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A longitudinal study of brain anatomy changes preceding dementia in Down syndrome

Jesus Pujol[a,b,*], Raquel Fenoll[a], Núria Ribas-Vidal[c], Gerard Martínez-Vilavella[a], Laura Blanco-Hinojo[a,b], Javier García-Alba[d], Joan Deus[a,e], Ramón Novell[c], Susanna Esteba-Castillo[c]

[a] MRI Research Unit, Department of Radiology, Hospital del Mar, 08003 Barcelona, Spain
[b] Centro Investigación Biomédica en Red de Salud Mental, CIBERSAM G21, 08003 Barcelona, Spain
[c] Specialized Service in Mental Health and Intellectual Disability, Institut Assistència Sanitària (IAS), Parc Hospitalari Martí i Julià, 17190 Girona, Spain.
[d] Adults with Down Syndrome Department, Hospital Universitario de La Princesa, 28006 Madrid, Spain.
[e] Department of Clinical and Health Psychology, Autonomous University of Barcelona, 08193 Barcelona, Spain

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ABSTRACT

Background: We longitudinally assessed Down syndrome individuals at the age of risk of developing dementia to measure changes in brain anatomy and their relationship to cognitive impairment progression.
Methods: Forty-two Down syndrome individuals were initially included, of whom 27 (mean age 46.8 years) were evaluable on the basis of completing the 2-year follow-up and success in obtaining good quality MRI exams. Voxel-based morphometry was used to estimate regional brain volumes at baseline and follow-up on 3D anatomical images. Longitudinal volume changes for the group and their relationship with change in general cognitive status and specific cognitive domains were mapped.
Results: As a group, significant volume reduction was identified in the substantia innominata region of the basal forebrain, hippocampus, lateral temporal cortex and left arcuate fasciculus. Volume reduction in the substantia innominata and hippocampus was more prominent in individuals whose clinical status changed from cognitively stable to mild cognitive impairment or dementia during the follow-up. Relevantly, longitudinal memory score change was specifically associated with volume change in the hippocampus, prospective memory with prefrontal lobe and verbal comprehension with language-related brain areas.
Conclusions: Results are notably concordant with the well-established anatomical changes signaling the progression to dementia in Alzheimer's disease, despite the dense baseline pathology that developmentally accumulates in Down syndrome. This commonality supports the potential value of Down syndrome as a genetic model of Alzheimer's neurodegeneration and may serve to further support the view that Down syndrome patients are best candidates to benefit from treatment research in Alzheimer's disease.

1. Introduction

Down syndrome (DS) or chromosome 21 trisomy is the most common genetic cause of intellectual disability (Ballard et al., 2016). In addition to interference with brain development, aging is also disturbed in DS with an early presence of neurodegenerative changes (in virtually all DS individuals aged 40 or over) and clinical dementia in up to 70% of cases by the age of 60 (Dekker et al., 2015; Wiseman et al., 2015). The brain in older DS individuals displays many of the neuropathological features found in Alzheimer's disease (Head et al., 2016). This commonality is of capital importance in the research context, as it indicates a direct link between a genetic anomaly and neurodegeneration that may potentially contribute to elucidating the pathogenesis of Alzheimer's disease (Wiseman et al., 2015).

Previous neuroimaging research is prominent in indicating that demented DS patients do indeed show brain alterations in systems with typical degeneration in Alzheimer's disease (Emerson et al., 1995; Teipel and Hampel, 2006; RJ1 et al., 2008; Beacher et al., 2009; Powell et al., 2014; Sabbagh et al., 2015; Rafii et al., 2015; Lin et al., 2016). Nevertheless, existing cross-sectional studies are still not conclusive in distinguishing baseline DS dense brain pathology established during brain development from ongoing degenerative changes when progressing towards dementia. We present a longitudinal study on DS patients at the age of risk to developing dementia aimed to measure changes in

* Corresponding author at: MRI Department, Hospital del Mar, Passeig Marítim 25-29, 08003 Barcelona, Spain.
E-mail address: 21404jpn@comb.cat (J. Pujol).

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Table 1
Characteristics of study participants and cognitive testing.

	Primary sample (n = 42)	Final sample (n = 27)
Age (mean, SD years)	46.0 (5.3)	46.8 (5.6)
Gender (male/female)	21/21	12/15
Medical background (%)		
Cardiovascular	28.6%	37.0%
Respiratory	11.9%	11.1%
Metabolic/Endocrine	57.1%	48.1%
Ophthalmological	71.4%	70.4%
Otorhinolaryngological	4.8%	7.4%
Disability levels (%)[DSM-IV-TR]		
Mild	33.3%	29.6%
Moderate	66.7%	70.4%
Severe	0%	0%
Profound	0%	0%
Performance IQ, K-BIT (mean, SD)[a]	59.3 (9.2)	60.7 (9.0)
Knowledge (%)		
Illiterate	33.3%	29.6%
Read/Write	66.7%	70.4%

