Looking into the eye of ADHD. Investigating the relationship between ADHD, the delayed circadian rhythm and the functioning of the eye.

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The aim of this project is to investigate associations between visual system functioning, ADHD, and the circadian rhythm. We will also investigate the effects on the functioning of the visual system of commonly used treatments for ADHD and related…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vision disorders
Study type	Interventional

Summary

ID

NL-OMON55884

Source
ToetsingOnline

Brief title
Looking into the eye of ADHD.

Condition

- Vision disorders
- Cognitive and attention disorders and disturbances

Synonym
Attention-deficit/hyperactivity disorder (ADHD); eye functioning

Research involving
Human

Sponsors and support

Primary sponsor: Parnassia Bavo Groep (Den Haag)
Source(s) of monetary or material Support: Uit ASPASIA gelden van dr. Sandra Kooij aan VUmc,PsyQ Kenniscentrum ADHD bij volwassenen; ADHDFund

Intervention

Keyword: Adult ADHD, Circadian disturbances, Diagnostic test for ADHD, Eye functioning

Outcome measures

Primary outcome

Phase 1: A difference in the prevalence of refractive errors between the ADHD group and existing data from the general population; a difference in type and extent of refractive errors between patients and controls.

Phase 2: The Post-Illumination Pupil Response (PIPR) is the primary outcome measure.

In order to evaluate if the functioning of the ipRGCs is involved in ADHD and any reported oversensitivity to light, the pupillary reflex is used. In the pupillary reflex the pupil*s diameter is adjusted to light intensity, protecting the retina from damage and optimizing vision. The Post-Illumination Pupil Response (PIPR) after red and blue light, is a measureable parameter of the functioning of the ipRGC system, and therefore an interesting outcome measure in our study. The PIPR of each person is unique, with very high intra-individual test-retest consistency. Any change in the PIPR can thus be allocated to an intervention with high probability.

Secondary outcome

Phase 2:

- A change in outomes on the refractive error test for myopia

(nearsightedness), hyperopia (farsightedness), astigmatism (cylindrical error),

presbyopia (focus difficulty), and strabismus (alignedness of the eyes);

- A change in colour discrimination ability;

- A change in colour deficiency;

- A change in perimetry score (visual field);

- A change in the self-reported oversensitivity to light.

- A change in the performance on the QbTest, which measures ADHD symptoms

objectively;

- A change sleep/wake cycle as measured with actigraphy;

- A change in the self-reported ADHD symptoms on the ADHD Rating Scale

(ADHD-RS);

- A change in chronotype as measured by the Munich Chronotype Questionnaire

(MCTQ) and Morningness-Eveningness Questionnaire (MEQ);

- A change in fatigue as measured by the Multidimensional Assessment of Fatigue

(MAF);

- A change on the Seasonal Pattern Assessment Questionnaire (SPAQ);

- A change on the Quick Inventory of Depressive Symptoms (QIDS).

Study description

Background summary

The visual system may be affected in Attention-Deficit/Hyperactivity Disorder (ADHD). As much as 70-80% children with ADHD have ophthalmologic deficiencies including near- and farsightedness, cylindrical errors, cross-eyedness, depth detection problems, convergence insufficiency, and deviant optic disc size [1,

2]. Adults with ADHD have problems with depth and blue-spectrum colour perception, visual search and processing, and peripheral vision [3]. Moreover, visual problems in ADHD can be reduced with ADHD-medications [4]. The visual system deficiencies in individuals with ADHD may be related to a delayed circadian rhythm, which is already apparent in childhood ADHD [5], and is prevalent in 78% of adults with ADHD [6]. The circadian rhythm is orchestrated by the suprachiasmatic nuclei (SCN) in the brain, that receive input a.o. from the intrinsically photosensitive retinal ganglion cells (ipRGCs) in the retina. The ipRGC system responds to light intensity, especially blue wavelengths, and modulates a.o. the pupillary reflex and melatonin (*sleep hormone*) release [7]. We found an increased prevalence of oversensitivity to light in adults with ADHD as compared to controls [8], an indication for a deficiency of the ipRGC system in ADHD. In order to study the role of the ipRGCs and the visual system functioning in ADHD and healthy controls, we will measure the pupillary reflex, conduct ophthalmologic assessments, and objective eye functioning tests. We will determine the prevalence and type of visual system deficiencies, and their relationship with circadian rhythm, ADHD symptoms, and comorbid psychiatric disorders. The effects of a single-dose and a 3-week intervention of commonly used treatments in adults with ADHD and delayed sleep on the visual system functioning will be evaluated. Results give us insight into the relationship between ADHD, visual system functioning, and circadian rhythm, all by looking into the eye of ADHD. This may lead to a new and simple test for ADHD.

REFERENCES

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Study objective

The aim of this project is to investigate associations between visual system functioning, ADHD, and the circadian rhythm. We will also investigate the effects on the functioning of the visual system of commonly used treatments for ADHD and related disorders: methylphenidate and light therapy. In case we find visual system deficiencies that are specific to ADHD, the development of an objective diagnostic test for ADHD will come closer.

