

Assessing the relation between medication, eye movements, and Autonomic Nervous System (ANS) functions in children and adolescents with ADHD.

Purpose and aims:

How objective measures such as measures of the autonomic nervous system (ANS) and eye movements are related to ADHD is insufficiently studied. Further, it is largely unknown how ADHD medication affects these biomarkers. The overarching purpose of the proposed study is to increase the understanding of mechanisms underpinning effects (symptom reduction, as well as side effects) of medication in children and adolescents with ADHD.

Specifically, we aim to examine the following research questions (RQs):

RQ1) Are there associations between:

- 1) symptom level and eye movement measures?
- 2) medication and changes in eye movement measures?
- 3) eye movement measures and symptom level changes?
- 4) eye movement measures and side effects?

RQ2) Are there associations between:

- 1) symptom level and pupil dilation?
- 2) medication and changes in pupil dilation?
- 3) pupil dilation and symptom level changes?
- 4) pupil dilation and side effects?

RQ3) Are there associations between:

- 1) symptom level and pupillary light reflex?
- 2) medication and changes in pupillary light reflex?
- 3) pupillary light reflex and symptom level changes?
- 4) pupillary light reflex and side effects?

RQ4) Are there associations between:

- 1) symptom level and heart rate variability (HRV)?
- 2) medication and changes in HRV?
- 3) HRV and symptom level changes?
- 4) HRV and side effects?

Survey of the field:

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder manifested by core symptoms of inattention and hyperactivity/impulsivity and associated with a range of negative consequences (American Psychiatric Association, 2013). It is one of the most prevalent psychiatric conditions, affecting 5-7% of children/adolescents (twice as many boys as girls), and consumes a large proportion of the resources in psychiatric care (Willcutt, 2012).

Medication in ADHD

Medications for ADHD (mostly psychostimulants) are efficient in reducing ADHD symptoms, although effectiveness studies do not show equally good results (Cortese, 2018; Posner 2020). Psychostimulant prescription rates have increased the latest decades (Gomez-Lumbreras et al., Psychopharmacology 2021), but there are differences in prescription rates between countries (Gomez-Lumbreras, 2021) and between domestic regions that cannot be solely explained by prevalence differences of ADHD (Socialstyrelsen, 2018). Very little is

known about predictors for treatment response and side effects. Considering the large burden that ADHD medication has for the psychiatric care, and the lack of knowledge on long-term effects, it would be preferable to be able to identify possible responders and non-responders beforehand. Although some possible predictors have been suggested to be associated with positive or negative treatment response, studies have not been conclusive (Raman et al., 2015; Pagerols et al., 2018; Elsayed et al., 2020; Lilja et al., 2025). Tools for treatment prediction within psychiatric care should preferably be objective biomarkers that are easy to measure.

Autonomic Nervous System (ANS) and ADHD

The ANS is part of the central nervous system and is involved in regulation of bodily functions such as heart rate, respiration, and pupil dilation. Dysfunction of the ANS, particularly hypo-activation has been proposed in ADHD (Bellato et al., 2020). For example, HRV concerns variation in the interval between heartbeats, and is regulated by the ANS. HRV increases during relaxation and decreases during stress, and these processes may be altered in individuals with ADHD (Bellato et al., 2020). Pupil dilation concerns increases in pupil size as an index of arousal, is also related to the ANS and assumed to be altered in ADHD (Kleberg et al., 2021a). A related promising but relatively unexplored biomarker is the pupillary light reflex (i.e. the constriction and dilation of the pupil in response to light) that seems to be altered in children with ADHD (Hamrakova et al., 2021). The relation between ANS markers and ADHD have however not been clear-cut, and one plausible reason for obscuring the results so far has been suggested to be different medications statuses of study participants (Bellato, 2020). Information on how ADHD medication affects the above suggested biomarkers is insufficient.

