaptative behaviors characterize this population (Schalock et al., 2010). This definition is proposed by the American Association on Intellectual and Developmental Disabilities (AAIDD). It highlights the importance of the social and ecological models focused on the person and the environment. At the same time, it recognizes the importance of the individualized support application to improve the person's functioning. The conception toward people with ID has changed, and nowadays, it is not only focused on intellectual functioning (Tassé et al., 2016).

The recognition of the three intelligence components and their correlation with adaptative behavior (conceptual, social, and practical skills) has brought up a new approach toward people with ID that offers new perspectives and intervention models linked with supports. Due to the individualized support mediation, optimal environments for the development and well-being of the person with ID can be promoted (Luckasson et al., 2002). Nowadays, there is a firm conviction that with adequate support application, a person's functional abilities can be enhanced, and his or her results and quality of life can be improved.

From this perspective of ID and considering that it answers to the environmental demands thanks to the support's mediation, we ask ourselves if the brain functioning of people with ID could present some irregularities. In other words, due to the adaptative behavior and the individualized supports, people with ID can develop and have a quality of life, despite their low intellectual functioning. The brain connectivity patterns of people with ID could be different from the brain connectivity patterns of people without ID.

To study brain connectivity, our principal aim is to study the different publications in functional magnetic resonance imaging (*f*MRI) and people with ID.

As it is well-known, *f*MRI estimates functional connectivity, which describes the temporal dependence between different brain areas (Friston et al., 1993). The study of the brain as an integrative network of functional connections contributes to the human behavior knowledge and also provides helpful information for the comprehension of the neuropsychiatric disease (Greicius et al., 2007; Greicius, 2008), as well as the influence of aging in cognitive function (Damoiseaux et al., 2008). The study of specific populations, as ID population, assumes that limitations in different areas result in similar functional abnormalities in brain signal (Reiss et al., 2000).

In this sense, neuroimaging studies have been published over the last three decades (Azuma et al., 2009, 2015; Bernardino et al., 2014) in ID field. For instance, Vega and associates (2015) compared the resting-state functional connectivity in three different populations: Down syndrome (DS), Williams syndrome (WS), and healthy controls. Their findings suggest that

differences in brain connectivity can be found within neurodevelopmental populations with ID compared with controls.

In general, sample sizes in these types of studies are tiny, and therefore, the effects found in the different studies are often low and inconsistent (Button et al., 2013). Consequently, researchers are driven into different methodologies as thresholding and analysis that may increase the type I errors (Eklund et al., 2016). In addition, these single imaging studies do not assemble the whole concept of ID, they are about a specific ID population, and they aim to find a specific pattern of the concrete ID population (Azuma et al., 2009, 2015; Bernardino et al., 2014).

Therefore, the neural correlates of ID persist unknown. In the field of neuroimaging, we can only find few meta-analyses that describe a single population with ID focused only on 22q11.2 deletion syndrome (22q11 DS; Scarpazza et al., 2019) or WS (Binelli et al., 2014).

From our perspective, some explanations justify why there is no meta-analysis found in *f*MRI with ID. First, problems that take place when using *f*MRI register may be exacerbated for the ID population (Carbó-Carreté et al., 2020). For instance, regarding the DS population, movements during registration can be highly increased. Consequently, experimental issues can arise (Pujol et al., 2014). In ID population, it can be a challenging task to be quiet and stay focused during the registration (Lightbody and Reiss, 2009).

Nevertheless, with considerable training and instruction for the scan (Fassbender et al., 2017), movements can be reduced. Therefore, in the last few years, some researchers have achieved the study of brain signal in the ID population. Second, it is not easy to sample this population (Carbó-Carreté et al., 2020), and people with more common disabilities will probably be more represented than people with more rare disabilities.

To date, it is therefore unclear if common aberrant connectivity patterns associated with ID can be found (Walter et al., 2009).

In this sense, as it has been mentioned above, the findings of Vega and colleagues (2015) show an altered between network connectivity common in WS and DS. They suggest that this could be characteristic of different disorders coursing with ID. Their findings highlight the utility of using a task-based procedure, a noninvasive technique that measures brain activity while participants perform different types of tasks (e.g., executive functions, language, memory, motor, among others). This technique could help resolve the association between brain function and intellectual functioning across different disorders coursing with ID (Vega et al., 2015).

Therefore, based on previous literature, this article aims to study the different publications in task-*f*MRI and different ID populations to make a qualitative and quantitative analysis in this field. Previous studies sustain the reason to study task *f*MRI designs such as the one of Vega and associates (2015), outlining this procedure's utility. We hope to find a pattern in different brain abnormalities with ID compared with healthy controls. Moreover, to guarantee solid and valid

results, additional heterogeneity and jackknife sensitivity analysis were estimated. In this study, Seed-based d mapping (SDM) was used. It is a meta-analysis tool for neuroimaging data that has proved high levels of validity and consistency (Iwabuchi et al., 2015; Li et al., 2019; Radua and Mataix-Cols, 2009; Radua et al., 2012; Sheng et al., 2015).

### *2.2.4 Method*

***Inclusion of studies***

Following PRISMA guidelines, an extensive review was performed to identify studies published from January 2009 until September 3, 2020. Also, the search, the inclusion criteria, and the article selection were made by three independent investigators and there was a complete agreement between them for the study search and selection. The search was carried out in PubMed and Web of Science (WoS) databases, and the Boolean algorithm with the keywords used is presented in the Supplementary Appendix SA1. This Boolean algorithm was created based on a systematic search conducted on the six principal journals of ID. The more frequent diseases coursing with ID were included in the search.

Moreover, all the meta-analyses published in the last 5 years in those journals were revised to find the best Boolean algorithm. However, autism spectrum disorder was excluded because there is a significant variability in this population's characteristics, and ID is not the principal one. We consider that this population deserves a unique study for its characteristics. Moreover, it is still discussed the presence of ID (Thurm et al., 2019).

The inclusion criteria for the studies were as follows: (1) functional MRI scan was conducted with a specific task during the register, (2) functional activation in the brain was compared between ID persons and the control group without ID, and (3) only studies that report the specific whole-brain coordinates in Talairach or Montreal Neurological Institute (MNI) spaces were included. The selection process is shown in Figure 7.

The literature review yielded 775 studies found in the WoS database and 84 studies in the PubMed database. One hundred seventy-six records were removed due to duplication in both databases. Six hundred forty-seven studies were excluded after title/abstract screening because they did not accomplish the inclusion criteria.

After this process, only 35 articles remained. However, after the full-text screening, 9 articles were excluded because they did not inform about the peak's activation coordinates, 5 articles were excluded because they did not analyze the whole brain, 6 studies did not compare groups or did not have a second-level analysis, 2 articles were excluded because the participants did not have ID, 1 article was excluded because it was not an original research,1 record was excluded because it was resting-state *f*MRI and no task was performed. Finally, 1 article was

excluded because it had no control group. Only 10 studies matching our inclusion criteria were included and are marked with an * in the reference list.

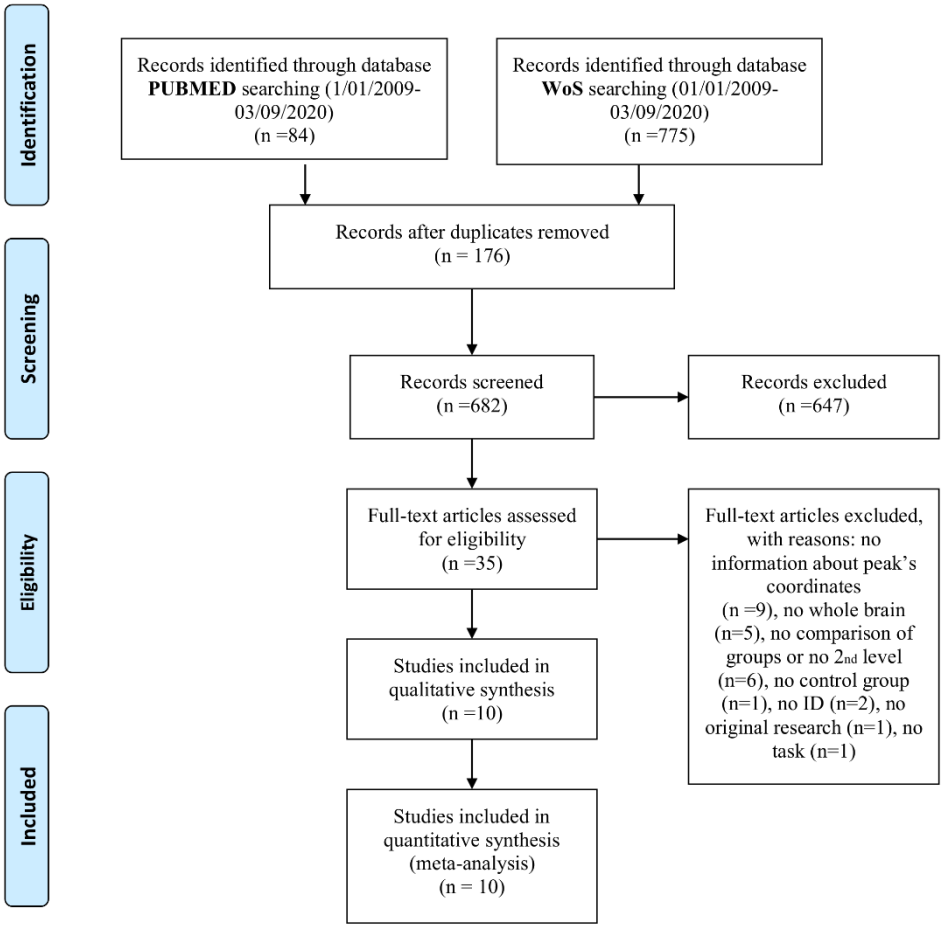


*Figure 7. Flow chart of the meta-anlysis search conducted. .*

***Voxel-Wise metanalysis***

SDM software was used to estimate the differences between the ID population and control people without ID. The procedure and methods of the tool have been described elsewhere (Iwabuchi et al., 2015; Li et al., 2019; Radua and Mataix-Cols, 2009; Radua et al., 2012; Sheng et al., 2015). The SDM uses the peak coordinates found in every included article to reproduce an effect size map of the differences between ID and controls.

First, the areas that were statistically significant differentiating between ID and controls were reported. All the included studies must have the same thresholding at the whole-brain level to assure possible future comparison. Second, the coordinates previously reported were established with a standard MNI map of the group difference effect size based on their peak t value through a non-normalized Gaussian kernel to the voxels near the peak. This procedure

assigns larger values to the voxels nearby peaks. By trying to avoid voxels from appearing both positive and negative simultaneously, the same map was used to represent the positive and negative coordinates (Radua and Mataix-Cols, 2009). The aforementioned positive coordinates imply increased brain activation, whereas the negative coordinates estimate the decreased brain activation.

Considering the sample size, the variance of each study, and the between-study heterogeneity, the mean map was estimated. Finally, a usual p-value of 0.05 was used as a threshold with an additional peak height of z = 127.

Furthermore, we performed a descriptive analysis according to the ID sample and the *f*MRI tasks of the included studies. Concretely, after the calculation of the cohen's d and the confidence intervals (CIs), a descriptive analysis of every article's results was resumed in different images and tables to clarify the results obtained in every included study, separately by the type of task and by the type of ID. We pretend, with this description, to summarize and report the different results distinguishing by ID type and task type.

To validate and test the replicability of the results, a jackknife sensitivity analysis was performed. This analysis systematically excludes one study of the data set and establishes whether the results remained significant.

***Quality Assessment***

A 10-point checklist based on previous meta-analyses (Chen et al., 2015; Du et al., 2014; Shepherd et al., 2012) was used to assess the quality of the included studies through an evaluation of the imaging-specific methodology and some demographic and clinical areas of the included studies. The quality assessment is shown in the supplementary appendix SA2 Two authors reviewed the included articles and independently determined a complete rating. An 80% rate agreement was found between both investigators in the quality assessment. In those articles where different scores were obtained, an agreement score was obtained after discussing the two different scores. Some variables at this point were coded for each chosen study to make the quality assessment and to be able to study the possible heterogeneity. Type of population, sample size in each group, % of women, and mean age are some variables codified in Table 14. Moreover, the quality assessment is also found in Table 14.

### *2.2.5 Results*

***Studies included in the metanalysis***

In Table 14, the different characteristics of the studies are shown. Four studies had 22q11 DS population; two studies had Prader–Willi syndrome, one DS, one WS, one fragileX syndrome, and finally, one Williams–Beuren syndrome. All these disorders course with ID. Regarding the tasks conducted in the resonator, these were classified in visual, audition, language perception,

and executive function tasks. The specific task in every experiment is found in Table 14. As shown in the same table, some studies had different tasks that included different regions. In this case, the study was separated to analyze the coordinates separately. In Table 14, we can also find the imaging modality used in every study, and in addition, we can see the sample size of every sample. Finally, in the last column, we can see the quality assessment made by two investigators separately.

*Table 14. Demographic and clinical characteristics of the participants in the 10-neuroimaging data included in this metanalysis.*

| Study | Imaging modality | n | | ID type | % Females | | Mean Age | | Task | Classification of task | Quality Assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | ID | Controls | | ID | Controls | ID | Controls | | | |
| Azuma et al. (2009) | 1.5 T MRI | 8 | 13 | 22q11DS | 50 | 35.71 | 12 | 13 | Visuospatial memory task | Visual perception and executive functions | 8.5 |
| Azuma et al. (2015) | 1.5 T MRI | 14 | 14 | 22q11DS | 100 | 38.46 | 13 | 13 | Facial emotion processing | Emotion recognition and visual perception | 9.5 |
| Bernardino et al. (2014) | 3.0 T MRI | 7 | 9 | WS | 57.14 | 44.40 | 21.57 | 21.22 | High-level visual categorical task | Visual perception and executive functions | 9 |
| Binelli et al. (2016) | 1.5 T MRI | 20 | 20 | WBS | 45 | 40 | 25.42 | 25.65 | Control and facial emotion processing task | Visual Perception | 9.5 |
| Hall et al. (2009) | 3.0 T MRI | 10 | 10 | FXS | 100 | 100 | 18.67 | 14.74 | Auditive perception task | Auditive perception | 8.5 |
| Montojo et al. (2013) | 3.0 T MRI | 16 | 25 | 22q11DS | 63 | 60 | 22.5 | 23 | Stop-signal task | Executive functions | 9.5 |
| Montojo et al. (2014) | 3.0 T MRI | 15 | 30 | 22q11DS | 40 | 40 | 23.88 | 24.36 | Spatial capacity working memory | Executive functions | 9.5 |
| Reynolds-Losin et al.(2009) | 3.0 T MRI | 9 | 9 | DS | 44.4 | 44.4 | 22 | 17.8 | Story listening task | Language, auditive and visual perception | 7 |
| Wan et al. (2017) | 3.0 T MRI | 38 | 38 | PWS | 28.9 | 28.9 | 13.17 | 13.07 | T-HVOT and FPMT | Visual perception | 8 |
| Woodcook, et al. (2010) | 3.0 T MRI | 8 | 8 | PWS | 37.5 | 37.5 | 20.7 | 21 | Switching and location | Visual perception and executive functions | 7.5 |

Note: n, sample size of every group.22q11DS, 22q11.2 deletion syndrome; DS, Down syndrome; FPMT, full picture matching test; FXS, fragile-X syndrome; ID, intellectual disability; MRI, magnetic resonance imaging; PWS, Prader–Willi syndrome; T-HVOT, two choice revised version of Hooper visual organization test; WBS, Williams–Beuren syndrome; WS, Williams syndrome

***Qualitative study***

As mentioned above, to our knowledge, it is the first time that a meta-analysis is done using different types of ID. Therefore, we first analyze all the articles' results and then expose the meta-analysis results.

Table 15 shows the principal results obtained in the first step of the program. In this sense, for each study, both the smallest and higher possible effect size of each voxel are estimated, fixing a lower and upper bound of the possible effect sizes (Albajes-Eizagirre et al., 2009).

*Table 15. Peak coordinates obtained in the different studies included in the metanalysis.*

| Study | Cohen's d | Coordinates | Area | Peak | Comparison |
|---|---|---|---|---|---|
| Azuma et al. (2009) | 1.003 | 24, -78, 12 | Occipital Precuneus right | Max | 22q11DS<C |
| Azuma et al. (2015) | 1.246 | -34, -80, -20 | Left cerebellum, | Max | 22q11DS<C |
| Bernardino, et al. (2014) | 1.480 | 24, -54, 30 | Caudal Intraparietal sulcus right hemisphere | Max | WS<C |
| | -1.402 | -56, -58, 4 | Left middle temporal gyrus, | Min | WS>C |
| Binelli et al. (2016) | 1.106 | 44, -62, 8 | Right Lateral Occipital Area | Max | WBS<C |
| | -1.024 | 64, -18, -16 | Right middle temporal gyrus | Min | WBS>C |
| Hall et al. (2009) | -1.859 | -4, -24, -38 | Left Pons | Min | FXS>C |
| Montojo et al. (2013) | 1.576 | -46, -52, 44 | Left occipital cortex, angular gyrus, supramarginal gyrus, superior parietal lobule | Max | 22q11DS<C |
| | -1.219 | 36, 22, 32 | Right inferior/middle frontal gyrus | Min | 22q11DS>C |
| Montojo et al. (2014) | 1.530 | -26, -66, 54 | Left superior parietal lobule, intraparietal sulcus, supramarginal gyrus, angular gyrus | Max | 22q11DS<C |
| Reynolds-Losin, et al. (2009) | 2.835 | 52, -30, 0 | Right middle temporal gyrus, | Max | DS<C |
| | -1.879 | 16, -66, 48 | Right precuneus | Min | DS>C |
| Wan et al. (2017) | 0.697 | 24, -56, 42 | Right precuneus | Max | PWS<C |
| Woodcook et al. (2010) | 2.513 | -26, -6, 26 | Middle frontal gyrus/subgyral white matter/ insula left | Max | PWS<C |
| | -1.476 | -18, 64, -16 | Inferior, anterior frontal pole Right | Min | PWS>C |

Note: Max, maximum peak; Min, minimum peak.

Figures 8-11 were visualized with the BrainNet Viewer (Xia et al., 2013). Figure 8 represents the different positive and negative coordinates of the results in every article after the

first analysis made with SDM. Moreover, the size of every node is proportioned to Cohen's d calculated through the meta-analysis, and so, the bigger the node is, the more total the effect. More concretely, Table 16 shows the same results classified by type of ID. Figure 9 represents the different peak coordinates separating by type of ID. Another time, the node's size is proportioned to Cohen's d.

We can see that the activated areas in 22q11 DS syndrome in front of controls were both the right inferior and middle frontal gyrus. The deactivation areas of 22q11 DS syndrome in front of controls were right occipital precuneus, left cerebellum, left occipital cortex, angular gyrus, supramarginal gyrus, superior parietal lobe, and intraparietal sulcus. In the case of Prader–Willi, the more activated areas were inferior and the anterior frontal pole right compared with controls, and the more deactivated areas were right precuneus and middle frontal gyrus. Finally, in the same way, Table 17 shows the peak coordinates classified by type of tasks. Figure 10 shows the results regarding the type of tasks used following the classification in Table 14.

Compared with controls, people with ID in visual perception and executive function tasks demonstrated increased brain activation in left middle temporal gyrus and inferior anterior frontal pole right. However, they showed decreased activation compared with controls in occipital precuneus right, caudal intraparietal sulcus of the right hemisphere, and middle frontal gyrus. In visual perception tasks, people with ID appeared to have higher activation in the right middle temporal gyrus and lower activation in the right lateral occipital area and right precuneus. Concerning executive functions tasks, people with ID displayed a higher activation in the right inferior/ middle frontal gyrus and decreased activation in left occipital cortex, angular gyrus, supramarginal gyrus, superior parietal lobe, and intraparietal sulcus.

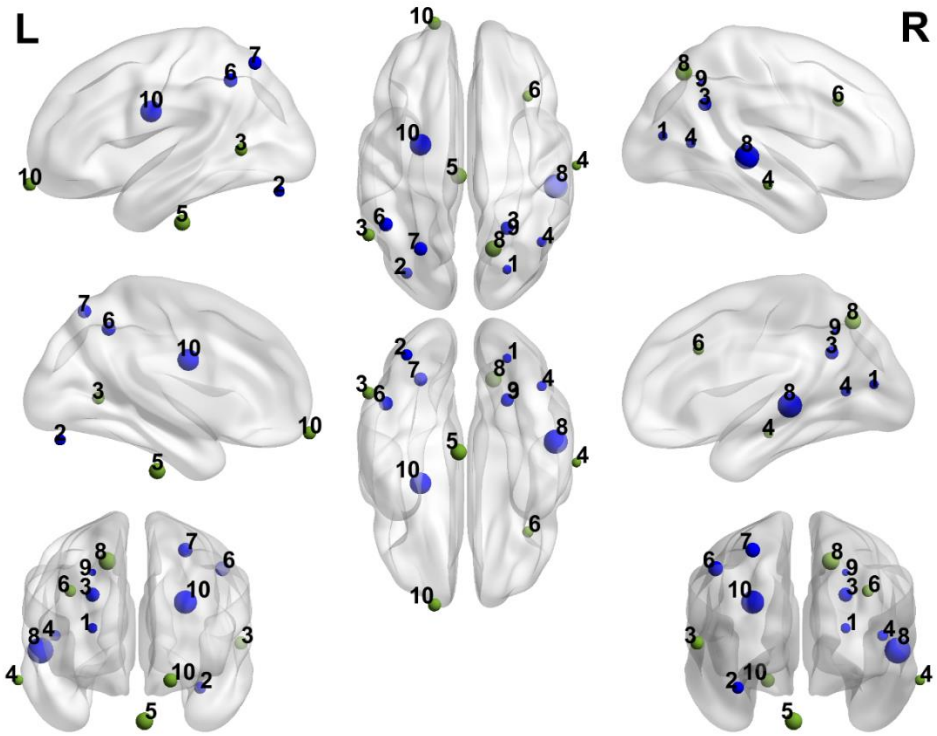


*Figure 8. Representation of the positive and negative peak coordinates obtained in the different studies included in the metanalysis.*

*Table 16. Peak coordinates classified by Intellectual Disability type*

| Study | Cohen's d | Coordinates | Area | Peak | Comparison |
|---|---|---|---|---|---|
| 22q11DS | 1.003 | 24, -78, 12 | Occipital Precuneus right | Max | 22q11DS<C |
| | 1.246 | -34, -80, -20 | Left cerebellum | Max | 22q11DS<C |
| | 1.576 | -46, -52, 44 | Left occipital cortex, angular gyrus, supramarginal gyrus, superior parietal lobule | Max | 22q11DS<C |
| | -1.219 | 36, 22, 32 | Right inferior/middle frontal gyrus | Min | 22q11DS>C |
| | 1.530 | -26, -66, 54 | Left superior parietal lobule, intraparietal sulcus, supramarginal gyrus, angular gyrus | Max | 22q11DS<C |
| WS | 1.480 | 24, -54, 30 | Caudal Intraparietal sulcus Right Hemisphere | Max | WS<C |
| | -1.402 | -56, -58, 4 | Left middle temporal gyrus, | Min | WS>C |
| WBS | 1.106 | 44, -62, 8 | Right Lateral Occipital Area | Max | WBS<C |
| | -1.024 | 64, -18, -16 | Right middle temporal gyrus | Min | WBS>C |
| FXS | -1.859 | -4, -24, -38 | Left Pons | Min | FXS>C |
| DS | 2.835 | 52, -30, 0 | Right middle temporal gyrus | Max | DS<C |
| | -1.879 | 16, -66, 48 | Right precuneus | Min | DS>C |
| PWS | 0.697 | 24, -56, 42 | Right precuneus | Max | PWS<C |
| | 2.513 | -26, -6, 26 | Middle frontal gyrus/sub gyral white matter/ insula left | Max | PWS<C |
| | -1.476 | -18, 64, -16 | Inferior, anterior frontal pole Right | Min | PWS>C |

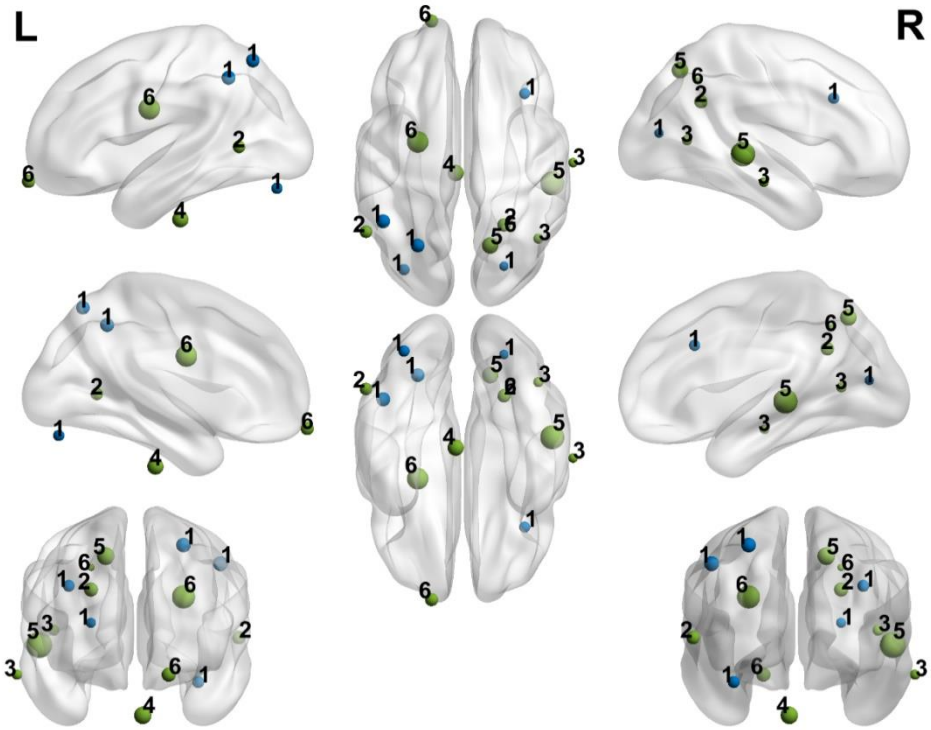


*Figure 9. Coordinates obtained in the different studies included in the metanalysis classified by the different types of ID.*

*Table 17. Peak coordinates classified by type of task used in the different studies.*

| Study | Cohen's d | Coordinates | Area | Peak | Comparison |
|---|---|---|---|---|---|
| Visual Perception and executive functions | 1.003 | 24, -78, 12 | Occipital Precuneus right | Max | 22q11DS<C |
| | 1.480 | 24, -54, 30 | Caudal Intraparietal sulcus Right Hemisphere | Max | WS<C |
| | -1.402 | -56, -58, 4 | Left middle temporal gyrus, | Min | WS>C |
| | 2.513 | -26, -6, 26 | Middle frontal gyrus/sub gyral white matter/ insula left | Max | PWS<C |
| | -1.476 | -18, 64, -16 | Inferior, anterior frontal pole Right | Min | PWS>C |
| Emotion recognition and visual perception | 1.246 | -34, -80, -20 | Left cerebellum, | Max | 22q11DS<C |
| Visual Perception | 1.106 | 44, -62, 8 | Right Lateral Occipital Area | Max | WBS<C |
| | -1.024 | 64, -18, -16 | Right middle temporal gyrus, | Min | WBS>C |
| | 0.697 | 24, -56, 42 | Right precuneus | Max | PWS<C |
| Auditive perception | -1.859 | -4, -24, -38 | Left Pons | Min | FXS>C |
| Executive functions | 1.576 | -46, -52, 44 | Left occipital cortex, angular gyrus, supramarginal gyrus, superior parietal lobule | Max | 22q11DS<C |
| | -1.219 | 36, 22, 32 | Right inferior/middle frontal gyrus | Min | 22q11DS>C |
| | 1.530 | -26, -66, 54 | Left superior parietal lobule, intraparietal sulcus, supramarginal gyrus, angular gyrus | Max | 22q11DS<C |
| Language, auditive and visual perception | 2.835 | 52, -30, 0 | Right middle temporal gyrus, | Max | DS<C |
| | -1.879 | 16, -66, 48 | Right precuneus | Min | DS>C |

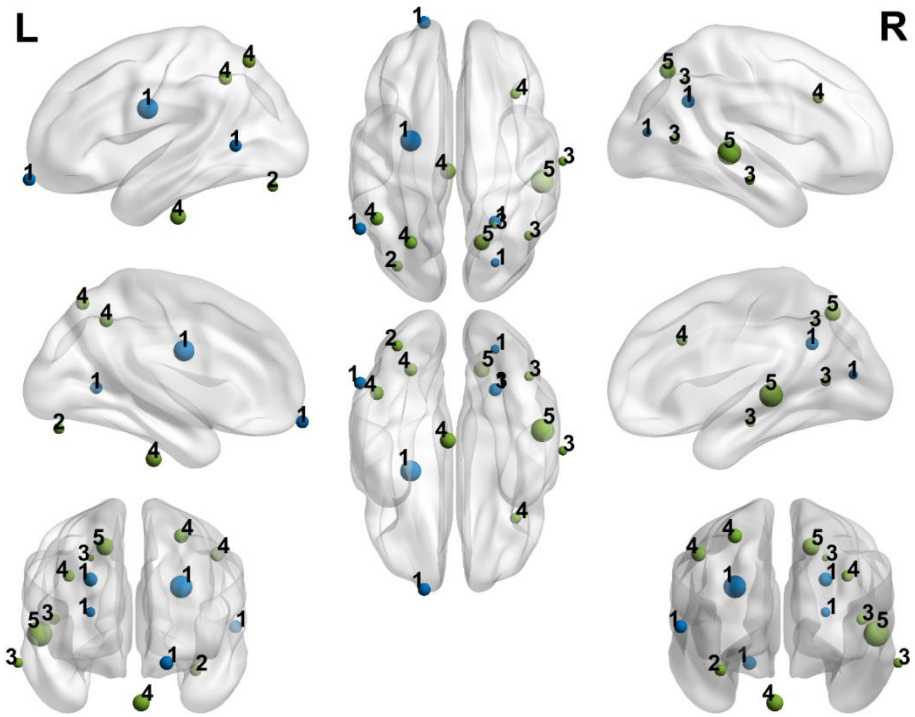


*Figure 10. Coordinates obtained in the different studies included in the metanalysis classified by the different tasks used in the different studies.*

***Metanalysis result***

In Supplementary Appendix SA3, the forest plot of the studies with their effect size, low CI, and high CI is shown. As we can see, the more significant effects are found in the study of Woodcock and colleagues (2010), and as in all articles CI 0 is not included, there are significant effects in all the studies.

In the meta-analysis, people with ID did not show any increased brain activation compared with controls. However, people with ID showed decreased activation in right temporal gyrus, concretely, in the right middle temporal gyrus, in Brodmann area (BA) 37, compared with controls. Two clusters were found in this same area, one of two voxels and one of four voxels. The results are shown in Table 18. Moreover, in Figure 11, we can see the represented areas of the study.

To determine the possible heterogeneity across studies, $Q$ and $I^2$ statistics were calculated. The results are shown in Supplementary Appendix SA4. In positive and negative peaks, nonsignificant Q statistics were found, and so, the results demonstrate that the variability is due to random variation rather than study heterogeneity. Due to the nonexistence of heterogeneity in the effect sizes, it is unnecessary to study the possible moderate variable effects. Therefore, it was decided not to conduct a meta-regression with external variables.

***Reliability analysis***

The jackknife sensitivity analysis (Supplementary Appendix SA5) reported that the right middle temporal gyrus (with coordinates in 48, 62, 69, and BA 37) was replicable in all 16 data sets. However, the same right middle temporal gyrus in different coordinates (46, 66, 6, and BA 37) was replicable in 14 data sets. This reveals a significant reliability of the results reported in this study.

*Table 18. Differences of brain activation between ID patients and controls in the main metanalysis.*

| Region | MNI coordinates | | | SDM-Z score | p value | Voxels | Cluster breakdown (voxels) |
|---|---|---|---|---|---|---|---|
| | x | y | z | | | | |
| ID<HC | 48 | -62 | 6 | -1.688 | 0.045716286 | 4 | Right middle temporal gyrus, BA 37 |
| (A)Right Temporal gyrus | | | | | | | |
| (B)Right Temporal Gyrus | 46 | -66 | 6 | -1.675 | 0.047921253 | 2 | Right middle temporal gyrus, BA 37 |

Note: MNI coordinates, Montreal Neurological Institute.

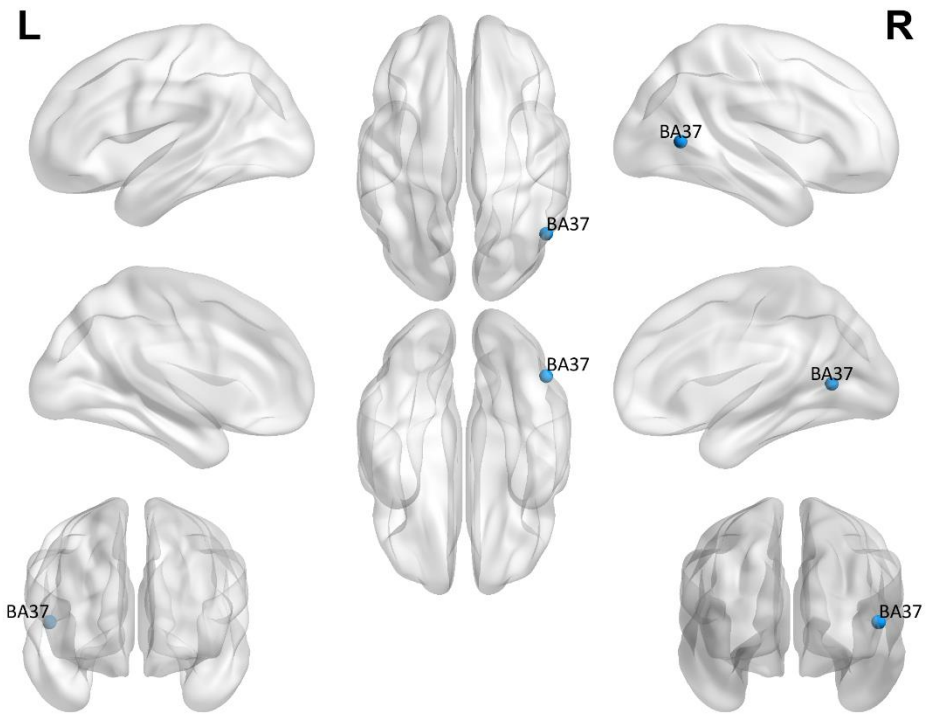


*Figure 11. Representation of the differences in brain activation between ID patients and controls in the metanalysis.*

### *2.2.6 Discussion*

This study aimed to identify brain abnormalities mainly associated with ID. To the best of our knowledge, it is the first meta-analysis exploring differences in brain activation between people with ID and control subjects. In this sense, it is important to highlight that although our aim and our search were centered on all types of ID, our search concludes that only studies with *f*MRI in different genetical syndromes associated with ID exist. The inclusion of genetic syndromes only could be because of the facility identifying the genetic syndromes and increasing the possibilities to control the different variables. The studies in *f*MRI with this population are very recent, and we hope that more studies with different types of ID are published in some years.

