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Erica Jostrup

LUND UNIVERSITY

DOCTORAL DISSERTATION

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Title and subtitle: Sensory noise as a possible non-pharmacological intervention for children with attention-deficit/hyperactivity disorder

Abstract:
Background: Children diagnosed with attention-deficit/hyperactivity disorder (ADHD) commonly exhibit academic underachievement. The condition is thought to be linked to a dysregulation of the dopamine (DA) and norepinephrine (NE) systems, which are normalized with pharmacological medication. While pharmacological and non-pharmacological interventions are available, more than 50% abort treatment after one year, and children with ADHD continue to struggle to achieve academic performance levels comparable to their typically developing peers.

Previous research suggests that white noise stimulation may enhance cognitive performance in children with ADHD. While many of the existing studies have used auditory white noise, the theoretical framework of this thesis suggest that noise stimulation in any sensory modality could yield similar benefits as from auditory noise. This thesis also investigates potential regulatory effects from white noise stimulation on DA and NE through the measurement of blink rate and pupil diameter, which serve as proxies for these neurotransmitter systems.

Methods: Three distinct noise modalities – auditory, visual, and vestibular – were examined regarding their ability to affect cognitive performance, pupil diameter and blink rate in children with ADHD and typically developing children (TDC). Each noise modality was compared against a no-noise condition, during tasks previously validated for their sensitivity in discerning differences between children with ADHD and TDC. Performance on the tasks was evaluated in relation to the different groups (ADHD and TDC), while blink rate and pupil diameter were assessed regarding their relationship to ADHD symptom severity in the entire sample.

Results: No beneficial effects on cognitive performance attributable to noise stimulation were observed, irrespective of noise modality. Furthermore, no relationship between blink rate or pupil diameter and ADHD symptom severity was found. The level of symptoms experienced did not predict pupil diameter or blink rate without noise. Neither did it interact with the noise stimulation in any way. However, boys had significantly larger pupil diameters compared to girls during both the no-noise condition and during auditory white noise stimulation. The boys were significantly affected by the noise stimulation.

Conclusions: White noise stimulation seems to be ineffective in improving cognitive performance for children with ADHD in several tasks related to working memory and executive function. Additionally, blink rate and pupil diameter do not seem to be reliably associated with ADHD symptom severity, nor modulated by auditory white noise stimulation. However, the pupil diameter in boys was consistently larger throughout the entire task as a result of the noise stimulation. The fact that only boys, and not girls, were significantly affected by the auditory white noise stimulation suggests that individual differences may influence responsiveness, warranting further investigation into potential influencing factors.

Key words: Attention-deficit/hyperactivity disorder, auditory white noise, visual white pixel noise, stochastic vestibular stimulation, cognitive performance, eye tracking, pupil diameter, blink rate.

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To Oliver and Elias

"The only way to achieve the impossible
is to believe it is possible"
Alice in Wonderland

Table of Contents

Abstract

Background

Children diagnosed with attention-deficit/hyperactivity disorder (ADHD) commonly exhibit academic underachievement. The condition is thought to be linked to a dysregulation of the dopamine (DA) and norepinephrine (NE) systems, which are normalized with pharmacological medication. While pharmacological and non-pharmacological interventions are available, more than 50% abort treatment after one year, and children with ADHD continue to struggle to achieve academic performance levels comparable to their typically developing peers.

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Three distinct noise modalities – auditory, visual, and vestibular – were examined regarding their ability to affect cognitive performance, pupil diameter and blink rate in children with ADHD and typically developing children (TDC). Each noise modality was compared against a no-noise condition, during tasks previously validated for their sensitivity in discerning differences between children with ADHD and TDC. Performance on the tasks was evaluated in relation to the different groups (ADHD and TDC), while blink rate and pupil diameter were assessed regarding their relationship to ADHD symptom severity in the entire sample.

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No beneficial effects on cognitive performance attributable to noise stimulation were observed, irrespective of noise modality. Furthermore, no relationship between blink rate or pupil diameter and ADHD symptom severity was found. The level of symptoms experienced did not predict pupil diameter or blink rate without noise. Neither did it interact with the noise stimulation in any way. However, boys had significantly larger pupil diameters compared to girls during both the no-noise condition and during auditory white noise stimulation. The boys were significantly affected by the noise stimulation.

