Cognitive rigidity and risperidone in children with autism spectrum disorders

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational non invasive

Summary

ID

NL-OMON34499

Source
ToetsingOnline

Brief title
Rigidity and risperidone in autism spectrum disorders

Condition

- Other condition
- Psychiatric disorders NEC

Synonym
'Autism Spectrum DIsorders' or 'autism'

Health condition

Autisme spectrum stoornissen

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Anterior Cingulate Cortex, Autism, Risperidone, Self-monitoring

Outcome measures

Primary outcome

The Error-Related negativity (ERN) is a peak in the ERP signal measured directly after the participant makes a mistake; in the case of the Go/ NoGo task, this means that the ERN is measured when the participant inadvertently presses the response button with a NoGo trial. The ERN is a measure of self-monitoring, which is hypothesized to be low in children with ASD with rigid behavior at baseline. The use of risperidone enhances cingulate cortex activity, resulting in larger ERN amplitudes. Response times, and particularly the delay in reaction time after making a mistake, are also measured. Usually, the reaction times after an erronous response are slower; we expect that this post-error slowing at baseline is relatively small in children with ASD, but that it increases due to the use of risperidone. Both effect measures will be correlated with the degree of rigid behavior in the children with ASD, here we expect stronger effects with higher levels of rigid behavior at baseline.

Secondary outcome

Source localizations of the ERN are applied, meaning that it is measured whether the ERN can actually be located in the anterior cingulate cortex. This source localization is done by using Brain Electrical Source Analysis software.

Previous studies have shown that using 64 electrodes, as it is the case in our study, will provide robust signals that are appropriate for measuring ERN source localization (Vlamings et al, 2008).

Study description

Background summary

Behavioral rigidity is an important restricting factor in the development of adaptive social functioning. However, it is also a characteristic of early childhood; very young children, beginning in the first year of life, increasing around three years of age and typically declining after age four, display ritualistic and rigid behaviors in daily life, such as ordering and arranging objects in circumscribed ways or insisting on specific bedtime rituals. Although in typical development this behavioral rigidity gradually declines, it remains a significant and exaggerated characteristic in individuals with autism spectrum disorders (ASD).
Both in human and animal research, dopaminergically innervated interactions in the fronto-striatal brain network have been implicated in rigid and stereotypic behavior, with a prominent role for the anterior cingulate cortex (ACC). Indeed, there is recent evidence for a relation between clinical measures of behavioral rigidity in ASD and the fronto-striatal system. E.g. it was shown that impairments in fronto-striatal white matter tracts are present in individuals with ASD which relate to their clinical rigidity (Thakkar et al., 2008). Also, a recent study showed a relation between clinically defined rigidity in ASD, formal measures of rigid and stereotypic behavior, i.e. set shifting abilities in neuropsychological tests, and ACC functioning (Shafritz et al., 2008).
Functioning of the fronto-striatal network can be studied in humans by measuring the event-related brain response to errors, the so-called error-related negativity (ERN). The origin of ERN activity has been repeatedly localized within the ACC (Dehaene et al., 1994). It is thought that ERN activity reflects self monitoring, a prerequisite to flexible and adaptive behavior, and it is therefore conceptually related to behavioral rigidity. We have shown atypical ERN activity in children with ASD (Vlamings et al., 2008). There is evidence that the fronto-striatal system shows a protracted development in healthy children, as indicated by changes in childhood in ACC functioning, but it is not known whether rigid and stereotypic behavior in individuals with ASD is qualitatively different from that seen in typically developing children, and how this relates to the abnormal development of the fronto-striatal system.
Developmental changes in ERN activity indicate an increase in ACC activity and

therefore maturity of the DA innervated connections (Segalowitz et al., 2009). The putative role of dopamine in behavioral rigidity is further suggested by the fact that in clinical practice, the atypical antipsychotic risperidone is often used to treat individuals with ASD, as it ameliorates the rigid and repetitive behavior associated with this disorder. Its mode of action, however, is not clear. We hypothesize that risperidone enhances activity of the ACC-dopamine midbrain network, as reflected in the ERN, and that this is directly related to clinically relevant measures of rigidity. In this study we want to find evidence for this hypothesis.