Regarding the qualitative part of the study, there are common patterns regarding the type of ID and the type of task that are important to highlight.

About the type of ID, in 22q11 DS, we can find an overall deactivation in different areas of the left occipital cortex and lobule, as well as of the superior parietal lobule. This is congruent with some abnormalities in the thickness of the occipital cortex found in this population in a group with psychosis (Sun et al., 2020). In the case of Prader–Willi syndrome, we can find a deactivation in comparison with the control population near the insula in both hemispheres.

Regarding the type of task used in the study, in visual perception and executive functions, deactivation in the occipital and parietal areas, left and right, was found. These areas have been identified as necessary in visual perception (Kaas et al., 2010). However, there is an activation in ID compared with controls in the middle temporal gyrus and in the frontal pole right. The most interesting result is in executive functions, where we can find a clear common pattern. We can see that there is deactivation in the left occipital cortex, supramarginal gyrus, superior parietal gyrus, and angular gyrus, also congruent with certain studies about executive functions (Fassbender et al., 2017).

Compared with controls, people with ID did not show any increased activation in the quantitative analysis of every study. However, people with ID showed decreased activation in two areas located in the right middle gyrus compared with controls. This area comprised the BAs 21, 22, 37, and 39. In particular, in our case, only the BA number 37 was deactivated in the case of ID population compared with controls. Early functional neuroimaging articles have demonstrated that the middle temporal gyrus is involved in specific cognitive domains (Cabeza and Nyberg, 2000; Laufer et al., 2011; Raposo et al., 2006; Sass et al., 2009), for instance, semantic memory processing or language (Cabeza and Nyberg, 2000; Chao et al., 1999; Tranel et al., 1997). These domains can be associated with 70% of the tasks used in the studies included in the meta-analysis.

In schizophrenia, functional deficits in these cognitive domains, that is, language (Kuperberg et al., 1998), semantic memory (Nestor et al., 1998), and complex visual perception

(Tek et al., 2002), have been demonstrated. In the same line, functional deficits, concretely, in the middle temporal gyrus (Chang et al., 2016; Fusar-Poli et al., 2011) have been found in current studies with samples at high risk of psychosis.

In a recent meta-analysis where the aim was to study the differences between 22q11 DS and controls, some regional differences were identified. Specifically, the results reported that the 22q11 DS population has structural and functional abnormalities. In particular, these abnormalities were mainly found within the right precuneus and superior temporal gyrus, bilateral inferior parietal lobe, and posterior cingulate cortex (Scarpazza et al., 2019). This could be congruent with our findings because 40% of our sample has 22q11 DS.

Moreover, two articles were shared between this paper and the meta-analyisis from Scarpazza et al. (2019). In the same line, a recent study (Marshall et al., 2017) conducted with 321 participants identified the 22q11 DS gene as one of the most linked to psychosis (Marshall et al., 2017). Consequently, the middle temporal gyrus and inferior temporal gyrus could be related to the appearance of schizophrenia and therefore may have a relationship with 22q11 DS.

#### *Limitations*

This study has several limitations. First, there exists a scarcity of studies in task-*f*MRI with the ID population. This is probably attributable to the relatively low commonness of this population and, in addition, the difficulties of using a resonator in this particular disease. Therefore, all our studies analyzed consisted of a tiny sample, and also, there are few studies in these meta-analyses. It is important to remark that the available studies do not allow us to draw clear conclusions about brain functional irregularities in ID. We should interpret our results with caution. Therefore, functional connectivity in the ID population remains unexplored.

Second, and due to the limited data, the effects of some variables such as type of ID, type of task used, % of women, or mean age of the participants have not been analyzed due to the low heterogeneity found. Our heterogeneity indexes were very low, and this can be due to the limited sample. Finally, the studies included used different tasks. In general, it is essential to highlight the low heterogeneity in all the included articles of this study. Therefore, we are not able, with these preliminary results, to generalize to the ID population. To address the functional brain abnormalities in this population, more task-*f*MRI studies are needed, and a task specific meta-analysis should address this topic more directly.

### *2.2.7 Conclusions*

Previous studies in ID and neuroimaging suggest an altered between-network connectivity that could be common of different disorders involving ID, including DS and WS. Considering the perspective of ID based on the individualized supports and the adaptative

behavior, this study aimed to examine if differences in the connectivity pattern exist in this population compared with healthy controls. However, this population faces different problems that complicate the register. This article aims to integrate the last years of knowledge in this field in a meta-analytic review.

Only 10 articles met the inclusion criteria, and all the disabilities were associated with genetical syndromes. Regarding the qualitative part of the study, common patterns of dysconnectivity and connectivity versus controls are found in specific populations such as 22q11 DS and Prader–Willi syndrome. Also, in the type of task, and considering that all the different syndromes are mixed, common patterns were found in executive functions and visual perception.

In conclusion, this meta-analysis revealed changes in brain activation in the right middle temporal gyrus regarding the quantitative part of the study. This area is implicated in cognitive areas, including semantic memory processing and language. These results can be highly influenced by the type of task that has been made in all the studies included in the meta-analysis, including 70% of tasks that would include the domains mentioned before. However, other issues can influence.

For instance, the high percentage of the 22q11 DS population that we have included in the studies (a 40%) could mediate the functional disconnection seen in the right middle temporal gyrus (Scarpazza et al., 2019). This region is linked with schizophrenia and psychosis, and 22q11 DS is at high risk of presenting this pathology (Nestor et al., 1998). Despite the efforts of the present study to provide state-of-the-art on this issue, it was not possible to demonstrate the differences in brain irregularities of the ID population and controls. Indeed, the current results are based on the available literature and do not allow the assumption of differences between the two populations. Clarifying if a pattern underlying the different types of ID exists compared with healthy controls would lead to a better understanding of the ID population.

### *2.2.8 References*

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### *2.2.9 Supplementary appendix*

*Supplementary Appendix SA1 (Study 3): Words searched in Pubmed and Web of science*

1. Pubmed (01/01/2009-03/09/2020):

(("Intel* Disab*"[Title/Abstract] OR "mental retard*"[Title/Abstract] OR "develop* disab*"[Title/Abstract] OR "develop* disor*"[Title/Abstract] OR "angelman* syndr*"[Title/Abstract] OR "Rett syndr*"[Title/Abstract] OR "22q11.2"[Title/Abstract] OR "Down* syndr*"[Title/Abstract] OR "Fragile X syndr*"[Title/Abstract] OR Williams-Beur*[Title/Abstract] OR William* syndr* [Title/Abstract] OR "Prader Will*"[Title/Abstract] OR "cri du chat synd*"[Title/Abstract] OR "sotos syndrom*"[Title/Abstract] OR "Apert syndr*"[Title/Abstract] OR "tuberous sclerosis"[Title/Abstract] OR "Cornelia de Lange syndr*"[Title/Abstract])) AND (fMRI[Title/Abstract] OR "functional magnetic resonance imag*"[Title/Abstract] OR "functional MRI"[Title/Abstract]))

2. Web of Science

TS= (("Intel* Disab*"OR"mental retard*"OR"develop* disab*"OR"develop* disor*"OR"angelman* syndr*"OR"Rett syndr*"OR"22q11.2"OR"Down* syndr*"OR"Fragile X syndr*"OR"William* syndr*"OR"Prader Will*"OR"cri du chat synd*"OR"sotos syndrom*"OR"Apert syndr*"OR"tuberous sclerosis"OR"Cornelia de Lange syndr*")) AND TS= ((fMRI OR functional magnetic resonance imag*"OR"functional MRI"))

*Supplementary Appendix SA2 ( Study 3): Quality assessment checklist (score 0/0.5/1 per item; total score out of 10)*

Category 1: Participants

1. Patients were evaluated prospectively, specific diagnostic criteria were applied, and demographic data were reported.

2. Healthy comparison participants were evaluated prospectively, psychiatric and medical illnesses were excluded.

3. Important variables (e.g., age, sex, illness duration, onset, medication status, comorbidity, severity of illness) were checked either by stratification or statistically.

4. Sample size per group > 10.

Category 2: Methods for image acquisition and analysis

1. Whole brain analysis was automated with no a priori regional selection.

2. Coordinates reported in a standard space

3. The imaging technique used was clearly described so that it could be reproduced.

4. Measurements were clearly described so that they could be reproduced.

Category 3: Results and conclusions

1. Statistical parameters for significant and important nonsignificant differences were provided.

2. Conclusions were consistent with the results obtained and the limitations were discussed.

*Supplementary Appendix SA3*

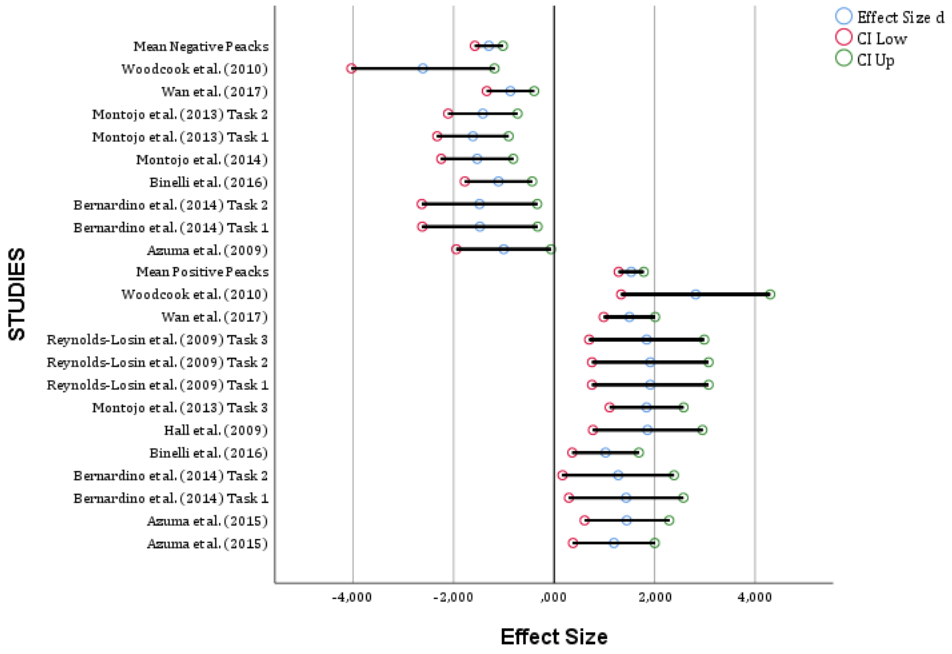


*Figure 12. Studies Forest plot with their effect size, low CI and up CI.*

*Supplementary Appendix SA4 (Study 3)*

*Table 19. Heterogeneity assessment in positive and negative peaks.*

| Peaks | $\tau$ | $Q$ | $df$ | $p$ | $I^2$ |
|---|---|---|---|---|---|
| Positive peaks | 0.000 | 8.242 | 11 | 0.6914 | -0.81 ≈ 0% |
| Negative peaks | 0.026 | 8.558 | 8 | 0.3809 | -0.75 ≈ 0% |

Note: τ, Tau, amount of heterogeneity; df, degrees of freedom.

*Supplementary Appendix SA5 (Study 3)*

*Table 20. Jackknife sensitivity analysis*

| All studies but… | A | B |
|---|---|---|
| Azuma et al. (2009) | | |
| Azuma et al. (2015) Task 1 | Yes | Yes |
| Azuma et al. (2015) Task 2 | Yes | Yes |
| Bernardino, Rebola, Farivar, Silva and Castelo-Branco (2014) Task 1 | Yes | Yes |
| Bernardino, Rebola, Farivar, Silva and Castelo-Branco (2014) Task 2 | Yes | Yes |
| Binelli et al. (2016) | Yes | Yes |
| Hall, Walter, Sherman, Hoeft and Reiss (2009) | Yes | Yes |
| Montojo et al. (2013) Task 1 | No | Yes |
| Montojo et al. (2013) Task 2 | Yes | Yes |
| Montojo et al. (2013) Task 3 | Yes | No |
| Montojo et al. (2014) | Yes | Yes |
| Reynolds-Losin, Rivera, O'Hare, Sowll and Pinter (2009) Task 1 | Yes | Yes |
| Reynolds-Losin, Rivera, O'Hare, Sowll and Pinter (2009) Task 2 | Yes | Yes |
| Reynolds-Losin, Rivera, O'Hare, Sowll and Pinter (2009) Task 3 | Yes | No |
| Wan, Chiang, Chen and Wuang (2017) | Yes | Yes |
| Woodcook, Humphreys, Oliver and Hansen (2010) | Yes | Yes |

Note: A, Right temporal gyrus (48,-62,6) ; B, Right temporal gyrus (46, -66, 6); Yes, the region is reported if we extract the mentioned study of the analysis; No, the region is not reported if we extract the mentioned study of the analysis.

## 2.3 Study 3: Using *f*MRI to Assess Brain Activity in People With Down Syndrome: A Systematic Review


### *2.3.1 Identifying data*

Title: Using *f*MRI to Assess Brain Activity in People With Down Syndrome: A Systematic Review

Authors: Maria Carbó-Carreté, Cristina Cañete-Massé, Maribel Peró-Cebollero & Joan Guàrdia-Olmos

Year of publication: 2020

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- Rank for Journal Citation Indicator: 150/293 Quartile: Q3, Category: Neuroscience
- Rank for Journal Citation Indicator: 41/85 Quartile: Q2, Category: Psychology

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### *2.3.2 Abstract*

***Background:*** In the last few years, many investigations have focused on brain activity in general and in populations with different pathologies using non-invasive techniques such as electroencefalography (EEG), positron emission tomography (PET), functional magnetic resonance imaging (fMRI) and magnetic resonance imaging (MRI). However, the use of non-invasive techniques to detect brain signals to evaluate the cognitive activity of people with Down syndrome (DS) has not been sufficiently addressed. The objective of this study is to describe the state-of-the-art in fMRI techniques for recording brain signals in people with DS. ***Methods:*** A systematic review was performed based on PRISMA recommendations; only nine papers on this topic have been published. Three independent researchers selected all relevant information from each paper. Analyses of information concordance showed a high value of agreement between researchers. ***Results*** Although few relevant works have been published, the use of fMRI in people with DS is becoming an appropriate option to study brain function in this population. Of the nine identified papers, five used task designs, and four used resting-state paradigms. ***Conclusions:*** Thus, we emphasize the need to incorporate rigorous cognitive activity procedures in evaluations of the DS population. We suggest several factors (such as head correction movements and paired sample techniques) that must be considered when designing an fMRI study with a task or a resting-state paradigm in a DS population.

**Keywords:** Down Syndrome, *f*MRI, Brain Signal, Brain Activity, Systematic Review

### *2.3.3 Introduction*

Analysis of the cognitive activity of people with Down Syndrome (DS) is extraordinarily relevant, and it has become a foundation for better understanding the development of neurodegenerative diseases, mainly Alzheimer's disease (AD) (Prasher et al., 1996; Lamar et al., 2011; Neale et al.,2018; Pujol et al., 2018; Musaeus et al., 2019); studying the development and morphological characteristics of the brains of individuals with DS (Baburamani et al., 2019; Lao et al., 2019; Rodrigues et al., 2019; Shiohama et al., 2019); and evaluating cognitive functioning (Virji-Babul et al., 2013). All these cited researchers used non-invasive brain registration techniques and extended studies that had the same objectives but used traditional paradigms (Contestabile et al., 2010; Wiseman et al., 2015). Early studies that focused on examining, for example, the relationship between AD and people with DS, identified certain limitations. The most notable limitation is the variability of the degree of intellectual disability of the assessed person and the problems understanding the verbal instructions of the test among people with severe or profound intellectual disability (Crayton et al., 1998; Oliver, 1999). In addition, the behavioral differences associated with dementia have an impact not only on the person with DS but also on the professionals who administer the tests, so the reliability of these responses must be examined and psychometrically guaranteed (Oliver et al., 2011). Finally, it should be noted that many psychometric scales have not been validated in populations with AD and SD, but some studies have made progress in addressing these gaps (Dekker et al., 2015).

Thus, our proposal in the present work is to advance in the knowledge of all the present contributions of brain signal neuroimaging techniques in the DS population. Many studies have shown the advantages of using non-invasive brain registration techniques, as these measurements have no response bias or learning processes because when tasks are used, they have already been learned in the preregistration phases. The use of the main techniques such as EEG (electroencephalography), MRI (magnetic resonance imaging), PET (positron emission tomography), DTI (diffusion tensor imaging), and fMRI (functional magnetic resonance imaging) provide information on structural mechanisms and functional aspects, explaining the connectivity networks that can be found in healthy subjects as well as those suffering from diseases (Massoud and Gambhir, 2003; Hoehn and Aswendt, 2013; Aswendt et al., 2017).

Regarding the SD population, the systematic review presented by Neale et al. (2018) indicates that PET techniques allow the identification of amyloid accumulation prior to the onset of Alzheimer's disease (AD), while techniques based on EEG and MRI identify cognitive impairment and can be assessed as biomarkers for the detection and diagnosis of AD in this population.

In addition to the already cited signals, in the general population, fMRI registers have been used in the last 20 years as derivatives of the images obtained from MRI data, and certainly, the use of fMRI to assess brain activity and functioning, as well as the use of various study designs, has become common (Welvaert and Rosseel, 2014). Despite the amount of published works, we believe that it is urgent to advance this field since the data obtained from fMRI are highly valuable and their use provides unique and remarkable results in general and specific populations.

One of the most interesting advantages of studying the DS population with resting-state fMRI, as with other non-invasive techniques, is that the resting-state fMRI register does not depend on the intellectual level of the person being evaluated. In this approach, the person should only be at rest inside a resonator, without doing anything special, with his or her eyes open and without moving. In contrast, in other study designs, the fMRI signal is recorded when a specific cognitive task (e.g., language, memory, motor, among others) is being performed. Clearly, based on the uses and potential of the fMRI signal in resting-state designs (Lu et al., 2007; Biswal et al., 2010), this approach may be an interesting option because it allows the analysis of the cognitive activity of people with ID and, as in the general population, facilitates the systematic study of spontaneous fluctuations of the BOLD signal. Notably, information from studies that involve a task is derived from a direct source of activation when the participant is faced with the task set, and the resting-state data are derived from an indirect source that is not associated with the task.

It seems clear that some of the problems that occur when using fMRI signals may be aggravated for the DS population. This observation is based on the difficulties that people with DS have been reported to have when MRI data is being obtained, which suggests that with fMRI techniques, such the occurrence incidents can increase. Reviews of MRI in the DS population indicate several questions that can be applied to fMRI studies, which we can summarize in the following points. (1) It is feasible that the brain connectivity network in DS persons is more weakened than that in healthy persons of the same chronological age. We must interpret exactly what we mean by the weakening of a network, as the points of interest to determine it are diverse (e.g., density, laterality, entropy, and complexity, among other possible topics). It is also possible that the manifestation of cognitive impairment in persons with DS will, in some cases, be compensated by the intervention of other brain areas. (2) Brain volume and head size are smaller in DS persons than in healthy populations (Pinter et al., 2001; Rodrigues et al., 2019), and a smaller number of neurons and fewer synaptic extensions and altered neuronal differentiation in fetuses with DS are detected (Takashima et al., 1981; Bhattacharyya et al., 2009; Kanaumi et al., 2013). This issue has led to the use of DARTEL (Ashburner, 2007) as a template in some studies with persons with DS (Lin et al., 2014). DARTEL (Diffeomorphic Anatomical Registration

through Exponentiated Lie Algebra) is a specific brain template used in the preprocessing phase or analysis of fMRI data to take into account deformations that must be parameterized by a single flow field, which is considered to be constant in time. (3) The DS population moves excessively during the registration of the signal, which leads to many experimental difficulties (Pujol et al., 2014). In this sense, Lao et al. (2019) point out an extremely important fact: the MRI signals acquired with motion correction below 1% allow the use of a general template for one of the general populations, which facilitates the study of PET signals, among others. If these assessments are documented by MRI data, it seems logical to consider them with respect to fMRI records.

Given the aforementioned points, it seems that the use of MRI data in the DS population is an interesting matter. Consequently, the question whether fMRI signals are adequate for use in this population must be addressed. The study of spontaneous fluctuations of the fMRI BOLD signal has become the goal of investigating connectivity and understanding how brain networks are organized, whether based on a stimulus response or simply at rest (Fox and Raichle, 2007; Raichle, 2009). Moreover, resting-state fMRI (rs-fMRI) has become an increasingly popular method of MRI that investigates synchronous activity across regions in the absence of an explicit signal correlation-based task (Corbetta, 2012; Snyder and Raichle, 2012). Data acquired by fMRI provides valuable information for explaining the determinants of network dysfunction, either with task designs to evaluate the person's different cognitive abilities (Hampson et al., 2006) or with rs-fMRI in populations that may have some diseases such as epilepsy (Centeno and Carmichael, 2014).

Therefore, based on the extensive contributions that have been shown in robust fMRI studies and the detailed review of non-invasive neuroimaging techniques in the population with DS (Baburamani et al., 2019), it is now important to establish the best experimental option to guarantee the validity and reliability of the brain signals recorded in individuals with DS. Moreover, our intention is to provide a reference point that allows us to systematically accumulate and order the available information and the findings derived from the fMRI and DS binomial (other signals such as PET or EEG are contemplated in the review of Neale et al., 2018, but this is not the case for fMRI signals.) Therefore, we want to review the works published to date in relation to fMRI data and people with DS, provide useful insights that identify the main difficulties and findings that researchers could utilize, and discuss the different ways to solve these difficulties.

### *2.3.4 Method*

#### *Search of Published Studies*

The articles included in the present study were searched in the Web of Science (WoS), PubMed and PsycInfo databases. The following inclusion criteria were applied: the articles had to be original fMRI papers that included a sample of persons with DS and that were published from 1992 to October 17, 2019. The literature search was conducted using a Boolean algorithm with the following keywords: (“DOWN SYNDROME” OR “DOWN’S SYNDROME”) in the title and (“Functional Magnetic Resonance Imag*” OR FMRI) in any part of the paper. If we added the keyword Alzheimer, no works were found in the three databases; consequently, in the present study, we worked with a combination of DS and fMRI studies. The search was performed independently by three researchers, and we obtained a 100% rate of agreement between them for the search; all papers found by the three researchers were considered in the study. Following these search criteria, we identified a total of 15 papers in WoS, 2 papers in PubMed and 19 records in PsycInfo. After duplicates were removed, a total of 9 papers were screened. None of these papers were discarded; thus, 9 articles were fully reviewed and were included in the current study (identified with an * in the bibliography). Figure 13 presents a graph that summarizes this search process.

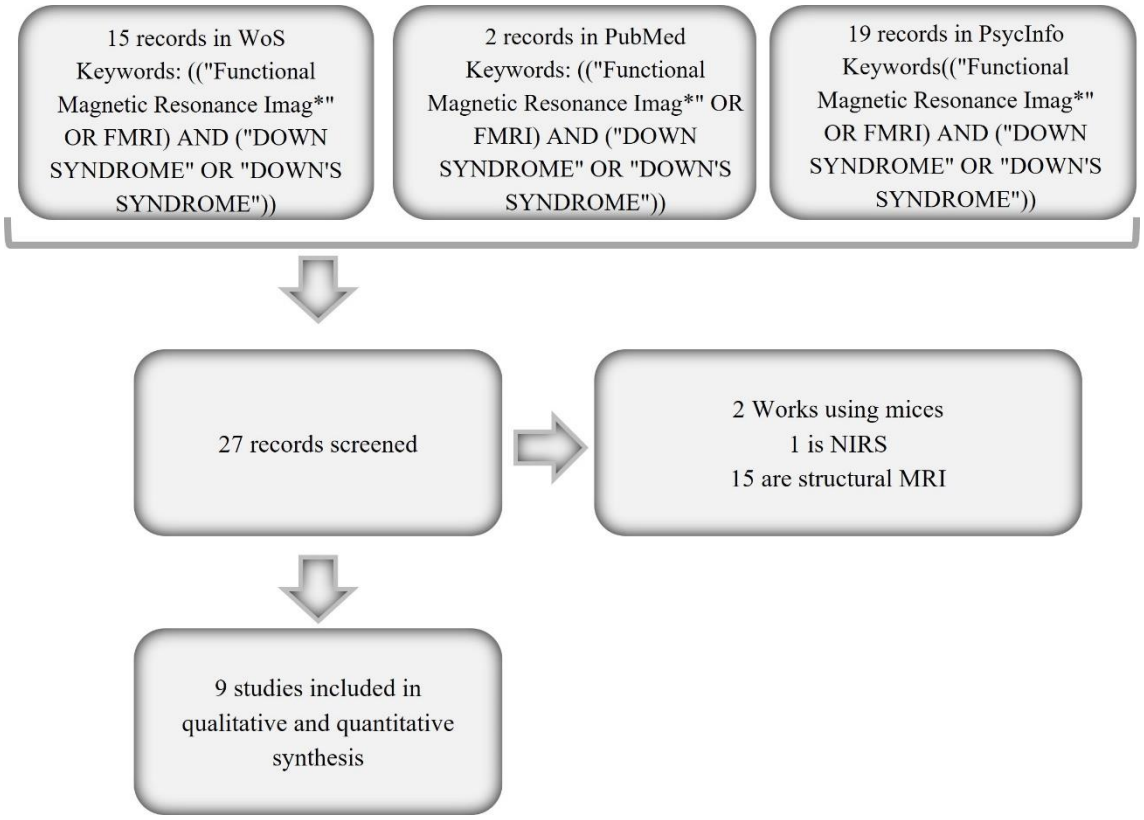


*Figure 13. Flow chart of the analyzed papers.*

Three independent researchers analyzed each paper to estimate the most important information from each of the included articles. Table 21 shows the main characteristics of these articles.

*Table 21. Main characteristics of the analyzed papers.*

| Title | Authors | Year | Journal |
|---|---|---|---|
| Abnormal brain synchrony in Down Syndrome. | Andesrson J. S., Nielsen J. A., Ferguson M. A., Burback M. C., Cox E. T., Dai L. et al. | 2013 | NeuroImage |
| Violence: heightened brain attentional network response is selectively muted in Down syndrome. | Anderson J. S., Treiman S. M., Ferguson M. A., Nielsen J. A., Edgin J. O., Dai L. et al. | 2015 | Journal of Neurodevelop mental Disorders |
| Functional Magnetic Resonance Imaging of cognitive processing in young adults with Down Syndrome | Jacola, L. M., Byars, A.W., Chalfonte-Evans, M., Schmithrst, V.J., Hickey, F., Patterson, B., Hotze, S., Vannest, J., Chiu, C.Y., Holland, .K., & Schapiro, M.B. | 2011 | American Journal on Intellectual and Developmental Disabilities |
| Functional magnetic resonance imaging of story listening in adolescents and young adults with Down syndrome: evidence for atypical neurodevelopment | Jacola, L.M., Byars, A. W., Hickey, F., Vannest, J., Holland, S.K., & Schapiro, M.B. | 2014 | Journal of Intellectual Disability Research |
| Abnormal fMRI activation pattern during story listening in individuals with Down Syndrome | Reynolds Losin, E.A., Rivera, S.M., O'Hare, E.D., Sowell, E.R., & Pinter, J.D. | 2009 | American Journal on Intellectual and Developmental Disabilities |
| Functional Magnetic Resonance Imaging shows aberrant language lateralization in Down Syndrome | Seyffert, M., Field, K., & Pinter, J. | 2002 | Annals of Neurology |
| Resting-state functional connectivity in individuals with Down syndrome and Williams syndrome compared with typically developing controls. | Vega J. N., Hohman T. J., Pryweller J. R., Dykens E. M., and Thornton-Wells T. A. | 2015 | Brain Connectivity |
| The effectiveness of the computerized visual perceptual training program on individuals with Down syndrome: An fMRI study | Wan, Y-T., Chiang, C-S., Chen, S. C-J., & Wuang, Y-P | 2017 | Research in Developmental Disabilities |
| Differential effects of Down's syndrome and Alzheimer's neuropathology on default mode connectivity. | Wilson L. R., Vatansever D., Annus T., Williams G. B., Hong Y. T., Fryer T. D. et al. | 2019 | Human Brain Mapping |

As shown in Table 21, the nine works were published after 2002, and seven studies were published in the last 9 years. Finally, the work of Seyffert et al. (2002) is a conference proceeding and therefore provides little information.

### *2.3.5 Results*

#### *Main Characteristics of the Studies*

Table 22 shows the main characteristics of the samples used in the nine analyzed works. As shown in the table, seven of the works are American, one is Taiwanese, and one is from the United Kingdom. The total sample sizes range between 6 and 76 participants belonging to two groups, a DS group and a control group; however, in Jacola et al. (2014) and Vega et al. (2015), three groups are used. In Jacola et al. (2014), there are two control groups, one paired by chronological age and the other by mental age; in Vega et al. (2015), there is a group of DS individuals, a group of Williams syndrome (WS) participants and a control group. In general, no characteristics of the total sample are provided; however, sample characterization is performed for each of the groups. The percentage of males, in general, is higher than 50% in both analyzed groups, even reaching 71.05% in the study by Wan et al. (2017). Notably, in the eight studies in which information on the age of the participants is available, the ages range between 5 and 47 years old. In the majority of the papers, the groups were paired by chronological age and/or sex.

Notably, in the work of Wan et al. (2017), the DS group is divided into two groups, an intervention group (n = 18) and a non-intervention group (n = 20). Because of this subdivision, the groups are not equal in terms of sex and age, so the proportion of men in the DS intervention group is 61.11%, while in the DS nonintervention group, the proportion of men is 80%; the average age in the DS intervention group is 14.09 years, while in the DS non-intervention group, it is 12.35 years. Finally, none of the nine studies present information on the degree of disability of the persons with DS.

*Table 22. Sample description of the analyzed papers.*

| Paper | Sample Country | n | % men | Groups | n by group | % men by group | Age mean by group | Sampling | Matching |
|---|---|---|---|---|---|---|---|---|---|
| Anderson et al. (2013) | USA | 29 | 58.62 | 2 | DS: 15<br>C: 14 | DS: 60.00<br>C: 57.14 | DS: 20.20<br>C: 23.70 | Accidental | Chronological age and sex |
| Anderson et al. (2015) | USA | 29 | 58.62 | 2 | DS: 15<br>C: 14 | DS: 60.00<br>C: 57.14 | DS: 20.20<br>C: 23.70 | Accidental | Chronological age and sex |
| Jacola et. al. (2011) | USA | 25 | 60.00 | 2 | DS: 13<br>C: 12 | DS: 61.54<br>C: 58.33 | DS: 18.3<br>C: 19 | Accidental | Chronological age and gender |
| Jacola et. al. (2014) | USA | 36 | 47.22 | 3 | DS: 11<br>C_CA: 13<br>C_MA: 12 | DS: 54.54<br>C_CA: 53.85<br>C_MA: 33.33 | DS: 18.3<br>C_CA: 18.3<br>C_MA: 5.4 | Accidental | C_CA: chronological age<br>C_MA: mental age |
| Reynolds et. al. (2009) | USA | 18 | 50.00 | 2 | DS: 9<br>C: 9 | DS: 44.44<br>C: 55.56 | DS: 16.5<br>C: 17.8 | Accidental | Chronological age |
| Seyffert et. al. (2002) | USA | 6 | | 2 | DS: 3<br>C: 3 | | | Accidental | |
| Vega et al. (2015) | USA | 68 | 60.29 | 2 | DS: 10<br>WS: 18<br>C: 40 | DS: 40<br>WS: 72.22<br>C: 60.00 | DS: 38.98<br>WS: 25.89<br>C: 46.95 | Accidental | |
| Wan et. al. (2017) | Taiwan | 76 | 71.05 | 2 | DS: 38<br>C: 38<br>Intervention (n=18) and control (n=20) | DS: 71.05<br>C: 71.05 | DS: 13.17<br>C: 13.07 | Accidental | Chronological age and gender |
| Wilson et al. (2019) | United Kingdom | 54 | 50.00 | 2 | DS: 34<br>C: 20 | DS: 55.00<br>C: 47.00 | DS: 43.5<br>C_CA:43.5 | Accidental | Chronological age |

Note: DS: Down syndrome group; C: control group; C_CA: control group matched by chronological age; C_MA: control group matched by mental age; WS, Williams syndrome group.

### *fMRI Description and Main Results*

As shown in Table 23, in eight of the works, the resonator used is 3 Teslas, while in the oldest work (Seyffert et al., 2002), the resonator is 1.5 Teslas. In five studies, the block design is used; therefore, the subjects must perform a task while undergoing BOLD signal acquisition. The rest of the works use the resting state paradigm, but two of them employ unusual strategies, such as presenting visual stimuli during signal acquisition (Anderson et al., 2013, 2015). Jacola et al. (2011, 2014) and Reynolds Losin et al. (2009) use semantic listening type tasks, whereas in the Wan et al. (2017) study, visual perception tasks are used. The amount of time that persons are in the resonator performing the task is generally short, ranging from 5min 30 s in the shortest case to 50 min in the longest case. In general, the objective of the analyzed works is to determine if there is a differentiated activation pattern between the DS group and the analyzed control group. Clearly, the papers estimating functional connectivity networks try to show the difference between groups in relation to network patterns and characteristics.

