Structural and functional connectivity in relation to cognitive and social functioning of children with Neurofibromatosis Type 1

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON32474

Source
ToetsingOnline

Brief title
Brain-behavior relationships in NF1

Condition

- Neurological disorders congenital
- Structural brain disorders

Synonym
Von Recklinghausen's Disease; NF1

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Leiden
Source(s) of monetary or material Support: Ministerie van OC&W,Neurofibromatose Vereniging Nederland

Intervention

Keyword: cognition, MRI, Neurofibromatosis Type 1, social functioning

Outcome measures

Primary outcome

Task performance, questionnaire data on social functioning, white matter integrity (i.e. Fractional Anisotropy (FA) measured with Diffusion Tensor Imaging (DTI) scan), T1-images to assess gray and white matter volumes (measured with structural anatomy scan), T2-images to assess activity (i.e. blood oxygen level dependent (BOLD) responses) during tasks (measured with functional MRI scans), and measures of functional connectivity between brain regions (cross-correlations), based on activity measured during the resting state scan and during task performance (i.e. using the fMRI-scans).

Secondary outcome

Performance and verbal IQ estimations as measured by Block Patterns and Word Knowledge from the WISC. Behavior data from the Child Behavior Checklist.

Study description

Background summary

Neurofibromatosis type 1 (NF1), also known as Von Recklinghausen*s disease, is a genetic disorder affecting about 1 in 3000 people. Physical manifestations of NF1 include café-au-lait spots, skin fold freckling, optic nerve glioma, osseous (bone) abnormalities, iris Lisch nodules, and cutaneous and plexiform

neurofibromas. The most common complications however are cognitive and social impairments. Recent studies indicate that, despite the fact that some more basic skills such as motor speed appear to be affected as well, the most evident deficits are present in the area of cognitive control. As social functioning requires increasing levels of cognitive control with increasing age, it is important to determine whether cognitive control and its associated networks of brain regions underlie social functioning in general and social impairment in NF1 in particular. The transition into adolescence is characterized by increasing and changing demands in social functioning. This period is also an important developmental stage for cognitive control. Therefore, this represents the best possible stage to investigate development of cognitive control and social functioning and its neural correlates. There is reason to believe that a suboptimal development of networks of brain regions may underlie cognitive control- and social problems in NF1. NF1 leads to a decreased production of the protein neurofibromin, which acts as a tumor suppressor and is associated with processes that are of general importance to cortical development, such as synaptogenesis and neuronal differentiation. Different abnormalities in the brains of NF1-patients have been demonstrated, including T2-hyperintensities, macrocephaly, and abnormal gray to white matter ratios (driven by small gray matter- and large white matter volumes), but these have not (yet) been convincingly related to social and cognitive function in this population. Further investigations are required, but these should be supplemented with studies into the relation between the quality of communication between different brain regions on the one hand and the quality of cognitive control and social functioning on the other. Cognitive and social problems are often cited by NF1-patients themselves as having the greatest impact in daily life. In order to be able to understand and treat these problems better it is necessary to reveal the underlying pathological mechanisms. For example, whereas behavioral interventions might aim at the organization of different cognitive abilities rather than separate cognitive abilities, medicine-based treatment might want to focus on transmitters that are specifically important for communication between brain regions such as glutamate and GABA.

Study objective

Our general objective is to find out whether impaired communication within networks of specific brain regions underlies the cognitive control- and social problems of individuals with NF1. It is very important to examine these relations in children who are in the transition towards adolescence, as this is a developmental stage characterized by complex and changing social demands as well as one where cognitive control abilities undergo a rapid development. Moreover, it has been shown that children with NF1 differ strongly from normally-developing children of the same age with respect to social functioning and cognitive control abilities. We have further operationalized our general objective with the following specific hypotheses:

