Effects of deep brain stimulation on eye movements

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Primary Objective: Is there an effect of DBS on eye movements?Secondary Objective: Are there different effects of DBS on eye movements by targeting different structures in the brain?

Ethical review	Approved WMO
Status	Pending
Health condition type	Neurological disorders of the eye
Study type	Observational non invasive

Summary

ID

NL-OMON36854

Source
ToetsingOnline

Brief title
DBS and eye movements

Condition

- Neurological disorders of the eye

Synonym
eye movement disorders

Research involving
Human

Sponsors and support

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

Intervention

Keyword: deep brain stimulation, Dytonia, essential tremor, eye movements, Parkinson□s disease, Tourette Syndrom

Outcome measures

Primary outcome

1) saccades:

a. latency: time between the onset of the target (i.e. the point of light) and

the beginning of the eye movement.

b. accuracy of saccadic eye movements: final eye position over the final

position of the point of light

2) smooth pursuit:

max. speed of the eye over the speed of the point of light at 0.2 Hz & 0.4 Hz

3) gaze-holding functioning:

fixation nystagmus while looking straight ahead, left, right, up and down

4) head impulse test:

max. speed of the eye over the max. speed of the head in the opposite

Secondary outcome

The above mentioned parameters of one subgroup will be compared with the

parameters of another subgroup (i.e. Parkinson*s disease versus essential

tremor, Parkinson*s disease versus dystonia)

Study description

Background summary

Several different pathways in the brain are involved in the control of eye movements. For instance, they are important to look quickly from one object of interest to another (i.e. saccades), to follow slowly moving objects (i.e. smooth pursuit) or to keep a stationary object of interest focused (i.e. gaze). The pathways important for eye movements are located in close proximity to pathways in the brain important for limb movements. For example, there are the basal ganglia-thalamocortical pathways connecting the cortex with the basal ganglia based on the classic concept by Alexander et al. (Ann. Rev. Neurosci 1986). In close proximity to the motor circuit, important for limb movements, is the oculomotor circuit of the basal ganglia-thalamocortical pathways, connecting the frontal eye field to the basal ganglia (incl. nucleus caudatus, globus pallidus and substantia nigra) and projecting via the mediodorsal thalamus back to the cortex. Diseases of the basal ganglia such as Parkinson*s disease or Dystonia affect the functioning of several circuits (Pinkhard et al. BMC Neurology 2012, Stell et al. JNNP 1990). Thus, limb motor and eye movement deficits such as deficits with saccadic eye movements and smooth pursuit can be found in patients with Parkinson*s disease. Another system important for limb and eye movements is the cerebello-thalamo-cortical pathways (Macchi and Jones et al. J. Neurosurg. 1997). These pathways originate in the cerebellar nuclei and lead into the ventrolateral thalamus which is right lateral to the mediodorsal thalamus. The ventrolateral thalamus projects predominantly to the motor cortex, but also to the prefrontal and vestibular cortical areas. The cerebello-thalamo-cortical pathways are also important for saccadic eye movements and smooth pursuit. For instance vascular lesions of the ventrolateral thalamus cause an impairment of saccades in the contralateral direction and smooth pursuit deficits to the ipsilateral direction (Brigell et al. Ann Neurol 1984; Rosseaux et al. Rev. Neur. 1985; Hirose et al. Neurology 1985). Furthermore, diseases such as essential tremor with its pathophysiology being closley connected to a disturbance of cerebello-thalamo-cortical pathways go along with smooth pursuit deficits (Helmchen et al. Brain 2003). A third system important for controlling eye movements is the medial longitudinal fasciculus connecting the midbrain with the brainstem. This fasciculus runs close to the midline, that is medial to the mediodorsal nucleus, and is important for gaze. For instance, patients with very medial thalamic lesions cannot keep looking their eyes on one object (Deleu, Acta Neurol Scan 1997; Joni and Gregory, Stroke 1995).
Some of these systems appear to have distinct functions while others share some of their properties. However, direct comparisons of their functions (or malfunctions as part of an underlying disease process) in eye movements have not been studied in detail.
Deep Brain Stimulation targeting different subcortical structures such as the

subthalamic nucleus, Globus pallidus or ventrolateral thalamus is a well established treatment for patients with movement disorders such as Parkinson*s disease, essential tremor or Dystonia. Furthermore, reports on the effects of DBS in patients with Tourette Syndrome as an experimental approach are promising (Ackermans et al. Brain 2011). For Deep Brain Stimulation, stimulation electrodes are implanted in the brain, which are connected to a pacemaker implanted in the subclavian region. It is believed that Deep Brain Stimulation reduces pathological over-activity in the neuronal network adjacent to the targeted structure (McIntyre et al. Clin. Neurophysiol 2004). For instance, this causes a clear cut improvement of bradykinesia and rigidity at the limbs in Parkinsonian patients. The advantage of Deep Brain Stimulation over lesioning the targeted structure comes from the adaptability of the programming to maximize symptom control and to avoid side effects. Furthermore, the effects of Deep Brain Stimulation are completely and immediately reversible, as it can get switched *off* and *on* any time. In some cases the patients do that themselves at night to save battery life time.