*Table 23. Principal characteristics of the fMRI design and principal results obtained.*

| ID | Teslas | Design | Task | Task time | Main aim | Principal results |
|---|---|---|---|---|---|---|
| Anderson et al. (2013) | 3T | Resting-state imaging with visualizing cartoons | | 50’ | Compare fMRI scans of 15 individuals with Down syndrome to 14 typically developing control subjects while they viewed cartoon video clips | Measurements of subject motion were significantly higher in Down syndrome subjects than in controls. Down syndrome subjects showed higher levels of synchrony between distributed brain networks as well as between the vast majority of gray matter regions. Down syndrome subjects exhibited weaker correlations only for a relatively small subset of the most correlated regions, whether negatively or positively related. Regardless of the distance separating the regions, pairs of regions that showed anticorrelation in a large control sample showed increased correlation (reduced anticorrelation) in Down syndrome. |
| Anderson et al. (2015) | 3T | Resting-state imaging with visualizing cartoons | | 50’ | Examine functional brain activation in response to stylized violence stimuli in Down syndrome and in typically developing individuals to determine whether regional brain activation patterns could be characterized, as well as whether atypical neural activation might be present that could provide clues to a basis for the deficits seen in Down syndrome | In typically developing individuals, the brain’s dorsal attention network was most active during violent scenes in the cartoons; this was significantly and specifically reduced in Down syndrome participants. Individuals with Down syndrome exhibited significantly reduced activation in the primary sensory cortices, and such perceptual impairments may constrain their ability to respond to more complex social cues such as violence |

| ID | Teslas | Design | Task | Task time | Main aim | Principal results |
|---|---|---|---|---|---|---|
| Jacola et al. (2011) | 3T | Block design | Paradigm that required participants to make a decision based on semantic information derived from visually presented stimuli | 5’30’’ | Understand the relationship between cognitive processing and brain activation in individuals with Down syndrome on tasks that measured aspects of both verbal and visual-spatial abilities | A significant difference was present in task performance between the mean of DS and control individuals; the mean of DS individuals was inferior to that of controls. In relation to fMRI, controls had 13 areas activated, whereas DS had 20 areas activated. |
| Jacola et al. (2014) | 3T | Block design | Language processing: a passive story listening paradigm | 5’30’’ | Explore neural activation during language processing in participants with DS compared with typically developing groups matched for chronological and mental age | Random effects group analyses documented a reduced activation magnitude in the DS cohort than in both control groups. The pattern of activation within the DS cohort additionally included significantly greater activation in the midline frontal regions (BA 9 and 10) and cingulate gyri (BA 23, 24, 30 and 32). |
| Reynolds Losin et al. (2009) | 3T | Block design | Passive story-listening task (Blocks: forward, backward and rest) | 6’08’’ | Investigate whether individuals with DS exhibit aberrant language-related activation patterns compared to an approximately age-matched typically developing control group during an easily performed passive story-listening task | Control > DS: Forward > Backward—Right middle temporal gyrus. DS > Control: Forward > Rest—Right precuneus; Backward > Rest—Right precuneus. |
| Seyffert et al. (2002) | 1.5T | Block design | Silent naming of pictures of common objects presented through fiber- | | Unspecific objective related to language deficits in Down syndrome | Greater activation was observed in the right inferior frontal and right superior temporal gyrus in the DS group than in the controls. |

| ID | Teslas | Design | Task | Task time | Main aim | Principal results |
|---|---|---|---|---|---|---|
| | | | optic goggles. As a control condition, subjects viewed pixilated images of the same objects with instructions to look without attempting to name them. | | | |
| Vega et al. (2015) | 3T | Resting State | | 5’ | First aim: confirm previous findings of increased between-network connectivity in DS individuals compared with TD controls and determine whether such differences are specific to DS or are also observed in another developmental disability disorders, such as WS. Characterize how the within-network connectivity profiles of DS and WS could be compared with each other and with TD participants. Together, these aims are intended to support the replication of previous work while providing new insights into resting-state brain | The results showed that alterations of between-network connectivity, particularly in the DMN, are a characteristic of a number of neurodevelopmental disorders involving intellectual disability, including DS and WS. Perhaps within-network connectivity is a feature that shows more variable patterns across different neurodevelopmental disorders. |

| ID | Teslas | Design | Task | Task time | Main aim | Principal results |
|---|---|---|---|---|---|---|
| | | | | | function across two different neurodevelopmental disorders. | |
| Wan et al. (2017) | 3T | Block design | Two types of visual perceptual tasks: two-choice revised version of Hooper Visual Organization Test (T-HVOT) and Full Picture Matching Test (FPMT) | 6’42’’ | (1) Develop and implement a one-year computerized visual perceptual training (CVPT) program for DS, (2) use a standardized visual perception assessment to evaluate the effectiveness of the CVPT program, and (3) examine the changes of cortical activation patterns of DS individuals after one-year of CVPT intervention by utilizing fMRI. | The results showed that the DS intervention group had significant improvements in TVPS-3 after the intervention. The fMRI results indicated more activation in the superior and inferior parietal lobes (spatial manipulation), as well as the precentral gyrus and dorsal premotor cortex (motor imagery) in the DS intervention group. In the T-HVOT vs. FPMT comparison, TD individuals showed highly significant bilateral activations in the middle occipital gyrus, middle temporal gyrus, middle frontal gyrus, and inferior frontal gyrus. |
| Wilson et al. (2019) | 3T | Resting state | Eyes closed while awake | 10’ | (a) Determine the potential functional connectivity alterations of the DMN in people with Down syndrome; (b) examine the relationship between DMN connectivity and age, IQ and performance on memory and executive function tasks in people with Down syndrome; and (c) investigate differences in | The Down syndrome (all) group did not display a typical profile of DMN connectivity; almost no anti-correlation with other cortical regions was observed. Disrupted functional connectivity of the DMN is an early biomarker of Alzheimer’s disease neuropathology. |

| ID | Teslas | Design | Task | Task time | Main aim | Principal results |
|---|---|---|---|---|---|---|
| | | | | | DMN connectivity in people with Down syndrome with and without fibrillar Aβ accumulation, indicative of Alzheimer's disease neuropathology | |

A summary of the results found in the different works is also provided in Table 23. The task description of these works is noteworthy since none of them mention the previous learning periods, and the level of difficulty of the task is not indicated in all of them. In fact, in older works using a resting-state approach, visualization is used to avoid excessive movement. The extent to which these sequences would be considered resting is debatable, since these types of records, as we have reiterated, occur in the absence of any external stimulation. An examination of the concrete results of each of the papers indicates some common characteristics, even though the papers are not strictly comparable. In general, differential activation patterns are seen in the DS samples compared to the control groups. This pattern is not regular, and statistically significant differences are observed in unilateral comparisons in both the Down > Control and Control > Down assessments. Most likely, depending on the characteristics of the tasks, distinct and small extrapolated activation patterns were obtained. For example, Seyffert et al. (2002) found greater activation in the DS sample than in the control group in a task to silently name pictures of common objects. On the other hand, Reynolds Losin et al. (2009), in a passive story-listening task (Blocks: Forward and Backward and Rest), found similar effects in some comparisons. For example, in the Forward > Backward task, statistically significant effects were found in the unilateral comparisons of the Control > DS groups. However, in other tasks (Forward>Rest), the statistically significant difference was in the opposite direction DS>Control. The works of Jacola et al. (2011, 2014) were especially consistent since they only found statistically significant effects in the Control > DS comparisons in all the areas studied. Inconsistent and irregular activation patterns, as we mentioned, can be seen in the remaining works (Vega et al., 2015; Wan et al., 2017; Wilson et al., 2019). The two works carried out with a resting-state approach (Anderson et al., 2015) showed less activation in the functional connectivity networks presented in the DS samples. However, these results are not comparable since both studies used resting-state techniques with the presentation of visual stimuli.

### *2.3.6 Discussion*

We should wait a few more years for more studies using fMRI techniques to be published and to include various specific populations. Even so, it is quite pertinent to promote the use of these techniques, which deserve special attention in the DS population for their singularities in relation to their cognitive functioning and intellectual level. Generally, the increase in the use of neuroimaging techniques has led to the appearance of many underpowered studies with small sample sizes, which leads to many missed results (Button et al., 2013). This leads us to continue to explore the different findings.

Presently, it is optimistic to talk about generalized conclusions given the small amount of evidence available (eight or nine papers depending on the consideration of Seyffert et al., 2002).

In any case, we aim to provide useful reference points to support future work that utilizes fMRI techniques with the DS population.

First, there is evidence of functional and structural differences between populations. Lower brain volume and lower activity (activation) recorded by fMRI appear to be typical in the DS population. It is evident that the morphological differences in the brain of a person with DS brain fuel the discussion about the normalized atlases, which were also revealed in the MRI studies of persons with DS. For instance, Pujol et al. (2018) used SPM voxel-based morphometry (VBM) with DARTEL algorithms in the image preprocessing phase.

Second, related to the last point, in fMRI sessions, we have already reiterated that the recording problems stem primarily from the movement of the person within the resonator. This problem is common in children and in populations with pathologies that compromise motor control (Aranyi et al., 2017). This tendency is observed among DS persons. As a consequence, some records have to be eliminated, or statistical routines are required to correct broadband movement in the preprocessing phase. It is a source of noise to consider in this type of work.

Except for the work of Wilson et al. (2019), this issue is not mentioned in the rest of the works. In this regard, the proposals of Ciric et al. (2017) should be taken into account in all fMRI studies and with more intensity in high-movement populations such as persons with DS. Even if their suggestions do not provide specific corrections for DS samples, they have been shown to be effective in reducing the perverse effects of excess movement. The work of Wilson et al. (2019) may be a reference for the appropriate application of these corrections.

Third, in the same manner, the sample sizes are small. This finding is not new; it is a recurring theme in many works, not necessarily just DS studies. Therefore, this factor is not a distinctive aspect of these samples. The difficulties of sampling are well-known but are not different from many other proposals for fMRI. From a classical perspective, the expected minor sampling error in this work would not be inferior to 0.1124 assuming a CI of 95% and a theoretical parameter $p = 0.5$.

From a methodological point of view, and as the fourth issue, we can identify certain doubts in the configuration of control groups of healthy people in the employed designs. It is important to note that the mental development of subjects with intellectual disability is not the same as that of healthy subjects of equal chronological age but should not differ significantly when matched for their mental age (Carducci et al., 2013). The focus is on the selection of an appropriate control group, and the options are matching by chronological age or by mental age. In the first case, we consider a non-specific maturation process, and in the second, we address cognitive skills, which are also developmental but focus fundamentally on performance. Notably,

in the case of studies that involve tasks, it would be appropriate to promote having control groups matched by mental age, as it is a question of comparing cognitive performance and brain signals (Jacola et al., 2014). Only one study analyzed described two paired control groups, one by chronological age and another by mental age, because basal functioning was being evaluated rather than factors associated with an explicit cognitive task or component.

In this respect, there is one aspect that is of little or no consideration. If a control group is generated from the estimation of mental age matching, strict matching must be performed (consisting with having an exact mirror in the control group of each case in the experimental group). If a poorly matched group is used due to sampling difficulties, the control is usually verified by comparing the means of the mental age between the two groups; relevantly, IQ ranges differ greatly between individuals with and without DS. In people without ID, the IQ ranges between 85 and 115 in almost 66% of people (according to the normal curve properties); the population of ID individuals is usually distributed into those that exhibit slight or medium delays, that is, those with IQs up to 70 in most cases. In addition, IQs are stable in the adult population but much less stable in the child population; thus, comparison with this type of matching can be misleading (Amador and Forns, 2019). No matching analyses have been reported with empirical evidence of homoscedasticity between groups paired with lax criteria.

In this sense, as a fifth point, the works analyzed here show comparisons between groups of statistically significant activations or networks obtained from the fMRI records during a semantic recognition task, passive listening, non-verbal denomination of objects, a visual perception task or a resting state (see Table 23). In all cases, activation differences are reported in certain areas of the brain with intergroup comparison. The fact that the visual areas are activated less in the DS sample than in the control group or that there are differences in other areas due to visual stimuli does not indicate specific properties of the DS population. The same consideration must be addressed in network differences. In fact, in general, all studies agree in reporting a lower activation intensity in DS groups than control groups, and the study by Wan et al. (2017) presents an interesting intragroup comparison that does describe intrinsic properties of the DS population. However, the lower activation level obtained in the DS group than in the controls confirmed the effects of brain impoverishment described above. We can make many comparisons with many different stimuli; however, these comparisons will not directly lead us to discovering unique brain behavior properties of the DS population. In fact, an activation increment is described in some connections, and a decrement is noted in others in the comparisons between networks in DS samples and the paired control groups. However, these differences do not allow the establishment of a stable and regular pattern typical of DS people.

These findings lead us to another crucial point. The use of tasks that previously published papers have used are tasks adapted to the peculiarities of the target population. Comparison with a healthy control group of similar chronological age does not in any way support characteristic outcomes among the DS population. The comparison between DS and non-DS groups does not provide relevant evidence regarding individuals with DS. It seems more methodologically reasonable to make intragroup comparisons than intergroup comparisons and, when feasible, use internal classification criteria for the identification of subgroups. For instance, to compare older and younger individuals, those with higher cognitive competence and those with lower competence, those with a higher cognitive reserve level and those with a lower level and so on within the DS population, any other criteria that allows characterization of cognitive competence by signals and study of its distribution should be utilized.

Intragroup comparisons present other types of statistical issues that extend beyond the objective of this paper but are reasonably resolved and can be used in DS studies. We can observe examples of these issues in AD or Parkinson's populations or in populations with other pathologies with characteristic intellectual deficits, such as Williams syndrome, Fragile FXS syndrome, Rett syndrome and Turner's syndrome (Beaton et al., 2010; Thornton-Wells et al., 2010; Chai et al., 2012; Stevenson et al., 2012; Venuti et al., 2012; Klabunde et al., 2015; Reynolds et al., 2015).

While previously mentioned, it is surprising that there are scarce resting-state fMRI records. Several studies have shown the relationship between the default mode network (DMN) and healthy aging processes; thus, the estimation of this type of wellknown network should also be a good vehicle for the study of brain functioning through fMRI in the DS population (Farràs-Permanyer et al., 2019), which leads to a final point that we must propose. The study of brain signals in pathologies with cognitive deficits is common; however, it is not commonly used to evaluate people with DS, and the lack of studies with this approach cannot be explained by the difficulties of sampling or the workload of registration alone. The sampling difficulties and workload are the same those for other pathologies, but there are more published studies on people with other diagnosis than on people with DS.

The issue is that if fMRI (or other types of signals) data are used as indicators of cognitive status, they are likely to be perceived as being unnecessary in these (and other) cases. However, this is not the essential question. The conception of the brain signal cannot currently be conceived as the study of a specific activity associated with a stimulus. The nature of brain function requires a much broader consideration than designs associated with tasks in which the statistical detection of increased activation in a specific area of the brain through intergroup or intragroup comparisons is a priority. Our proposal is based on the need to study functional and effective connectivity

networks for the whole brain at rest and in series that are not less than 5min, according to the recommendations of Cole et al. (2010) and Van Dijk et al. (2010). This recommendation provides a measure of brain functionality (i.e., connectivity networks) in a short and feasible time and with no bias.

### *2.3.7 Conclusions*

To conclude, we want to summarize the notable points discuss above. First, it is feasible to use fMRI signals in a population with DS, as long as measures are provided with the utmost rigor. Second, it seems preferable to use the resting-state paradigm in this population. Third, it would be beneficial to invest time and effort in studying how the brain signal in the population with DS could be used as a biomarker of cognitive activities. Fourth, this type of data must be exhaustively analyzed to estimate classification and discrimination functions between differential groups within the same population of DS. Techniques such as linear or non-linear discriminant analysis and latent profile analysis, among others, may be especially relevant. Finally, we must remember that the techniques related to movement reduction can help improve recruitment and sampling, especially reducing experimental mortality due to register errors. All these questions are very limited thus far with respect to the effort to meta-analyze data from fMRI signal studies in populations with DS.

### *2.3.8 References*

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## 2.4 Study 4: Altered spontaneous brain activity in Down syndrome and its relation with cognitive outcome


### *2.4.1 Identifying data*

Title: Altered spontaneous brain activity in Down syndrome and its relation with cognitive outcome

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### *2.4.2 Abstract*

Although Down syndrome (DS) is the most common genetic cause of neurodevelopmental delay, few neuroimaging studies have explored this population. This investigation aimed to study whole-brain resting-state spontaneous brain activity using fractional amplitude of low-frequency fluctuation (fALFF) and regional homogeneity (ReHo) strategies to find differences in spontaneous brain activity among young people with DS and controls and to correlate these results with cognitive outcomes. The sample comprised 18 persons with DS (age mean=28.67, standard deviation=4.18) and 18 controls (age mean=28.56, standard deviation=4.26). fALFF and ReHo analyses were performed, and the results were correlated with other cognitive variables also collected (KBIT-2 and verbal fluency test). Increased activity was found in DS using fALFF in areas involving the frontal and temporal lobes and left cerebellum anterior lobe. Decreased activity in DS was found in the left parietal and occipital lobe, the left limbic lobe and the left cerebellum posterior lobe. ReHo analysis showed increased activity in certain DS areas of the left frontal lobe and left rectus, as well as the inferior temporal lobe. The areas with decreased activity in the DS participants were regions of the frontal lobe and the right limbic lobe. Altered fALFF and ReHo were found in the DS population, and this alteration could predict the cognitive abilities of the participants. To our knowledge, this is the first study to explore regional spontaneous brain activity in a population with DS. Moreover, this study suggests the possibility of using fALFF and ReHo as biomarkers of cognitive function, which is highly important given the difficulties in cognitively evaluating this population to assess dementia. More research is needed, however, to demonstrate its utility.

**Keywords:** Down syndrome, intellectual disability, resting-state functional magnetic resonance imaging, fractional amplitude of low-frequency fluctuation, regional homogeneity

### *2.4.3 Introduction*

Down syndrome (DS) is the most common genetic cause of neurodevelopmental delay and affects one out of 700 live births[1]. Although the life expectancy of people with DS has increased dramatically[2,3], age-related comorbidities in this group have appeared, specifically Alzheimer's disease (AD)[4]. In the last few years, new quantitative approaches using brain magnetic resonance imaging (MRI) have characterized brain development in diseased and healthy populations[5]. In the field of DS, although clinical and genetic characteristics have been described, few neuroimaging studies have been performed[6].

Regarding structural MRI, brain abnormalities have been demonstrated in the DS population. Koenig et al.[7] demonstrated differences in the hippocampus in the DS group compared with the non-DS group. Similarly, Beacher et al.[8] demonstrated that the frontal, temporal, and parietal lobes show more significant age-related reduction in DS than in the general population. Additionally, white matter integrity has been found to be decreased in DS and correlates with cognitive dysfunction[9,10]. Benjanin et al.[11] found an association between cognitive decline and the APOE e4 allele, the earlier loss of cortical metabolism and hippocampal volume; these results were congruent with previous studies on brain volume loss[12-14]. APOE e4 is the most established genetic risk factor for sporadic AD and has been related to earlier symptoms in the general population and in DS[11].

Less is known about functional MRI (*f*MRI) in DS; nevertheless, a systematic review[6] highlighted the importance of studying resting-state functional MRI (rs-*f*MRI) in this population. The rs-*f*MRI paradigm captures intrinsic functional spontaneous brain activity and allows the evaluation of the brain baseline function and has been used to elucidate differences between diseased populations and control participants[15]. This paradigm has been suggested as a suitable biomarker for abnormal brain function and predicting later adverse neurodevelopment in DS [16]. The majority of studies using rs-*f*MRI in this population have focused on specific areas or predetermined networks, such as the default mode network[17-19] (DMN) or the hippocampus[7]. However, few studies have focused on the whole brain[20].

Unclear findings in functional connectivity (FC) have been found in this field for various reasons. First, there is heterogeneity in the age of the participants. In this sense, it is crucial to consider that AD neuropathology is universal by 40 years of age in people with DS [21,22], and therefore, significant changes in the brain can occur in this population in an interval of very few years. It has been demonstrated that the DS population exhibits a β-amyloid (Aβ) burden prior to dementia diagnosis, and this deposition can begin in the late teens [23-25]. Therefore, it is vital to focus investigations on young DS participants who have not yet developed the neuropathology of AD. These studies can help to elucidate the abnormalities of the DS phenotype and aid in finding biomarkers of neurodegeneration[16]. Second, the use of predetermined seeds or regions of interest

limits the comparison of results between studies. Third, methodological decisions, for instance, different head motion corrections or approaches of analyses, can also limit the generalization of the findings[26]. Finally, the limited number of studies and the small sample size typically used have also limited the reliability of these findings[27,28].

Despite these limitations, studies have demonstrated altered FC in this population. Increased brain synchrony was found between distributed brain regions, including grey matter, visual-frontoparietal regions, somatomotor regions, and different regions of the DMN and frontal lobes[29-31]. The DMN is related to high structural and FC while a person is at rest and has been demonstrated to be disrupted in several diseases[32], such as DS. Results indicating abnormalities in DS through the DMN were found[17-19]: first, a disrupted connectivity between posterior brain regions, and second, hyperconnectivity and hypoconnectivity, including different subregions of the DMN. Finally, they found weaker strength in frontal regions, consistent with other studies[29]. Recently, Csumitta et al.[20] found increased whole-brain FC in DS.

Some studies have also tried to link the abnormalities with different neurocognitive impairments typically found in DS. In this sense, the cognitive domains that are particularly impaired in individuals with DS, apart from an intelligence quotient (IQ) usually ranging from 30 to 70, include language (particularly expressive language), memory, executive function and motor coordination[33]. Anderson et al.[29] found an inverse relationship between network synchrony performance and IQ in the DS group, whereas Vega et al.[31] found no relationship between the abnormalities in network connectivity and IQ. Pujol et al.[30] evaluated whether the differences found in FC could be related to communication skills and found direct relationships between FC in the ventralial frontal cortex, amygdala and communication skills. They also found indirect relationships between communication skills and decreased FC in the left posterior insula and right sensorimotor cortex. These results are in accordance with Csumitta et al.[20], who demonstrated that differences found in connectivity in DS could be related to verbal abilities.

Functional neuroimaging findings until now have suggested alterations in connectivity in DS. However, the vast majority of studies are linked with finding differences between controls and DS in FC. However, FC only depicts the relationship between two or more regions and thus does not provide information on which exact single region is abnormal within networks. In contrast, regional spontaneous brain activity analysis may provide this helpful information[34] and thus could help disentangle differences in regional activity[35].

The amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (ReHo) are data-driven methods that reveal different regional characteristics of rs-fMRI data and are useful when the studies in the population are very limited; therefore, there are no hypotheses on specific regions. ALFF and ReHo have recently been used in many psychiatric diseases[36-38], neurodevelopmental disorders [39,40], and dementias[41,42]; however, to our knowledge, these methods have not yet been applied in the DS population, and both methods seem promising for detecting

regional signal changes in spontaneous activity. Both tools have been suggested as potential biomarkers for tracing changes in the brain while it develops, as well as in relation to behaviours and diseases, as both techniques present high temporal stability [43,44].

On the one hand, ALFF measures the strength of the regional intensity of spontaneous fluctuations in the BOLD signal[45] but has often been criticized because it could be sensitive to physiological noise. Therefore, Zou et al.[34] suggested fractional amplitude of low-frequency fluctuations (fALFF), which enhances the sensitivity and specificity of spontaneous brain activity detection. On the other hand, ReHo estimates the temporal homogeneity of the signal between a given voxel and neighbouring voxels. Basically, ReHo estimates local neural activity. Both approaches are complementary, while fALFF is focused on measuring local spontaneous activity, and ReHo estimates regional abnormalities[34]. Thus, combining ReHo and fALFF to assess spontaneous brain activity among the DS population could provide more information about brain function in people who present an intellectual disability (ID).

In addition to the interesting use of ReHo and fALFF to explore the brain mechanism of DS, it could be interesting to examine the relationship with other external, as it has been done in other populations. Li et al.[40] studied ALFF and ReHo with a sample of individuals with low-functioning autism spectrum disorder (ASD) and found increased ReHo and ALFF in different brain regions. However, no correlation was found with clinical symptoms in the ASD group. Lee & Hsiesh [46] studied fALFF and ReHo in a healthy population and showed a significant relationship with cognitive outcome using a stop-signal task and found negative correlations with different areas using both approximations. In the AD and mild cognitive impairment (MCI) field, Yang et al. [47,48] found significant correlations between fALFF and ReHo values and neuropsychological assessment in both populations. More interestingly, Li et al.[49] studied the relationship between fALFF and ReHo and amyloid-β accumulation in a sample with subjective cognitive decline (SCD) and found higher ReHO in the precuneus and superior parietal areas in amyloid-positive patients. Lu et al.[50] also found significant correlations between fALFF and executive function in a sample of childhood trauma in young adults. Fryer et al.[51] also found significant correlations between fALFF measures and cognitive function in schizophrenia. Consequently, both fALFF and ReHo seem to be promising techniques related to cognitive or clinical symptoms.

The present paper aimed to study the whole-brain resting state using fALFF and ReHo strategies to find differences in spontaneous brain activity among young people with DS and controls. We hypothesized that significant differences would be found between both groups, as seen in other rs-fMRI studies. As both techniques are data-driven methods and have never been used in DS, there was no need for a hypothesis. However, both techniques have been found to be highly related to FC[52]; therefore, the study of regional activity could elucidate already discovered

FC abnormalities. Consequently, we expected to find differences in the frontal lobe and in the DMN[17-19,30], following other resting-state studies in this population. Moreover, as there are cognitively impaired domains in DS[33], we expected that the neural correlates associated with these functions would be altered in spontaneous activity. For instance, the temporal and frontal lobes seem to play an important role in language and executive functions[53], as well as the frontoparietal brain regions in memory[54]. In addition, we expected the differences in fALFF and ReHo between DS and controls to be related to cognitive outcomes, as in other studies[20, 29].

### *2.4.4 Method*

#### *Participants*

The sample was comprised of 20 persons with DS and 20 non-DS controls matched by chronological age and gender. However, due to excessive movement in the *f*MRI registration, the final sample was comprised of 18 persons with DS (5 females, mean age=28.7, standard deviation (SD) of age=4.18) and 18 controls (mean of age= 28.56, SD of age=4.26). In both groups, the same protocol was applied. The recruitment of the DS group was conducted through different centres attending people with ID in Catalonia, Spain. The recruitment of the control participants was made from the community through advertisements. Regarding the inclusion criteria of the participants, the DS group had to be between 16 and 35 years old, and all of them had to have a diagnosis of DS. The participants with DS were excluded if: other comorbid diagnoses implying cognitive dysfunction were present apart from the DS diagnosis itself, the legal guardian's consent could not be obtained, and the person with DS had medication that could affect cognitive function (for example, anxiety medication). Control participants had to be matched by gender and age (±2 years) with DS participants. They were excluded if they had any psychiatric diagnoses or other disorders affecting cognitive function. For both groups, if excessive movement was present in the registration of the *f*MRI sequences, information for that participant was discarded. IQ was estimated for both groups with the Kaufman Brief Intelligence Test, Second Edition (KBIT-2)[55]. In the DS group, the mean KBIT-2 Full Scale IQ score was 43.94 ± 6.2 (range 40-66). The demographic information of the sample appears in Table 24.

#### *Procedure*

The Bioethical Committee of the Universitat de Barcelona approved the project (03/16/2017), and all methods were performed in accordance with the relevant guidelines and regulations. For minors and the participants with DS, informed consent of the guardians in legal charge of every person with DS was obtained. Informed consent was also acquired from all DS and control participants.

As the data of this project belong to a more extensive protocol, more data than the one presented here were registered. In this sense, the data used in this study only comprised the following: a usual sociodemographic questionnaire and a checklist for the MRI scanner. A cognitive test, KBIT-2[55], and a simple verbal fluency test were performed. The KBIT-2 test has been used to evaluate people with DS and controls in multiple studies [20, 29] and was chosen because of its ability to ensure items were age-appropriate, as the age rank for the administration is sufficiently large. Moreover, it evaluates verbal and nonverbal IQ. The measures used were raw scores in matrices (nonverbal), vocabulary (verbal) and total IQ. Moreover, the standardized score for total IQ was also used. It is important to mention that data were missing for one subject with DS to whom the KBIT-2 was not administered. Hence, the total sample with the KBIT-2 test was n=35.

Finally, regarding the verbal fluency test, three measures were performed: a) phonological verbal fluency: evaluated by the number of words produced beginning with the letter "p" during 1 min; b) semantic verbal fluency: evaluated by the number of words produced during 1 min related to things that can be bought in a supermarket; and c) semantic verbal fluency: evaluated by the number of words produced during 1 min related to the names of colours. The total score for semantic verbal fluency was estimated by adding the b) and c) scores.

Participants were evaluated in two sessions, and the sequence was the same for the DS and control participants. Questionnaires were administered, and images were acquired in the first session. The second session was dedicated to another part of the general research design.

***MRI acquisition***

Brain imaging was performed in a Philips Ingenia 3 MRI scanner T system located in the Fundació Pasqual Maragall in Barcelona, Spain. All participants underwent a *f*MRI recording sequence: T1, T2, Flair, and resting state. Regarding the resting-state registration, participants with DS only underwent a total of 6 minutes in the MRI scanner. Participants with DS underwent a short training to improve their familiarization with the scan and acclimate to the noise and environment. The control participants underwent a sequence of 10 minutes, but for this study, only the first 220 volumes of registration were used to guarantee a possible comparison between both groups. All participants were told to try to stay quiet without movement. Moreover, they should remain awake and with their eyes opened and fixed on a cross symbol on the screen. Participants could choose music to hear during all recordings except in the resting-state scan. Although individuals in the eyes-closed condition are more likely to become drowsy and fall asleep[56], none of the subjects included fell asleep during scanning, as self-reported after scanning. A T1-weighted turbo field echo (TFE) structura image was obtained for each subject with a 3-dimensional protocol (repetition time (TR) = 2300 ms, echo time (TE) = 2980 ms, 240 slices, and field of view (FOV) = 240 × 240 × 170). The image acquisition was in the sagittal plane. For the functional images, a T2 *-weighted (BOLD) image was obtained (TR = 1750 ms, TE=30 ms,

FOV=230×230×160, and voxel size=3×3×3 mm, 46 slices). The image acquisition was in the transverse plane.

***Data preprocessing***

Image preprocessing was performed using the Data Processing Assistant for Resting-State fMRI [57] (DPARSF; http://rfmri.org/DPARSF). Basically, it is based on MATLAB, SPM12 (http://www.fil.ion. ucl.ac.uk/spm) and DPABI[58].

The first 10 functional images were removed to allow magnetization equilibration and to allow participants to adapt to the scanner. Then, a correction was made for the remaining functional images for slice acquisition timing difference and head motion. Nuisance signals were regressed out, including white matter signals, cerebrospinal fluid signals, linear trends and signals associated with the 24 Friston head-motion parameters[59]. The derived functional images were coregistered with the corresponding structural images, which were segmented and normalized to Montreal Neurological Institute (MNI) space using diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL). The functional images were normalized to MNI space with warped parameters and resampled to 3 mm cubic voxels. For the ReHo analysis, the normalized functional images were then bandpass filtered (0.01–0.1 Hz). As DS is a specific population that can present excessive movement, the criterion used to exclude subjects in the sample was that the participants could not exceed the mean of the group plus 2 SD[60], estimated with Jenkinson's framewise displacement[61] (FD) owing to its consideration of voxelwise differences in motion in its derivation[60]. Overall, two persons with DS were excluded, and the final sample included 18 people with DS and 18 controls. Both groups differed in movement ($Z$ = -4.46, $p$ <.001, $\bar{x}_{DS}$=0.22 (SD=0.16); $\bar{x}_{C}$=0.08 (SD=0.028)), presenting more movement in the DS group. The DS group presented a total of 1040 (out of 3780) volumes exceeding 0.2 mm in Jenkinson FD, whereas the control participants presented a total of 172 volumes exceeding 0.2 mm in Jenkinson FD. Therefore, scrubbing regression was performed[60,62,63] in the final step of the preprocessing to control the movement exceeding 0.2 Jenkinson's FD. We further addressed the residual effects of motion in group analyses by including mean FD derived from Jenkinson's FD as a nuisance covariate[64].

***Calculation of fALFF and ReHo***

The estimation of fALFF and ReHo values was performed using DPABI[58]. To estimate ALFF, spatial smoothing was performed with a 4 mm full width at half maximum (FWHM) Gaussian Kernell. To compute the power spectrum, the time series of each voxel was transformed to the frequency domain via fast Fourier transform (FFT). This power spectrum, which has a frequency range of 0–0.25 Hz, was square-rooted at each frequency and then averaged across 0.01–0.08 Hz at each voxel, which was taken as ALFF. To obtain fALFF, the ALFF values were divided by the whole frequency range observed in the signal[34] (0–0.25 Hz).

Regarding the ReHo estimation, Kendall's concordance coefficient (KCC) of the time series of all voxels and their neighbours was calculated[35]. All ReHo maps were smoothed with a Gaussian kernel of four mm FWHM. Finally, individual fALFF and ReHo maps were standardized into z score maps by subtracting the mean and dividing by the standard deviation.

***Statistical Analysis***

The data analysis was performed with IBM SPSS (v26) to compare both groups. More specifically, two-group comparisons were performed using nonparametric tests due to the nonapproximation to the normal distribution of the quantitative variables, and $p$ <.05 was set as significant.

For statistical analysis of both groups in fALFF and ReHo, DPABI was used with a voxelwise two-sample t test. As mentioned above, both groups differed significantly in head motion; therefore, Jenkinson's FD[61] was included as a covariant in all analyses. Significant differences in the study were reported using the criteria of multiple comparisons with the threshold-free cluster enhancement (TFCE), which reached the best balance between familywise error and test-retest reliability[27]. In total, 10000 permutations were performed, and the Cluster *p value* was set to $p$ <.05. An additional threshold with a minimum extent threshold of 30 voxels for ReHo and 10 voxels for fALFF was set to exclude very small clusters, although they passed the strict permutation test with TFCE correction.

Moreover, R Studio (R 4.1.2) was used for the correlations, regression analysis, and visualization matrices. Extraction of the cluster values with DPABI was performed in the clusters where a significant t value was found in the comparisons between DS and controls. Then, they were separately correlated with the cognitive outcome. For this analysis, participants with DSs who did not have KBIT-2 scores were excluded.

### *2.4.5 Results*

In Table 24, the participants' characteristics are shown. As no normality was found in the quantitative variables, the statistical analysis was performed with nonparametric tests. As shown, significant differences were found in head motion, phonological and semantic verbal fluency, and all subtests of KBIT-2.

*Table 24. Participant characteristics.*

| | DS (mean; SD) | Controls (mean; SD) | Test (*p value*) |
|---|---|---|---|
| Age (years) | 28.67 (4.18) | 28.56 (4.26) | $Z$ = -0.03 ($p$ = .975) |
| Gender (% male) | 72.22% | 72.22% | |
| Head motion | 0.19 mm (0.10) | 0.08 mm (0.03) | $Z$ = -4.46 ($p$ < .001) |

| | DS (mean; SD) | Controls (mean; SD) | Test (*p value*) |
|---|---|---|---|
| Phonological verbal fluency | 4.28 (3.30) | 18.11 (5.41) | *Z* = -5.14 (*p* < .001) |
| Semantic verbal fluency | 17.50 (10.86) | 51.16 (12.05) | *Z* = -4.84 (*p* < .001) |
| KBIT-2 Vocabulary (DS group, n=17) | 25.41 (12.23) | 71.72 (4.10) | *Z* = -5.06 (*p* < .001) |
| KBIT-2 Matrices KBIT-2 (DS group, n=17) | 13.17 (5.44) | 39.33 (3.34) | *Z* = -5.06 (*p* < .001) |
| KBIT-2 raw total (DS group, n=17) | 96.88 818.18 | 223.5 (13.73) | *Z* = -5.05 (*p* < .001) |
| KBIT-2 Full IQ standarized (DS group, n=17) | 43.94 (6.23) | 111.05 (7.83) | *Z* = -5.31 (*p* < .001) |

Note: Z: Z score linked to the Mann–Whitney test; SD: standard deviation

***fALFF results between groups***

Table 25 shows the significant differences between groups in fALFF with the coordinates of the MNI. Figure 14 shows the graphical representation of the results in fALFF visualized with DPABI[58].

Compared with matched controls, on the one hand, DS showed significantly increased fALFF in the frontal and temporal lobes and the left cerebellum anterior lobe. On the other hand, the DS showed decreased activity in some parts of the left parietal, occipital and limbic lobes and in the left cerebellum posterior lobe.