Eye tracking

Eye tracking is a rapidly evolving technology that is time efficient, relatively inexpensive, and completely non-invasive. Eye tracking measures gaze allocation and changes in pupil size that appear at a very short time scale (typically 120-1000 HZ). Eye movements indicate where a person attends, whereas task-related changes in pupil size (the pupil dilation response) is a physiological index of attention and arousal, strongly influenced by activity in the brain's locus coeruleus noradrenergic (LC-NE) system. The LC-NE system is one of the brain's most important attention networks, closely linked to processing of motivationally important stimuli (Aston et al., 2005). In a recent study of a population-based twin sample, premature eye movements in an anti-saccade task were shown to be associated with severity of ADHD traits, and to inattentive traits specifically (Siqueiros Sanchez et al., 2020). The eye region is the most informative part of the face (Senju et al., 2009). Recent research suggests that children with ADHD may show specific impairments related to processing of other's eye gaze. For example, children with ADHD often fail to attend to others' eyes during emotion recognition (Airdrie et al., 2018), and are not using others' gaze direction to guide their attention (Marotta et al., 2017). Using eye-tracking, we have recently studied how ADHD traits are linked to eye preference in children with and without ADHD, aged 8-13 years (N = 82, 40% with ADHD) (Frick et al., 2022). We used the eye preference task (EPT) in which the study participants were primed to look towards the eyes or the mouth of depicted faces and found that a reduced latency to *orient away* from the eyes was associated with high levels of inattention. We found that longer looking in the eyes before reorienting was independently associated with concurrent symptoms of inattention with control for comorbid symptoms (both internalizing and externalizing symptoms). This was also significantly correlated with inattention and externalizing symptoms two years later. The eye-preference measure in the study showed excellent internal psychometric consistency (Cronbach's $\alpha = 0.93$), suggesting that it may be feasible as a marker task in treatment research. How eye movements, the pupillary light reflex and pupil dilation are associated with ADHD medication has to our knowledge not been investigated.

Project description

Theory and method

The study has a quasi-experimental pretest posttest design that will be performed within child and adolescent psychiatry (CAP) in Västerbotten. At least $n=150$ individuals aged 6-17 years diagnosed with ADHD will be invited to participate in the study. Power analyses accounting for the hierarchical nature of the data (with variation within and across individuals) were conducted using Monte Carlo simulations using the *simr* package (Green & MacLeod, 2016) implemented in R (R Core Team, 2013). These analyses were conducted based on observed covariances between trials from the same individuals (random effect covariances) from eye tracking studies in children of similar ages conducted by collaborators (e.g., Kleberg et al., 2021a; Kleberg et al., 2021b). Based on previous data collected by the applicant (Lilja et al., 2025), it was assumed that 1/3 of participants could be categorized as responders. Based on these assumptions, the study has 96% power to detect moderate effects (Cohen's $f^2 > 0.15$) at a sample size of 175, 85% with a sample size of 150, 84% with $n = 125$, and even 73% with a small sample size of $n = 100$. Exclusion criteria will be diagnoses of arrhythmia, cardiovascular disease, or ongoing substance abuse, concomitant use of non-steroid asthma medications or beta-blockers, and the inability to fulfill the study participation before the participant's 18th birthday. No caffeine intake will be allowed 4 h prior to ANS and eye tracking measurements.

Data collection:

Eye movement and ANS measures will be collected before medication start and at a follow-up measurement approximately 2-3 months after the first measurement. Symptom screenings, and screening of side effects will be collected before the first measure, and at the follow-up. For a subset of children the eye movement and ANS measurements will be made before and after the intake of ADHD medication, both at baseline and at the follow-up.

Assessment:

Rating scales

SNAP-IV-parent- and teacher-rated (Bussing et al., 2008), and the World Health Organization Adult ADHD Self-Report Scale for adolescents (Sonnby et al., 2015) will be used to measure ADHD symptoms. The Pediatric side-effects checklist (P-SEC) will be used to screen for side effects. To measure other psychiatric symptoms we will use SCAS, ASSQ, SDQ-Sve, ACE-Q SE, and ARI.

Equipment

ATobii Pro Spectrum 1200 HZ eye tracker (Tobii, Stockholm, Sweden) will be used to measure eye movements, pupil dilatation and the pupillary light reflex. Bio-tracer NeXus 10 device with bipolar ECG channels (MindMedia, Herten, the Netherlands) will be used to measure HRV with 10 min baseline registration with no intervention in supine position, after 15 min rest.

Analyses:

To judge if the child is a responder to ADHD medication the SNAP-IV rating of ADHD symptoms (before and at three-month follow-up after medication start) is used. Children, who at three months have a minimum of 40% reduction in SNAP-IV score, are classified as "responders". According to previous studies, 40% threshold has shown well coherence with the degree of change in the SNAP-IV rating scale score that predominantly correspond to a substantial clinical effect, in regards of ADHD characteristic symptoms (Newcorn et al., 2008; Newcorn et al., 2009). Those who have a smaller than 20% change in SNAP-IV score are classified as "non-responders".

- 1) The associations between ADHD symptoms and the ANS and eye movement measures will be explored with linear regression models with ADHD symptom load as independent variable, and the ANS or eye movement measures as dependent variables.
- 2) The associations between medication and changes in the ANS or eye movement measures will be measured with linear regression models with the time-point as independent variable and the change in the measure as independent variable
- 3) The associations between the ANS or eye movement measure changes and ADHD symptom changes will be explored both with logistic regression (for the primary outcome of the study) with the ANS or eye movement measures as independent variables and medication responder status as dependent variable, as well as with linear regression with the ANS or eye movement measures as independent variables and the change in ADHD symptoms as dependent variable after correction for symptoms at baseline.
- 4) The associations between the ANS or eye movement measure changes, and side effects, will be explored with logistic regression with the ANS or eye-tracking measures as independent variables and side-effects as the dependent variable.

