The influence of symptom provocation on glutamate in obsessive-compulsive disorder - a functional magnetic resonance spectroscopy study

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The primary goal of this study is to gain insight into the role of glutamate in the LOC of OCD patients while observing symptom-inducing visual stimuli. This will be investigated by using fMRS on an ultra-high field strength MRI scanner (7T). This...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Impulse control disorders NEC
Study type	Observational non invasive

Summary

ID

NL-OMON49350

Source
ToetsingOnline

Brief title
fMRS during symptom provocation in OCD

Condition

- Impulse control disorders NEC

Synonym
alcoholism, contamination fear | alcohol addiction, Obsessive-compulsive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: fMRS, Glutamate, Lateral occipital cortex, Obsessive-compulsive disorder

Outcome measures

Primary outcome

The change in the concentration of glutamate in the LOC when viewing disorder-specific visual stimuli (versus neutral stimuli) in patients with OCD compared to healthy controls.

Secondary outcome

* The change in the concentration of GABA in the LOC when viewing disorder-specific visual stimuli (versus neutral stimuli) in patients with OCD compared to healthy controls.

* Changes in brain activity in the LOC when viewing disorder-specific visual stimuli (versus neutral stimuli) by patients with OCD and healthy controls.

* Relationship between change in glutamate and GABA concentration and change in brain activity in the LOC when viewing disorder-specific visual stimuli in patients with OCD compared to healthy control participants.

Study description

Background summary

An obsessive compulsive disorder (OCD) is a neuropsychiatric disorder that is characterized by obsessive and intrusive thoughts that cause fear or anxiety

(American Psychiatric Association, 2013). To relieve these fears, patients perform repetitive and ritual behaviors (compulsions). These compulsions include among others a compulsion to organize, check or clean. The prevalence of OCD is around 1% in the Netherlands (de Bruijn, Beun, de Graaf, ten Have, & Denys, 2010) and has a chronic course with only 20% of patients who, despite current drug and behavioral treatments after 10- 20 years of follow-up remission (Bloch et al., 2013). These figures support the need for new effective treatments.

Multiple studies implicate dysfunction of fronto-striatal circuits - which connects the (pre) frontal cortex to striatal areas - in the pathophysiology of this disorder, possibly due to an imbalance in the concentration of neurotransmitters such as dopamine and serotonin (Milad & Rauch , 2012; Perani et al., 2008; van der Wee et al., 2004). Research in more recent years, however, shows that dysregulation of glutamate and GABA - the primary exciting and inhibiting neurotransmitters in the fronto-striatal circuits, and beyond, such as the visual cortex * also play an important role in the pathophysiology of disorders within the impulsive compulsive spectrum (Boedhoe et al., 2017; Moreira et al., 2017; Pittenger, Bloch, & Williams, 2011).

Within the visual cortex, the lateral occipital cortex is one of the areas where emotionally salient stimuli are processed (Garcia-Garcia et al., 2016; Kuniecki, Woloszyn, Domagalik, & Pilarczyk, 2018). A recent meta-analysis showed that this area in OCD patients, compared to healthy controls, is more strongly activated by OCD-related visual stimuli (Thorsen et al., 2018). The stronger response to disorder-specific stimuli in OCD patients can possibly be explained by top-down regulation from the limbic system (Pessoa & Adolphs, 2010; Thorsen et al., 2018; Vuilleumier, 2005). The OCD-related hyperactivation of the limbic system during symptom provocation and abnormal functional connectivity between the fronto-striatal circuits and the LOC could be responsible for this (Moreira et al., 2017; Thorsen et al., 2018). In this way, the LOC may contribute to the pathophysiological changes seen in OCD.

Despite previous studies showing abnormal activation in the LOC of OCD patients during symptom provocation, little research has been done into glutamate in the LOC of OCD patients. The concentration of glutamate can be measured in vivo using Magnetic Resonance Spectroscopy (MRS) - a Magnetic Resonance Imaging (MRI) technique based on the magnetic properties of glutamate and other neurometabolites (Figure 1C). Previous MRS studies in patients with OCD have shown changes in glutamate concentration in different brain areas compared to healthy controls (for reviews, see (Brennan, Rauch, Jensen, & Pope, 2013; Naaijen, Lythgoe, Amiri, Buitelaar , & Glennon, 2015) The direction of the effect, however, depends on the characteristics of the patient group (medicated versus non-medicated, duration of disease, etc.).