*Table 25. Significant between-group differences in fALFF.*

| Comparison | Area | Number of voxels | *t* (peak) | Peak MNI coordinates (mm) | | | AAL peak region |
|---|---|---|---|---|---|---|---|
| DS>C | Cluster1: Frontal and temporal lobe | 636 | 6.36 | -18 | 12 | -27 | ~Temporal_Pole_Sup_L |
| | Cluster2: Left cerebellum anterior lobe | 10 | 6.19 | -27 | -33 | -33 | Cerebellum_4_5_L |
| | Cluster3: Left inferior temporal lobe | 13 | 5.39 | -60 | -30 | -33 | ~Temporal_Inf_L |
| | Cluster4: Left frontal lobe | 40 | 5.09 | -15 | 63 | -9 | Frontal_Sup_Orb_L |
| DS<C | Cluster5: Left parietal and occipital lobe | 41 | -5.97 | -42 | -75 | 33 | Occipital_Mid_L |
| | Cluster6: Left limbic lobe | 25 | -5.71 | 0 | -39 | 21 | ~Cingulum_Post_R |
| | Cluster7: right cerebellum posterior lobe | 215 | -5.61 | 30 | -66 | -36 | Cerebellum_Crus_1_R |
| | Cluster8: left cerebellum posterior lobe | 120 | -5.17 | -39 | -66 | -45 | Cerebellum_Crus2_L |
| | Cluster9: Left limbic lobe | 23 | -4.77 | 0 | -63 | 30 | Precuneus_L |

Note: C: Controls; MNI: Montreal Neurological Institute; ~: approximately, AAL atlas area closer to the t peak.

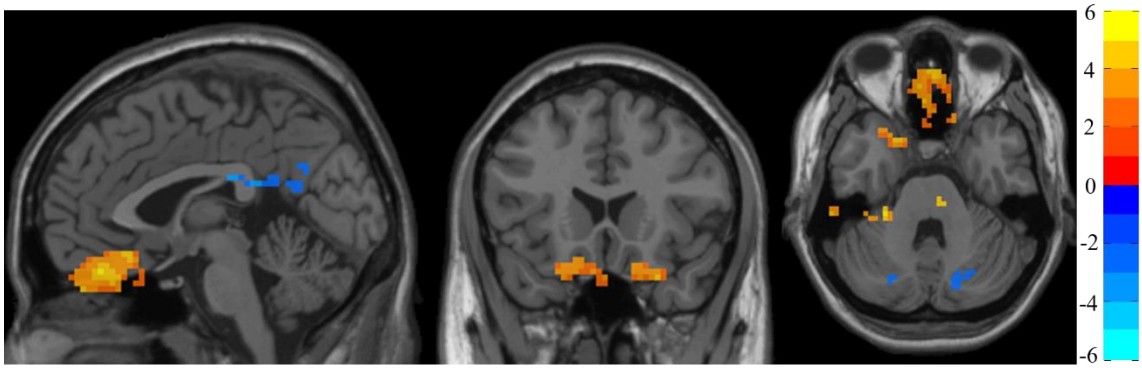



*Figure 14. fALFF analysis. Two-sample t test results are presented, corrected by a permutation test with TFCE, p < 0.05.*

Note: The area in blue represents a significantly decreased ALFF value in DS patients compared with controls; the area in yellow and red represents

***ReHo results between groups***

Table 26 shows the significant differences between groups in ReHo with MNI coordinates. Figure 15 shows the graphical representation of the ReHo results visualized with DPABI[58].

Compared with matched controls, on the one hand, people with DS showed significantly increased ReHo in some parts of the left frontal lobe and inferior temporal lobe. On the other hand, controls showed significantly increased activity in parts of the frontal lobe and right limbic lobe.

*Table 26. Significant between group differences in ReHo.*

| Comparison | Area | Number of voxels | *t* (peak) | Peak MNI coordinates (mm) | | | AAL peak region |
|---|---|---|---|---|---|---|---|
| DS>C | Cluster1: Right inferior temporal lobe | 43 | 5.84 | 48 | -27 | -27 | Temporal_Inf_R |
| | Cluster2: Left frontal lobe and left rectus | 746 | 5.75 | -3 | 30 | -15 | Rectus_L |
| | Cluster3: Left inferior temporal lobe | 40 | 5.16 | -42 | -30 | -21 | Fusiform_R |
| DS<C | Cluster4: Frontal lobe | 1947 | -7.42 | -45 | 45 | 0 | Frontal_Mid_Orb_L |
| | Cluster5: Left limbic lobe | 92 | -6.73 | 0 | -30 | 24 | ~Cingulum_Post_L |

Note : C: Controls; MNI: Montreal Neurological Institute.;~: approximately, AAL atlas area closer to the t peak.

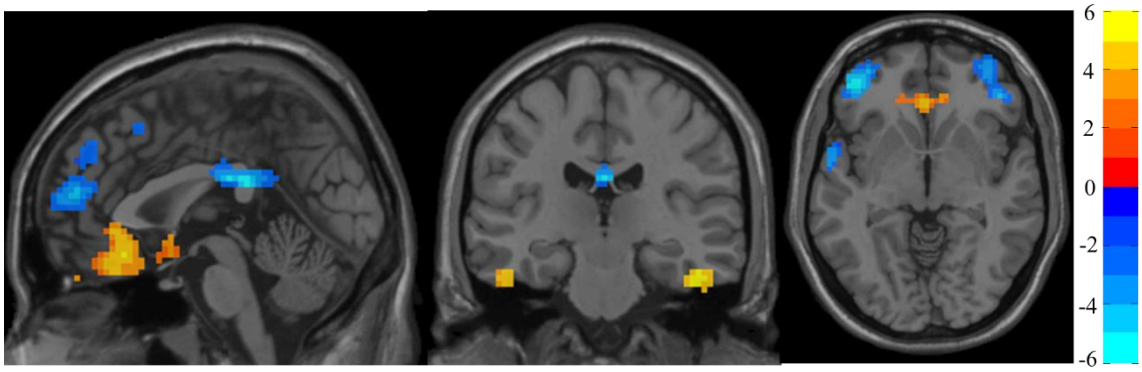



*Figure 15. ReHo analysis. Two-sample t test results corrected by TFCE are presented.*

Note: The area in blue represents a significantly decreased ReHo value in DS patients compared with controls; the area in yellow and red represents a significantly increased ReHo value in DS patients compared with controls.

***Correlations and regression analysis***

As large differences were found between the control and DS groups through both the ReHo and fALFF techniques, the possible relationship between the significant clusters and cognitive scores/measures was analysed via a correlation test.

Figure 16 represents a correlation matrix between the different significant clusters in fALFF and ReHo and cognitive scores. As expected, a high correlation was found between all cognitive measures and between the cluster signals. More interestingly, Figure 16 highlights the high correlations between the cognitive measures and the cluster values.

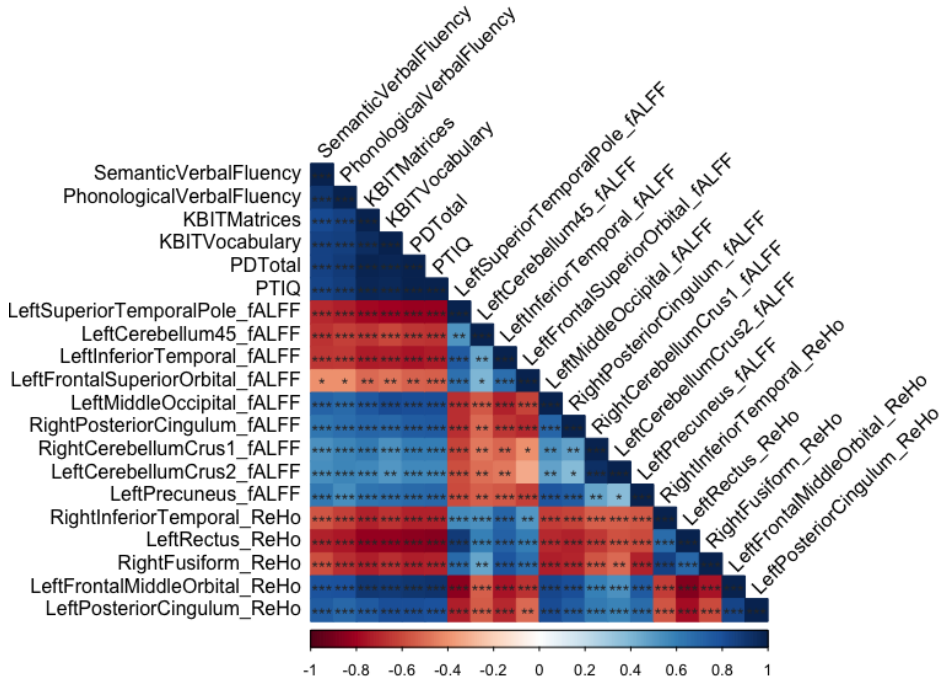



*Figure 16. Correlation matrix regarding the cognitive outcome and significant clusters in fALFF and ReHo.*

Regarding fALFF, at a $p$ <.001 significance level, all clusters correlated with most of the cognitive measures. The first four clusters of fALFF correlated negatively with cognitive scores, and the five final clusters were positively correlated with cognitive scores. Moreover, the directions of the correlations were consistent with the sign of the comparison, indicating that, when DS had increased activity in a cluster, the signal in that cluster was negatively correlated with the cognitive outcome. Similarly, when the controls had increased activity in a cluster, then the signal in that cluster was positively correlated with the cognitive outcome.

Regarding ReHo measures, similar to fALFF at a $p$ <.001 significance level, all clusters correlated with most of the cognitive measures. The first three clusters of ReHo correlated negatively with the cognitive scores, and the two final clusters were positively correlated with the

cognitive scores. The directions of the correlations were consistent with the sign of the comparison, indicating that, when DS had increased activity in a cluster, the signal in that cluster was negatively correlated with the cognitive outcome. Similarly, when the controls had increased activity in a cluster, the signal in that cluster was positively correlated with the cognitive outcome.

As the correlations in both the fALFF and ReHo clusters were high, a regression analysis was performed for every cognitive measure. It is important to highlight that the total measures of IQ in KBIT-2 were excluded from the regression models because the two groups were easy to distinguish and were not logical. Therefore, only the cognitive measures with sufficient variability, such as phonological and semantic verbal fluency, matrices, and vocabulary, were used to predict the cluster signal.

In Table 27, the regression models predicting cognitive scores are presented. They all met the conditions (no error autocorrelation, linearity, normality, and homoscedasticity of errors tested). All of them had high $R^2$ values, meaning that a high level of prediction was achieved. All of them were multiple linear regressions, and all of the variables included in the model were significant.

*Table 27. Parameter estimation (β) of the best stepwise linear model for each significant cluster in fALFF.*

| Signal | KBIT-2 Matrices | KBIT-2 Vocabulary | Phonological Verbal Fluency | Semantic Verbal Fluency |
|---|---|---|---|---|
| | $F$ = 53.65<br>$R^2$ = .86<br>*AIC* = 221.51 | $F$ = 43.17<br>$R^2$ = .83<br>*AIC* = 269.07 | $F$ = 34.22<br>$R^2$ = .66<br>*AIC* = 214.56 | $F$ =37.17<br>$R^2$ = .68<br>*AIC* = 276.38 |
| Intercept | 5.91 | 13.58 | 3.59 | 15.02 |
| Left Cerebellum 4,5 fALFF | -7.98 | | -6.82 | -20.73 |
| Left Superior Temporal Pole fALFF | | -25.32 | | |
| Left Frontal Superior Orbital fALFF | 5.63 | 13.92 | | |
| Left Middle Occipital fALFF | | 16.13 | | |
| Right Inferior Temporal ReHo | -6.73 | | | |
| Left Frontal Middle Orbital ReHo | 25.17 | 27.687 | 12.14 | 28.32 |

Note: F: ANOVA; AIC: Akaike information criterion. They all had a p <.001 in the model (df =1;33) and a p >.05 in Anderson's Darling test of normality, the Ramsey Regression Equation Specification Error (RESET) test, Durbin Watson's test, and the Breusch–Pagan test.

Supplementary Figure 1 and Supplementary Figure 2 show the scatter plots for the prediction of KBIT-2 Matrices and Vocabulary, as well as verbal fluency.

### *2.4.6 Discussion*

There is a scarcity of neuroimaging studies involving people with DS, especially in rs-*f*MRI techniques for detecting regional signal changes in spontaneous activity. Therefore, this study aimed to study the whole-brain resting state using fALFF and ReHo strategies to find differences in spontaneous brain activity among young people with DS and controls. Moreover, this study aimed to correlate the results of the differences between controls and DSs with cognitive outcomes.

Regarding fALFF analysis, the results showed significant differences in these frequencies in the whole brain between both compared groups. The areas that showed increased activity in DS included some parts of the frontal and temporal lobes and the left cerebellum anterior lobe. The areas that showed decreased activity in DS compared with controls were regions of the left parietal and occipital lobe, the left limbic lobe and the left cerebellum posterior lobe.

In relation to the ReHo analysis, significant differences between both groups were found. The areas that showed increased activity in DS participants compared with controls were certain areas of the left frontal lobe and left rectus, as well as the inferior temporal lobe. The areas with decreased activity in the DS participants were regions of the frontal lobe and the right limbic lobe.

There was high congruence between the areas in which differences were found using both techniques, which is consistent with previous studies [65] in other populations. Regarding the higher activity in the DS population than in the controls, the congruent regions of both analyses were the frontal and temporal lobes. Compared with the controls, the limbic lobe was decreased in DS participants. The areas that show widespread differences between controls and DS are clearly abnormal in DS, finding increased and decreased activity. Moreover, as no neuropathology of AD was present in our sample, these differences were not due to the clinical features of AD.

As we hypothesized, DS participants showed decreased fALFF and ReHo in the limbic lobe, a region that conforms to the DMN. Rosas et al.[17] also found differences in connectivity in this region. Moreover, they found an increased level of local connectivity within the frontal lobe in DS, which is consistent with our results showing increased fALFF and ReHo in the frontal lobe in DS compared with controls. Wilson et al.[19] also found weaker connectivity in the DS group than controls with the DMN seed and several regions, some of which were also reported in our study. More specifically, the precuneus, reported in our research as having decreased fALFF in the DS group than in the controls, and part of the cerebellum also showed significant results in our study.

Moreover, increased fALFF and ReHo have also been found in the frontal and temporal lobes. Both lobes are relevant for executive and language functions and memory[53,54], functions highly altered in DS[33,66,67]. This increase in spontaneous activity, despite being in a rs-*f*MRI paradigm, could be a mechanism of compensation for their disrupted networks and functions, as

has been suggested in other pathologies that present cognitive impairments[68] or visual disabilities[69].

Structural brain abnormalities have been found in DS compared with controls, and the areas in which they are found are consistent with our study. For instance, Beacher et al.[8] and Newton [13] found a specific volume reduction in the frontal, temporal, and parietal lobes and the cerebellum, areas also appearing abnormal in our study. Beacher et al.[8] demonstrated that these areas show more significant age-related reduction than the general population. Additionally, decreased white matter integrity has been found in the frontal tracts, and correlations with cognitive dysfunction have been demonstrated [9,10]. In this study, differences in fALFF and ReHo involving white matter and frontal areas were found. Therefore, white matter appears to play an important role in the neuropathology of people with DS. Cerebellar alterations have been reported in this population. An investigation in foetuses with DS found that the cerebellum had an immature pattern, a reduced volume and notably fewer cells in all cerebellar layers[70]. Other authors have reported similar results [71-73]. Recently, the importance of cerebrocerebellar networks in the clinical manifestations of DS has been highlighted. More specifically, researchers found hypoplasia of cerebellar afferent systems in DS using DTI-driven tensor-based morphometry[74]. In our study, differences in fALFF were found, but interestingly, increased fALFF was found in the anterior region of the cerebellum, and decreased fALFF was found in the posterior region of the cerebellum. Rosas et al.[17] found an anterior-posterior dissociation in this population in the DMN, and perhaps this could also be widespread in the cerebellum.

Regarding grey matter, Anderson et al.[29] found that DS presented higher levels of synchrony between most grey matter regions. DS also exhibits higher fALFF and ReHo in the fusiform gyrus. This abnormality may be explained because this region plays a crucial role in visual recognition memory, a function that is impaired in children and adults with DS. Guidi et al.[75] found reduced thickness in this region in foetuses with DS compared with controls.

Despite the young sample of DS used in this study, it has been demonstrated that the DS population without dementia exhibits β-amyloid (Aβ) burden that can begin in the late teens[24,25]. Orbitofrontal regions have proven to be areas affected by this early deposition in DS presenting MCI but also in cognitive stable DS[76,77]. The abnormalities found in the orbitofrontal lobe (increased fALFF in DS) could be a prelude of this deposition in our sample, but more studies are needed to demonstrate this association by linking the amyloid deposition with fALFF values. To date, this association has only been demonstrated with ReHo[49], with higher values of ReHo indicating amyloid deposition.

These results should also be compared with AD studies using fALFF and ReHo. Yang et al.[48] found decreased fALFF in the right precuneus in AD and MCI participants compared with controls. In our study, this area also presented decreased activity in fALFF in DS. Cha et al.[78] also found significant differences in the precuneus between AD patients and controls, finding

increased values of fALFF in controls, as in our study. As mentioned before, although the results with AD could be consistent in some areas with the results of this study, the younger population used in this study can guarantee that the symptomatology of AD is not present in the sample. However, neuropathology in the brain can begin years before clinical symptoms are evident, and amyloid deposition is already present in young DS[76,77]. Moreover, differences in brain structure development can increase vulnerability to AD in DS[79]. Because of the high incidence of AD in DS, the DS population provides an extraordinary opportunity for understanding the temporal progression of AD and the different facets that contribute to the age of dementia onset and for applying this knowledge to the general population[4].

Interestingly, there was a high correlation between all of the significant clusters in fALFF and ReHO and cognitive measures. We can affirm that the differences between DS and controls in fALFF and ReHo measures have a significant relationship with the cognitive profile of both groups and are linked to verbal and nonverbal intelligence, as measured with KBIT-2. Moreover, these correlation analyses were consistent with the sign of the relationship found between DS and the controls. This study demonstrates that the differences in congruity and low-frequency fluctuations seen between the controls and DS depend on its cognitive profile because high correlations have been found between the signal in fALFF and ReHo in the different respective clusters of cognitive outcomes. Yang et al.[48] found a relationship between fALFF and cognitive outcome in a sample with an AD spectrum. They found significant correlations between the whole sample (including controls) and neuropsychological outcomes. As high correlations were found between cognitive measures and cluster activity through both analyses, a regression was performed using only the variables that had high variability in their distribution, such as KBIT-2 Vocabulary and Matrices raw scores as well as semantic and phonological verbal fluency. It is important to remark that KBIT-2 total outcomes are not presented as predictors in any model because the dispersion found in the variables clearly allows identification of both types of populations. As predicted, the results found in DS and the controls in those variables were truly different, and both groups were located in the opposed tail of the distribution. Notably, the differences found in the clusters of fALFF and ReHo can be explained by some cognitive variables, such as verbal- and nonverbal-related measures. All of the regression models were highly predictable, with high $R^2$ values, and all of the models had values of fALFF and ReHo. Studies using task procedures in *f*MRI have demonstrated the engagement of the left cerebellum in nonverbal tasks[80]. Studies have also highlighted the role of the left middle orbital superior frontal gyrus in phonological processing accuracy in children with dyslexia[81]. Finally, regarding the engagement of the left hemisphere in vocabulary, studies have demonstrated a language lateralization to the left part of the brain in healthy adult participants[82].

Taken together, significant differences in fALFF and ReHo were found between DS and controls. Some of the differences encountered could be related to the neuropsychological profile

of the DS (engagement of the frontal and temporal lobes as hubs for executive and language functions). We suggest that this increased fALFF could be a compensatory mechanism, as has been suggested in other studies with participants who present cognitive impairments[68] or visual disabilities[69] or in healthy ageing[83]. Other differences could be due to the already demonstrated amyloid deposition that takes place within the ages of our sample in cognitive stable DS. Some of the results found are also linked with the structural abnormalities already found in this population in the frontal, temporal, parietal and cerebellar lobes. Moreover, abnormalities have also been found in the DMN, a network that has already been demonstrated to be disrupted in DS.

Finally, as both techniques used in this study are data-driven, it is not necessary to have a prior hypothesis of the seed regions in the analysis[84]. Specifically, in the DS population, as there is a scarcity of studies in rs-*f*MRI, both techniques are valuable tools for studying this population without knowing the specific underlying pathology. Both techniques have localized brain areas that are different in both populations. The specific regions that have shown differences between both groups could be targeted brain regions for future lines of research, using them as seeds to explore the FC to other regions in the brain. Moreover, this exploratory study demonstrates the regions that are abnormal in this population and is the first step to disentangle the pathological functions and connectivity of the DS brain due to lifelong abnormal development. This study is also important for understanding ageing in DS and the incidence of AD pathology in this population.

The correlations and regression analysis performed in this study demonstrate that differences in both groups depend highly on their cognitive profile, and the level of prediction of the cognitive evaluation is high.

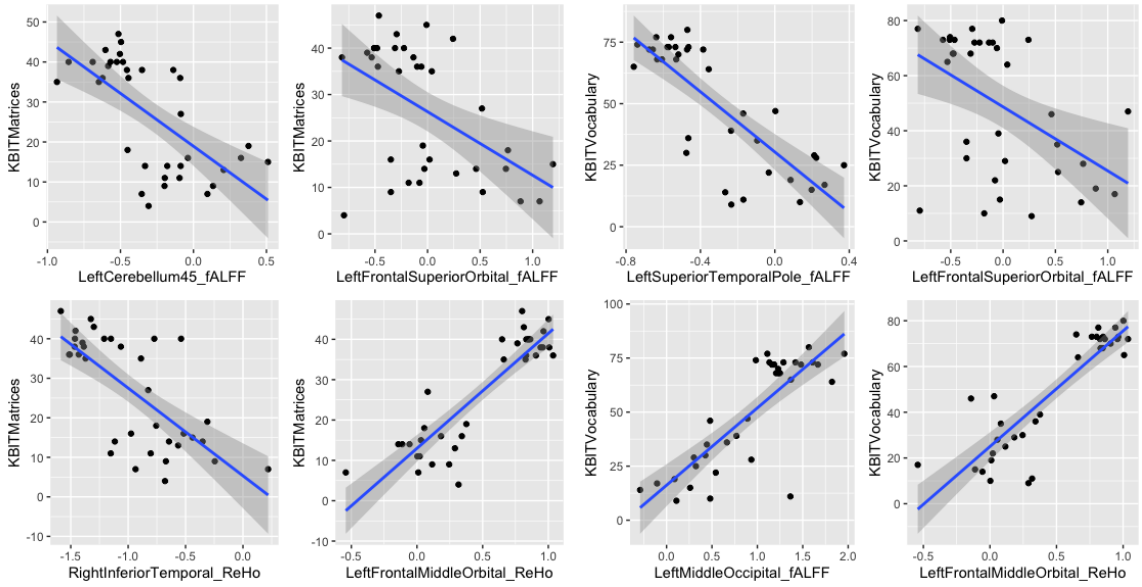
This study is not exempt from some limitations. In this sense, the difficulties in recruiting samples in this particular population and, of course, the high degree of movement during scanning in the DS population limited the study's sample size. However, it is important to highlight that this study's sample size is in accordance with the typical sample size used in neuroimaging [28]. Therefore, more studies using FC and other methodological approaches, such as graph analysis or ReHo and fALFF, in this population are needed, targeting the areas found to be disrupted in this study as seeds. The lack of a replication dataset may have also limited the results. Finally, motion, even if well controlled, could have affected the results.

There are also some strengths of the study that are worth mentioning. To our knowledge, this is the first study to explore regional spontaneous brain activity in a population with DS compared to controls. Moreover, the high control of the age of the study is valuable because of the early onset of AD in this population. This study allows us to affirm that the differences found between the two populations are not because of the clinical symptomatology of AD. Finally, a highly restricted correction for multiple comparisons was performed in this analysis, and multiple corrections for movement were performed. The results had a large effect size; thus, we could

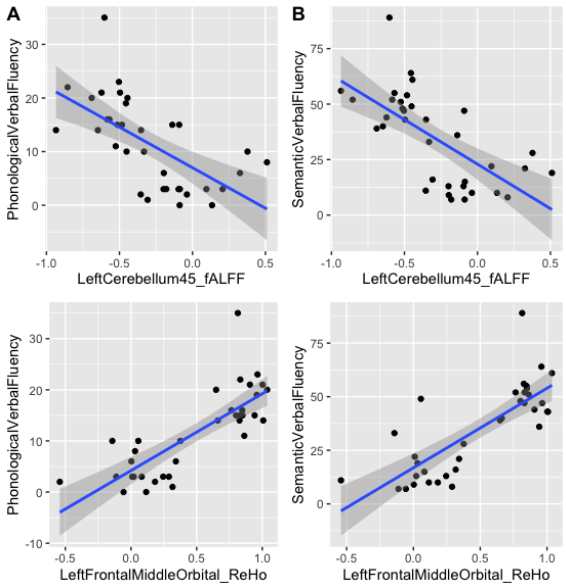
affirm significant differences in regional spontaneous brain activity between controls and DS using fALFF and ReHo. Moreover, this study suggests the possibility of using fALFF and ReHo as biomarkers of cognitive function, which is highly important given the difficulties in cognitively evaluating this population and assessing dementia[6]. Both techniques have been suggested to be potential biomarkers owing to their high test-retest reliability[43,44]. More research is needed, however, to demonstrate its utility.

### *2.4.7 Supplementary material*

**Supplementary Figure 1.** Scatter plot and regression for KBIT Matrices and Vocabulary. In the left, Matrices raw score is predicted, and in the right, Vocabulary raw score is predicted.




**Supplementary Figure 2.** Scatter plot and regression for verbal fluency. A represents the prediction of phonological verbal fluency and B represents the prediction of semantic verbal fluency.



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## 2.5 Study 5 Abnormal degree centrality and Functional Connectivity in Down syndrome: a resting-state functional MRI study


### *2.5.1 Identifying data*

Title: Abnormal degree centrality and Functional Connectivity in Down syndrome: a resting-state functional MRI study

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### *2.5.2 Abstract*

***Background/Objective:*** Neuroimaging studies have shown brain abnormalities in Down syndrome (DS) but have not clarified the underlying mechanisms of dysfunction. Here, we investigated the degree centrality (DC) abnormalities found in the DS group compared with the control group, and we conducted seed-based functional connectivity (FC) with the significant clusters found in DC. Moreover, we used the significant clusters of DC and the seed-based FC to elucidate differences between brain networks in DS compared with controls. ***Method:*** The sample comprised 18 persons with DS (M=28.67, SD=4.18) and 18 controls (M=28.56, SD=4.26). Both samples underwent resting-state functional magnetic resonance imaging. ***Results:*** DC analysis showed increased DC in the DS in temporal and right frontal lobe, as well as in the left caudate and rectus and decreased DC in the DS in regions of the left frontal lobes. Regarding seed-based FC, DS showed increased and decreased FC. Significant differences were also found between networks using Yeo parcellations, showing both hyperconnectivity and hypoconnectivity between and within networks. ***Conclusions:*** DC, seed-based FC and brain networks seem altered in DS, finding hypo- and hyperconnectivity depending on the areas. Network analysis revealed between- and within-network differences, and these abnormalities shown in DS could be related to the characteristics of the population.

**Keywords:** Down syndrome, degree centrality, seed-based functional connectivity, brain networks.

### *2.5.3 Introduction*

Down syndrome is the most common genetic condition associated with intellectual disability (ID; Bull, 2020). With medical advancements, life expectancy has greatly increased and has led to the appearance of Alzheimer's disease (AD; Fortea et al., 2020). Recent studies regarding structural and functional magnetic resonance imaging (*f*MRI) have started to emerge, but neuropathology is still unknown, and neuroimaging could be a useful technique to understand brain abnormalities in DS (Baburamani et al., 2019).

Structural studies have demonstrated reduced volume in some regions of the brain (Guidi et al., 2011; McCann et al., 2021). Regarding *f*MRI studies, research using whole brain has highlighted disrupted network connectivity in this population (Anderson et al., 2013; Vega et al., 2015), finding local functional connectivity (FC) differences compared with their peers without ID.

Recent investigations have studied FC in DS using a seed-based approach. In this sense, the default mode network (DMN) has been studied in populations with DS, and a global disruption of FC has been found (DiProspero et al., 2022; Koenig et al., 2021; Rosas et al., 2021; Wilson et al., 2019). Nevertheless, the scarcity of studies in this field hinders the possibility of formulating a prior hypothesis, and therefore, an alternative method that does not assume a prior hypothesis could be more adequate in this population, as the recent study of Csumitta et al. (2022) which studies whole-brain FC and network selectivity in youth with DS.

Degree centrality (DC) is a graph metric that assesses the importance of each node in a brain network, evaluating the connectivity strength to every voxel (Telesford et al., 2011; Zuo et al., 2012). DC offers the opportunity for an unbiased general search of abnormalities within the entire connectivity matrix of the full-brain functional connectome (Zhou et al., 2014), and study functional brain abnormalities at the whole-brain level without prior hypotheses.

FC seems disrupted in DS, but findings until now are not clear, finding in some studies increased FC (Csumitta et al., 2022) and in others reduced FC in DS (Rosas et al., 2020; Wilson et al., 2019). Moreover, the great variability in the age of the participants could hinder the results because of the dementia appearance. Therefore, the aim of this investigation is to 1) perform DC analysis to identify voxels that show altered FC with other voxels, 2) conduct seed-based FC with the areas showing differences between DS and controls to disentangle the underlying mechanism of DS, and 3) perform network analysis using the obtained results of the significant voxels of DC between both populations and the results of the seed-based FC analysis as regions of interest (ROIs).

As main hypothesis in this study, we believe that DC values in whole brain will be different that in controls, as Pujol et al. (2015). The areas that will be settled as seeds (coming from the DC clusters) will also show different FC with other areas of the brain in DS, as this graph metric evaluates the significance of each node in the brain, and therefore it is directly linked with FC (Rubinov & Sporns, 2010; Watts & Strogatz, 1998). Between and within network FC using Yeo et al. (2011) parcellations will be altered in DS involving regions of the cerebellum, frontal lobes and DMN following other findings in this population (DiProspero et al., 2022; Koenig et al., 2021; McCann et al., 2022 Rosas et al., 2020; Wilson et al., 2019). Other authors have found also an anterior-posterior dissociation in the DMN in DS (Rosas et al., 2021) and therefore we expect to find results in the same line.

### *2.5.4 Method*

#### *Participants*

Data collection for this project was approved by the Bioethical Committee of the Universitat de Barcelona (03/16/2017). Informed consent was also acquired from all DS and control participants, as well as from the guardians in legal charge of every person with DS.

Twenty persons with DS and twenty non-DS controls matched by chronological age (±2 years maximum in difference of age) and gender were recruited, and the same protocol was applied for both.

For DS participants, recruitment was conducted through different centers attending people with IDs in Catalonia, Spain. The inclusion criteria for this group were as follows: 1) age between 16 and 35 years old and 2) a formal diagnosis of DS. The exclusion criteria for this group were: 1) presence of other comorbid diagnoses implying cognitive dysfunction 2) if the legal guardian's consent could not be obtained, and 3) the person with DS had medication that could affect cognitive function.

Regarding control participants, recruitment was made from the community through advertisements. They had to be matched by gender and age with DS participants and were excluded if they had any psychiatric diagnoses or other disorders affecting cognitive function.

For both groups, if excessive movement was present in the registration of the *f*MRI sequences, the participant was discarded. In the preprocessing section the methods used to exclude a subject for movement will be further explained. IQ was estimated for both groups with the Kaufman Brief Intelligence Test, Second Edition (KBIT-2; Kaufman, 1990). The demographic information of the sample appears in Table 1.

#### *Measures*

Participants were evaluated in two sessions, and the sequence was the same for the DS and control participants.

The data used in the study comprise the following: 1) a usual sociodemographic questionnaire; 2) a checklist for the *f*MRI scanner; and 3) KBIT-2 evaluation. It is important to mention that data were missing for one subject with DS, to whom the KBIT-2 was not administered. Hence, the total sample with KBIT-2 evaluation was n=35 despite the sample for the resting-state *f*MRI measures is 18 persons for each group.

***Imaging acquisition***

Brain imaging was performed in a Philips Ingenia 3 MRI scanner T system (Fundació Pasqual Maragall, Barcelona, Spain). All participants underwent a *f*MRI recording sequence: T1, T2, Flair, and resting state. Participants with DS only underwent a total of 6 minutes (exactly 6.41 mins) in the MRI scanner, whereas control participants underwent a sequence of 10 minutes. However, to enable group comparison, for this study, only the first 220 volumes of registration were used. Participants with DS underwent a short training to improve their familiarization with the scan and acclimate to the noise and environment. All participants were told to try to stay quiet without movement. Moreover, they should remain awake and with their eyes opened and fixed on a cross symbol on the screen. Participants could choose music to hear during all recordings except in the resting-state scan. None of the subjects included fell asleep during scanning, as self-reported by them after scanning. A T1-weighted turbo field echo (TFE) structural image was obtained for each subject with a 3-dimensional protocol (repetition time (TR) = 2300 ms, echo time (TE) = 2980 ms, 240 slices, and field of view (FOV) = 240 × 240 × 170). The image acquisition was in the sagittal plane. For the functional images, a T2 *-weighted (BOLD) image was obtained (TR = 1750 ms, TE=30 ms, FOV=230×230×160, and voxel size=3×3×3 mm, 46 slices). The image acquisition was in the transverse plane.

***Preprocessing***

Image preprocessing was performed using the Data Processing Assistant for Resting-State fMRI (DPARSF; Yan & Zang, 2010). Basically, it is based on MATLAB, SPM12 and DPABI (Yan et al., 2016). The preprocessing procedure is described elsewhere (Li et al., 2021).

As DS is a specific population that can present excessive movement, the criterion used to exclude subjects in the sample was that the participants could not exceed the mean of the group plus 2 standard deviations (Yan et al., 2013), estimated with Jenkinson's framewise displacement (FD; Jenkinson et al., 2002). Overall, two persons with DS were excluded, and the final sample was 18 people with DS and 18 controls. Both groups differed in movement as shown in Table 28.

The DS group presented a total of 1040 (out of 3780) volumes exceeding 0.2 mm in Jenkinson FD whereas the control participants presented a total of 172 volumes exceeding 0.2 mm in Jenkinson FD. Therefore, scrubbing regression was performed (Yan et al., 2013; Power et al., 2012, Power et al., 2013) in the final step of the preprocessing in order to control the movement exceeding 0.2 Jenkinson's FD. Moreover, further statistical analyses were performed with the covariate of mean Jenkinson's FD for every subject.