Hypothesis 1: Children with NF1 will perform more poorly than age- and IQ-matched controls on the N-back task and the Facial Affect Recognition task (both administered in the scanner, see section 6.3).
Hypothesis 2: Children with NF1 will have more social problems than age- and IQ-matched controls. For questionnaires measuring social skills, see section 6.3.
Hypothesis 3: Children with NF1 will show less activation of individual brain regions associated with performance of the N-back- and Facial Affect Recognition tasks (see Figure 2) than age- and IQ-matched controls. However, based on previous studies, it is expected that reduced activation in these brain regions can only explain a marginal proportion of the variance in performance differences with controls.
Hypothesis 4: Children with NF1 will have reduced gray matter and increased white matter volumes throughout the brain compared to healthy controls, but again it is expected that this will explain a marginal proportion of the variance in performance differences with controls.
Hypothesis 5: Children with NF1 will show less functional connectivity between brain regions of interest for the N-back task and the Facial Affect Recognition task (see Figure 2) and this will be related to performance deficits.
Hypothesis 6: Both tasks have different levels of complexity, presumably related to the required levels of connectivity and possibly related to additional connectivity (e.g. with other brain regions). It is hypothesized that NF1-patients will particularly demonstrate connectivity-related performance deficits in more complex task parts.
Hypothesis 7: Hypotheses #6 and #7 propose that reduced functional connectivity will become particularly evident when specific networks of brain regions should be actively communicating because of task demands. Hypothesis #8 proposes that such networks should already show increased connectivity at rest, as the brain regions they are composed of often work together in everyday life. It postulates that among NF1-patients such connections will be less developed than in healthy controls, leading to reduced connectivity at rest.
Hypothesis 8: With respect to structural connectivity, it is expected that decreased white matter integrity in NF1-patients will explain a substantial proportion of the variance in their cognitive and social difficulties.
Hypothesis 9: It is expected that associations between structural connectivity abnormalities and social and cognitive outcomes will be mediated by functional connectivity abnormalities.

Study design

Observational study, case-control study. See also the answer to question E4.

Study burden and risks

The requested time investment is a total of 1.5 hours (1 visit), of which 45 minutes will be spent in the scanner, for the NF1-patients. Control data will

be provided by the aforementioned parallel study (NL25924.058.08). With respect to the MRI session, other studies from the LIBC in which children participate in MRI research give us confidence that children will have no problems with this study. Participants will be also thoroughly screened (using standard procedures) before scanning. Even though the MRI scans will not be diagnostically screened for abnormalities, we will ask the neuroradiologists, who always screen the scans made at the LIBC, to be alert to the fact that abnormalities in brain matter of individuals with NF1 are more likely than in most other people. We will convene a meeting where the neuroradiologists will be briefed about often-occurring abnormalities in the brains of individuals with NF1, such as optic nerve glioma. The procedure in case of unexpected findings will be explained (in person and in writing) to parents of participants. Specifically, it will be explained that such findings will be communicated to their General Practitioners, who will discuss them further with the participants and their families.

Contacts

Public
Universiteit Leiden

Wassenaarseweg 52
2333 AK, Leiden
NL
Scientific
Universiteit Leiden

Wassenaarseweg 52
2333 AK, Leiden
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

General inclusion criteria: age between 9 and 13 at time of study; Dutch speaking and signed informed consent from parents and participants. NF1 participants fulfill the diagnostic criteria specified by the National Institutes of Health Consensus Conference (National Institutes of Health, 1988), i.e. they meet two or more of the following criteria: six or more café-au-lait spots, two or more neurofibromas, skinfold freckling, an optic glioma, two or more Lisch nodules, or a first degree relative with NF1.

Exclusion criteria

-history of psychiatric illness (other than ADHD), closed-head injury, endocrinological dysfunction, or neurological illness (other than NF1). Use of psychotropic medication (other than stimulants to treat ADHD-symptomatology). Many individuals with NF1 receive an ADHD-diagnosis (there are reports of an ADHD-incidence of up to 40-50% in NF1). Most of them will receive stimulant medication. Because of the high incidence we will not exclude individuals with an ADHD-diagnosis. Instead, we will control for ADHD and use of stimulant medication in our analyses.
-contraindications for fMRI
-premature birth

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	31-10-2010

Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	23-04-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL30665.058.09