Glutamate, GABA and cognition in subjects with 22q11.2 CNVs

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We hypothesize that: I) ACC glutamate concentrations are higher in 22q11.2 CNVs compared to healthy controls as a result of haplo-insufficiency for PRODH seen in 22q11.2 CNVs which in turn could result in excessive glutamate release. II) The ACC...

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON24163

Bron
NTR

Verkorte titel
TBA

Aandoening

22q11.2 copy number variants

Ondersteuning

Primaire sponsor: azM
Overige ondersteuning: azM

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Primary outcomes will be metabolite concentrations including glutamate and GABA assessed using 1H- MRS in the anterior cingulate cortex as well as performance on the

neuropsychological tests battery: The CNB, a Computerized Neurocognitive test Battery .

Toelichting onderzoek

Achtergrond van het onderzoek

22q11.2 copy number variants (22q11.2 CNVs) are genetic disorders caused by a microdeletion or duplication on the long arm of chromosome 22 and are associated with an increased risk of developing a variety of psychiatric disorders, including psychotic disorders, and cognitive dysfunction. One of the genes located at within the deleted or duplicated region in 22q11.2 CNVs is known to be involved in glutamatergic neurotransmission. This gene encodes proline dehydrogenase (PRODH), also known as proline oxidase. This enzyme is implicated in converting proline to glutamate. Increased proline levels have been observed in patients with 22q11.2DS and it is hypothesized that this increase is the result of reduced PRODH enzyme activity in 22q11.2DS due to haploinsufficiency of the PRODH gene. Decreased PRODH enzyme activity can thus lead to increased proline levels and, subsequently, excessive glutamate release. Glutamate is the major excitatory neurotransmitter in the brain, and has been
implicated in the pathophysiology of psychosis, as well as in cognitive functioning due to its mediating role in long term potentiation. Since 22q11.2 CNVs are associated with progressive cognitive and functional deterioration in combination with psychosis, it could be hypothesized that a neurodegenerative process, as a consequence of chronic high (neurotoxic) concentrations of glutamate could result in neuronal damage. Glutamate function is closely correlated with gamma- aminobutyric acid (GABA): the main inhibitory neurotransmitter in the brain. Glutamatergic N-methyl-D-aspartate (NMDA) receptors are located on GABA interneurons for example and therefore, altered glutamate transmission affects GABA-ergic function as well. GABA has been implicated in psychosis based on most-mortem and animal studies showing reduced expression of pre- and postsynaptic markers of GABAergic neurotransmission in subpopulations of GABAergic interneurons. There is accumulating evidence relating glutamate and GABA to cognitive functioning in psychosis through cortical hyperexcitation. Although a balance between both glutamate and GABA is necessary for optimal brain functioning, both systems are often studied in isolation and little is known about GABA in 22q11.2 CNVs. Research on the role of glutamate and GABA in cognition in 22q11.2 CNVs may reveal biological substrates with novel insights into molecular mechanisms underlying cognitive functioning in psychosis. Research can lead to possible targets for pharmacological treatment which in turn could potentially enhance cognitive functioning in patients with 22q11.2 CNVs, and possibly reduce disease-associated cognitive decline. Therefore, we aim to study glutamate and GABA concentrations, as well as cognition in subjects with 22q11.2 CNVs.

The main objective of this study is to investigate the role of glutamate and GABA in cognition in healthy subjects with 22q11.2 CNVs and healthy subjects without 22q11.2 CNVs using high-field Magnetic Resonance Spectroscopy (MRS). Additionally, we will exploratively investigate the role of neuromelanine, which is an indirect measure of dopamine and

noradrenaline, in relation to cognition in 22q11.2 CNVs and healthy subjects without 22q11.2 CNVs using MRS.

This study is a cross- sectional study measuring in-vivo glutamate and GABA concentrations in relation to cognition in subjects with 22q11.2 CNVs and healthy subjects without 22q11.2 CNVs.

Doel van het onderzoek

We hypothesize that:
I) ACC glutamate concentrations are higher in 22q11.2 CNVs compared to healthy controls as a result of haplo-insufficiency for PRODH seen in 22q11.2 CNVs which in turn could result in excessive glutamate release. II) The ACC glutamate/GABA balance is altered in 22q11.2 CNVs compared to healthy controls as a result of a disruption in the glutamatergic pathway. III) Based on the results of our pilot study, showing an inverse correlation of glutamate and GABA with cognitive performance, we hypothesize that performance on the cognitive test battery will be negatively associated with ACC glutamate and GABA concentrations in 22q11.2 CNVs. IV) Neuromelanine concentrations in the SN and LC are higher in 22q11.2 CNVs compared to healthy controls as a result of haploinsufficiency of COMT seen in 22q11.2 CNVs. V) Performance on the cognitive test battery will be negatively associated with SN and LC neuromelanine concentrations in 22q11.2 CNVs.

Onderzoeksopzet

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Contactpersonen

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Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

For subjects with 22q11.2 CNVs
• Confirmed diagnosis of 22q11.2 deletion or duplication syndrome established by FISH, microarray or MLPA analysis.
• 16 year or older of age and mentally competent (determined by an experienced physician) to give informed consent.
• No presence of a physical/medical condition that may interfere with the study.
• No contraindication for MRI.

For healthy controls:
• Healthy subjects will be matched for age and gender.
• No presence of a physical/medical condition that may interfere with the study.
• No contraindication for MRI.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

For subjects with 22q11.2 CNVs:
• Other chromosomal abnormalities.
• Current substance abuse / dependence.
• A psychiatric or neurologic disorder.
• Pregnancy.

For Healthy controls:
• Any chromosomal abnormalities.
• Current substance abuse / dependence.
• A psychiatric or neurologic disorder.
• Pregnancy.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders

Toewijzing: N.v.t. / één studie arm

Controle: N.v.t. / onbekend

Deelname

Nederland

Status: Werving nog niet gestart

(Verwachte) startdatum: 01-09-2020

Aantal proefpersonen: 80

Type: Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum: 23-07-2020

Soort: Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

ID: 52428
Bron: ToetsingOnline
Titel:

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL8794
CCMO	NL73420.068.20
OMON	NL-OMON52428

Resultaten