The following objectives and hypotheses are formulated:
Objective 1: To determine the prevalence and type of visual system deficiencies in adults with ADHD and in healthy controls.
Hypothesis 1: Adults with ADHD will have more visual system deficiencies.

Objective 2: To study the relationship between visual system deficiencies, ADHD symptoms, executive functioning, circadian rhythm, and comorbid psychiatric disorders.
Hypothesis 2: Any relationship between visual system deficiencies and ADHD will be mediated by a circadian rhythm disturbance.

Objective 3: To evaluate the single-dose effect of methylphenidate and bright light on the visual system functioning in adults with ADHD.
Hypothesis 3: These single-dose interventions will lead to changes in visual functioning.

Objective 4: To evaluate the effect of a 3-week treatment with these agents on the visual system functioning in adults with ADHD.
Hypothesis 4: Longer duration of treatment will result in larger effects on the functioning of the visual system.

Study design

The study consists of two phases, (1) exploring eye functioning in ADHD and healthy controls in an observational case-control design, and (2) an experimental randomized controlled trial on the effect of a single dose and a 3-week treatment period of these commonly used treatments on eye functioning.

Phase 1: Exploring eye functioning in ADHD and healthy controls

- Meeting objective 1: To determine the prevalence and type of visual system deficiencies in adults with ADHD and in healthy controls.
- Meeting objective 2: To study the relationship between visual system deficiencies, ADHD symptoms, circadian rhythm, and comorbid psychiatric disorders.

In Phase 1, the prevalences of eye abnormalities and characteristics of the visual system will be explored in ADHD patients (n=41) and in healthy controls (n=41), using the full battery of assessments (total N=82), which are summed in paragraph E4.

Phase 2: Effect evaluation of a single dose and a 3-week treatment period of these commonly used treatments on retinal functioning

- Meeting objective 3: To evaluate the single-dose effect of methylphenidate and bright white light on the visual system functioning in adults with ADHD.
- Meeting objective 4: To evaluate the effect of a 3-week treatment with these agents on the visual system functioning in adults with ADHD.
ADHD patients that have participated in Phase 1 will be randomized for any of the interventions or for a placebo condition (as a control condition for Mph) or for a waiting list group (as a control condition for LT). Participants that have already participated in Phase 1, with major substance abuse, or any contra-indication for the interventions will be excluded. Each group will have n=20 participants per group. All conditions and medication intake schedules are designed according usual treatment regimes.
There will be a placebo condition for Mph, and a waiting list group as a control condition for LT. Thus, in this example the following conditions will be evaluated, N=40:

i. Methylphenidate vs. placebo: Randomization is double blind.
- 1A) Mph, 3 x 20 mg/day at 8 AM, 12 PM and 4 PM during 3 weeks, n=10
- 1B) Placebo, 3 x 20mg/day at 8 AM, 12 PM and 4 PM during 3 weeks, n=10

ii. Light Therapy vs. waiting list: Randomization is open because there is no alternative good control condition for LT.
- 2A) LT, 30 minutes/day in the morning during 3 weeks, n=10
- 2B) Waiting list during 3 weeks, n=10

After a single dose, the PIPR will be re-assessed. After the 3-week intervention period, the total assessment battery (see paragraph E4) will be re-assessed. The intra-individual change of the outcomes between the Phase 1 and the Phase 2 measurements will be compared between the Mph and the placebo group, and between the LT and waiting list group.

Intervention

In Phase 2:
- 3 x daily 40 mg immediate release Methylphenidate (Ritalin) at 8 AM, 12 PM, and 4 PM
- once daily 30 minutes of bright light therapy (10.000 lux at 20 cm from the eyes) between 7 and 10 AM

Study burden and risks

The time needed to test one individual is estimated at 2.5 hours, of which 1.5h for eye functioning assessments. If an individual is tested twice, the total duration of the assessments is 5 hours. The eye assessments may lead to tired eyes. Wearing an actiwatch is deemed minimally burdening. The questionnaires are in nature not burdening to the participants. In Phase 2, the participant will get a 3-week intervention period of placebo or methylphenidate, or has a half hour of bright light therapy. These interventions are very common in adults with ADHD.

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

Patient group and control group: Age 18 to 40 years old.
Patient group: Diagnosis of ADHD.
Control group: matched for age (+/- 5 years) and sex to included patient.

Exclusion criteria

Patient group and control group: Severe psychiatric comorbidity; substance abuse; contraindication for the intervention.
Control group: ADHD; use of stimulant medication.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-10-2016
Enrollment:	82
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ritalin
Generic name:	Methylphenidate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-02-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	31-03-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	24-11-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	14-10-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	15-11-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	09-06-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	10-07-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	14-01-2019

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	14-07-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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
EudraCT	EUCTR2013-005017-12-NL
CCMO	NL47188.058.14

Study results

Date completed:	10-05-2021
Actual enrolment:	41