***Degree centrality Analysis***

Basically, based on the preprocessed data, voxel wise DC was performed using DPABI software. Owing to the uncertainty of interpretation, only positive Pearson correlation coefficients were considered in the DC calculations. As a threshold is usually applied to the typical correlation matrices (van den Heuvel et al., 2008), in this sense, DC was estimated for nodes over a range of thresholds (sparsity range 0.05-0.50). The best threshold was chosen using the area under the curve (AUC). This procedure has been used in previous studies (Yang et al., 2021), and is sensitive at detecting topological alterations of brain disorders (Achard & Bullmore, 2007).

***Seed-based FC***

Seed-based FC was estimated using DPABI software. Regions with significant group differences in DC analysis between controls and DS were used as seeds for further resting-state FC. Seed regions were spheres with a radius of 6 mm around the center voxels, and the reference time series for seeds were obtained by averaging the time series of all voxels within the seed region. Correlation analysis was then performed between the seeds and the remaining voxels. Finally, the correlation coefficients were converted into Fisher z values to obtain a z-FC map for further statistical analysis.

***Edge-based functional connectivity***

For the network-based analysis, first, the ROIs signals were used to perform the network construction with DPABI. The ROI signals were extracted using the results of the DC significant coordinates (12 coordinates) and the 28 significant coordinates of the seed-based FC. All of them were extracted with a sphere with a radius of 6 mm around the center voxels, and they were used as the nodes to estimate FC.

To better describe significant clusters obtained in network-based contrast, we also classified suprathreshold edges by their membership in the networks defined by Yeo et al. (2011) networks using a script (MATLAB), which identifies the Yeo networks using Buckner and Choi parcellations (Buckner et al., 2011; Choi et al., 2012). The seven networks are the visual network

(VN), somatosensory-motor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network (LN), frontoparietal network (FPN), and DMN.

***Statistical analysis***

The data analysis was performed with IBM SPSS (v26) to compare both groups' characteristics. More concretely, two-group comparisons were tested using nonparametric tests due to the nonapproximation to the normal distribution of the quantitative variables, and $p$ <.05 was set as significant.

Statistical analysis regarding DC, seed-based FC and network analysis were performed using DPARSF.

First, to determine if significant differences were found between groups in DC, DPABI was used with a voxel wise two-sample t test. As mentioned above, both groups differed significantly in head motion; therefore, Jenkinson's FD (Jenkinson et al., 2002) was included as a covariant in all analyses. Significant differences in the study were reported using the criteria of multiple comparisons with the threshold-free cluster enhancement (TFCE), which reaches the best balance between familywise error and test-retest reliability (Chen et al., 2018). A total of 10000 permutations were performed, and the cluster *p value* was set to $p$ <.05.

Second, to determine if significant differences were found in seed-based FC, voxel wise two-sample t tests were performed using the z-FC map, Gaussian random field (GRF) correction of multiple comparisons and Jenkinson's FD as a covariant.

Finally, to perform network-based FC analysis, the network matrix of each subject was used, and a t-test was performed using false discovery rate (FDR) correction (Chen et al., 2018) with nonparametric permutation for the 40 coordinates used. Jenkinson's FD was also set as a covariant.

### *2.5.5 Results*

***Participant characteristics***

In Table 28, the participants' characteristics are shown. As shown, significant differences were found in head motion and all subtests of KBIT-2.

*Table 28. Participant characteristics.*

| | DS (mean; SD) | C (mean; SD) | Test (*p value*) |
|---|---|---|---|
| Age (years) | 28.67 (4.18) | 28.56 (4.26) | $Z$ = -0.03 ($p$ = .975) |
| Head motion | 0.19 (0.10) | 0.08 (0.03) | $Z$ = -4.46 ($p$ < .001) |
| Vocabulary KBIT-2 | 25.41 (12.23) | 71.72 (4.10) | $Z$ = -5.06 ($p$ < .001) |

| | DS (mean; SD) | C (mean; SD) | Test (*p value*) |
|---|---|---|---|
| (DS group, n=17) Matrices KBIT-2 (DS group, n=17) | 13.17 (5.44) | 39.33 (3.34) | $Z$ = -5.06 ($p$ < .001) |
| Total IQ KBIT-2 (DS group, n=17) | 43.94 (6.23) | 111.05 (7.83) | $Z$ = -5.31 ($p$ < .001) |

Note: DS: down syndrome participants; C: control participants; Z: Z score linked to the Mann–Whitney test; SD: standard deviation.

***Degree centrality***

Table 29 shows the significant differences between groups in DC with MNI coordinates. Figure 17 shows the graphical representation using DPARSF.

Compared with matched controls, people with DS showed significantly increased DC in the temporal lobe, the right frontal lobe and left caudate and rectus. Controls showed significantly increased DC compared with DS in the left frontal lobe.

*Table 29. Significant between group differences in DC.*

| Comp. | Area | Nr. Vox | *t*(peak) | Peak MNI coordinates (mm) | | | AAL peak region |
|---|---|---|---|---|---|---|---|
| DS>C | Left temporal lobe | 10 | 6.00 | -48 | -27 | -27 | Temporal_Inf_L |
| | Right frontal and temporal lobe | 157 | 5.89 | 12 | 24 | -21 | Rectus_R |
| | Left caudate | 343 | 5.59 | -6 | -9 | 18 | Thalamus_L |
| | Left rectus | 2 | 3.95 | 0 | 45 | -27 | ~Rectus_L |
| C>DS | Left frontal lobe | 21 | -5.57 | 0 | 54 | 18 | Frontal_Sup_Medial_L |
| | Left frontal lobe | 12 | -5.42 | -27 | 66 | 6 | Frontal_Mid_L |

Note: DS: down syndrome participants; C: control participants; MNI: Montreal Neurological Institute; ~: approximately, AAL atlas area closer to the t peak.

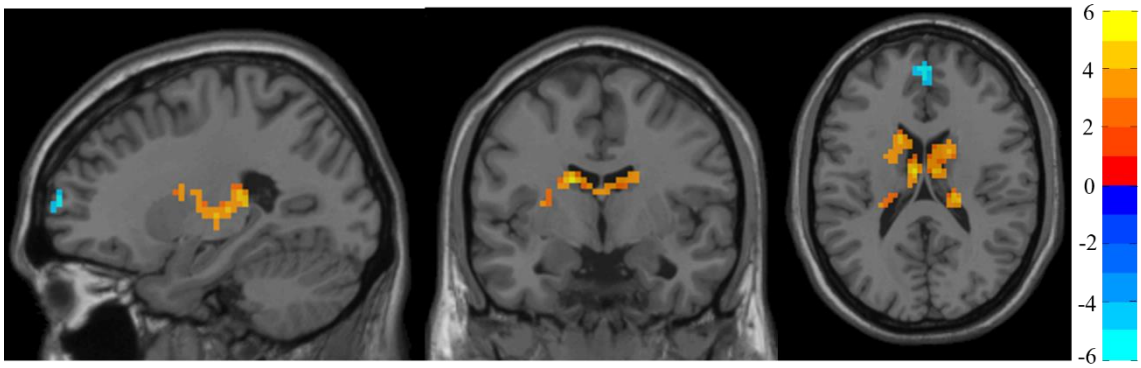


*Figure 17. DC analysis. Two-sample t-test results corrected by TFCE are presented.*

Note: The area in blue represents a significantly decreased DC value in DS patients compared with controls; the area in yellow and red represents a significantly increased DC value in DS patients compared with controls.

***Seed-based FC analysis***

Table 30 shows the significant clusters found in seed-based FC. It is important to highlight that the right rectus and the left thalamus did not present any significant difference between both groups.

*Table 30. Significant between-group differences in seed-based FC using the significant clusters of DC results as seed regions.*

| Seed region | Significant differences | T (voxels) | Comp. |
|---|---|---|---|
| Temporal_Inf_L | Cerebellum_Crus_1_R | 4.46 | DS>C |
| | Temporal_Sup_L | 4.84 | DS>C |
| | Lingual_R | 5.62 | DS>C |
| | Precuneus_L | 5.77 | DS>C |
| | Precuneus_R | 6.63 | DS>C |
| Thalamus_L | Cerebellum_9_R | 4.89 | DS>C |
| | Hippocampus_L | 6.28 | DS>C |
| | Lingual_R | 4.72 | DS>C |
| | Occipital_Mid_L | 5.19 | DS>C |
| | Lingual_L | 5.16 | DS>C |
| | Frontal_Inf_Oper_L | 4.18 | DS>C |
| | Cuneus_L | 5.14 | DS>C |
| | apr Postcentral_L | 4.22 | DS>C |
| | Precentral_R | 4.32 | DS>C |
| | Cingulum_Mid_L | 4.38 | DS>C |
| | Supp_Motor_Area_L | 5.02 | DS>C |
| Frontal_Sup_Medial_L | Cingulum_Ant_L | -4.86 | C>DS |
| | Precuneus_L | 4.97 | DS>C |
| | Angular_L | -5.03 | C>DS |
| | Frontal_Sup_Medial_L | -4.86 | C>DS |
| | Frontal_Mid_R | -5.33 | C>DS |
| Frontal_Mid_L | Precuneus_R | -4.42 | C>DS |

Note: DS: down syndrome participants; C: control participants

***Network-based analysis***

As previously stated, network-based analysis was performed using the 6 significant DC clusters and the 22 significant clusters of the seed-FC analysis.

All regions were classified using the Yeo et al. (2011) parcellations. Table 31 shows the classification.

*Table 31. Classification of the regions in Yeo networks.*

| Others | VN | SMN | DAN | VAN | LN | FPN | DMN |
|---|---|---|---|---|---|---|---|
| Thalamus_L | Lingual_R | Temporal_Sup_L | Precuneus_L | Cingulum_Mid_L | Temporal_Inf_L | Frontal_Mid_R | Frontal_Sup_Medial_L |

| Others | VN | SMN | DAN | VAN | LN | FPN | DMN |
|---|---|---|---|---|---|---|---|
| Precuneus_R | Lingual_R | apr Postcentral_L | Precentral_R | | Rectus_R | | Frontal_Mid_L |
| Hippocampus_L | Occipital_Mid_L | Supp_Motor_Area_L | | | apr Rectus_L | | Cerebellum_Crus_1_R |
| Cingulum_Ant_L | Lingual_L | | | | Cerebellum_9_R | | Frontal_Inf_Oper_L |
| | Cuneus_L | | | | | | Precuneus_L |
| | | | | | | | Angular_L |
| | | | | | | | Frontal_Sup_Medial_L |
| | | | | | | | Precuneus_R |

Note: VN: visual network; SMN: somatosensory motor network; DAN: dorsal attention network; VAN: ventral attention network; LN: limbic network; FPN: frontoparietal network; DMN: default mode network.

Figure 18 shows the edge plot matrix, Figure 19 shows the spatial connectogram, and Figure 20 shows the brain network representation.

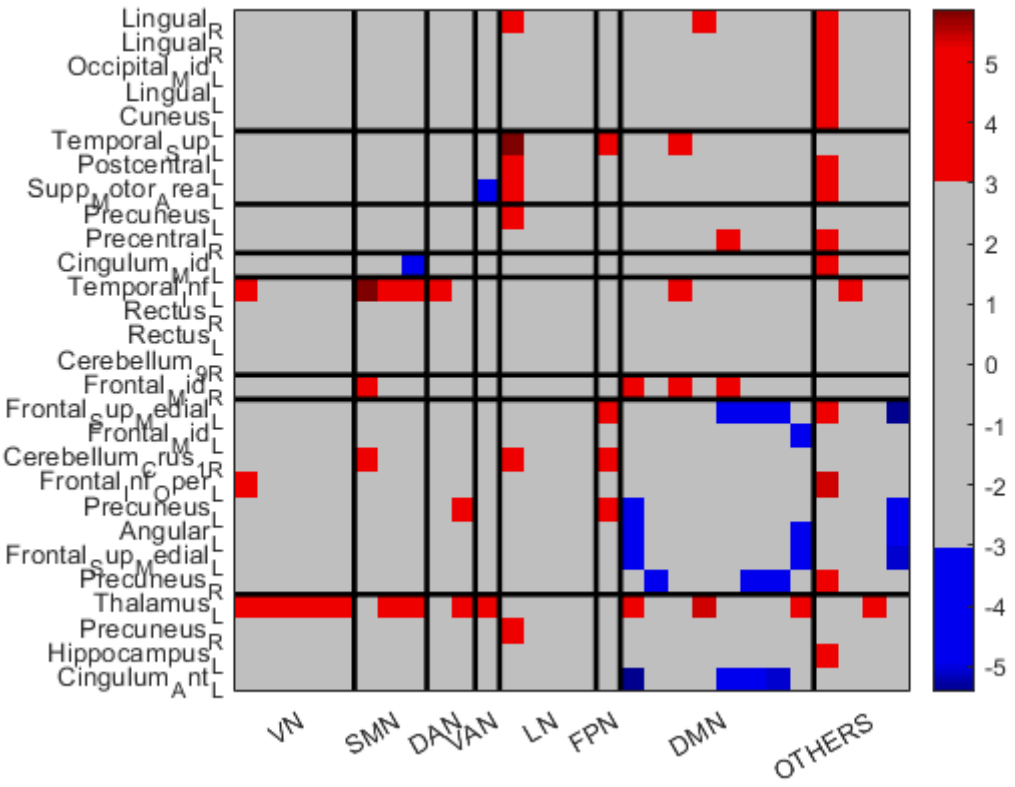


*Figure 18. Edge plot matrix. Blue colors show areas that have significantly increased connectivity in control participants compared to DS.*

Note: Red areas show significantly increased connectivity in DS patients compared with controls.

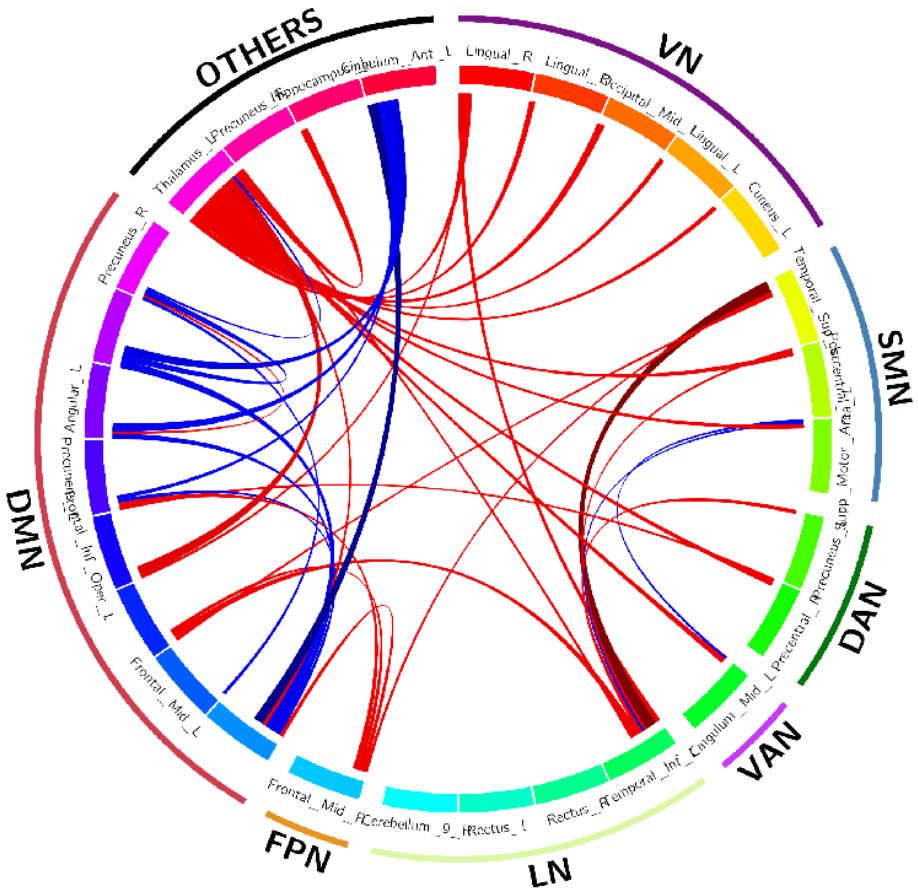


*Figure 19. Spatial connectogram of differences in connectivity between DS and controls generated using the Circos tool (Krzywinski, et al., 2009).*

Note: Blue lines show areas that have significantly increased connectivity in control participants compared to DS. Red lines show areas that have increased connectivity in DS patients compared with controls.

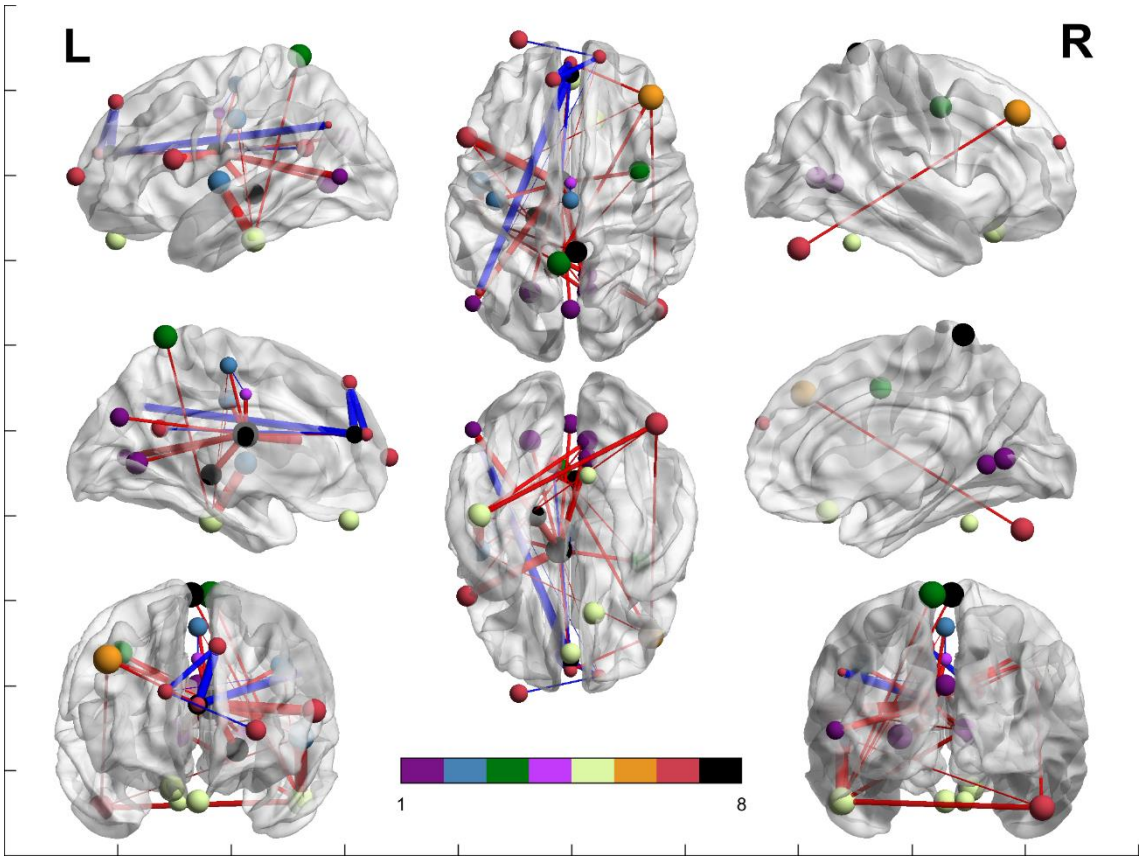


*Figure 20. Network analysis between both groups. Colors represent the Yeo et al. (2011) networks, following their legend.*

Note: Purple represents the ROIs included in the VN; blue represents the ROIs included in the SMN; green represents the ROIs included in the DAN; light purple represents the ROIs included in the VAN; yellow represents the ROIs included in the LN, orange represents the ROIs included in the FPN; red represents the ROIs included in the DMN; and black represents the ROIs not belonging to Yeo's network. Blue lines show areas that have significantly increased connectivity in control participants compared to DS. Red lines show areas that have increased connectivity in DS patients compared with controls. The brain networks were visualized with BrainNet Viewer (Xia et al., 2013).

Regarding the nodes of other regions, the left thalamus shows widespread increased FC in the DS group: with all the nodes included in the VN, with some nodes of the SMN, DAN, VAN, DMN and the left hippocampus, which is not included in the Yeo parcellations. The right precuneus demonstrates also increased FC in the DS group with a node that conforms the LN, whereas the left hippocampus, as mentioned above, also shows increased FC with the left thalamus. Finally, the left cingulum anterior shows decreased FC in the DS group with areas of the DMN.

Regarding the VN, all the ROIs seem to be increased in the DS group. The first right lingual (shown in figure 18) shows increased FC in the DS group with a region of the LN, a region of the DMN and with a region which is not included in the Yeo parcellations. The rest of the areas included in the VN show increased FC in the DS group with the left thalamus.

Regarding the SMN, the FC of the left superior temporal appears strongly increased with an area of the LN, an area of the FPN and an area of the DMN. The left Postcentral gyrus shows increased connections in the DS with an area of the LN and a ROI that do not pertain to the Yeo parcellations. Finally, the left supplementary motor area appears increased in the control group with the VAN's ROI whereas increased in the DS group with a ROI that pertains to the LN.

Concerning the DAN, all the connections seem increased in the DS group: the left precuneus with a region of the LN, and the right precentral gyrus with a region that do not pertain to the Yeo parcellations.

In relation to the VAN, the left cingulum mid appears to be decreased in DS with a region that pertains to the SMN, and decreased with the left thalamus.

Regarding the LN, only the temporal inferior left seems strongly increased in the DS group, with a region of the VN, with all the regions of the SMN, with a region of the DAN and DMN and finally with the right precuneus.

Referring to the FPN, the connections appear to be increased in the DS group. The right frontal mid show increased FC in the DS group with the SMN and with some regions of the DMN.

Finally, regarding the DMN, the left superior medial appears to be increased with the region of the FPN and with a region that does not pertain to the Yeo parcellations (left thalamus). However, shows decreased FC in the DS group with some regions of the DMN and with the left cingulum anterior. The left middle frontal gyrus appears increased with a region of the DMN. The cerebellum Crus 1 right appears increased in the DS group with a region of the SMN, a region of the LN and a region of the FPN. The inferior frontal gyrus opercular part appears increased in the DS group with a region of the VN and a region that is not included in the Yeo parcellations (left thalamus). The left precuneus appears increased in the DS group with a region of the DAN and the region of the FPN, whereas decreased with a region of the DMN and with the cingulum anterior left. The left angular only appears increased in the control group, in regions of the DMN and also with the cingulum anterior left. The left superior medial gyrus appears also increased in the control group with some regions of the DMN and also with the cingulum anterior left. Finally, the right precuneus appears increased in the DS group with the left thalamus (a region not included in the Yeo parcellations) whereas decreased with some regions of the DMN.

### *2.5.6 Discussion*

To our knowledge, this is one of the few studies on brain networks to investigate the FC of resting-state *f*MRI in DS. The present paper aimed to disentangle brain FC differences between DS and control participants.

Generally, the study showed the following results. a) Alterations in DC were found. Increased DC was found in the temporal lobe, right frontal lobe, left caudate and left rectus. Decreased DC in the DS was found in the left frontal lobe. b) Seed-based analysis revealed significant differences in many clusters. c) Brain network analyses showed significant group differences between different areas of the Yeo et al. (2011) networks.

More concretely, in the first stage, DS participants showed increased DC in the temporal lobe, right frontal lobe, left caudate and left rectus. However, they showed decreased DC compared with controls in the right frontal lobe.

Decreased frontal lobe volume has been demonstrated in older and young adults with DS (Teipel et al., 2004, Powell et al., 2014). Moreover, structural abnormalities have been also reported in structures involving the thalamus and the caudate, regions that appear to be increased in DC in the DS group ((McCann et al., 2021). It seems that decreased volume in this population can lead to FC abnormalities. In other populations, a link between structural and functional abnormalities has been demonstrated (Rogers et al., 2018; Valenti et al., 2020). Moreover, the structures that display abnormal DC are engaged in functions that are altered in DS, as language and executive functions (Hamburg et al., 2019).

It is also important to compare our results with those of Pujol et al. (2015), who also studied DC. In this sense, they found increased DC in the DS in the ventral anterior cingulate cortex (ACC) and decreased DC in the dorsal ACC. Both regions were also increased in DS (cluster of the left caudate) and decreased (cluster of the left frontal lobe) in our study. Moreover, the decreased DC in the medial frontal cluster reported by Pujol et al. (2015) was also found in our study (cluster left frontal lobe). Pujol et al. (2015) reported higher DC in DS in the right amygdala, which also is congruent with our study (cluster left caudate) and decreased DC in DS in areas of the posterior insula.

Regarding seed-based FC analyses, hyper connectivity in DS was found in most of the seeds used, finding high congruence with the results of DC analyses. It is important to highlight the importance that may have the left thalamus in the neuropathology of DS, because of the hyper connectivity found with other structures of the brain. This structure is implied in executive and memory functions (Stagni et al., 2020), which are impaired in DS, and it seems that is particularly sensitive to effects of aging, finding a loss of neurons and volume (Perry, Pakkenberg & Vann, 2019) in older persons with DS, as well as other abnormalities related to brain amyloid (Keator et al., 2020). These structural alterations could be related to the hyperconnectivity found regarding this structure with other areas. It is important also to highlight the big presence of subcortical structures in the significant differences between both populations as the thalamus and the caudate, which are especially important for the cortico-striatal-thalamo-cortical (CSTC) circuits. These

regions have been linked with important neuropsychological deficits and neurodevelopmental diseases such as Autism Spectrum Disorder or Attention deficit/Hyperactivity Disorder (Riva, Taddei & Bulgheroni, 2018).

Significant differences were found between DS and controls regarding brain network analyses. Within network connectivity was only found to be altered in the DMN, but significant differences were found between all the networks regarding between network connectivity.

More concretely, regarding the VN, hyperconnectivity was found in the links between the VN and some regions of the DMN and LN, as well as with the left thalamus. When we used the SMN as a seed, the brain networks also seemed altered in DS; concretely, they were increased with the LN, FPN, DMN and the left thalamus, whereas decreased in the VAN. The DAN also seems disrupted in DS, finding increased between network FC: The connections of the DAN with the LN, DMN and the left thalamus seemed to be increased in DS. When using the VAN as a seed, those networks linked with the left thalamus appeared to be increased in the DS while the networks linked with the SMN appeared to be decreased. Concerning the LN, only increased connections were found in DS involving areas of the VN, SMN, DAN, DMN and other regions. Regarding the FPN, links with regions of the SMN and DMN are increased in DS

Finally, concerning the DMN, on the topic of between network connectivity, networks that link with the DAN, SMN, VAN, VN, LN and FPN seem to be increased in DS, as well as the left thalamus- Interestingly, significant differences in within network connectivity were found in this network, only decreased in DS. Finally, the FC between the DMN and the structure of the left anterior cingulum was also decreased in DS.

Vega et al. (2015) also found results congruent with those presented in this study, despite their study including whole-brain Yeo et al. (2011) networks and with a small sample (n=10). In this sense, they also found increased FC between the SMN and the DMN as well as increased FC between the SMN and the FPN. Moreover, they found increased FC between the LN and the DAN. However, Vega et al. (2015) found increased FC between the SMN and FPN, as well as between the DAN and FPN, whereas in our study these results were not reported. These different results could be explained because in our study there is only one ROI included that pertains to the FPN, which shows increased FC with areas of the SMN and DMN, but in the study of Vega et al. (2015) the whole network is included. The FPN could be underrepresented in our study and this fact could explain the differences between our study and the one published by Vega et al. (2015). Finally, regarding the three hyperconnected links of the FPN in DS demonstrated in our study, could be consistent with the results of the Arizona Cognitive Test Battery (Edgin et al., 2010), showing cognitive deficits in the frontal lobe functions, as pointed by Vega et al. (2015).

Interestingly, it is important to highlight the disrupted FC pattern in the DMN found in the DS group. Intrinsic FC in the DMN is certainly altered, finding a clear pattern of hypoconnectivity in the DS group within areas of the anterior DMN (including frontal medial areas). Rosas et al. (2021) also studied the intrinsic FC of the DMN in this population, and found abnormalities also congruent with our study, finding an anterior-posterior dissociation in the DMN: the anterior parts of the DMN (in our study, the left frontal superior medial gyrus and the left frontal middle gyrus) were disconnected in the DS group from the posterior parts of the brain (precuneus and left angular gyrus). Koenig et al. (2021) also found decreased FC in the majority of connections between the anterior and posterior aspects of the cingulate cortex. These results could be linked to the structural abnormalities found in this population in the cerebellum (Guidi et al., 2011; Lee et al., 2020). Contrarily, between network connectivity of the DMN with the other networks seems increased in the DS group, finding a clear pattern of hyper connectivity with all of the other Yeo et al. (2012) networks (VN, SMN, DAN, LN and FPN). This pattern was congruent with Wilson et al (2019), who found increased FC in the DS group from the DMN to the rest of the brain.

At this point, it is important to mention a recently published study by Csumitta et al. (2022) also with young DS using resting-state *f*MRI. They found significant differences in 18 ROIs, and they classified them also using Yeo et al. (2011) parcellations. Left inferior temporal, right fusiform, left middle frontal and left inferior frontal, among others, were also found to be significant in our study. Moreover, their regions also included cerebellar ROIs, which also were significantly different among controls and DS. However, they found in all the areas increased FC in DS, whereas our findings are depending on the area, congruent with other studies.

Findings in this study confirm some of the results of already published papers, innovating in some points. However, there are some limitations that are worth mentioning, such as the sample used in this study, which is similar to other neuroimaging studies but still is poor. Two subjects were discarded for movement, which is also typical in this population, and movement, despite being well controlled, could hinder the results. Therefore, more studies in this line should be published to confirm the results.

Despite the limitations, to our knowledge, this is the first study of brain networks in DS. Some studies have used seeds to study FC, but no one has used brain networks. Despite using a small sample, the corrections applied in this analysis for multiple comparisons are stringent, and the effect sizes of all the comparisons are large. Moreover, the results are in line with those of another study performed in this field.

### *2.5.7 Conclusions*

The results of this study demonstrate DC alterations in frontal and temporal areas that could be related with the neuropsychological profile of DS (with major dysfunction in executive functions and language). Moreover, the results that show abnormalities in DC and seed-based FC analyses are related with structural abnormalities already proven in this population. More studies linking structural and functional brain abnormalities are needed to demonstrate this association in this population. Regarding brain networks analyses, results show a disrupted pattern of between network connectivity involving all the Yeo networks, but only in the DMN there is altered within-network FC, finding hypoconnectivity in many areas of the DMN. Regarding the results in within network connectivity of the DMN, we confirm an anterior-posterior dissociation in this network already described in other studies. This means that connectivity in DS is altered, and these abnormalities could be related to the characteristics of the disease (low ID, physiological features, decreased volume of different areas of the brain such as the cerebellum, etc.). It is important to mention that most differences found in connectivity between DS and controls are located within the Yeo parcellations. Moreover, regions that seem more disconnected should be targeted to plan therapeutic interventions to promote increased connections. The three methods used in this study (DC, seed-based FC and brain network analysis) have proven to be useful tools to disentangle brain abnormalities in this population.

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# 3. Discussion

As mentioned above, the aim of this thesis is twofold. In the first place, the first objective is to overcome methodological issues that arise from working with a DS population, missing data, and small sample sizes. This first aim will solve some methodological issues before starting to work with the second aim. The second objective is to study resting-state *f*MRI in DS. Firstly, the present thesis involves a systematic review investigating the state-of-art of *f*MRI in DS population. Secondly, two techniques highly used to disentangle brain differences in clinical and healthy populations will be applied to the DS data recollected. On the one hand, spontaneous brain activity, and on the other hand, degree centrality, seed-based FC, and the study of brain networks. As both aims of the present thesis are very different, the following discussion section will present both these aims separately. This section has comments on each study and its results in light of the analyzed literature.

### 3.1 Missing data and small samples sizes

Recruitment in special and clinical populations is challenging (Huang et al., 2018) due to the low prevalence of the sampled population and the difficulties in collaborating when any type of impairment is present. In addition, enrollment in clinical trials and research is often incomplete, and missing data from some participants is typical. Therefore, small sample sizes and missing data are usual in health and social sciences (McNeish, 2018). In the *f*MRI field, this phenomenon is worse because of the properties of the methodological designs, which are very expensive and demand time and motivation from participants. Secondly, in these types of studies, movement in the scan is a very determinant issue to consider, and the loss of sample once recruited is also common (Maziero et al., 2020). Consequently, in studies related to *f*MRI, sample sizes are tiny (Smith & Nichols, 2018; Szucs & Ioannidis, 2020). In this sense, the first two studies of the thesis try to find strategies that could overcome those limitations from two very different overviews.

In the first place, the first study tries to find strategies to overcome both limitations, small sample sizes, and missing data when resampling is not possible. In this case, some methodological issues are proposed from a technical point of view employing an example of application, which in the context of the present thesis is pertinent: the operationalization of the CR's concept in the DS population.

In the second place, the second paper included in this aim tries to overcome also the limitation of small sample sizes in the context of neuroimaging. Generally, as mentioned above, sample sizes are tiny in these study types (Smith & Nichols, 2018; Szucs & Ioannidis, 2020) due to the considerable expense associated with collecting *f*MRI data (Turner et al., 2018) or the difficulties finding samples. Therefore, the effects found in the different studies are often low and inconsistent (Button et al., 2013). Consequently, the studies are underpowered (Turner et al., 2018), and this drives researchers into different methodologies, including thresholding and

analysis, which could increase type I errors (Eklund et al., 2016). Thus, there is a need to quantitatively consolidate effects across individual studies to overcome problems associated with individual neuroimaging studies. In this context, meta-analyses are helpful because they combine and summarize the data of interest and potentially offer insights that are not immediately apparent from individual studies (Radua & Mataix-Cols, 2012). Moreover, there is a scarcity of studies using neuroimaging techniques because of the difficulty of finding samples or movements during the registration in the ID context. Despite this, with training, some researchers have accomplished studying brain signals in the ID population. However, to date, it is unclear if there are common aberrant connectivity patterns associated with ID (Walter et al., 2009). Therefore, the principal aim of this study is to find common aberrant connectivity patterns associated with the ID, using a quantitative technique that reduces the impact of small sample sizes in the neuroimaging field. Although resting-state techniques have proven to be more sensitive than task-*f*MRI to elucidate differences in the brain, especially between the ID population and the compared population, a search was conducted using both techniques, and more studies were found at that moment using task-*f*MRI in ID. Therefore, to increase the impact of the meta-analysis, task-*f*MRI was chosen.

As mentioned above, the first study proposes ways to overcome two main methodological problems typical in research, specifically in social and health sciences (McNeish, 2018). The main difficulties are missing data and the small sample sizes, usually found in clinical and special population research. For our case in the broader project, we collected hundreds of variables from persons with DS with complicated register techniques (*f*MRI or physical activity evaluation) where missing data is very typical. The sample size is also problematic: their tutor's consent is hard to achieve, and finding sample with DS is difficult due to the small population. There are other problems in studying ID, as participants have the arduous assignment in completing the research tasks (for example, cognitive evaluation). In this sense, this paper provides a methodological proposal to overcome both problems. The second aim was to estimate a CR model for DS people. In this population, as in the general population, individual trajectories of cognitive changes are highly heterogeneous, with some declining rapidly and others declining slowly or even improving (Bull 2020; Temple et al., 2001). Given the variability that exists in DS, the implications of CR for individuals with DS deserve special attention to generate a more systematic definition.

