



## Clinical neuroanatomy

# Anomalous brain functional connectivity contributing to poor adaptive behavior in Down syndrome



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## ABSTRACT

Research in Down syndrome has substantially progressed in the understanding of the effect of gene overexpression at the molecular level, but there is a paucity of information on the ultimate consequences on overall brain functional organization. We have assessed the brain functional status in Down syndrome using functional connectivity MRI. Resting-state whole-brain connectivity degree maps were generated in 20 Down syndrome individuals and 20 control subjects to identify sites showing anomalous synchrony with other areas. A subsequent region-of-interest mapping served to detail the anomalies and to assess their potential contribution to poor adaptive behavior. Down syndrome individuals showed higher regional connectivity in a ventral brain system involving the amygdala/anterior temporal region and the ventral aspect of both the anterior cingulate and frontal cortices. By contrast, lower functional connectivity was identified in dorsal executive networks involving dorsal prefrontal and anterior cingulate cortices and posterior insula. Both functional connectivity increases and decreases contributed to account for patient scoring on adaptive behavior related to communication skills. The data overall suggest a distinctive functional organization with system-specific anomalies associated with reduced adaptive efficiency. Opposite effects were identified on distinct frontal and anterior temporal structures and relative sparing of posterior brain areas, which is generally

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consistent with Down syndrome cognitive profile. Relevantly, measurable connectivity changes, as a marker of the brain functional anomaly, could have a role in the development of therapeutic strategies addressed to improve the quality of life in Down syndrome individuals.

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## 1. Introduction

Research in Down syndrome has substantially progressed in the understanding of basic mechanisms via which gene overexpression interferes with brain development, although the available data mostly involve molecular and neuropathological alterations (Capone, 2001; Dierssen, 2012; Dierssen, Herault, & Estivill, 2009; Gardiner et al., 2010; Lott & Dierssen, 2010). There is a paucity of information on the consequences of the molecular changes on overall brain functional organization.

Functional MRI permits testing the integrity of relevant brain functional networks on the basis of region synchrony – typically defined as “functional connectivity” (Fox & Raichle, 2007). One recent MRI study assessed the overall architecture of brain functional connectivity in Down syndrome individuals during the viewing of cartoon video clips (Anderson et al., 2013). The connectivity measurements revealed a global enhancement in brain synchrony with a simplified functional structure in Down syndrome. The subset of strong connections, however, distinctively showed the most severe effects that involved both connectivity increases and decreases. Other graph connectivity approaches using near-infrared spectroscopy (Imai et al., 2014) and EEG-based small-world metrics (Ahmadlou, Gharib, Hemmati, Vameghi, & Sajedi, 2013) also suggested that the global changes may combine with specific connectivity anomalies, although the neural systems implicated were not identified.

We have assessed the functional status of the brain in Down syndrome using resting-state functional connectivity MRI with the aim of identifying system-specific functional anomalies. Whole-brain “connectivity degree” maps (Buckner et al., 2009) were generated for Down syndrome patients and control subjects to locate brain regions showing net increases or decreases in their functional synchrony with other areas. A subsequent region-of-interest functional connectivity mapping served to detail the anomalies within the networks implicated. Brain maps were generated to show the correlation of functional connectivity changes with representative measurements of adaptive behavior.

## 2. Materials and methods

### 2.1. Participants

Twenty-six Down syndrome individuals participated in this study. Candidates were recruited from the community via parent organizations and received comprehensive medical,

psychiatric, neuropsychological and laboratory evaluation. Individuals with seizure or neurological disease (other than Down syndrome), psychiatric disorder (including autism spectrum disorder), non-stable medical conditions and current psychoactive medication were not eligible for the fMRI assessment. Candidates were selected from a large group of 87 Down syndrome individuals on the basis of their capability to understand MRI instructions, follow the commands and remain still, as well as optimal attitude and the willingness (participants and parents) to participate. Six subjects were ultimately excluded on the basis of actual head motion during MRI (see further) and the final sample included 20 Down syndrome participants (10 females) with genotype-confirmed trisomy 21 and a mean  $\pm$  SD age of  $24.4 \pm 4.1$  years, range 18–32. Mean education was  $13.5 \pm 1.6$  years (range 11–17), IQ estimated with the Kaufman Brief Intelligent Test, Second Edition (KBIT-II) (Kaufman, 1990), was  $45.8 \pm 7.1$  (range 40–66), and adaptive skills according to total scoring (excluding “Work” subscale) on the Adaptive Behavior Assessment System—Second Edition (ABAS-II) (Harrison & Oakland, 2003) showed  $472 \pm 82$  (range 296–627). Maternal ethnicity was Caucasian in all cases. No participant was taking psychotropic medication.

The ABAS-II was used as a measurement of patients' efficient use of their intellectual capabilities to be correlated with brain functional connectivity. This instrument was selected as potentially adequate to comprehensively assess the ultimate repercussion of both cognitive and general behavioral disturbances on daily functioning in Down syndrome individuals (as opposed to using specific cognitive testing). The ABAS-II indeed is a reliable and valid norm-based measurement (Harrison & Oakland, 2003; Rust & Wallace, 2004) that generates scores consistent with the American Association on Intellectual and Developmental Disabilities (AAIDD) (Schalock et al., 2010) definition of intellectual disability and rates the 10 daily living skills specified in the DSM-IV-TR (APA, 2000). The ABAS-II has been previously used in Down syndrome subjects to document and monitor the individual's overall functioning (Harrison & Oakland, 2003; Zis, Dickinson, Shende, Walker, & Strydom, 2012). The adaptive areas evaluated are Communication Skills, Community Use, Functional Academics, Home Living, Health and Safety, Leisure Skills, Self-Care, Self-Direction, Social Skills and Work (working individuals). The Parent/Primary Caregiver Form of rating was used in this study.

A group of 20 control individuals was selected matching in age ( $25.1 \pm 4.0$  years, range 19–33) and sex distribution (10 females) with the patient sample. Subjects with relevant medical or neurological disorder, substance abuse, psychiatric

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