Time plan

2025:	Application for ethical approval Training in equipment use PhD Student recruitment
2026:	Pilot study Preparation of Database and data entry interface Enrollment of study participants
2027:	Enrollment of study participants
2028:	Enrollment of study participants Data analysis
2029:	First publication

Implementation

Data collection will be performed in the premises of the Child and Adolescent Psychiatry Västerbotten. A 50% project nurse/project assistant will help coordinate the data collection, and transfer of the data into the database. To proceed more efficiently, the proposed study will recruit a PhD student.

Project organization:

The applicant Associate Professor Linda Halldner Henriksson will be PI for the proposed project. Halldner Henriksson is a senior consultant in child and adolescent psychiatry at BUP Västerbotten as well as adjunct lecturer at Umeå University. She has initiated the project and designed the study. She will be leading the project forward and supervise the PhD student in the study

Associate Professor Johan Lundin Kleberg is a researcher at the Department of Clinical Neuroscience, Karolinska Institutet, and senior lecturer at the Department of Psychology, Stockholm University, and a clinical psychologist. He is an expert in eye tracking and pupillometry and has extensive experience from studies using these methods in children with ADHD and other neurodevelopmental disorders.

Associate Professor Lundin Kleberg is participating researcher in this project. He has already contributed with his vast experience from this research field when designing the study. He will continuously be assisting in the ongoing designing of the set-up of the study, and future analyses of collected data.

Significance

There are so far, to our knowledge, few or no studies on the relation between ANS functioning (including eye-tracking technology) and ADHD medication. Although medication status is often referred to as a possible confounder or limitation in studies of ANS and eye-tracking measures in ADHD. Thus, the proposed study would ease the interpretation of previously inconclusive studies on the subject. The design of the proposed project will allow for studying both associations between ANS, eye-tracking measures, and ADHD medication, as well as how observed treatment responses can be predicted by baseline eye-tracking, ANS, and/or symptom measures.

The information that the proposed study has potential to produce, will further elucidate the physiological underpinnings of clinical ADHD, and may detect new clinical phenotypes of ADHD. This will help ameliorate future medication trials and development of personalized medicine in the field of ADHD management.

Equipment

To answer the research questions an eye tracker with high resolution and the ability to measure both eye movements, pupil dilation, as well as pupillary light reflex is needed. The ATobii Pro Spectrum 1200 HZ (Tobii, Stockholm, Sweden) is well suited for these tasks. Funding of part of the cost for an eye tracker was granted by ALF Investeringar for 2022 and procured during 2023.

Bio-tracer NeXus 10 device with bipolar ECG channels (MindMedia, Herten, the Netherlands) has already been acquired by Associate Professor Henje, Child and Adolescent Psychiatry Umeå university, and will be accessible also for the here described project.

International and national collaboration

This study is a collaboration with researcher Associate Professor Lundin Kleberg, at Stockholm universitet and Karolinska Institutet. In case the study participant recruitment is too slow, collaboration with other CAP/BUP units in Sweden may be needed. Initial contacts with several Swedish CAP clinics have been made, resulting in positive response and interest in the future study participation.

Clinical significance

The three-month follow-up enables investigation of if baseline-measures and/or the short-term effects of medication on ANS and eye-tracking measures, could be used to predict the effectiveness or side effects of the medication. To date, predictors of treatment outcome are non-existent for staff in clinical practice. Nevertheless, ADHD medication trials constitute a large part of the operational child and adolescent psychiatry leading to shortage of resources for other clinical needs. In the light of recurrent reports on increasing mental health problems in adolescents it is of utmost importance to direct the right treatments to the right patients as efficiently as possible.

Ethical considerations

Eye-tracking technology and assessment of HRV using a bio tracer are non-invasive methods and associated with no risks for the participants. The methods are well used, by us and others. The participants will be patients that were assessed to be candidates for, and offered treatment with, ADHD medication within the ordinary CAP practice. That is, participants will not be exposed to substances they would otherwise not take. Some participants may experience the filling in of rating forms and the assessment time tedious.

Regarding the large knowledge gap on the relation between ANS and eye movement measures and ADHD medication and the vast yearly number of children starting ADHD medication trials we judge that the possible gains with this study exceed the risks it may entail. Application for ethical permit of the proposed study from the ethics review authority (etikprövningsmyndigheten) will be submitted.

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