Regarding the aim of the first study, figure 21 shows the steps used to overcome both problems. The use of Multiple Imputation (MI) techniques solved the first problem (missing data on the applied protocol) and is used widely in research investigations (Huque et al., 2018). Following Montenegro-Montenegro et al. (2015) recommendation, the two types of MI - linear regression and predictive mean matching were used, obtaining 10 simulated samples iterating from the initial solution. However, to evaluate which was the best MI (using both methodologies

and the 10 iterations of everyone), Rubin's estimation (1976) was used. This technique does not allow for a direct comparison of the mean's Standard error (SE) obtained in the original distribution and the solution after the imputation mechanisms. Therefore, to overcome these limitations, an adjusted index associated with the original SE and imputed distributions was estimated (Imputation fit index; IFI). This indicator lets us know the point at which imputation generates a variable that behaves similarly to the original one. This IFI index worked better than Rubin's (1976) proposal, and it is a suitable tool to evaluate the quality of imputed data. After solving the missing data problem, the next challenge was working with a small sample size in operationalizing the CR in DS using Confirmatory Factor Analysis (CFA). Instead of using classical frequentist inference at this point, we choose the Bayesian Structural Equation Model (BSEM), which works better when working with small samples (Smid & Winter, 2020). However, is strongly recommended to use this estimation with informative priors (Smid et al., 2020). As literature is scarce in the DS field, the use of BSEM was without informative priors. In addition, to cover some of the limitations of the small sample sizes, we followed Jian and Yuan's (2017) schema, which provides additional corrections for the CFA. This approach is used widely in multiple research studies (Garnier-Villarreal & Jorgensen, 2020; Hogreve et al., 2019). Moreover, we also performed a Jackknife correlation correction to solve the sample size problem. The proposed correction based on Jiang and Yuan's (2017) seems to be in good approximation to study the global fit of BSEM, despite being Adhoc (Yuan et al., 2018). In the same line, our results show the capacity of conservative strategies such as the Jackknife correlation (in particular, the use of the low confidence interval value) to estimate the R matrix as an input to BSEM. The combination of both strategies makes it possible to generate a statistical framework that is more suitable to solve the small sample problem and limitations derived from them.


*Figure 21. Steps followed to solve missing data and small sample size problems.*

Finally, as an applied point of view, and regarding the second aim of this paper, the acceptable fit of the CFA model suggests the possibility of operationalizing the latent factors of CR to measure it in the DS population. The results of both the individual Bayesian parameter estimation and the global fit are evidence of this possibility. Figure 22 shows a graphical

representation of the model. As shown, Quality of Life, Cognitive Outcome, Personal conditions, and Physical Activity can influence and mediate the concept of CR in DS. Although years of formal education have been the principal variable studied to operationalize this concept (Arola et al., 2021; Umarova et al., 2019), it is tough to measure in the ID population. The perspective of conceptualizing CR as a latent construct defined with different measures seems to be the clearer option. Obviously, according to the real properties of the sampling, this model does not allow any extrapolation for the general population and must be used strictly as an operational definition by our sample. However, it is an empirical confirmation and therefore an optimal measure for the operationalization of CR in persons with DS, at least in our sample. As mentioned above, the prevalence of dementia in this population is much higher than in other ID populations and the general population (Fortea et al., 2021). This study could be an initial phase in studying the significant differences encountered in the DS population regarding the appearance of dementia. In the general population, there is evidence that cognitive, social activities and effective dementia prevention strategies may preserve the cognitive functioning of life (Hachinski & Avan, 2022). In addition, in the field of ID, some recent studies prove the relationship of the severity of ID, included in the personal conditions of our model, with the prevalence of dementia (Anderson et al., 2020). Therefore, it is crucial to operationalize the concept of CR in this population and know which factors may decrease the impact of aging and prevent the appearance of dementia.

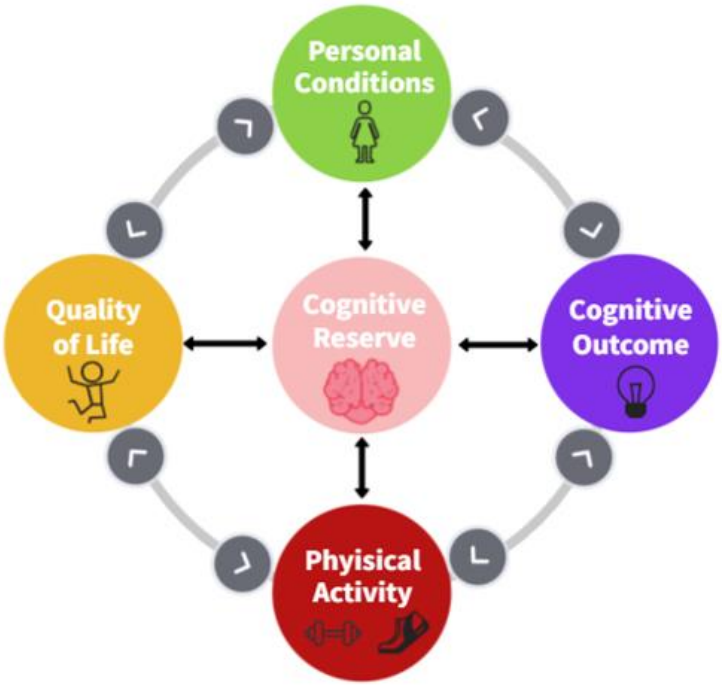


*Figure 22. Graphical representation of the CR model in DS.*

Regarding the second study of the present thesis, the study aimed to identify brain abnormalities mainly associated with ID. To the best of our knowledge, it is the first meta-analysis

exploring differences in brain activation between people with ID and controls. In this sense, it is crucial to highlight that although our aim and our search was centered on all types of ID, our search concluded that only studies with *f*MRI in different genetic syndromes associated with ID exist. The inclusion of genetic syndromes only could be because of the facility identifying the genetic syndromes. This identification can increase the control possibilities for the different variables. The studies in *f*MRI with this population are very recent, and we hope there will be more published studies with different types of ID in years to come. The present study has two approaches: qualitative and quantitative approach.

Regarding the qualitative part of the study, there are common patterns regarding the type of ID and the task types that are important to highlight. In 22q11 DS, we can find a general deactivation in different areas of the left occipital cortex, lobule, and superior parietal lobule. This deactivation is congruent with some abnormalities in the thickness of the occipital cortex found in this population in a group with psychosis (Sun et al., 2020). In the case of Prader–Willi syndrome, we can find a deactivation when compared to the control population near the insula in both hemispheres.

Regarding the type of task used in the study, in visual perception and executive functions, deactivation in the left and right of both occipital and parietal areas is found. These identified areas are necessary for visual perception (Kaas et al., 2010). However, there is an activation in ID compared with controls in the middle temporal gyrus and the frontal pole right. The most interesting result is in executive functions, where we can find a clear pattern. We can see that there is deactivation in the left occipital cortex, supramarginal gyrus, superior parietal gyrus, and angular gyrus, also congruent with certain studies about executive functions (Fassbender et al., 2017).

Compared with controls, people with ID did not show any increased activation in the quantitative analysis of every study. However, people with ID showed decreased activation in two areas located in the right middle gyrus compared with controls. This area comprised the BAs 21, 22, 37, and 39. In particular, in our case, only the BA number 37 was deactivated in the case of the ID population compared with controls. Early functional neuroimaging articles have demonstrated that the middle temporal gyrus is involved in specific cognitive domains (Cabeza and Nyberg, 2000; Laufer et al., 2011; Raposo et al., 2006; Sass et al., 2009). These domains can be associated with 70% of the tasks used in the studies included in the meta-analysis. In schizophrenia, functional deficits in these cognitive domains, that is, language (Kuperberg et al., 1998), semantic memory (Nestor et al., 1998), and complex visual perception (Tek et al., 2002), have been demonstrated. In the same line, functional deficits, concretely, in the middle temporal gyrus (Chang et al., 2016; Fusar-Poli et al., 2011) have been found in current studies with samples

at high risk of psychosis. A recent meta-analysis, which aimed to show the differences between 22q11 DS and controls, identified some regional differences. Specifically, the results reported that the 22q11 DS population has structural and functional abnormalities. These abnormalities are found mainly within the right precuneus and superior temporal gyrus, bilateral inferior parietal lobe, and posterior cingulate cortex (Scarpazza et al., 2019). This result could be congruent with our findings because 40% of our sample has 22q11 DS. Moreover, two articles were shared between this paper and the meta-analysis from Scarpazza et al. (2019). In the same line, a recent study (Marshall et al., 2017) conducted with 321 participants identified the 22q11 DS gene as one of the most linked to psychosis (Marshall et al., 2017). Consequently, the middle temporal gyrus and inferior temporal gyrus could be related to the appearance of schizophrenia, and this may have a relationship with 22q11 DS.

Finally, it is crucial to highlight that the metanalysis technique has proven to be a practical tool to elucidate differences between both populations and find a common pattern in ID. In this sense, the use of this technique increases the impact of the results found, due to the low sample sizes used in this type of studies and also due to the scarcity of studies found in this population. There is a need for more task-*f*MRI studies for this population, and within the years between the publication other researches have been published in the field that should be included in posterior meta-analyses (Hsu, 2020; Omisade et al., 2021).

On the one hand, MI, with the correct corrections, jackknife correlation, and using the Bayesian paradigm for conducting the CFA have proven robust enough to solve missing data and sample size problems when using statistical analysis. On the other hand, meta-analyses techniques can solve the sample size problems used throughout the field of neuroimaging. We must assume that working with missing data and a small sample size is not a good scenario. Even if we add some recommendations, it is still not a perfect stage for the working environment. Therefore, what we aim to present is valid only when resampling is not viable and with a reduced population of interest. Both points of view can be applied to scarce sample sizes when resampling is not feasible. Finally, it is crucial to highlight that both resources could be applicable for further studies. The first could be for the posterior study of CR adding another variable (resting-state analysis) if we demonstrate that FC depends on the CR level. The strategies of MI could also be applied when head movements are present in the scan, as proposed by other studies (Calhas & Henriques, 2021).

### 3.2 Resting-state *f*MRI in Down syndrome

There is a scarcity of neuroimaging studies involving people with DS, especially in resting-state *f*MRI. Therefore, the third study of the present thesis aims to describe the state-of-art *f*MRI techniques for recording brain signals in people with DS. This systematic review will aid the further steps of analysis. Studies four and five aim to elucidate brain differences in

connectivity between DS and controls using different techniques already applied to other populations. Both studies are complementary.

The third study reviews the main works published until October 2019 concerning *f*MRI data and people with DS and aims to provide valuable insights that identify the main difficulties and findings that researchers could use. It aims to discuss the different ways to solve these difficulties. This study includes task and resting-state paradigms. However, it has been three years since the last search of this paper (therefore, it may not be up to date). Hence, we conducted a new search covering papers focusing only on resting-state with DS shown in table 7.

The fourth study aims to detect regional signal changes in spontaneous brain activity using fALFF and ReHo. Both are data-driven methods that are very useful when the studies have a limited population, and therefore there is no prior hypothesis on specific regional abnormalities. Moreover, the study aims to explain the differences in fALFF and ReHo between controls and persons with DS relating to cognitive outcomes.

Finally, the fifth study aims to study DC and identify the voxels that show altered FC with other voxels and conduct seed-based FC with the areas showing differences between DS and controls to disentangle the underlying mechanism of DS. Finally, performing brain network analysis using the obtained results of the significant voxels of DC between both populations and the results of the seed-based FC analysis as ROIs.

Regarding the third study, only nine studies matched our inclusion criteria. The findings are not enough to draw definitive conclusions about *f*MRI in DS, as in the second study of the thesis which involves task-*f*MRI studies in ID. As mentioned above, it is a challenge to evaluate the cognitive performance of the DS population. It is also an obstacle in assessing the presence or absence of dementia in this population. Therefore, *f*MRI could be a valued tool to evaluate the cognitive state of a person with DS. Even with the included studies, it is difficult to draw definitive conclusions. There are some relevant facts that we have to highlight when using this technique with the DS population. Firstly, as summarized in tables six and seven, there is evidence of functional and structural differences between DS and controls, demonstrating the lower cerebral volume in some areas and differences in FC. However, in light of the literature in FC, differences found are not congruent within studies and do not enable the establishment of a stable and regular pattern typical of DS people. Second, excess movement is present when working with DS samples. It is crucial to mention it when the working samples have special excessive motion. Third, it is vital to consider which type of control group is comparative to the DS sample: a chronological matched control or mental age-matched control. When the specific case relates to task procedures, it is better to use mental age controls, which could address cognitive skills correctly. Fourth, the use of resting-state procedures could better describe the functioning of the

DS brain. Finally, it would be beneficial to invest time and effort in studying how the brain signal functions in the DS population. All these findings were crucial for the consecution of the protocol and the following analyses.

After summarizing the main findings and difficulties of using *f*MRI, some of the main resting-state techniques were chosen to find abnormalities in DS. Due to the limited literature found in this field, these techniques were chosen because they were data-driven methods without prior hypotheses. The data from the presented protocol was used to perform the analyses. The findings of the fourth study guide us to highlight the importance of movement when working with both populations. The movement was statistically different for both populations in our sample, as in all the studies found in the systematic review (Carbo-Carreté et al., 2020) performed with the DS population. Therefore, head movements were set as a covariant in all further analyses. Moreover, scrubbing also was performed in the preprocessing of the images to guarantee no influence of head motion on the results.

Generally, both of the studies showed the following results: a) findings of alterations in fALLF and ReHo, b) findings of the alterations in DC, c) Seed-based analysis revealed significant differences in many clusters and d) Brain network analyses showed significant group differences between different areas of the Yeo et al. (2011) networks.

It is crucial to highlight that fALFF, ReHo, DC, and seed-based FC are voxel-wise approaches. The significant clusters found are conformed by hundreds of voxels. Therefore, the labels that correspond to them are also extensive areas with activity in some areas that can be increased and decreased simultaneously. For more detailed areas, the information of the voxel's coordinates in the peak can be found in the manuscript, as well as the label of the AAL where they correspond.

More concretely, in the fALFF analysis, figure 23a shows the significant differences between both groups. The areas that showed increased activity in DS included some parts of the frontal and temporal lobes and the left cerebellum anterior lobe. The areas showing decreased fALFF activity in DS were regions of the left parietal, occipital and limbic lobes and in the left cerebellum posterior lobe.

In the ReHo analysis, figure 23b shows the significant differences between both groups. The areas that showed increased activity in DS participants compared with controls were certain areas of the left frontal lobe and inferior temporal lobe. The areas with decreased activity in DS were regions of the frontal lobe and right limbic lobe.

Interestingly, there was a high correlation between the most significant clusters in fALFF and ReHo and cognitive measures. Therefore, we can affirm that the differences between DS and

controls are related to the cognitive profile of both groups and linked to verbal and nonverbal intelligence, as measured with KBIT-2. It is crucial to mention that this test has been applied to assess neuropsychological performance in DS on multiple occasions (Anderson et al., 2013; Hamburg et al., 2019; Csumitta et al., 2022). As DS is one of the most commonly identifiable causes of ID (Goeldner et al., 2022), all substantial differences found in the whole-brain analysis were mainly related to the cognitive profile of DS. As high correlations were found between cognitive measures and cluster activity through both analyses, using both populations, a regression was performed using only the variables that had high variability in their distribution. In this sense, four regression models for each analysis were highly predictable of the cognitive outcome, with high $R^2$ values. The areas of the clusters were congruent with other studies using other approaches and in other populations (Eimontaite et al., 2018, Trimmel et al., 2021, Zavala-Crichton et al., 2020). Other studies have also found a relationship between these measures and cognitive outcomes in AD (Yang et al., 2020), in a healthy sample (Lee & Hsieh, 2017), or in those with schizophrenia (Fryer et al., 2015).

The intense relationship between cognitive outcome and spontaneous brain activity measured by fALFF and ReHo is vital to emphasize. As stated by Carbó-Carreté et al. (2020) in the third study of the present thesis, resting-state techniques could allow the analysis of the cognitive activity of people with ID. Whereas evaluating cognitive functioning in DS is a challenging task due to the problems understanding the verbal instructions of the test among people with severe or profound ID, resting-state *f*MRI analyses could be an attractive option. Moreover, it is also an arduous task to evaluate the presence of AD in DS due to the variability in the degree of ID and clinical features in DS (Fragoso et al., 2021). Therefore, biomarkers of AD and highly correlated measures using resting-state *f*MRI measures can be valued tools. Consequently, the high correlations with the cognitive outcome of resting-state measures could be the first step to increasing the validity and reliability of the neuropsychological evaluation of DS people. Therefore, it is important to suggest, that, fALFF and ReHO could be used as biomarkers of cognitive function, which is crucial given the difficulties in cognitively evaluating this population and assessing dementia (Carbó-Carreté et al., 2020). It is also crucial to find biomarkers related to cognitive function given the practice effects that the currently available tests to perform neuropsychological assessment or cognitive evaluations can present. The decrease in the test-retest reliability of the traditional neuropsychological evaluations increases the need to seek novel paradigms, which could be related to neuroscience (Kessels, 2019).

Regarding DC analysis figure 23c shows the significant differences between both groups. DS participants showed increased DC in the temporal lobe and right frontal lobe, and the left caudate. However, they showed decreased DC compared with controls in the left frontal lobe.

There is a high congruency found between fALFF, ReHo, and DC. Figure 23 shows the significant areas for allowing the comparison, visualized with DPABI. Other studies have pointed out this high congruence with fALFF and ReHo (Shen et al., 2020). Increased fALFF and ReHo is found in prefrontal regions of the frontal lobe, whereas decreased ReHo and DC is found in frontal regions. Increased fALFF, ReHO and DC is found in temporal lobes. Decreased fALFF and ReHo is found in regions that compose the limbic lobe, whereas decreased ReHo and DC is found in the left frontal lobe.

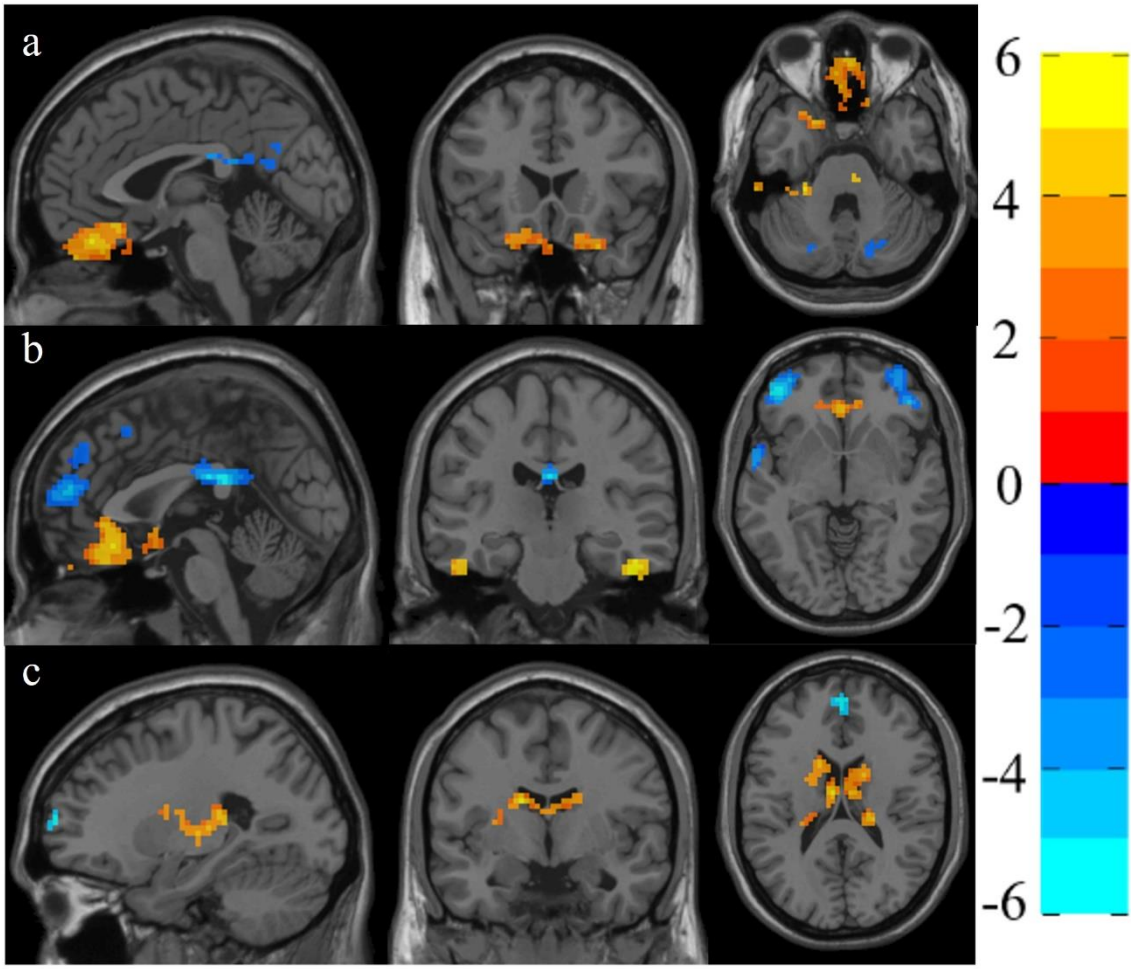


*Figure 23. Two sample t-test analyses between DS and controls with TFCE correction.*

Note: Image a represents fALFF analysis, image b represents ReHo analysis, and image c represents DC analysis.

Structural brain abnormalities have been reported in this population congruent with the areas that were significant in our study using fALFF, ReHo, and DC. Decreased brain volume has been reported in this population in the frontal and temporal lobes, as well as in the cerebellum (Fragoso et al., 2020). Beacher et al. (2010) demonstrated that these areas show a more significant age-related reduction in DS than the general population. Additionally, the findings show a

decrease in white matter integrity in the frontal tracts and correlations with cognitive dysfunction (Fenoll et al., 2017; Powell et al., 2014). This study found the differences in fALFF, ReHo, and DC involving white matter and frontal areas. Therefore, white matter appears to play a vital role in the neuropathology of people with DS. Moreover, the decreased volume for this population can lead to fALFF, ReHo, and DC abnormalities. In other populations, a relationship between structural and functional abnormalities has been reported (Rogers et al., 2018; Valenti et al., 2020).

It is also crucial to highlight that significant differences were found in the temporal and frontal lobes: these areas are vital for some cognitive functions such as executive and language functions and memory (Chai Abd Hamid & Abdullah, 2018; Oyegbile et al., 2019), functions highly altered in DS (D'Souza et al., 2020; Hamburg et al., 2019; Schworer et al., 2022;). This increase in spontaneous activity, despite being in a resting-state *f*MRI paradigm, could be a mechanism of compensation for their disrupted networks and functions, as has been suggested in other pathologies that present cognitive impairments (Xiong et al., 2020) or visual disabilities (Shao et al., 2019).

As hypothesised, it is crucial to highlight that DS showed decreased activity in fALFF, ReHo, and DC in some regions that conform to the DMN, and our results are in line with those reported by Rosas et al. (2021), who also found differences in connectivity in this region. Wilson et al. (2019) also found weaker connectivity in the DS group than controls with the DMN seed and several regions, some of which were also reported in our study. More specifically, the precuneus, reported in our research as having decreased fALFF in the DS group than in the controls, and part of the cerebellum also showed significant results in our study.

Despite the young sample of DS used in this study, it has been demonstrated that the DS population without dementia exhibits β-amyloid (Aβ) burden that can begin in the late teens (Perez et al., 2019; Snyder et al., 2020). Orbitofrontal regions have proven to be areas affected by this early deposition in DS presenting MCI but also in cognitively stable DS (Cha et al., 2015; Keator et al., 2020). The abnormalities found in the orbitofrontal lobe (increased fALFF in DS and increased/decreased DC in frontal lobes) could be a prelude to this deposition in our sample, but more studies are needed to demonstrate this association by linking the amyloid deposition with fALFF or DC values. To date, this association has only been demonstrated with ReHo (Li et al., 2021), with higher values of ReHo indicating amyloid deposition.

It is also crucial to compare our results with AD pathology, despite the high restrictions we have used in this study with the participant's age. Despite this fact, congruencies have been found with the significant regions in fALFF and ReHo between our study using DS and the one of Yang et al. (2020) or Cha et al. (2015), which use AD participants. As it has been mentioned,

we have guaranteed that our sample does not present signs of dementia or MCI, but brain's neuropathology of AD can begin years before clinical symptos are evident Moreover, Aβ deposition is already present in young DS (Keator et al., 2018; Keator et al., 2020).

To our knowledge, it is the first study to measure fALFF and ReHo in DS. However, DC was also studied in DS by Pujol et al. (2015) in a sample of DS. In this sense, they found increased DC in the DS in the ventral anterior cingulate cortex (ACC) and decreased DC in the dorsal ACC. Both regions were also increased in DS (cluster of the left caudate) and decreased (cluster of the left frontal lobe) in our study. Moreover, the decreased DC in the medial frontal cluster reported by Pujol et al. (2015) was also found in our study (cluster left frontal lobe). Pujol et al. (2015) reported higher DC in DS in the right amygdala, which also is congruent with our study (cluster left caudate) and decreased DC in DS in areas of the posterior insula.

Regarding seed-based FC analyses, hyper connectivity in DS was found in most of the seeds used, finding high congruence with the results of DC analyses. It is important to highlight the importance that may have the left thalamus in the neuropathology of DS, because of the hyper connectivity found with other structures of the brain. This structure is implied in executive and memory functions (Stagni et al., 2020), which are impaired in DS, and it seems that is particularly sensitive to effects of aging, finding a loss of neurons and volume (Perry et al., 2019) in older persons with DS, as well as other abnormalities related to brain amyloid deposition (Keator et al., 2020). These structural alterations could be related to the hyperconnectivity found regarding this structure with other areas. It is important also to highlight the big presence of subcortical structures in the significant differences between both populations as the thalamus and the caudate, which are especially important for the cortico-striatal-thalamo-cortical (CSTC) circuits. These regions have been linked with important neuropsychological deficits and neurodevelopmental diseases such as autism spectrum disorder or ADHD (Riva et al., 2018).

All the clusters found in DC and seed-based FC analyses were classified using the Yeo et al. (2011) parcellations. Figure 24 represents Yeo et al. (2011) parcellations using DPARSF. Remarkably, many regions conformed to Yeo et al. (2011) parcellations. There were only four ROIs that did not pertain to Yeo's network. Five ROIs were included in the visual network (VN), three regions in the Sensorimotor Network (SMN), two regions in the Dorsal Attention Network (DAN), one region in the ventral attention network (VAN), four related to the limbic network (LN), one in the frontoparietal network (FPN), and six in the DMN. It is important to mention that all the regions are not equally represented because the regions which were used were extracted from the DC analyses. Therefore, it is important to be carefull when discussing about networks as a whole, because the whole network is not included.

At this point, it is vital to mention a recently published study by Csumitta et al. (2022) with young DS using resting-state *f*MRI. They studied whole-brain connectivity at the voxel level and network selectivity. In this sense, they found significant differences in 18 ROIs and classified them also using Yeo et al. (2011) parcellations. It is crucial to mention that the aberrant FC findings of Csumitta et al. (2022) are similar to the ones found in our study when using DC and seed-based approaches. Regions of the temporal and frontal lobes, among others, were also found to be significant in our study. However, they found an increase in all areas of the FC in DS, whereas our findings are dependend on the area, congruent with other studies (Rosas et al., 2021; Wilson et al., 2020). DC and FC are related measures that can elucidate similar changes among DS and controls. Finally, the classification of the ROIs was similar to our study, but they did not perform brain network analyses.

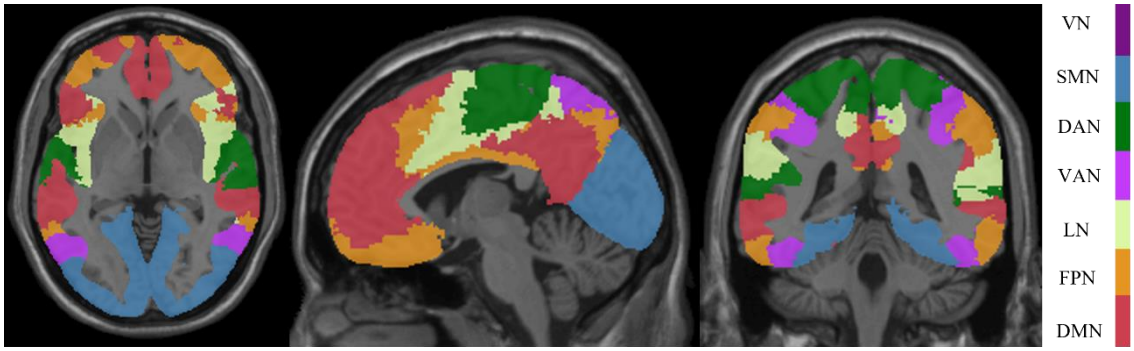


*Figure 24. Representation of Yeo et al (2011) networks.*

Note: Purple represents the ROIs included in the VN; blue represents the ROIs included in the SMN; green represents the ROIs included in the DAN; light purple represents the ROIs included in the VAN; yellow represents the ROIs included in the LN, orange represents the ROIs included in the FPN and red represents the ROIs included in the DMN.

Regarding brain network analyses, our study found significant differences between DS and controls, and figure 25 summarizes the results. Regarding within connectivity in the parcellations, only significant differences were found in the DMN, finding decreased FC within the DMN in the DS participants. The other networks studied did not differ regarding within connectivity.

Concerning between network connectivity, significant differences were found between all the networks included in Yeo et al. (2011) parcellations. We found hyperconnectivity in the links between the VN and some regions of the DMN and LN. When we used the SMN as a seed, the brain networks also seemed altered in DS; concretely, they were increased with the FPN and DMN,as well as with the LN, whereas decreased in the VAN. The DAN also seems disrupted in DS, increased with some areas of the DMN and LN. When using the VAN as a seed, those regions linked with the SMN were decreased. Regarding the FPN, links with regions of the SMN and

DMN show an increase in DS. Regarding the LN, the links with with the VN, SMN, DAN and DMN were increased in DS participants. Finally, concerning the DMN, networks that link with the DAN, SMN, VAN, VN, LN and FPN seem to be increased in DS. However, as mentioned above, within connectivity is also altered, finding decreased FC.

Clearly, disrupted intrinsic and between network FC is found in DS in the DMN. There is a clear pattern of hypoconnectivity in the DS group within the areas of the anterior DMN. Rosas et al. (2021) studied also the within-network FC of the DMN in DS and reported abnormalities congruent with our study. In this sense, they found an anterior-posterior dissociation in the DMN: the anterior parts of the DMN (in our study, left frontal superior medial gyrus and the left frontal middle gyrus) were disconnected in the DS group from the posterior part of the brain (in our study, precuneus and left angular gyrus). In the same line, Koenig et al. (2021) also found decreased FC in the majority of connections between the anterior and posterior aspects of the cingulate cortex. Contrarily, between network connectivity of the DMN with all other networks pertaining to the Yeo et al. (2011) parcellations are increased in DS. This pattern was congruent with Wilson et al. (2019), who found increased FC in the DS group from the DMN to the rest of the brain.

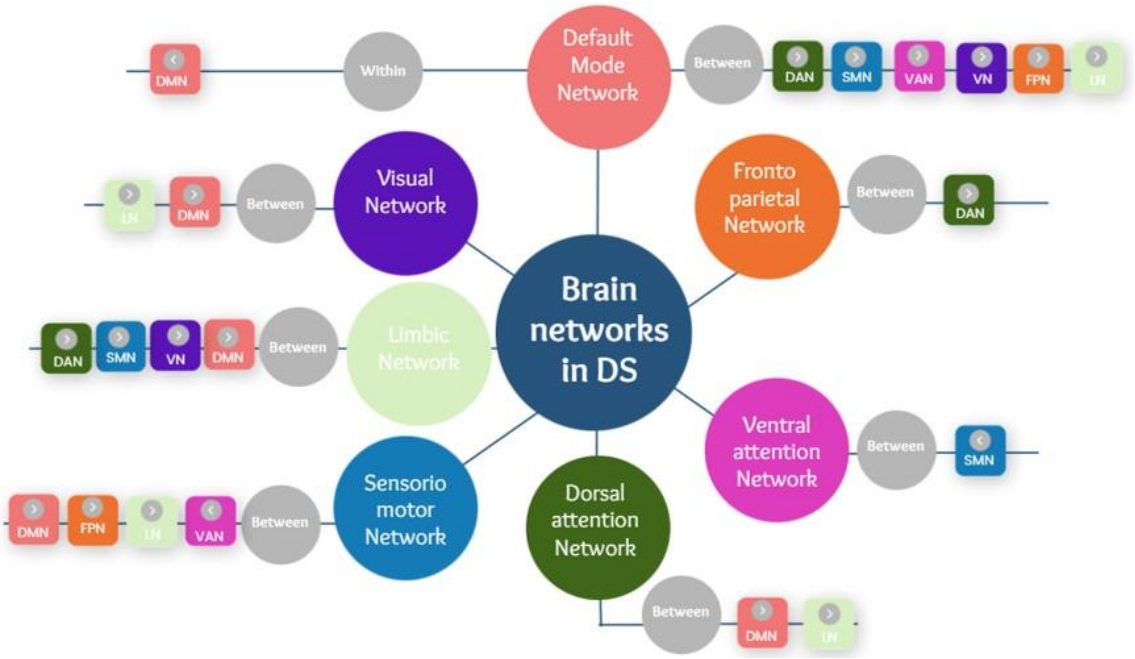


*Figure 25. Graphical representation of the results found in brain networks.*

Note: > means increased FC in DS participants; < means decreased FC in DS participants.

Despite Vega et al. (2015) study includes the whole brain networks of Yeo et al. (2011) and with a smaller sample than in our study, there are consistencies between the studies. In this sense, they also found increased FC between the SMN and the DMN as well as increased FC

between the SMN and the FPN. Moreover, they found increased FC between the LN and the DAN. However, Vega et al. (2015) found increased FC between the SMN and FPN, as well as between the DAN and FPN, whereas in our study these results were not reported. These different results could be explained because in our study there is only one ROI included that pertains to the FPN, which shows increased FC with areas of the SMN and DMN, but in the study of Vega et al. (2015) the whole network is included. The FPN could be underrepresented in our study and this fact could explain the differences between our study and the one published by Vega et al. (2015).