MRS studies also suggest involvement of GABA - the primary inhibitory neurotransmitter - in the pathophysiology of OCD (Naaijen et al., 2015). The number of MRS studies that investigated GABA concentrations is limited, however, because these were mostly performed on MRI scanners with a field strength of 3 Tesla or lower, on which the GABA peak in the spectrum is difficult to distinguish from the surrounding peaks of other neurometabolites.

Another disadvantage of previous "resting-state" MRS studies is that it gives a static picture of the neurometabolite concentrations, without taking into account the temporal fluctuations. Functional MRS (fMRS) is a relatively new technique in which it is possible to determine the neurometabolite fluctuations (Stanley & Raz, 2018). By having a participant perform a task during scanning, task-induced fluctuations in neurometabolite concentrations can be measured. It is also technically possible to simultaneously measure brain activity during the task by alternating (interleaving) the fMRS sequence with a functional Magnetic Resonance Imaging (fMRI) sequence that is sensitive to the blood oxygenation level dependent (BOLD) response (Bednarik et al., 2015; Ip et al., 2017; Mangia et al., 2007). In this way, the relationship between task-induced chemical changes and task-induced activation patterns can be studied (Bednarik et al., 2015; Ip et al., 2017; Mangia et al). The provocation of symptoms by means of disorder-specific visual cues while measuring fluctuations in neurometabolite concentrations can therefore offer important insights into the neurochemical background of symptom development (Figure 1C). In addition, these insights can give direction to new pharmacological interventions to normalize neurotransmitter concentrations.
Recent fMRS studies in the healthy population focus primarily on the visual cortex because of the robust stimulus-related BOLD effects that are observed there. the same studies also show a relationship between neurotransmitter dynamics of glutamate and the BOLD response (Bednarik et al., 2015; Ip et al., 2017; Mangia et al., 2007). Given this relationship and the findings of the abnormal activation patterns in the LOC due to OCD-related stimuli, we expect that offering disorder-relevant visual stimuli in patients with OCD will lead to a greater increase in glutamate concentrations as well as a greater increase in brain activity, compared with healthy controls.

Study objective

The primary goal of this study is to gain insight into the role of glutamate in the LOC of OCD patients while observing symptom-inducing visual stimuli. This will be investigated by using fMRS on an ultra-high field strength MRI scanner (7T). This allows us to measure the concentration of glutamate in the LOC and how the concentration changes in response to viewing of disorder-relevant visual stimuli in OCD patients relative to age, gender and training matched healthy controls. The manufactured fMRS spectra also contain information about the (fluctuating) concentrations of GABA, the primary inhibitory neurotransmitter, and other neurometabolites. One of the secondary goals of this study is therefore to investigate the fluctuation in concentration of these neurometabolites. By alternating the acquisition of fMRS spectra (interleaving) with echo-planar imaging (EPI) volumes, the BOLD response - a proxy for brain activity - can be measured simultaneously while participants perform a symptom provocation task. The second secondary goal of this study is therefore to measure symptom provocation-related brain activity in the LOC. Based on this combined fMRS / fMRI sequence, the relationship between brain activity and metabolite dynamics in the LOC can also be examined during the

performance of the symptom provocation task.
In addition, using this technique in combination with high-resolution structural anatomical scans and diffusion tensor imaging (DTI), the relationship between neurometabolite dynamics and OCD-specific structural characteristics can also be examined

Study design

If patients want to participate, after sending the patient's information letter and after the relevant reflection period has elapsed, the researcher will contact the subject to discuss the purpose of the study by telephone and to answer any questions from the potential participant. An informed consent will be sent to request permission for an initial screening for MRI contraindications and the collection of demographic information (Social history). After successful (pre) screening, participants will be invited to come to the Spinoza Center in Amsterdam for a clinical evaluation, neuropsychological examination and the production of brain scans (total duration of five hours, including one hour of scanning). If possible and willing, participants from another ongoing study in OCD patients (NL61982.029.17) will also be invited to participate in the current study. The clinical scales and neuropsychological tests have been harmonized over these two studies so that the results can be exchanged. When this happens, participants would only come to sign informed consent and undergo the scan (total duration: 75 minutes). During the clinical evaluation, additional (screening) questionnaires will be filled in / taken that relate to the severity, duration and development of the OCD symptoms (Yale-Brown Obsessive Compulsive Scale [Y-BOCS], The Dimensional Yale-Brown Obsessive-Compulsive Scale [DY-BOCS] and OCD Age of Onset questionnaire). The presence of possible comorbid psychiatric disorders (Structured Clinical Interview for DSM-5 [SCID-5]), depression (Hamilton Rating Scale for Depression [HAM-D]), Tic disorder / Gilles de la Tourette will also be examined (Tic form), anxiety (Hamilton Rating Scale for Anxiety [HAM-A]) or sleep problems (Epworth sleepiness Scale [ESS] and Pittsburgh Sleep Quality index [PSQI]). In addition, additional questionnaires will be taken to map out various characteristics of the participant and to rule out possible contraindications for participation in the study, including: possible psychological disorders of first-degree family members (Family History Form), treatment history (Treatment history form)) and possible neurological or severe somatic disorders (General Medical history form).
After successful screening, the study will be continued with the neuropsychological examination. Three short neuropsychological tasks are performed on paper to determine cognitive functions (Montreal Cognitive Screening Assessment [MOCA] and Dutch Reading Proficiency Test for Adults [NLV]). Participants will then perform three computer tasks that again look at cognitive functions planning and response inhibition (Tower of London task [TOL], stop signal task [SST] and Temporal discounting task [ICT]. These neuropsychiatric tasks are taken to measure the cognitive functioning of

