Impaired sensory processing in Autism Spectrum Disorder: Towards better phenotyping and cellular models*

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Ethical review	Approved WMO
Status	Pending
Health condition type	Developmental disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON48762

Source
ToetsingOnline

Brief title
BECAUSE: From Behavior to Cell in Autism Sensory Processing.

Condition

- Developmental disorders NEC

Synonym
Autism ASD

Research involving
Human

Sponsors and support

Primary sponsor: VU
Source(s) of monetary or material Support: ZonMW TOP subsidie

Intervention

Keyword: Autism, E/I inbalance, Induced Pluripotent Stem cells (iPSCs), Sensory Processing

Outcome measures

Primary outcome

1. Self-reported behavioural questionnaire on sensory processing

2. Self-reported behavioural questionnaire on daily life functioning, such as

clinical severity, social problems, educational attainment, and wellbeing

3. Neuropsychological tasks on sensory processing

4. Neurophysiological (i.e., EEG) parameters

5. Polygenic Risk Scores

6. Cellular assays

Secondary outcome

nvt

Study description

Background summary

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with a >1% prevalence characterized by impairments in social skills and flexibility and by a complex aetiological heterogeneity. The neurobiological mechanisms underlying ASD are still poorly understood and the aetiological heterogeneity complicates their elucidation. Recently, sensory processing sensitivities, such as extreme sensitivity to light, sound, or touch, were added to the ASD diagnostic criteria (DSM5) as negative and prevalent symptoms (reported up to 87%). These symptoms are now considered *a critical cornerstone for characterizing and understanding ASD*. A new network theory explains ASD by a disturbed excitation/inhibition (E/I) balance in synaptic networks in the brain. We aim to test this theory using behavioral, neuropsychological, europhysiological and synaptic analyses of sensory processing deficits in ASD.

We will first exploit our Netherlands Autism Register to pre-select extreme

cases of high and low sensory sensitivity among ASD participants (currently 683) and control subjects and examine the relationship between sensory sensitivity and other clinical characteristics and daily functioning skills. Secondly, we will assess 80 pre-selected participants further, using customized sensory processing tasks and EEG, which we have previously optimized to analyze sensory sensitivity and E/I balance. Thirdly, we will utilize our unique expertise to generate small, standardized neuronal networks in vitro, made of human neurons derived from induced pluripotent stem cells (iPSCs) and to record differences in synaptic and network properties. The sensory sensitivity and E/I balance tests will be exploited to generate these standardized in vitro networks of the most extreme cases. Finally, it has been proposed that the (unknown) neurobiological mechanisms underlying sensory processing deficits are similar to those underlying higher order social function deficits. Therefore, we will test whether the outcomes of our neuropsychological and neurophysiological tests are predictive for the reported higher order function deficits.

This project brings together unique expertise to bridge across behavioral, neuropsychological, neurophysiological and cellular research domains of ASD, focusing on a symptom that is only recently recognized as a central symptom, also in relation to other indicators of ASD, but for which integrated studies across research domains are still lacking. Whereas higher order social functions are difficult to measure quantitatively, sensory processing can be easily quantified in a manner that is less biased for age, gender, or cultural background. This quantification is expected to lead to a more objective, unbiased and homogeneous ASD subtyping which is again expected to improve ASD diagnosis and facilitate cellular studies with neurons derived from ASD participants. Such iPSC-derived neuronal models, in contrast to current (monogenic) animal- or cell-models, present the full polygenic complexity of ASD. Given the expected subtle cellular effects and the heterogeneity in ASD, current IPSCs-studies are often underpowered. We will exploit the precise classification of the disease subtypes to overcome this problem and arrive at homogenously phenotyped ASD subgroups. Together, this project provides a unique opportunity to bring together information from these different research domains, enhance our understanding of the complexity of ASD, and provide intervention targets to alleviate the burden of ASD.

Study objective

The main aim of this proposal is to characterize the neurobiological basis of sensory processing deficits in ASD.

The first key objective is to exploit our Netherlands Autism Register to pre-select extreme cases of high- and low sensory sensitivity among ASD- and control subjects and examine the relationship between sensory sensitivity and social and daily functioning skills.