Finally, the effect sizes of all comparisons were large, despite having applied strict corrections for multiple comparisons using the covariate of movement. It is important to mention that the control of head motion in this population is a challenge, and we have tried to address this fact by: a) Scrubbing in the preprocessing; b) Adding movement as a covariate in all the analyses. As the techniques used in both studies are data-driven, it is not necessary to have a prior hypothesis of the seed regions in the analysis. Specifically for the DS population, there is a scarcity of studies on resting-state *f*MRI procedures, with only three techniques used as valuable tools for studying this population without knowing the specific underlying pathology. The three techniques have localized brain areas that are different in both populations. The specific regions that have shown differences between both groups could be targeted brain regions for new researches and treatment (Martínez-Cué & Dierssen, 2020).

Regarding the results of the fifth study, to our knowledge, this is one of the few studies on brain networks to investigate the FC of resting-state *f*MRI in DS. The study aimed to disentangle brain FC differences between DS and control participants. We examined the intrinsic connectivity pattern of whole-brain functional networks in DS participants by combining DC at the voxel level and seed-based FC analysis. Moreover, the significant voxels of DC and the seed-based FC clusters found were used as ROIs to study network-based analysis, and the results are congruent with other published papers in the field (Csumitta et al., 2022; Koenig et al., 2021; Rosas et al., 2021; Vega et al., 2015).

### 3.3 Common considerations

Two very different aims direct the present thesis. Therefore separate sections are used to discuss all the studies, specifically. However, it is vital to discuss some facts commonly found in all the studies.

Firstly, it is crucial to suggest the possibility of using the procedures proposed in the first study to solve missing data in *f*MRI. As mentioned above, head movements are one of the most challenging facts in *f*MRI, which leads to discarding a high percentage of the sample for a peak

of movement. Further investigations should address this matter and it is presented in further investigations.

It is crucial to discuss the results of the meta-analysis with the other studies, despite only being with task-studies. Regarding the qualitative part of the study, the right middle temporal gyrus was found to be decreased in DS samples and also in the final result of the metanalysis (quantitative section) when using all the types of ID. This result is in line of our study, finding also a decrease in DS participants in this area (cluster: left parietal and occipital lobe, with the peak in the middle occipital gyrus). This area appears to link with cognitive demands, such as semantic processing and language (Cabeza & Nyberg, 2000; Chao et al., 1999; Tranel et al., 1997), and it is linked then with the majority of the tasks included in the metanalysis. Even though our study uses the resting-state paradigm, fALFF measures in this cluster are correlated positively with verbal and non-verbal measures evaluated with KBIT-2 and the phonological and semantic verbal fluency, meaning that higher activation was correlated to better performance in cognitive evaluation. ReHo is also congruent with this result, finding also a decrease in ReHo values in this area in the DS group (cluster: frontal lobe, with the peak in the frontal middle orbital left gyrus). The activation in this region is also highly correlated with all the cognitive outcome. However, DC doesn't display any differences in this area between controls and DS participants in our study.

Regarding the systematic review, it is crucial to mention that the present thesis demonstrates that resting-state measures are highly correlated with cognitive outcomes, therefore the present hypothesis could be to solve the low reliability of the actual proposals to evaluate people with DS using resting state measures, which have a high test-retest reliability (Chen et al., 2018) and solve the issues that present classical neuropsychological evaluations (Harvey, 2022) as the practice effects. Moreover, fALFF and ReHo measures have already been suggested as potential biomarkers owing to their high test-retest reliability (Zuo et al., 2013; Küblböck et al., 2014). More research is needed in this field to demonstrate their potential utility. It is vital to mention that within this thesis; there was no use of intragroup comparisons recommended by Carbó-Carreté et al. (2020). These intragroup comparisons among participants with DS should be adressed for further investigations.

Finally, regarding the utility of the CR model in DS, we have demonstrated that physical activity levels, cognitive outcome, personal conditions, and quality of life operationalize this concept. However, the present thesis demonstrates alterations in resting-state *f*MRI measures and that these alterations are linked to the cognitive profile in DS. Therefore, these measures could also belong to the operationalization of the CR model: it is crucial to try to operationalize this concept using fALFF and ReHo, as well as DC and brain network analyses, due to its important

role in the neuropathology of DS. This presented proposal should be presented for future lines of research in the field.

Finally, the implications of all the findings are linked to the AD pathology. Because of the high incidence of AD in DS, the DS population provides an extraordinary opportunity for understanding the temporal progression of AD and the different facets that contribute to the age of dementia onset, as well as for applying this knowledge to the general population (Fortea et al., 2020).

### 3.4 Limitations, strengths, and future research

The results of this thesis are not exempt from some limitations. First, regarding the first study, we did not study the statistical properties of the IFI to achieve a more adjusted significance or use simulations to estimate its sensitivity or specificity. Another major limitation of this study is the use of noninformative priors in the Bayesian estimation of the CFA. However, for the moment, with the scarcity of studies done in DS, there is no possibility to use informative priors.

The results of the second study have been limited due to the few studies using ID population in *f*MRI, resulting in low effect size in the meta-analysis. All our studies analyzed consisted of a tiny sample, with a few studies included in the meta-analyses. It is important to remark that the available studies do not allow us to draw clear conclusions about brain functional irregularities in ID. We should interpret our results with caution. Second, and due to the limited data, there was no analysis of the effects of some variables such as type of ID, type of task used, % of women, or mean age of the participants due to the low heterogeneity found. Our heterogeneity indexes were very low, and this can be due to the limited sample. Finally, the studies included used different tasks. Therefore, we are not able, with these preliminary results, to generalize to the ID population. There should be more task-*f*MRI and task-specific meta-analysis studies to address the functional brain abnormalities in this population.

Regarding the limitations found in the third study, the scarcity of studies involving DS and *f*MRI techniques led to difficulties in generalizing conclusions about activations.

Finally, the limitations found in studies four and five are difficulties recruiting samples in this particular population, the high degree of movement during scanning in the DS population, and the limited sample size. However, it is vital to highlight that this study's sample size is in accordance with the typical sample size used in neuroimaging. The lack of a replication dataset can also limit the results. Finally, motion, even if well controlled, could affect the results. Therefore, more studies using FC and other methodological approaches, such as graph analysis or ReHo and fALFF, in this population are needed.

Despite the limitations mentioned above, it is also crucial to state the strengths of the five studies. Firstly, as there is a scarcity of studies done with this population, the five studies stand as the first time done with a population with DS. In first place, the first paper provides the first approximation of CR concept to the DS population. It also provides a starting point in studying individual differences in both clinical and neuropathological appearance of dementias. In the second place, the second study is the first one to ensemble the whole concept of ID in a neuroimaging metanalysis, to clarify if a pattern underlying the different types of ID exists compared to a group of healthy controls. In the same line, the third study is the first systematic review using DS and *f*MRI techniques. Finally, the applied analyses in the fourth and fifth studies are novelty approaches for the first time applied to this population. Therefore, the novelty and impact of the thesis studies are evident.

Another major strength of this research is the high control of the age of the study, as it is valuable because of the early onset of AD in this population. Studies four, and five allow us to affirm that the differences found between the two populations are not because of the neuropathology of AD. Other studies in the literature shown in tables 6 and 7 use an older DS population, and the differences found with controls could be a prelude to AD appearance (Rosas et al., 2021; Wilson et al., 2020).

Regarding studies four and five, despite the limited samples, a highly restricted correction for multiple comparisons was performed in the analyses. The results show a large effect size, so we can affirm that there are significant differences in regional spontaneous brain activity using fALFF and ReHo, and in the FC using DC, seed-based FC, and brain network analyses between controls and DS. The results of both studies are in line with those of other studies performed in this field, using structural and *f*MRI.

Finally, the current thesis may open the scope for new research lines. Regarding the first study, it is necessary to put more effort into developing better-performing statistics with small sample sizes and missing data in the sample. Moreover, it is crucial to estimate the statistical properties of the IFI to achieve a more adjusted significance or use simulations to estimate its sensitivity or specificity. The evidence proves the importance of FC in this population, and we would like to add the variable FC to the model of CR. Other studies have included MRI variables in the study of CR (Lopez-Soley et al., 2020). Regarding the second study, firstly, meta-analysis is a valuable tool to enhance the power of individual studies. However, other strategies have started emerging, such as big shared data protocols in the field of neuroimaging (Smiths & Nichols, 2018). Secondly, it is essential to highlight that the scarcity of studies in the literature did not allow to clarify if there is a clear pattern existing in ID. Therefore, to address the functional brain abnormalities in this population, more task-fMRI studies are needed, and a task-specific

meta-analysis should address this topic more directly. There should also be more publication in resting-state *f*MRI studies for ID, and more meta-analyses with these studies could also aid in explaining brain abnormalities in this population.

With results from study four, this study suggests that fALFF and ReHo can serve as biomarkers of cognitive function. More research should be focused on these findings. Finally, study five has demonstrated that connectivity in DS is altered, and these abnormalities could be related to the characteristics of the disease (low ID, physiological features, decreased volume in the brain). Moreover, regions that seem more disconnected should be targeted to plan therapeutic interventions to promote increased connections. The abnormalities found in this population could be targeted as therapeutic interventions to enable plasticity to improve cognition and behavior in DS (Martínez-Cué & Dierssen, 2020).

Moreover, there are hundreds of approaches in resting-state *f*MRI. These approaches have not yet been applied to this population in resting-state fMRI, such as graph theoretical analyses, whole brain FC the study of the 7 complete Yeo networks. As the recollection of the sample is still being made in the project, future intragroup comparisons within the group of DS could be performed to try to find differences in FC due to the high variability in the clinical of DS.

The findings of the final two studies confirm that brain abnormalities can be demonstrated using different techniques in resting-state *f*MRI. Therefore, it is clear that in future research, we would like to interpret if all the techniques used in both studies could also be part of the CR investigated in the first study, together with quality of life, physical activity, and cognitive outcome.

# 4. Conclusions

Considering all the results obtained from the five studies conducted in the present thesis and the aims that delimitated the thesis, the extracted conclusions are the following:

1. Missing data and small sample sizes are present when using clinical and special populations that, due to their characteristics, cannot complete the whole protocol. Moreover, when talking about populations that are not very prevalent, and in this case, when the parent's consent is necessary, the difficulty increases. In the neuroimaging field, this issue is more serious because of the expensive costs and the complications of the register techniques.
2. When the possibility to resample is not real, there are some methodologies and techniques that could be useful: MI (using different techniques and iterations and evaluating the fit of them using IFI); the corrections of Jian and Yuan, Jacknife correlations, and Bayesian models instead of frequentist estimations, preferably using informative priors.
3. Sample sizes in neuroimaging techniques are small and meta-analyses tools can help to summarize, qualitative and quantitively, the findings found throughout different studies.
4. The operationalization of the CR concept in DS is possible considering factors such as quality of life, physical activity levels, cognitive outcome, and personal condition of the person with ID. This finding may provide a starting point in studying the individual differences in both clinical and neuropathological appearance of dementias.
5. Resting-state techniques could be valuable tools to study brain activity in DS. However, up-to-date findings are unclear, and do not establish regular pattern of disrupted FC in this population. There are reports of increased and decreased FC.
6. In the meta-analysis, a clear pattern of dysconnectivity was found in ID in the right temporal gyrus compared with controls. However, more task-*f*MRI studies on the ID must be published to add larger samples to address the pathophysiological questions more directly.
7. fALFF and ReHO are useful data-driven tools to disentangle brain abnormalities in DS
8. There are significant differences in DS spontaneous brain activity: increased and decreased fALFF and ReHo in different areas of the brain.
9. High correlations were found using the significant clusters found in fALFF and ReHo. Four regression models predicting KBIT-2 measure were highly predictable, using as predictors activations in the significant areas of fALFF and ReHo.
10. Significant differences were found using DC in the whole brain, with increased DC in DS in regions of the cerebellum and temporal and occipital lobes and decreased DC in the DS in regions of the frontal and parietal lobes.
11. Significant differences were also found when using the clusters found in DC for estimating seed-based FC.

12. Differences found in fALFF, ReHo, DC and seed-based FC could be related to the cognitive profile of DS, finding alterations in the frontal and temporal lobes. These regions are thought to be engaged in executive, language and memory functions, functions highly altered in DS. Moreover, the Aβ deposition, which can start in the late teens in the DS population, and has been demonstrated in cognitive stable adults with DS also can be an explanation of the differences found. Also, the structural abnormalities already demonstrated in this population can be related to the differences in FC found in the present thesis.
13. Findings show significant differences between networks and within networks using the significant clusters found with DC and seed-based FC.
14. The DMN displays disrupted FC, finding in DS increased FC between the DMN and all the other networks of Yeo et al. (2011) parcellations. However, a clear pattern of dysconnectivity has been found in this population when using within network connectivity of the DMN. This region seems to play an important role in the neural correlates of DS; and has been demonstrated in other diseases and mental health problems.
15. Remarkably, there were no differences in within connectivity in the VN, SMN, DAN , VAN, LN and FPN. However, between connectivity in DS is always altered. and hyper and hypoconnectivity was found.
16. Future studies should address the possibility of including resting-state measures in the CR model for DS to prove the differences with control people are remarkable and linked with their ID and further research on resting-state measures could find biomarkers of AD in DS.

Despite the difficulties recruiting sample and the presence of missing data when working with special populations that are not very prevalent, the present thesis demonstrates that DS courses with a disruption in spontaneous brain activity and in FC.

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# Appendices

## Appendix 1: Full protocol for DS participants of the study


UNIVERSITAT DE BARCELONA

# PROTOCOLO *f*MRI – SÍNDROME DE DOWN

# ANÁLISI DE SEÑAL CEREBRAL, ACTIVIDAD FÍSICA, HÁBITOS DE ALIMENTACIÓN Y RENDIMIENTO COGNITIVO

Dra. Maria Carbó. Universitat de Barcelona. Universitat Ramon Llull

Dr. Joan Guàrdia. Institut de Neurociències. Universitat de Barcelona

Dra. Myriam Guerra. Universitat Ramon Llull

Dr. Cristina Andrés. Universitat de Barcelona

*Barcelona, noviembre de 2017*

INFORMADOR: Família o professional

**EVALUACIÓN DE CRITERIOS DE INCLUSIÓN E EXCLUSIÓN**

| | |
|---|---|
| **Criterios de inclusión** | |
| | Edad entre 16 y 30 años |
| | Diagnóstico de síndrome de Down |
| | Escolarizado (texto de primaria para comprobar capacidad lectora o aritmética básica) |
| **Criterios de exclusión** | |
| | Otros diagnósticos que cursen con síndrome de Down |
| | Presencia de medicación que afecte a funciones cognitivas |
| | No aceptación de consentimiento informado |
| | Sospecha de demencia según el DSQIID: 3a parte (1 puntuación de 10 indicador de sospecha) |

**DSQIID (3ª parte):**

Contesta por favor las preguntas que siguen con un "si" o un "no"

| | Sí | No |
|---|---|---|
| Perdió algunas habilidades (ejemplo: cepillarse los dientes) | | |
| Habla menos (con señales) | | |
| Parece en general más cansado | | |
| Parece lloroso, se molesta más fácilmente | | |
| Parece más lento | | |
| Discurso más lento | | |
| Parece más perezoso | | |
| Camina más lento | | |
| Generalmente parece más olvidadizo | | |
| Generalmente parece más confuso | | |

**CONSENTIMIENTO INFORMADO**

El/La Sr./Sra.....,

con DNI nº....., como padre/madre o tutor/a legal

de.....

HAGO CONSTAR:

Que he sido invitado a participar en la investigación "**CONECTIVIDAD CEREBRAL PARA LA ESTIMACIÓN DEL EFECTO DE LA ACTIVIDAD FÍSICA Y DE LA DIETA EN LA MEJORA DEL RENDIMIENTO COGNITIVO EN ADOLESCENTES CON SINDROMES DE DOWN PARA LA MEJORA DE SU RESERVA COGNITIVA Y PREVENCIÓN DE DEMENCIAS PRESENILES**" que dirige el Dr. Joan Guàrdia Olmos de la Universitat de Barcelona.

Se me ha comunicado que el director del proyecto se compromete a utilizar mis opiniones, así como mis datos exclusivamente para este estudio y se guardaran de forma confidencial.

**Autorizo** la comunicación de los resultados y conclusiones de la investigación preservando el anonimato que he confiado al investigador[1].

**Tengo el derecho** de decidir que mi hijo/a o persona que tutelo abandone el estudio en el momento en que lo desee sin ningún perjuicio.

Dado que la información me ha sido expuesta de forma comprensible y que he podido formular preguntas para resolver dudas, **doy libremente mi conformidad** para participar en esta investigación y lo autorizo explícitamente en este documento.

Lugar y fecha:

| | | |
|---|---|---|
| Firma del/la participante | Firma del padre/madre o tutor/a legal | Firma del director del proyecto |

[1] De acuerdo con la Ley Orgánica de Protección de Datos de Carácter Personal 15/1999 del 13 de diciembre.

Proyecto aprovado por el Comité Ético de la Universidad de Barcelona, el 16 de marzo del 2017

HOJA de Autorización y Consentimiento

**RESONANCIA MAGNÉTICA (RM). Proyectos externos BBRC**

Este documento tiene como objeto solicitar y obtener su autorización expresa por escrito para la realización de una resonancia magnética (RM) cerebral.
La RM cerebral es una técnica de imagen que emplea campos magnéticos y ondas de radio (127Mhz) para obtener imágenes del cerebro.
Es una prueba NO agresiva, que no utiliza rayos X ni sustancias de contraste y no comporta efectos secundarios para el organismo. El escáner RM, durante su funcionamiento, produce ruido que puede llegar a ser molesto, por lo que se le proveerá de protección auditiva (tapones y auriculares). Durante la exploración, ocasionalmente puede producirse estimulación neuromuscular periférica, es decir, pequeños temblores en la piel y leve sensación de bochorno por el calor inducido por el escáner. Al salir del escáner puede sentir una ligera sensación de mareo que desaparece a los pocos segundos.

No se han descrito efectos adversos sobre el embrión/feto en mujeres embarazadas por la realización de una RM cerebral. No obstante, dado el caso, se evaluará individualmente para determinar la idoneidad o no de la realización de la prueba. Las imágenes de RM obtenidas se almacenarán en un sistema seguro de almacenamiento y transmisión de imágenes, que aplica las condiciones de protección de datos de carácter confidencial establecidas en la legislación vigente.

Si tiene dudas, le rogamos que solicite la información que desee a los miembros del equipo en cualquier momento.

Previo a la realización de la prueba, y a fin de velar por su seguridad, es preciso que usted conteste a las siguientes preguntas:

1. ¿Es usted claustrofóbico? (Padecer elevada ansiedad en espacios cerrados) ☐SI ☐NO
2. ¿Existe la posibilidad de que tenga en los ojos fragmentos o restos metálicos a consecuencia, por ejemplo, de un accidente o de su actividad laboral? (e.g. astillas metálicas, virutas, etc.) ☐SI ☐NO
3. ¿Está o podría estar embarazada? ☐SI ☐NO

**Por favor indique si tiene alguno de los siguientes ítems que podrían ser incompatibles:**

| | | |
|---|---|---|
| ☐SI | ☐NO | Marcapasos cardíaco |
| ☐SI | ☐NO | Válvulas cardiacas protésicas |
| ☐SI | ☐NO | Clip de aneurisma |
| ☐SI | ☐NO | Implante con desfibrilador para conversión cardíaca (ICD) |
| ☐SI | ☐NO | Implante electrónico o dispositivo electrónico |
| ☐SI | ☐NO | Implante o dispositivo activado magnéticamente |
| ☐SI | ☐NO | Sistema de neuroestimulación |
| ☐SI | ☐NO | Audífono, implante coclear, otológico, u otro implante de oído |
| ☐SI | ☐NO | Intervenciones oculares con implantes |
| ☐SI | ☐NO | Bomba de infusión de insulina o de otro medicamento |
| ☐SI | ☐NO | Cualquier tipo de prótesis (cadera, rodilla, etc.) o extremidad artificial |
| ☐SI | ☐NO | Cualquier objeto o fragmento metálico o cuerpo extraño dentro del cuerpo |
| ☐SI | ☐NO | Dispositivo intrauterino |
| ☐SI | ☐NO | Dentadura y dispositivos de ortodoncia extraíbles. |

**Por favor indique si tiene alguno de los siguientes ítems que no son incompatibles, pero que pueden afectar a la calidad de la imagen:**

| | | |
|---|---|---|
| ☐SI | ☐NO | Ortodoncia o implantes fijos. |
| ☐SI | ☐NO | Piercing, agujas (acupuntura) |
| ☐SI | ☐NO | Tatuajes o maquillaje permanente |

**Observaciones del profesional médico o técnico/a RM:**

HOJA de Autorización y Consentimiento

**Durante la prueba:**

1. Antes de entrar en la sala de exploración, debe quitarse cualquier objeto metálico que lleve consigo: audífono, puentes dentales extraíbles, llaves, teléfono móvil, gafas, horquillas de pelo, joyas (incluyendo "piercings"), reloj, tarjetas de crédito o cualquier otra tarjeta con banda magnética o chip, monedas, bolígrafos, ropa con enganches de metal, o con hilos metálicos. Por favor consulte con el Técnico Radiólogo si tiene alguna duda antes de entrar a la sala de exploración.
2. Deberá tumbarse en la camilla de exploración.
3. Mientras dure la prueba deberá permanecer inmóvil, respirando relajadamente. En cualquier momento podrá comunicarse con el equipo de la sala de control. Para que el ruido de la maquina no se tan molesto le facilitaremos unos tapones y unos auriculares adaptados
4. Las consecuencias derivadas de cualquier imprecisión o error en los datos facilitados por el voluntario no serán responsabilidad de la Fundación BarcelonaBeta Brain Research Center y/o Fundación Pasqual Maragall (en adelante "BBRC" y/o "FPM").

**Manifiesto voluntariamente que:**

He sido informado/a de las características de la Resonancia Magnética, de las consecuencias relevantes o de la importancia de la prueba, de sus posibles riesgos y de los efectos secundarios que se puedan presentar. La información me ha sido facilitada de forma comprensible y mis preguntas han sido contestadas, por lo que tomo libremente la decisión de autorizar el citado procedimiento. No obstante, podré revocar mi consentimiento en cualquier momento si esa es mi voluntad.

Así mismo, consiento que, si durante la prueba se precisara realizar alguna otra adquisición de imagen o procedimiento diferente a los que han sido previstos en el protocolo y se me han explicado, autorizo al equipo médico para que realice aquello que considere conveniente, dándome posteriormente las correspondientes explicaciones.

He sido informado del tratamiento de mis datos personales en los términos siguientes:
Información básica sobre protección de datos:
Responsable del tratamiento: Fundación BarcelonaBeta Brain Research Center para la Investigación sobre el Alzheimer.
Finalidad del tratamiento: contacto y gestión de las pruebas de Resonancia Magnética en la Plataforma de Neuroimagen de BBRC que incluye los datos de salud.
Base legal para el tratamiento: el consentimiento del interesado.
Destinatarios de los datos: no serán comunicadas a terceros excepto por obligación legal.
Derechos: para ejercer sus derechos de acceso, rectificación y supresión, así como otros derechos reconocidos en la normativa, puede enviar un correo electrónico a gdpr@barcelonabeta.org
Para más información y cómo ejercer sus derechos, le rogamos que consulten nuestra política completa de protección de datos al final del presente documento.

| **Persona participante de la prueba, Sr. / Sra:** | **Firma tutor/a legal:** |
|---|---|
| Nombre:<br>Apellidos:<br>DNI:<br>Fecha de nacimiento:<br>Firma: | Nombre:<br>Apellidos:<br>DNI:<br>Firma: |

| **ID PARTICIPANTE:** |
|---|

Barcelona, a_____ de _____ de 20 __

HOJA de Autorización y Consentimiento

¿El profesional médico autoriza la realización de la RM? ☐SI ☐NO

El profesional médico, designado por el grupo de investigación externo a BBRC, declara y garantiza que la persona participante signataria, no tiene ninguna de las incompatibilidades previstas para la realización de la RM, cumple los requisitos establecidos en el protocolo para la realización de la presente prueba y en caso de tratarse de personas con perfil vulnerable al COVID-19, su condición clínica le permite participar y someterse a la RM. En consecuencia, el profesional médico autoriza la realización de la RM y exime de cualquier responsabilidad a la BBRC y/o FPM.

**Profesional médico:**

| | |
|---|---|
| Nombre:<br>Apellidos:<br>DNI:<br>Nº Colegiado:<br>Fecha: | Firma: |

**El/La Investigador/a, coordinador/a o representante del estudio certifica:**

- Que el proyecto ha sido aprobado por un Comité Ético.
- Que el/la participante ha firmado el CI del estudio.
- La edad del/de la participante.
- Que el/la participante tiene capacidad natural para decidir.
- Si fuera necesario, ha comprobado que el/la firmante es el/la tutor legal del/de la participante.
- Los datos del/de la participante y del médico.

| | |
|---|---|
| Nombre:<br>Apellidos:<br>DNI:<br>Grupo Investigación:<br>Fecha: | Firma: |

**A rellenar por Técnico/a RM**

¿El/La participante ha realizado una RM anteriormente en BBRC, en un periodo inferior a tres (3) meses? ☐SI ☐NO

a. ¿El Check list de la RM anterior está firmado por un/una profesional médico? ☐SI ☐NO
b. Indicar fecha del CI anterior firmado por un profesional médico: ____/____/_____
c. Indicar profesional médico que firma el CI anterior:

**Técnico/a RM:**

| | |
|---|---|
| Nombre:<br>Apellidos:<br>DNI:<br>Fecha: | Firma: |

Responsable del tratamiento: Fundación BarcelonaBeta Brain Research Center; Finalidad del tratamiento: contacto y gestión de los profesionales implicados en las pruebas de Resonancia Magnética de la Plataforma de Neuroimagen; Base legal para el tratamiento: la relación contractual establecida; Destinatarios de los datos: no serán comunicadas a terceros excepto por obligación legal; Derechos: para ejercer sus derechos de acceso, rectificación y supresión, así como otros derechos reconocidos en la normativa, puede enviar un correo electrónico a gdpr@barcelonabeta.org; Para más información y cómo ejercer sus derechos, le rogamos que consulten nuestra política completa de protección de datos al dorso del presente documento.

HOJA de Autorización y Consentimiento

**POLÍTICA DE PROTECCIÓN DE DATOS**

En virtud de lo que dispone la legislación de la Unión Europea (UE) sobre datos personales, en concreto el Reglamento (UE) n.º 2016/679 del Parlamento europeo y del Consejo, de 27 de abril de 2016, de Protección de Datos (RGPD) y la Ley Orgánica 3/2018 de Protección de datos personales y garantía de derechos digitales, teniendo en cuenta que es necesario el tratamiento de sus datos personales, le informamos de nuestra política de protección de datos:

1. Identificación del titular responsable del tratamiento:

   Titular responsable del tratamiento de los datos: Fundación BarcelonaBeta Brain Research Center (en adelante, BBRC)
   Calle Wellington, 30, 08005 Barcelona
   NIF n.º G-65895401
   Correo electrónico: gdpr@barcelonabeta.org

2. Finalidad del tratamiento, base legal y plazos de conservación:

   Verificación de seguridad para el cuestionario de compatibilidad con la prueba de resonancia y relación del participante con el estudio al que pertenece y con su identificador así como contactar con el médico o investigador del estudio externo en caso de ser necesario.

   La base legal es su consentimiento, que se considera otorgado al rellenar y firmar la presente solicitud (si es papel) y la relación contractual establecida con los profesionales implicados en las pruebas de resonancia magnética.

   Los datos se conservarán durante 15 años desde el alta del proceso asistencial en cumplimiento de la Ley de Autonomía del paciente en Cataluña (ley 21/2000)

3. Destinatarios de los datos personales:

   Por obligación legal: jueces, tribunales que lo soliciten por vía judicial o en el marco de una investigación policial y la autoridad de control sanitario.

4. Derechos de los titulares de los datos:

   Cualquier persona tiene derecho a obtener información sobre cómo se tratan sus datos. A continuación, le explicamos sus derechos:

   - Las personas interesadas tienen derecho a acceder a sus datos personales, así como a solicitar la rectificación de los datos inexactos o, si procede, solicitar su supresión cuando, entre otros motivos, los datos ya no sean necesarios para las finalidades para las que fueron recogidos.
   - En determinadas circunstancias, los interesados podrán solicitar la limitación del tratamiento de sus datos; en este caso únicamente se conservarán para el ejercicio o la defensa de reclamaciones.
   - En determinadas circunstancias y por motivos relacionados con su situación particular, los interesados podrán oponerse al tratamiento de sus datos. BBRC dejará de tratar los datos, excepto por motivos legítimos imperiosos o para el ejercicio o la defensa de posibles reclamaciones.
   - Portabilidad: el interesado tendrá derecho a recibir los datos personales que le incumban, que haya facilitado a BBRC, en un formato estructurado, de uso común y lectura mecánica, cuando: a) el tratamiento esté basado en el consentimiento o en un contrato y b) el tratamiento se efectúe por medios automatizados.

   Le informamos de su derecho a presentar una reclamación ante la autoridad de control (AEPD - www.aepd.es) en caso de que no haya visto satisfecho el ejercicio de sus derechos aquí indicados.

   Para ejercer los derechos mencionados puede ponerse en contacto con nosotros a través de correo postal o electrónico en las direcciones indicadas en el apartado 1, indicando en su petición la siguiente información:

   - Datos del solicitante (nombre y apellidos)
   - Dirección de contacto
   - Derecho que quiere ejercer
   - Sobre qué datos concretos formula su petición

   En el plazo máximo de un mes resolveremos su petición a través del mismo medio que haya utilizado inicialmente.

5. Seguridad en el tratamiento:

   Teniendo en cuenta el estado de la técnica, los costes de aplicación y la naturaleza, alcance, contexto y finalidades del tratamiento, así como los riesgos de probabilidad y gravedad variables para los derechos y libertades de las personas físicas, BBRC aplicará medidas técnicas y organizativas apropiadas para garantizar un nivel de seguridad adecuado al riesgo, que eviten la destrucción, pérdida o alteración accidental o ilícita de los datos personales transmitidos, conservados o tratados de otro modo, o la comunicación o acceso no autorizados a estos datos.

INFORMADOR: Família o professional

## CUESTIONARIO SOCIODEMOGRÁFICO

**Identificación (nombre/código):**

**Fecha de nacimiento:** **Edad actual:**

**Género:**

☐ Hombre ☐ Diestro

☐ Mujer ☐ Zurdo

**Lugar de residencia (por favor, marque sólo una casilla según el número de habitantes):**

☐ Rural (menos de 5.000 hab. aprox.)

☐ Semi-urbano (entre 5.000 y 50.000 hab. aprox.)

☐ Urbano (más de 50.000 hab. aprox.)

**GRADO DE DISCAPACIDAD INTELECTUAL**

**Evaluación del grado de discapacidad intelectual**

☐ Capacidad intelectual límite ☐ Retraso mental moderado

☐ Retraso mental leve ☐ Retraso mental grave y/o profundo

Factores sociales complementarios:

Grado de disminución total (porcentaje total):

**SERVICIOS**

**Servicio diurno o entorno laboral** (por favor, marque una casilla según le corresponda):

☐ Empresa ordinària ☐ Centro de día

☐ Trabajo con apoyo ☐ Centro educativo

☐ Centro Especial de Empleo (CEE) ☐ Otros

☐ Servicio de Intermediación para la Inserción Sociolaboral

☐ Centro Ocupacional (CO)

**Servicio nocturno** (por favor, marque una casilla según le corresponda):

☐ Piso tutelado

☐ Residencia

☐ No asiste a servicio nocturno y vive en:

- ☐ Vivienda independiente
- ☐ Casa familiar

**Fecha administración:**
**Hora administración:**

INFORMADOR: Participante

**EVALUACIÓN NEUROPSICOLÓGICA**

| PRUEBA DE FLUENCIA | RECUENTO DE ENSAYOS CORRECTOS |
|---|---|
| ¿En 1 minuto cuantas palabras puedes decirme que empiecen por la letra p como la palaba pera? | |
| ¿En 1 minuto puedes decirme cosas que se pueden comprar en un supermercado, como por ejemplo fruta? | |
| ¿En 1 minuto puedes decirme nombres de colores como por ejemplo el azul? | |

ADMINISTRACIÓN KBIT-2: Por motivos de permisos, no han sido añadidos en el protocolo.

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Fort he first 10 administrations, the FAB was used. After, this test was replaced by the KBIT-2. People who was already evaluated were another time assessed with the KBIT-II.

Informador: Participante

La FAB (*Frontal Assessment Battery* o Batería de Evaluación del Lóbulo frontal) diseñada por Dubois *et al* (2000) evalúa en aproximadamente diez minutos las funciones ejecutivas mediante seis ítems que incluyen: tareas *go no-go*; de sensibilidad a la interferencia; de fluidez léxica y programación motora. El déficit en estas tareas facilita el diagnóstico diferencial de demencia frontotemporal. Se ha establecido que una puntuación igual o menor a 11 puntos puede indicar un deterioro en la función ejecutiva (*Chayer, 2002*). En la actualidad existen estudios en español en los cuales se ha traducido y aplicado la FAB, pero está aún sin estandarizar (*Rodríguez-del Álamo et al, 2003; Maluenda et al, 2005).*

**1. Semejanzas (Conceptualización)**
*"¿En qué se parecen…?"*
*a) Un plátano y una naranja.*
*b) Una mesa y una silla.*
*c) Un tulipán, una rosa y una margarita.*
Ayudar al paciente en caso de fracaso total: "no se parecen" o parcial: "los 2 tienen cáscara" en el primer ítem, no en los siguientes. Sólo las respuestas de categoría (frutas, muebles, flores) se consideran correctas.
Puntaje: 3 correctas = 3; 2 correctas = 2; 1 correcta = 1; ninguna correcta = 0 ___/ **3**

**2. Fluidez léxica (Flexibilidad mental)**
*"Diga todas palabras que pueda (por ejemplo, animales, plantas y objetos, pero no nombres propios ni apellidos) que comiencen con A".* Si no responde en los primeros 5 segundos decirle *"por ejemplo, árbol".* Si se detiene por más de 10 segundos, insista *"cualquier palabra que empiece con A".* Tiempo: 60 segundos. Las repeticiones, derivaciones árbol, arbolito), nombres propios y apellidos no cuentan.
Puntaje: 10 o más palabras = 3; 6 a 9 = 2; 3 a 5 = 1; menos de 3 = 0 ___/ **3**

**3. Secuencias**
*"Mire con atención lo que hago";* el examinador frente al paciente realiza 3 veces la prueba de Luria (golpear con nudillo, canto y palma) con su mano izquierda. *"Con su mano derecha haga lo mismo que yo, primero juntos, después solo".* El examinador hace la serie 3 veces con el paciente y le dice *"ahora haga lo mismo Vd. solo".*
Puntaje: 6 series consecutivas correctas = 3; a 5 series correctas = 2; no lo hace solo, pero sí 3 series consecutivas con el examinador = 1; no logra ni siquiera imitar 3 veces = 0 ___/ **3**

**4. Instrucciones Conflictivas (Sensibilidad a la interferencia)**
*"Cuando yo golpeo 1 vez, debe golpear 2 veces";* para asegurar que comprendió las instrucciones, se hace una serie de 3 ensayos: 1-1-1. *"Cuando yo golpeo 2 veces, debe golpear una";* para asegurar que comprendió las instrucciones, se hace una serie de 2-2-2. El examinador realiza la siguiente serie: 1-1-2-1-2-2-2-1-1-2.
Puntaje: sin errores = 3; 1 o 2 errores = 2; más de 2 errores = 1; si golpea igual que el examinador al menos 4 veces consecutivas = 0 ___/ **3**

**5. Go no Go (Control inhibitorio)**
*"Cuando yo golpeo 1 vez, debe golpear 1 vez";* para asegurar que comprendió la instrucción, se hace una serie de 3 ensayos: 1-1-1. *"Cuando yo golpeo 2 veces, no debe golpear";* para asegurar que comprendió la instrucción, se hace una serie de 3 ensayos: 2-2-2. El examinador realiza la siguiente serie: 1-1-2-1-2-2-2-1-1-2.
Puntaje: sin errores = 3; 1 o 2 errores = 2; más de 2 errores = 1; golpea igual que el examinador al menos 4 veces seguidas = 0 ___/ **3**

**6. Conducta de prehensión (Autonomía del ambiente)**
El examinador se sienta frente al paciente, que tiene las manos sobre sus rodillas, con las palmas hacia arriba. El examinador acerca lentamente sus manos hasta tocar las del paciente para ver si se las toma espontáneamente. Si lo hace, dice *"ahora, no me tome las manos"* y vuelve a tocárselas.
Puntaje: no le toma las manos = 3; duda o pregunta qué tiene que hacer = 2; las tomas sin vacilar = 1; las toma aún después de decirle que no lo haga = 0 ___/ **3**

**Puntuación total: ___/ 18**

INFORMADOR: Família o professional

## EVALUACIÓN ACTIVIDAD FÍSICA

### HÁBITOS DE ACTIVIDAD FÍSICA Y DEPORTE

Por favor, lee las siguientes preguntas y contesta con una sola opción. En el caso de que la persona practique más de un deporte, escoge la respuesta que consideres que representa más la práctica de actividad física de la persona.