	Primary sample (n = 42)		Final sample (n = 27)	
Cognitive testing (mean (SD) range)	Baseline	Follow-up	Baseline	Follow-up
Memory-Word List Learning	24.3 (7.7) 8–42	25.8 (8.8) 9–45	25.7 (7.2) 13–42	25.8 (8.5) 9–42
Verbal Comprehension	8.9 (2.4) 2–12	9.2 (2.4) 0–12	9.0 (2.6) 2–12	9.2 (2.0) 3–12
Block Construction	6.2 (2.3) 3–10	5.2 (1.9)* 2–8	6.1 (2.3) 3–10	5.2 (1.9)* 2–8
Object Recognition	3.3 (1.5) 1–6	3.8 (1.3) 2–6	3.2 (1.3) 1–6	3.8 (1.2) 2–6
Prospective Memory	3.0 (1.4) 0–6	2.6 (1.9) 0–6	3.2 (1.4) 0–6	2.7 (1.7) 0–6

SD, standard deviation.
[a] K-BIT, Kaufman Brief Intelligence Test (2nd edition); matrices test.
* Significant score reduction at $p < 0.01$.

brain anatomy and their relationship to cognitive deterioration.

2. Methods

2.1. Participants

Forty-two DS individuals were initially included in the study. Candidates were recruited from the community via parent organizations and were selected on the basis of age (40 years old upwards), DS confirmed by karyotype, capability to understand and follow MRI instructions, and also optimal attitude and willingness (participants and parents) to participate. Individuals with non-stable medical conditions were not considered eligible. Eight participants were excluded due to head motion during baseline MRI, 3 participants were lost in the follow-up period (follow-up cognitive testing was obtained, but they refused to be re-scanned) and 4 more were ruled out due to head motion during follow-up MRI exams. No subject was excluded on the basis of test performance. The final evaluable sample for MRI analysis included 27 DS individuals (15 females, 12 males) with genotype-confirmed trisomy 21 and a mean ± SD age of 46.8 ± 5.6 years, range 40–63 years (Table 1). The included (n = 27) and excluded (n = 15) participant subgroups did not significantly differ in terms of age, sex distribution, performance IQ and study-specific neuropsychological testing.

Our study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the Clinical Research Ethical Committee of the Parc de Salut Mar (Barcelona). Written informed consent was obtained from parents. Verbal or written assent was additionally obtained from Down syndrome individuals.

2.2. Clinical assessment

Each participant underwent comprehensive medical, neurological and psychiatric evaluations and subsequent tailored neuropsychological testing to clinically establish (or rule out) the diagnoses of mild cognitive impairment (MCI) and dementia in terms of cognitive deterioration overlapping with developmental cognitive deficits associated with DS. The diagnosis of MCI and dementia was based on expert clinical judgement as is recommended in DS (Sheehan et al., 2015; Krinsky-McHale and Silverman, 2013; Fenoll et al., 2017). Operatively, a diagnosis of MCI was established on the basis of (i) a report of cognitive impairment by the patient (confirmed by a reliable informant) or by a reliable informant implying a change from previous capacities and (ii) no clinically relevant deterioration in adaptive skills and general cognition. The diagnosis of dementia was established when the patient met MCI criteria (i) and showed a perceptible deterioration in adaptive skills associated with memory impairment and at least one of the following disorders: aphasia, apraxia, agnosia or disturbance in executive functioning. At baseline, 2 DS individuals met MCI criteria and none for dementia.

2.3. Specific neuropsychological testing

To establish the correlation between regional brain volume changes over time and cognitive decline, one neuropsychological test was selected for each major Alzheimer's disease domain: memory impairment, aphasia, apraxia, agnosia and disturbance in executive functioning.

2.3.1. Memory

A version of the Rey Auditory-Verbal Learning Test (Geffen et al., 1990) adapted for people with intellectual disability (Esteba-Castillo et al., 2017) was used. The test measures learning, delayed recall and recognition. Only performance on learning was used. Participants were read a list of 12 words and were asked to evoke as many words as they could remember. The same list was repeated over five trials. Word-list learning over trials was measured as the sum of recalled words in trials 1 to 5.

2.3.2. Verbal comprehension-verbal abstract reasoning

This test combines an adapted version of the conventional “similarities” subtest (4 items) used in many intelligence batteries (participants are given two words or concepts and have to describe how they are similar) with comprehension of verbal sentences (5 items) reflecting different social situations (Esteba-Castillo et al., 2017). Each response was rated as 0 (incorrect), 1 (partial) or 2 (correct) with total maximum score of 18.

2.3.3. 3D block construction

As a measurement of constructional apraxia, we used a variation of the cubes subtest of the Developmental Neuropsychological Assessment-NEPSY battery (Korkman et al., 1998) adapted for people with intellectual disability (Esteba-Castillo et al., 2017). The participants used hand movements to construct 3D block patterns with methacrylate cubes to match a model. A total of 10 models were consecutively presented and 1 point was given for each correct construction (maximum score = 10).

2.3.4. Object recognition

The recognition of objects (unusual views) subtest of the Cambridge Examination for Mental Disorders of Older People with Down's Syndrome and Others with Intellectual Disabilities-CAMDEX-DS (Ball et al., 2006), validated for the Spanish population, was used (Esteba-Castillo et al., 2013). The test involves the recognition of objects (6 items) on images taken from unusual angles. The number of correct