The second key objective is to perform a detailed assessment of 80 pre-selected ASD- and 80 control participants using sensory processing tasks and EEG, specifically targeting sensory sensitivity and E/I balance.

The third key objective is to generate small, standardized neuronal networks in vitro, made of human neurons derived from induced pluripotent stem cells (iPSCs) and to record differences in synaptic and network properties related to E/I balance.

We have defined two projects to reach these objectives. Project A will target objectives 1 and 2 and provides the classification in ASD subtypes using our two-step selection principle (pre-selection in key objective 1 and detailed assessment using sensory processing tasks and EEG in key objective 2). In addition, this project addresses to what extent altered sensory processing can be used as a proxy for other aspects of ASD. This project will provide new fast and robust diagnostic tools for ASD based on sensory processing tasks and EEG. Project B will target objective 3 and characterize the neurobiological basis of sensory processing deficits in standardized neuronal networks, with a focus on the excitatory/inhibitory balance. This project provides insight into the cellular basis of sensory processing deficits in ASD and new cellular models for ASD. Both objectives contribute to the awareness and recognition of ASD as a heterogeneous condition with sensory processing deficits as a defining criterion.

Study design

a) The NAR: a large, unique ASD sample
We use one of the largest clinical ASD samples to date with sensory processing data. All participants are recruited via the Netherlands Autism Register (NAR) (www.nederlandsautismeregister.nl) which is a longitudinal cohort of 2000 participants with ASD (1000 adults; IRB approved). Since 2013, NAR participants complete yearly online questionnaires that assess an extensive range of data, among which clinical severity, treatment and medication, comorbid psychiatric problems, education and wellbeing (Figure 2A). The NAR has added in 2016 a validated self-report questionnaire on sensory processing (Tavassoli et al., 2014). We will use the first results of this self-report to conduct the preselection of low and high sensitive individuals in NAR (see Figure 1). In addition we will utilize the extensive NAR data collection to explore how sensory processing sensitivities in adults correlates with (predicts) ASD severity.

b) Functional biomarkers for ASD: EEG
We will collaborate with NBT Analytics (www.nbt-analytics.com), a spin-off company from the Linkenkaer-Hansen lab in Amsterdam, to produce an ASD diagnosis tool, based on EEG measurements. This tool will be used for the second step in our selection procedure for extreme
sensory sensitivity, depending on the outcome of subsequent synaptic analyses

in project B, further optimized as a diagnostic tool for ASD. NBT Analytics has developed a unique approach to classify brain disease phenotypes based on EEG biomarkers (see project A below), which has been successfully applied for patient classification in other disease domains before (Figure 5). In addition, they have developed a novel computational method using Detrended Fluctuation Analysis (DFA) to quantify E/I ratio from brain oscillations measured with EEG (Figure 3). We will apply this method to investigate the differences in E/I balance in high- and low sensitivity in ASD. After finalizing the EEG study, participants will be approached to participate in a DNA study, based on saliva collection via mail.

c) The use of IPSCs in ASD research
In ASDs about 10% of the syndromes are monogenic, with reasonably good animal models available (Nelson and Valakh, 2015). However, it is not clear to what extent these animal models are relevant for the other 90% syndromes in ASD with highly polygenic origin, where many disease genes contribute only a small fraction to the total disease risk. Therefore, we chose to study these forms of ASD using micro-networks of human neurons derived from IPSCs from selected extreme cases of sensory processing.

Study burden and risks

see protocol

Contacts

Public
VU

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NL
Scientific
VU

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Amsterdam 1081HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Diagnosis of Autism Spectrum Disorder, parent or sibling of person with Autism Spectrum Disorder or Control
Scoring extreme high or low (7th percentile) on the Sensory Processing questionnaire.

Exclusion criteria

Control Participants are excluded if
-they have an IQ score below 80), based on educational attainment (Mavo/VMBO or higher);
-if they are younger than 20 or older than 55 years;
-if they have a diagnosis of autism, or score above the cutoff on the Autism Quotient Questionnaire, Participants with autisem are excluded if they are
-not clinically diagnosed with autisme

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2017
Enrollment:	240
Type:	Anticipated

Ethics review

Approved WMO Date:	20-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL61614.029.17