1. La persona con discapacidad intelectual, ¿realiza algún tipo de actividad física o deporte?

- ○ Sí
- ○ No

→ Si has contestado **Sí**, puedes continuar con la pregunta **2**.

→ Sólo si has contestado **No** responde a la siguiente pregunta y ya puedes abandonar el cuestionario. Muchas gracias por tu colaboración.

1.1. ¿Tiene algún problema de salud o de movilidad que le impida realizar actividad física o practicar algún deporte? (marca sólo una cruz)

- ○ No tiene ningún problema de salud ni de movilidad
- ○ Sí, y no puede realizar ningún tipo de actividad física ni deporte
- ○ No lo sé, no tengo constancia de ello

2. En general, ¿con qué intensidad realiza la actividad física?

- ○ Realiza actividad física ligera (como pasear o jugar al golf)
- ○ Realiza actividad física moderada (bailar o levantar pesas)
- ○ Realiza actividad física vigorosa (como correr o jugar a squash)

3. Habitualmente, ¿cómo practica la actividad física? (marca sólo una cruz)

- ○ Por su cuenta
- ○ Como actividad organizada dentro del horario del centro (CET, CO)
- ○ Como actividad organizada desde el servicio (CET, CO, ocio) pero realizada por profesionales externos y fuera del horario del centro laboral
- ○ Como actividades que comparte con la familia
- ○ Otros

4. ¿Dónde practica generalmente la actividad física o el deporte? (marca sólo una cruz)

- ○ En instalaciones deportivas públicas
- ○ En las instalaciones de un club o gimnasio privado
- ○ En las instalaciones del servicio donde pertenece (CET, CO)
- ○ Depende del deporte, en instalaciones de la comunidad o en el centro (CET, CO)
- ○ En su casa
- ○ En espacios públicos al aire libre (parque, calle, etc.)
- ○ Otros

5. ¿Cuánto tiempo hace que realiza actividad física o practica algún tipo de deporte? (marca sólo una cruz)

- ○ Hace más de 3 años
- ○ Entre 1 y 3 años
- ○ Hace menos de 1 año

6. ¿En qué época del año realiza más actividad física? (marca sólo una cruz)

- ○ Durante todo el año
- ○ Durante todo el año (excepto el mes de verano y vacaciones que no asiste al centro)
- ○ Sólo en verano
- ○ Otros períodos (otoño, invierno)

7. ¿Cuándo realiza más actividad o practica algún deporte? (marca sólo una cruz)

- ○ Entre semana
- ○ Fines de semana
- ○ Toda la semana

8. En general, ¿con qué frecuencia realiza actividad física? (marca sólo una cruz)

- ○ Tres veces o más por semana
- ○ Una o dos veces por semana
- ○ Una o dos veces al mes

9. El día que practica algún deporte o realiza algún tipo de actividad física, ¿cuánto tiempo le dedica? (marca sólo una cruz)

- ○ Menos de 30 minutos
- ○ Entre media hora y una hora
- ○ Más de una hora

10. Habitualmente, ¿con quién practica actividad física o deporte? (marca sólo una cruz)

- ○ Sólo, la mayoría de las veces
- ○ Con compañeros del centro donde trabaja (CET, CO, etc.)
- ○ Con amigos
- ○ Con algún miembro de la familia
- ○ Depende, a veces solo y a veces en grupo

11. ¿Ha hablado con su médico de la importancia de la práctica de actividad física para mejorar su salud? (marca sólo una cruz)

- ○ Sí, y lo tiene presente en el día a día
- ○ Sí, porque me han pasado la información, pero no lo tiene presente
- ○ No ha hablado de este tema con su médico
- ○ No lo sé, no tengo constancia de ello

INFORMADOR: Família o professional

## EVALUACIÓN CALIDAD DE VIDA

### Dimensión: desarrollo personal

El apartado de desarrollo personal se centra en la educación del individuo (incluyendo aprendizajes a lo largo de la vida) y sus competencias personales (incluyendo habilidades de aprendizaje y su ejecución). Antes de completar cada ítem de observación directa, se debería recopilar información sobre el individuo en relación con el desarrollo personal, intentando responder a las siguientes preguntas:

| **Parámetros objetivos** | |
|---|---|
| *1. ¿La persona está siguiendo algún curso o programa educativo en estos momentos?*<br>*2. ¿Lee algún periódico o revista?*<br>*3. ¿Va a la biblioteca?*<br>*4. ¿Tiene ordenador o sabe cómo utilizar uno?* | |

**Observación directa**

1. ¿Cómo valora el grado de realización de la persona en las siguientes actividades diarias: alimentarse, acostarse y levantarse de la cama, ir al baño, vestirse?

   Generalmente independiente | Con ayuda | No puede por sí solo

2. ¿Cómo valora el grado de realización de la persona en las siguientes actividades instrumentales diarias: cocinar, realizar las tareas del hogar, moverse con independencia, tomarse la medicación?

   Generalmente solo | Con ayuda | No puede por sí solo

3. ¿Cuántos tipos de habilidades ha adquirido la persona o cuántos programas educativos ha seguido en los últimos 6-12 meses?

   Muchos | Algunos | Pocos, si hay

4. ¿Con qué frecuencia ejerce las habilidades adquiridas (por ejemplo: en el trabajo, en la escuela, en casa)?

   A menudo | A veces | Raramente o nunca

5. ¿Qué grado de acceso tiene a información que le interese a través de, por ejemplo, periódicos, revistas, Internet, bibliotecas?

   Total | Limitado | Restringido o inexistente

6. ¿Con qué frecuencia utiliza tecnología de ayuda?

   A menudo | A veces | Raramente o nunca

**Dimensión: autodeterminación**

El apartado de autodeterminación incluye el autocontrol, las metas y objetivos personales, la capacidad de tomar decisiones y de elegir. Antes de completar cada elemento de observación directa, se debería recopilar información sobre la persona en relación con la autodeterminación, intentando responder a las siguientes preguntas:

**Parámetros objetivos**

*1. ¿La persona sueña con tener una carrera profesional (qué trabajo quiere tener en el futuro)?*
*2. ¿La persona tiene ideas concretas sobre algún trabajo?*
*3. ¿Qué debe cambiar para poder tener el trabajo soñado?*
*4. ¿Qué puede hacer para conseguirlo?*
*5. ¿La persona tiene planes de futuro?*
*6. ¿La persona cuenta con un presupuesto?*
*7. ¿Puede decidir por sí mismo/a cómo gastar ese presupuesto?*

**Observación directa**

1. ¿Hasta qué punto la persona controla cómo vestir, qué comer, dónde ir, etc.?

| Bastante | Un poco | Poco o nada |
|---|---|---|

2. Cuando se le ofrece la posibilidad de elegir, ¿la aprovecha?

| A menudo | A veces | Raramente o nunca |
|---|---|---|

3. ¿Hasta qué punto toma decisiones que son importantes para él/ella, aunque su opinión difiera de la de los demás?

| Con normalidad | Hasta cierto punto | Raramente o nunca |
|---|---|---|

4. ¿Hasta qué punto se respetan las decisiones que toma (independientemente de la decisión que sea)?

| Se aceptan y se respetan en gran medida | Se respetan hasta cierto punto | No se respetan |
|---|---|---|

5. ¿Hasta qué punto controla, al menos, una parte de su dinero?

| Control considerable | Cierto control | Ningún control |
|---|---|---|

6. ¿Hasta qué punto la persona tiene la oportunidad de expresar lo que quiere?

| Siempre | A veces | Raramente o nunca |
|---|---|---|

**Dimensión: relaciones interpersonales**

| |
|---|
| El apartado de relaciones interpersonales se centra en la familia, los amigos, el entorno social y el apoyo que la persona recibe de los demás. Antes de completar cada elemento de observación directa, se debería recopilar información sobre la persona en relación con las relaciones interpersonales, intentando responder a las siguientes preguntas: |

| **Parámetros objetivos** | |
|---|---|
| *1. ¿La persona tiene uno o más amigos con quién pasa el tiempo?*<br>*2. ¿La persona realiza algún tipo de actividad con uno o más amigos?*<br>*3. ¿La persona interactúa con los miembros de su familia?* | |

**Observación directa**

| | | | |
|---|---|---|---|
| 1. | ¿La persona tiene amigos conocidos con quienes mantiene un contacto regular y se refiere a ellos como tales? | | |
| | Sí | Más o menos | No |
| 2. | ¿Con qué frecuencia participa en actividades sociales, como recibir visitas de amigos, invitarlos a comer a casa o ir a fiestas o bailes? | | |
| | A menudo | A veces | Nunca |
| 3 | ¿Con qué frecuencia la persona interactúa con la familia o va a visitarla? | | |
| | A menudo | A veces | Nunca |
| 4. | ¿Con qué frecuencia interactúa con los amigos o va a visitarlos? | | |
| | A menudo | A veces | Nunca |
| 5. | ¿La familia lo trata con dignidad y respeto incondicionales, o le demuestra que es importante para ellos de cualquier otro modo? | | |
| | Por supuesto | Puede que sí | No |
| 6. | ¿La persona cuenta con un entorno social al que puede recurrir si necesita ayuda, respuestas o apoyo? | | |
| | Un entorno fuerte | Un entorno moderado | Ningún entorno |

**Dimensión: inclusión social**

| |
|---|
| El apartado de inclusión social se centra en la integración y la participación, los roles comunitarios y el apoyo social que recibe la persona. Antes de completar cada elemento de observación directa, se debería recopilar información sobre la persona en relación con la inclusión social, intentando responder a las siguientes preguntas: |

| | |
|---|---|
| **<u>Parámetros objetivos</u>**<br><br>*1. ¿Cuántos vecinos de la zona conocen a la persona por su nombre, y viceversa?*<br>*2. ¿Cuántos servicios de la comunidad ha utilizado en el último mes (bares, tiendas, peluquerías, pubs, bancos, cines, centros de culto religioso, autobuses públicos, salas de conciertos, instalaciones deportivas)?*<br>*3. ¿Qué ROLES diferenciados lleva a cabo la persona en su entorno?*<br>*4. ¿Cuál es su nivel de participación en la comunidad?* | |

**Observación directa**

| | | | |
|---|---|---|---|
| 1. | ¿Con qué frecuencia interactúa la persona con sus vecinos? | | |
| | A menudo | A veces | Raramente o nunca |

| | | | |
|---|---|---|---|
| 2. | ¿A cuántos vecinos de la zona conoce por su nombre? | | |
| | Muchos (5+) | Algunos (2-4) | Pocos (0-1) |

| | | | |
|---|---|---|---|
| 3. | ¿Utiliza servicios de la zona donde vive (cafeterías, tiendas, peluquerías, pubs, bancos, cines, lugares de culto religioso, autobuses públicos, salas de conciertos, instalaciones deportivas)? | | |
| | A menudo (a diario) | A veces (1 o 2 veces por semana) | Nunca |

| | | | |
|---|---|---|---|
| 4. | ¿Se ofrece voluntario para ayudar a otros miembros de la comunidad? | | |
| | A menudo | A veces | Raramente o nunca |

| | | | |
|---|---|---|---|
| 5. | ¿Con qué frecuencia la gente de la comunidad visita a la persona o la lleva a sitios? | | |
| | A menudo | A veces | Raramente o nunca |

| | | | |
|---|---|---|---|
| 6. | ¿Con qué frecuencia participa la persona en actividades de la comunidad? | | |
| | A menudo | A veces | Nunca |

**Dimensión: derechos**

| |
|---|
| El apartado de derechos se centra tanto en los derechos humanos (respeto, dignidad, igualdad) como en los derechos legales (ciudadanía, accesibilidad y trato justo). Antes de completar cada elemento de observación directa, se debería recopilar información sobre la persona en relación con los derechos, intentando responder a las siguientes preguntas: |

| **Parámetros objetivos** | |
|---|---|
| 1. *¿La persona va a votar?*<br>2. *¿Vive dónde y con quien él/ella ha elegido?*<br>3. *¿Tiene pareja?*<br>4. *¿Tiene permiso para pasar tanto tiempo como quiera con su pareja?* | |

**Observación directa**

| | | | |
|---|---|---|---|
| 1. | ¿La persona tiene una habitación o un espacio para su intimidad? | | |
| | Por supuesto | Puede que sí, aunque depende | No |
| 2. | ¿La persona dispone de llaves de su casa/piso? | | |
| | Sí, y las lleva siempre | Sí, pero con control parcial | No |
| 3. | ¿Podría tener un animal de compañía si quisiera? | | |
| | Por supuesto | Puede que sí, aunque depende | Nunca |
| 4. | ¿Podría tener pareja sentimental si quisiera? | | |
| | Sí | Puede, pero depende | No |
| 5. | ¿La persona y su pareja pueden estar juntos todo el tiempo que quieran?<br>Si no tiene pareja, puntuar: Sí | | |
| | Sí | Puede, pero depende | No |
| 6. | ¿Cuántas veces la persona ha ido a votar en los últimos años? | | |
| | Siempre o casi siempre | Alguna vez | Nunca |

**Dimensión: bienestar emocional**

| |
|---|
| El apartado de bienestar emocional se centra en la satisfacción, el concepto que se tiene sobre uno mismo y el grado de ausencia de estrés en la vida. Antes de completar cada elemento de observación directa, se debería recopilar información sobre la persona en relación con el bienestar emocional, intentando responder a las siguientes preguntas: |

| | |
|---|---|
| **Parámetros objetivos**<br><br>*1. ¿Qué expresiones utiliza para comunicar sus sentimientos?*<br>*2. ¿Hay elementos de peligro en el entorno donde pasa la mayor parte de su tiempo?*<br>*3. ¿Le/la molestan o se burlan de él/ella las personas de su entorno? ¿La incordian alguna vez por la calle o en el transporte público?*<br>*4. ¿Está inquieta o tiene preocupaciones serias sobre algún asunto en concreto? ¿Cuál?*<br>*5. ¿Cuán estable y predecible es su entorno?* | |

**Observación directa**

| | | | |
|---|---|---|---|
| 1. | ¿Cómo valora usted el grado de seguridad en el entorno diario de la persona? | | |
| | Muy seguro | Más o menos seguro | Nada seguro |
| 2. | ¿Con qué frecuencia vive la persona experiencias de éxito, como ganar en un juego, completar una actividad deseada y/o que le reconozcan su éxito? | | |
| | A menudo | A veces | Nunca |
| 3. | ¿Con qué frecuencia la persona expresa cariño o afecto hacia los demás? | | |
| | A menudo | A veces | Nunca |
| 4. | ¿Cuántas veces ha visto a la persona mostrando signos de felicidad (ej. con una sonrisa, riéndose)? | | |
| | A menudo | A veces | Nunca |
| 5. | ¿Cuántas veces expresa satisfacción a través de comentarios, gestos o expresiones faciales? (Esto significa que no está inquieto ni tiene preocupaciones serias sobre algún asunto en concreto.) | | |
| | A menudo | A veces | Nunca |
| 6. | ¿La persona confía en los demás, comparte sus sentimientos y se siente a gusto cuando está con otras personas? | | |
| | A menudo | A veces | Nunca |

**Dimensión: bienestar físico**

| |
|---|
| El apartado de bienestar físico se centra en la salud y la asistencia sanitaria de la persona, su nutrición, las habilidades de cuidado personal, movilidad y tiempo libre o de ocio. Antes de completar cada elemento de observación directa, se debería recopilar información sobre la persona en relación con el bienestar físico, intentando responder a las siguientes preguntas: |

| | |
|---|---|
| **<u>Parámetros objetivos</u>**<br><br>*1. ¿Cuál es su estado de salud y nutricional?*<br>*2. ¿En qué deportes o actividades de ocio participa la persona y con qué frecuencia?* | |

**Observación directa**

| | | | |
|---|---|---|---|
| 1. | ¿Cómo valoraría la salud de la persona en general? | | |
| | Muy buena | Aceptable | Pobre |

| | | | |
|---|---|---|---|
| 2. | ¿Con qué frecuencia practica algún deporte o participa en alguna actividad de ocio? | | |
| | A menudo | A veces | Raramente o nunca |

| | | | |
|---|---|---|---|
| 3. | ¿Con qué frecuencia la persona suele descansar bien y relajarse? | | |
| | A menudo | A veces | Raramente o nunca |

| | | | |
|---|---|---|---|
| 4. | ¿Cómo valoraría su estado nutricional? | | |
| | Bueno | Aceptable | Pobre |

| | | | |
|---|---|---|---|
| 5. | ¿Con qué frecuencia le preocupa la posibilidad de hacerse daño o sentir dolor? | | |
| | Raramente | A veces | A menudo |

| | | | |
|---|---|---|---|
| 6. | ¿Cómo valoraría el estado de la persona al despertarse y levantarse de la cama? | | |
| | Bien descansado | Un poco cansado | Cansado |

**Dimensión: bienestar material**

| |
|---|
| El apartado de bienestar material se centra en la situación financiera y laboral de la persona, sus planes de vida y sus pertenencias personales. Antes de completar cada elemento de observación directa, se debería recopilar información sobre la persona en relación con el bienestar material, intentando responder a las preguntas siguientes: |

| | |
|---|---|
| **<u>Parámetros objetivos</u>**<br><br>*1. ¿Cuánto dinero mensual ingresa la persona?*<br>*2. ¿Tiene objetos personales que él/ella considera importantes?*<br>*3. ¿Tiene un trabajo remunerado?*<br>*4. ¿Hay algún objeto o artículo que no se haya podido permitir en el último año debido a problemas financieros?* | |

**Observación directa**

| | | | |
|---|---|---|---|
| 1. | ¿La persona tiene suficientes ingresos disponibles para comprar lo que realmente <u>necesita</u>? | | |
| | Siempre | A veces | Nunca |

| | | | |
|---|---|---|---|
| 2. | ¿La persona tiene alguna cuenta de ahorro personal o alguna otra fuente de ahorros de la que pueda disponer? | | |
| | Siempre | A veces | Nunca |

| | | | |
|---|---|---|---|
| 3. | ¿Tiene pertenencias personales que considere importantes (radio, televisor, equipo de música, cuadros)? | | |
| | Suficientes | Algunas | Pocas o ninguna |

| | | | |
|---|---|---|---|
| 4. | ¿La persona tiene un trabajo remunerado? | | |
| | Con regularidad | Esporádicamente | Raramente o nunca |

| | | | |
|---|---|---|---|
| 5. | ¿La persona tiene la llave de su casa? | | |
| | Siempre | A veces | Nunca |

| | | | |
|---|---|---|---|
| 6. | ¿Tiene suficiente dinero para poder elegir lo que <u>quiere</u> (p. ej. cómo vestir o qué comprar)? | | |
| | Siempre | A veces | Nunca |

INFORMADOR: Família o professional

## 2. CUESTIONARIO DE ADHERENCIA A LA DIETA MEDITERRÁNEA ENKID

Para el tutor/a:

Este cuestionario consta de un total de 16 preguntas/afirmaciones. Escriba en la columna "Puntos participante" el mismo número i signo que aparece en la columna "Puntos referencia" (+1 o -1) en caso de que la pregunta/afirmación sea correcta. Importante: sólo en el caso que la afirmación sea cierta se obtendrá la puntuación de la columna "Puntos referencia").

| Adherencia a la DIETA MEDITERRANEA en la infancia | | |
|---|---|---|
| | Puntos referencia | Puntos participante |
| Toma una fruta o un zumo natural todos los días. | +1 | |
| Toma una 2ª pieza de fruta todos los días. | +1 | |
| Toma verduras frescas (ensalada) o cocinadas regularmente una vez al día. | +1 | |
| Toma verduras frescas (ensalada) o cocinadas de forma regular más de una vez al día. | +1 | |
| Consume pescado con regularidad (por lo menos 2-3 veces a la semana). | +1 | |
| Acude una vez o más a la semana a un centro de comida rápida (fast food) tipo hamburguesería. | -1 | |
| Le gustan las legumbres y las toma más de 1 vez a la semana. | +1 | |
| Toma pasta o arroz casi a diario (5 días o más a la semana) | +1 | |
| Desayuna un cereal o derivado (pan, etc.) | +1 | |
| Toma frutos secos con regularidad (al menos 2-3 veces a la semana). | +1 | |
| Se utiliza aceite de oliva en casa. | +1 | |
| No desayuna | -1 | |
| Desayuna un lácteo (yogurt, leche, etc.) | +1 | |
| Desayuna bollería industrial, galletas o pastelitos. | -1 | |
| Toma 2 yogures y/o 40 g queso cada día | +1 | |
| Toma golosinas y/o caramelos varias veces al día | -1 | |

**Para el investigador:**

El total de puntuación que obtenga en la columna “Puntos participante” se sumará para calcular el valor del índice KIDMED.

Para la posterior valoración del cuestionario KIDMED:

Valor del índice KIDMED

≤ 3: Dieta de muy baja calidad

4 a 7: Necesidad de mejorar el patrón alimentario para ajustarlo al modelo mediterráneo

≥8: Dieta mediterránea óptima

**RESONÁNCIA FUNCIONAL**

T1 volumétrico

T2

Flair

Resting 6 minutos

# EVALUACIÓN ACTIVIDAD FÍSICA

Variables de capacidad aeróbica

Variables de salud vascular

Variables de antropometría

Variables de equilibrio

Variables de fuerza

## Appendices 2: Changes for the protocol of control participants

The consent, the sociodemographical information as well as the questionnaire used for evaluate quality of life are the unique changes for the protocols of control participants compared with the ones of DS participants. Therefore, they will be here shown instead of using both protocols. However, for control participants, all the information was acquired directly from them.

## EVALUACIÓN DE CRITERIOS DE INCLUSIÓN E EXCLUSIÓN

☐ Edad entre 16 y 35 años

### CRITERIOS DE EXCLUSIÓN

☐ Diagnósticos que alteren la función cognitiva

☐ Presencia de medicación que afecte a funciones cognitivas

☐ No aceptación de consentimiento informado

**CONSENTIMIENTO INFORMADO**

**(participantes menores de edad)**

El/La Sr./Sra.....,

con DNI nº....., como padre/madre o tutor/a legal

de.....
.....

HAGO CONSTAR:

Que he sido invitado a participar en la investigación "**CONECTIVIDAD CEREBRAL PARA LA ESTIMACIÓN DEL EFECTO DE LA ACTIVIDAD FÍSICA Y DE LA DIETA EN LA MEJORA DEL RENDIMIENTO COGNITIVO EN ADOLESCENTES CON SINDROMES DE DOWN PARA LA MEJORA DE SU RESERVA COGNITIVA Y PREVENCIÓN DE DEMENCIAS PRESENILES**" que dirige el Dr. Joan Guàrdia Olmos de la Universitat de Barcelona.

Se me ha comunicado que el director del proyecto se compromete a utilizar mis opiniones, así como mis datos exclusivamente para este estudio y se guardaran de forma confidencial.

**Autorizo** la comunicación de los resultados y conclusiones de la investigación preservando el anonimato que he confiado al investigador[2].

**Tengo el derecho** de decidir que mi hijo/a o persona que tutelo abandone el estudio en el momento en que lo desee sin ningún perjuicio.

Dado que la información me ha sido expuesta de forma comprensible y que he podido formular preguntas para resolver dudas, **doy libremente mi conformidad** para participar en esta investigación y lo autorizo explícitamente en este documento.

Lugar y fecha:

Firma del director del proyecto

Firma del/la participante

Firma del padre/madre o tutor/a legal

UNIVERSITAT DE BARCELONA

[2] De acuerdo con la Ley Orgánica de Protección de Datos de Carácter Personal 15/1999 del 13 de diciembre.

Proyecto aprovado por el Comité Ético de la Universidad de Barcelona, el 16 de marzo del 2017

**CONSENTIMIENTO INFORMADO**

**(participantes mayores de edad)**

El/La Sr./Sra.....,

con DNI nº.....,

HAGO CONSTAR:

Que he sido invitado a participar en la investigación "**CONECTIVIDAD CEREBRAL PARA LA ESTIMACIÓN DEL EFECTO DE LA ACTIVIDAD FÍSICA Y DE LA DIETA EN LA MEJORA DEL RENDIMIENTO COGNITIVO EN ADOLESCENTES CON SINDROMES DE DOWN PARA LA MEJORA DE SU RESERVA COGNITIVA Y PREVENCIÓN DE DEMENCIAS PRESENILES**" que dirige el Dr. Joan Guàrdia Olmos de la Universitat de Barcelona.

Se me ha comunicado que el director del proyecto se compromete a utilizar mis opiniones, así como mis datos exclusivamente para este estudio y se guardaran de forma confidencial.

**Autorizo** la comunicación de los resultados y conclusiones de la investigación preservando el anonimato que he confiado al investigador[3].

**Tengo el derecho** de decidir en abandonar el estudio en el momento en que lo desee sin ningún perjuicio.

Dado que la información me ha sido expuesta de forma comprensible y que he podido formular preguntas para resolver dudas, **doy libremente mi conformidad** para participar en esta investigación y lo autorizo explícitamente en este documento.

Lugar y fecha:

Firma del/la participante Firma del director del proyecto

UNIVERSITAT DE BARCELONA

[3] De acuerdo con la Ley Orgánica de Protección de Datos de Carácter Personal 15/1999 del 13 de diciembre.

Proyecto aprovado por el Comité Ético de la Universidad de Barcelona, el 16 de marzo del 2017

**Fecha administración:**

**CUESTIONARIO SOCIODEMOGRÁFICO**

**Identificación (nombre/código):**

**Fecha de nacimiento:** **Edad actual:**

**Género:**

☐ Hombre ☐ Diestro

☐ Mujer ☐ Zurdo

**Lugar de residencia (por favor, marque sólo una casilla según el número de habitantes):**

☐ Rural (menos de 5.000 hab. aprox.)

☐ Semi-urbano (entre 5.000 y 50.000 hab. aprox.)

☐ Urbano (más de 50.000 hab. aprox.)

**Estado civil (por favor, marque sólo una respuesta):**

☐ Soltero/a ☐ Divorciado/a, separado/a

☐ … Casado/a, pareja de hecho ☐ Otros

☐ Viudo/a

**Nivel educativo (por favor, señale sólo una opción):**

☐ Sin estudios ☐ Estudiante Título Universitario

☐ Estudios de primaria …… ☐ … Título Universitario finalizado

☐ Estudios de Secundaria ….. ☐ ….. Título Universitario Superior (máster, doctorado)

**Hora** **administración:**

## ESCALA DE CALIDAD DE VIDA

## WHOQOL-BREF

**Instrucciones:** Este cuestionario sirve para conocer su opinión acerca de su calidad de vida, su salud y otras áreas de su vida. Por favor conteste todas las preguntas. Si no está seguro/a de qué respuesta dar a una pregunta, escoja la que le parezca más apropiada. A veces, ésta puede ser la primera respuesta que le viene a la cabeza.

Tenga presente su modo de vivir, expectativas, placeres y preocupaciones. Le pedimos que piense en su vida ***durante las dos últimas semanas***. Por ejemplo, pensando en las dos últimas semanas, se puede preguntar:

| | | Nada | Un poco | Moderado | Bastante | Totalmente |
|---|---|---|---|---|---|---|
| | ¿Obtiene de otras personas el apoyo que necesita? | 1 | 2 | 3 | 4 | 5 |

Rodee con un círculo el número que mejor defina cuánto apoyo obtuvo de otras personas en las dos últimas semanas. Si piensa que obtuvo bastante apoyo de otras personas, usted debería señalar con un círculo el número 4, quedando la respuesta de la siguiente forma:

| | | Nada | Un poco | Moderado | Bastante | Totalmente |
|---|---|---|---|---|---|---|
| | ¿Obtiene de otras personas el apoyo que necesita? | 1 | 2 | 3 | (4) | 5 |

Recuerde que cualquier número es válido, lo importante es que represente su opinión

Por favor, lea la pregunta, valore sus sentimientos y haga un círculo en el número de la escala que represente mejor su opción de respuesta.

| | | Muy mala | Regular | Normal | Bastante buena | Muy buena |
|---|---|---|---|---|---|---|
| 1 | ¿Cómo calificaría su calidad de vida? | 1 | 2 | 3 | 4 | 5 |

| | | Muy insatisfecho/a | Un poco insatisfecho/a | Lo normal | Bastante satisfecho/a | Muy satisfecho/a |
|---|---|---|---|---|---|---|
| 2 | ¿Cómo de satisfecho/a está con su salud? | 1 | 2 | 3 | 4 | 5 |

Las siguientes preguntas hacen referencia al grado en que ha experimentado ciertos hechos en las dos últimas semanas.

| | | Nada | Un poco | Lo normal | Bastante | Extremadamente |
|---|---|---|---|---|---|---|
| 3 | ¿Hasta qué punto piensa que el dolor (físico) le impide hacer lo que necesita? | 1 | 2 | 3 | 4 | 5 |
| 4 | ¿En qué grado necesita de un tratamiento médico para funcionar en su vida diaria? | 1 | 2 | 3 | 4 | 5 |
| 5 | ¿Cuánto disfruta de la vida? | 1 | 2 | 3 | 4 | 5 |
| 6 | ¿Hasta qué punto siente que su vida tiene sentido? | 1 | 2 | 3 | 4 | 5 |
| 7 | ¿Cuál es su capacidad de concentración? | 1 | 2 | 3 | 4 | 5 |
| 8 | ¿Cuánta seguridad siente en su vida diaria? | 1 | 2 | 3 | 4 | 5 |
| 9 | ¿Cómo de saludable es el ambiente físico a su alrededor? | 1 | 2 | 3 | 4 | 5 |

Las siguientes preguntas hacen referencia a si usted experimenta o fue capaz de hacer ciertas cosas en las dos últimas semanas, y en qué medida.

| | | Nada | Un poco | Lo normal | Bastante | Totalmente |
|---|---|---|---|---|---|---|
| 10 | ¿Tiene energía suficiente para la vida diaria? | 1 | 2 | 3 | 4 | 5 |
| 11 | ¿Es capaz de aceptar su apariencia física? | 1 | 2 | 3 | 4 | 5 |
| 12 | ¿Tiene suficiente dinero para cubrir sus necesidades? | 1 | 2 | 3 | 4 | 5 |
| 13 | ¿Dispone de la información que necesita para su vida diaria? | 1 | 2 | 3 | 4 | 5 |
| 14 | ¿Hasta qué punto tiene oportunidad de realizar actividades de ocio? | 1 | 2 | 3 | 4 | 5 |
| 15 | ¿Es capaz de desplazarse de un lugar a otro? | 1 | 2 | 3 | 4 | 5 |

SIGA EN LA PÁGINA SIGUIENTE

Las siguientes preguntas hacen referencia a si en las dos últimas semanas ha sentido satisfecho/a y cuánto, en varios aspectos de su vida

| | | Muy insatisfecho/a | Poco | Lo normal | Bastante satisfecho/a | Muy satisfecho/a |
|---|---|---|---|---|---|---|
| 16 | ¿Cómo de satisfecho/a está con su sueño? | 1 | 2 | 3 | 4 | 5 |
| 17 | ¿Cómo de satisfecho/a está con su habilidad para realizar sus actividades de la vida diaria? | 1 | 2 | 3 | 4 | 5 |
| 18 | ¿Cómo de satisfecho/a está con su capacidad de trabajo? | 1 | 2 | 3 | 4 | 5 |
| 19 | ¿Cómo de satisfecho/a está de sí mismo? | 1 | 2 | 3 | 4 | 5 |
| 20 | ¿Cómo de satisfecho/a está con sus relaciones personales? | 1 | 2 | 3 | 4 | 5 |
| 21 | ¿Cómo de satisfecho/a está con su vida sexual? | 1 | 2 | 3 | 4 | 5 |
| 22 | ¿Cómo de satisfecho/a está con el apoyo que obtiene de sus amigos/as? | 1 | 2 | 3 | 4 | 5 |
| 23 | ¿Cómo de satisfecho/a está de las condiciones del lugar donde vive? | 1 | 2 | 3 | 4 | 5 |
| 24 | ¿Cómo de satisfecho/a está con el acceso que tiene a los servicios sanitarios? | 1 | 2 | 3 | 4 | 5 |
| 25 | ¿Cómo de satisfecho/a está con los servicios de transporte de su zona? | 1 | 2 | 3 | 4 | 5 |

SIGA EN LA PÁGINA SIGUIENTE

La siguiente pregunta hace referencia a la frecuencia con que usted ha sentido o experimentado ciertos sentimientos en las dos últimas semanas.

| | | Nunca | Raramente | Moderadamente | Frecuentemente | Siempre |
|---|---|---|---|---|---|---|
| 26 | ¿Con qué frecuencia tiene sentimientos negativos, tales como tristeza, desesperanza, ansiedad, o depresión? | 1 | 2 | 3 | 4 | 5 |

¿Le ha ayudado alguien a rellenar el cuestionario?

¿Cuánto tiempo ha tardado en contestarlo?

¿Le gustaría hacer algún comentario sobre el cuestionario?