patients and healthy controls (sample description) and to include them as covariates in the static model Participants will also complete a few questionnaires to look at: OCD subtype (Obsessive Compulsive Inventory [OCI]), presence of autism (Autism Spectrum Questionnaire [ASQ]), childhood trauma (Childhood Trauma Questionnaire [CTQ]), Disgust (Disgust questionnaire), hand preference (PhenX Hand Dominance index) and insomnia and sleepiness (Pittsburgh Sleep Quality Index [PSQI] and Epworth Sleepiness Scale [ESS]).
As a final part of the study site, participants will undergo the MRI scans. All participants will be instructed not to take caffeine or nicotine at least two hours before the scan so as not to disturb the measurement of neurometabolite concentrations. Participants are once more screened for possible MRI contraindications (e.g. metal in the body). The scanning procedure consists of a T1-weighted structural MRI scan for the individual localization of the LOC, acquisition of the combined fMRS / fMRI sequence during the performance of the symptom provocation task (Protocol Figure 2) and an ultra-high resolution DTI scan. During the task, participants see photos of objects and situations that have been selected to provoke OCD symptoms. OCD patients are shown disorder specific stimuli that are contrasted with neutral stimuli (matched for color and contrast) plates (Figure 2). These visual stimuli were used earlier during an emotion regulation study and validated in the context of that study (de Wit et al. 2015). The photos are projected on a screen behind the 7T MRI scanner that participants can see through a mirror mounted on the MRI main coil. Immediately before and after performing the task, the participant will be asked how serious the symptoms are at that moment (on a scale from 0 to 100, respectively "very relaxed" to "extremely tense"). To ensure that participants view the visual stimuli carefully, they will be instructed to respond to each photo by pressing a button on an MRI-compatible button box in response to numbers shown at the bottom of every stimulus. Any eye abnormalities can be corrected by wearing MRI compatible glasses. Participants are instructed to remain as still as possible during scanning. To further reduce movement artifacts, the head will be immobilized with soft cushions. The scan protocol takes around 60 minutes in total.
*

Study burden and risks

In the context of this study, participants are asked a number of questionnaires that relate to the severity of the symptoms of OCD, mood (depression and anxiety) and sleep (problems). Part of these questionnaires can already be completed at home on paper or online before participants come to the research center. In addition, five short neuropsychological tests are performed for brain scan research to measure cognitive functions. Taking these tests and the questionnaires together take approximately four hours.
The brain scan examination also takes approximately 60 minutes. A number of different scans will be made during this investigation. With most scans, participants do not have to do anything except stay still. During a scan, participants perform a symptom provocation task to elicit OCD symptoms through

visual stimuli related to OCD. Healthy controls perform the same task.
No health risks are expected from participation in this study. This study does not involve any intervention. We screen for possible causes for damage due to the magnetic field of the MRI scanner (Appendix A in the research protocol). If the screening is positive, that particular participant is excluded from participation. Participants may experience slight dizziness when entering the scanner room and mild muscle twitching while scanning. This is normal.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients diagnosed with OCD (18 - 70 years) according to the DSM-5 criteria (American Psychiatric Association, 2013), with a Y-BOCS score of * 16.

Age, gender and education matched healthy control participants free from psychiatric, neurological or severe somatic disorders.

Exclusion criteria

Contraindications for MRI examination; e.g. metal in the body, claustrophobia.

Problems with or shortness of breath when lying flat for 60 minutes.

Traumatic brain injury involving a cerebral contusion with 1) loss of consciousness for more than 15 minutes and 2) post-traumatic amnesia of more than one hour.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-09-2018
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO

Date:	20-02-2017

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2019
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	NL59569.029.16