Study objective

The global aim of the proposal is to expand our knowledge on the functioning of the fronto-striatal system and the relation to behavioral rigidity, and how these are affected by dopaminergic modulation. The specific aim is to study the effects of risperidone on fronto-striatal functioning in individuals with ASD, and the effects on behavioral rigidity. We hypothesize that risperidone enhances activity of the fronto-striatal network, as reflected in the ERN, and that this is directly related to improvement on clinical measures of behavioral rigidity.

Study design

Participants will conduct a go/nogo task twice, the second one month after the first administration. They will conduct the task just before medication is started and one month after. During the task we will measure event-related brain potentials (ERPs) that will be analyzed with respect to latency and amplitude of the ERN, as well as to source localization. In addition, we will quantify rigidity in daily life. This will be done with diagnostic information obtained from the ADI-R.
A go/nogo task will be used (Durston et al., 2002). In this task the children will be asked to press a button in response to visually presented stimuli (go trials), but to avoid responding to rare non-targets (nogo trials). They will perform 5 blocks, each containing 108 stimulus presentations, with 75% go trials, resulting in a total of 135 nogo trials. Additionally, we vary the number of go trials preceding a nogo trial, with 1, 3, or 5 preceding go trials. Each type of nogo trial therefore contains 45 stimulus presentations.
To make the study better suitable for use with children, stimuli will be taken from the Pokemon cartoon series. Stimulus duration is 500 ms and the intertrial interval will vary randomly between 500 - 1500 ms, during which a central fixation stimulus is presented on screen. The children are asked to push a designated button every time a go trial occurs, but to withhold from responding as soon as the character 'Meowth' appears on screen.
Many studies using a go/nogo paradigm have found ACC activity following an erronous nogo-response, which makes this task ideally suited for our study (e.g. Hester et al., 2004).

EEGs will be recorded at a sample rate of 2048 Hz from 64 locations using standard Ag/AgCl pin-type active electrodes (BIOSEMI, Amsterdam, the Netherlands) mounted in an elastic cap, referenced to two additional electrodes (Common Mode Sense, and Driven Right Leg) during recording. The children are seated in a comfortable chair in front of a computer screen in an electrically shielded room. After a standardized instruction the children perform a short practice block consisting of 24 trials. After application of the electrodes the children perform the 5 experimental blocks (each lasting less than 3 min).

Study burden and risks

The EEG itself does not elicit any risk of complications. The burden for the participant is minimal as it only requires administration of two EEGs during planned visits to the clinic. Travel expenses will be reimbursed, and all participants will receive a 10 euro cheque after each visit to the UMC Utrecht. The benefits are twofold. First, the study will provide clinicians with neurobiological markers for behavioral rigidity related to ASD. Although repetitive behaviors are included in all major diagnostic criteria for ASD and can be reliably diagnosed in children, it is unclear, as yet, whether this relates to the abnormal development of ACC functioning and maturation of the dopaminergic neuronal connections between ACC and the limbic system. Second, the study is expected to provide clinicians with more knowledge about underlying mechanisms leading to successful treatment of rigid and stereotypic behavior. The daily clinical practice clearly requires such knowledge, as it is unknown beforehand who will respond positively to risperidone treatment and who will not.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Children aged 6 to 12, who are diagnosed with ASD at the department of child psychiatry. All children who will be prescribed risperidone for stereotypic behavior, but who are medication-naive at the beginning of the study, will be asked to participate. Based on the known male: female ratio of about 4:1 (Fombonne, 2002), we expect to include around 20 boys and 5 girls in our study. Diagnostic criteria are according to the DSM-IV (APA, 1994), and verified by the ADOS (Lord et al., 1989) and ADI-R (Lord et al., 1994). IQs of all participants will be measured by the Wechsler Intelligence Scale for Children, Dutch edition (WISC-III-NL).

Exclusion criteria

Individuals who are either not medication-naive at baseline, with a known brain dysfunction, total IQ score below 75 or with psychiatric pathology other than ASD will be excluded.

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-02-2011
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO

Date:	30-11-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL33261.041.10