As pathways in the brain important for limb movement run in close proximity to pathways involved in eye movements, one may expect that Deep Brain Stimulation has an effect on both limb and eye movement. First reports from international research groups and publications from the universities of Maastricht and Aachen suggest that Deep Brain Stimulation does indeed effects eye movements as well. For instance, Deep Brain Stimulation targeting the subthalamic nucleus improved the latency of saccadic eye movements in Parkinsonian patients (Temel et al., Exp. Neurol. 2009), while it impaired the accuracy of saccades in patients with essential tremor and Deep Brain Stimulation targeting ventrolateral thalamus (Kronenbuerger et al., Brain Stimulation 2010) or caused a vertical gaze palsy in a patient with Tourette Syndrome treated with Deep Brain Stimulation targeting the very medial thalamic nuclei (Ackermans et al. Neurosurgery 2007).
The direct comparison of eye movement functioning with Deep Brain Stimulation targeting different subcortical structures in patients with different diseases and with stimulation switched *on* and *off* may be helpful to better understand the role of subcortial pathways in the control of eye movements.

Thus we intend to study four patient populations: (1) patients with Parkinson*s disease treated with Deep Brain Stimulation targeting the subthalamic nucleus or Globus pallidus, (2) patients with essential tremor treated with Deep Brain Stimulation targeting the ventrolateral thalamus, (3) patients with Dystonia treated with Deep Brain Stimulation targeting the Globus pallidus internus and (4) patients with Tourette Syndrome treated with Deep Brain Stimulation targeting the medial thalamus or the Globus pallidus. The patients will be studied twice: once with Deep Brain Stimulation switched *on* and once with Deep Brain Stimulation *off* while performing different eye movement tasks (i.e. tasks of saccades, smooth pursuit and gaze). We would like to assess 12 patients with Parkinson*s disease, 12 patients with essential tremor, 6 patients with Tourette Syndrome and 6 patients with Dystonia. All patients are

patients that have obtained Deep Brain Stimulation either at the University Hospital in Maastricht or at the University Hospital in Aachen.
As Deep Brain Stimulation reduces pathological over-activity, we expect an improvement of eye movement deficits as part of the disease process. In contrast, we expect an impairment of eye movements with Deep Brain Stimulation in tasks that are not affected by the disease.

For the literature citated , please refer to the reference section of the Template Research Protocol on page 28.

Study objective

Primary Objective:
Is there an effect of DBS on eye movements?

Secondary Objective:
Are there different effects of DBS on eye movements by targeting different structures in the brain?

Study design

This study is a DBS-on versus DBS-off comparison (paired comparison). Thus eye movement parameters will be assess and compared when DBS is switched on and off. Additionally we will also compare the effects of DBS of different targets in the brain on different eye movements. Therefore different patient populations treated with DBS will be assessed and compared (comparison of different groups).

Study burden and risks

The equipment of the oculomotor laboratory of the ear, nose and throat clinic of the academisch ziekenhuis Maastricht are used for the eye movement recording. This equipment is also used in the routine care. The eye movement recording is done by attaching skin electrodes next to both eyes, which causes no discomport. Additionally the patients are seated on a comfortable chair and asked to look toward a screen where the light point is projected. This step up allows the recording of eye movements with great precision but without discomfort to the patients.
The examination of the eye movement will take about twice 30 minutes (once with DBS switched on and once with DBS switched off). When stimulation is switched off, the patients will have their symptoms similarly to the extent before the DBS was started. Thus during the DBS-off test period they will have bradykinesia, rigidity, tremor, dystonia or tics. This starts about 5 minutes after the DBS is switched off and disappears within 5 minutes when DBS is again switched on. Studying the patients when DBS is switched off is important to assess the eye movements without DBS and to compare the above mentioned

parameter to the situation when DBS is switched on. Only with this approach we can find out, if DBS has effects on eye movements.
The eye movement analysis will be performed on the days when the patients have their regular outpatient control visits to the AZM. Thus the patient will not spend too much extra time for participation in this study (time investment for the patient for participation altogether: 80 minutes).
There are no medical risks involved by having the DBS turned off. However, there will be discomfort when the DBS is turned off. This is by far the only way to find out if DBS has an effect on the different eye movements. The knowledge about the effects of DBS on eye movements is important to get a deeper understanding of how the brain works and this may be the basis for new or better treatment options for patients with movement disorders or eye movement disorders. Furthermore, as DBS is increasingly applied for patients with movement disorders and is presently under the investigation for the treatment of psychiatric disorders, the knowledge about the effect of DBS in eye movements is important. This is because if may help to identify additional benefits of the DBS treatment or identifying side effect of DBS that may be important for the care of patients.

Minors and incapacitated patients will not be included into this study.

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 (age: 40 - 80) have Parkinson*s disease, essential tremor, Dystonia or Tourette Syndrom treated with DBS.
*The surgery took place at least 3 months prior to this eye movement study without complications.

Exclusion criteria

*Patients with other disease than the above mentioned
*Intraocular disease such as macular degeneration
*Strabismus
*Deformities of the eye bulb
*Minors and incapacitated patients

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2012
Enrollment:	36
Type:	Anticipated

Ethics review

Approved WMO Date:	08-11-2012
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL40933.068.12