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Populärvetenskaplig sammanfattning

Bakgrund

Attention-deficit/hyperactivity disorder (ADHD) är en vanlig neuropsykiatrisk diagnos som påverkar ungefär 5% av jordens barn, med en större andel pojkar än flickor. Diagnosen debuterar oftast i barndomen och kännetecknas av svårigheter med uppmärksamhet, hyperaktivitet och impulsivitet. Dessa symtom gör det svårt för barn att hantera vardagens krav, särskilt i skolmiljöer som ställer höga krav på koncentration, självkontroll och samspel med andra. För många unga med ADHD innebär detta inte bara en försämrad skolfunktion, utan också en ökad risk för långvariga svårigheter i livet, såsom lägre akademiska prestationer och problem med att etablera stabila sociala och yrkesmässiga relationer.

ADHD tros vara kopplat till en dysreglering av hjärnans signalsystem, framför allt dopamin och noradrenalin, två neurotransmittorer som är viktiga för uppmärksamhet, impulskontroll och belöningssystem. Farmakologisk behandling med läkemedel, såsom stimulerande medel, hjälper till att normalisera dessa system, vilket kan leda till förbättrad koncentration och minskad impulsivitet. Trots denna symptomlindring fortsätter många barn att kämpa med akademiska utmaningar, och även om den medicinska behandlingen ofta ger positiva effekter, leder den inte alltid till förbättrade resultat i skolan. Det finns därmed ett stort behov av nya behandlingsmetoder som kan komplettera de nuvarande insatserna och hjälpa barn med ADHD att nå sin fulla potential, särskilt när det gäller akademisk prestation.

Tidigare forskning har visat att stimulering med vitt brus kan förbättra arbetsminne och exekutiva funktioner hos barn med ADHD. En fördel med denna typ av icke-farmakologisk intervention är att den potentiellt kan bidra till att stärka kognitiva funktioner utan de biverkningar som ibland är förknippade med medicinsk behandling. Trots lovande resultat från tidigare studier, finns det dock fortfarande osäkerheter kring de underliggande mekanismerna för hur vitt brus fungerar samt hur de påverkar olika individer och uppgifter. Inte alla barn eller uppgifter verkar svara på brusstimulering, och mer forskning behövs för att fastställa om denna metod kan utvecklas till en alternativ icke-farmakologisk intervention för barn med ADHD.

De flesta tidigare studier har fokuserat på auditivt vitt brus, men teorierna bakom effekterna föreslår att stimulering med brus i andra sensoriska modaliteter, så som visuell, taktil eller elektrisk, också kan ge liknande fördelaktiga resultat – något som denna avhandling undersöker. För att försöka få en bättre förståelse för de underliggande mekanismerna bakom effekterna av vitt brus undersöker denna avhandling även de möjliga regulatoriska effekterna av vitt brus på dopamin- och noradrenalin-systemen genom att mäta blinkfrekvens och pupillstorlek, som fungerar som indikatorer för dessa neurotransmittorer.

Material och metoder

Denna avhandling har undersökt effekterna av vitt brus i tre olika brusmodaliteter–auditiv, visuell och vestibulär–och deras inverkan på arbetsminnesprestation och exekutiva funktioner hos barn med ADHD och jämnåriga kontroller utan neuropsykiatriska funktionsnedsättningar. Målet var att utforska om brusstimulering, i olika sensoriska former, kan förbättra kognitiva funktioner hos barn med ADHD och om denna typ av stimulering har olika effekter på barn med ADHD jämfört med friska jämnåriga.

I Studie I undersöktes 43 barn med ADHD och 28 kontroller för att bedöma effekterna på arbetsminnesprestation av elektrisk stimulering av det vestibulära systemet. I Studie II deltog 52 barn med ADHD och 45 friska kontroller, som genomförde två ögonrörelseuppgifter som utvärderar exekutiva funktioner, medan de samtidigt blev stimulerade med antingen auditivt eller visuellt brus. Uppgifterna i Studie I och II har tidigare visat sig vara känsliga i sin förmåga att skilja mellan barn med och utan ADHD. Prestation under brusstimulering jämfördes med prestation utan brusstimulering för att undersöka om och i vilken grad stimuleringen påverkade de exekutiva funktionerna och arbetsminnesprestation.

Utöver detta har blinkfrekvens och pupillstorlek undersökts hos barn med olika nivåer av ADHD-symptom både utan brusstimulering samt hur dessa påverkas av stimulering med auditivt vitt brus.

Resultat

Varken den auditiva, visuella eller vestibulära stimuleringen förbättrade arbetsminnesprestationerna eller de exekutiva funktionerna hos barn med ADHD jämfört med kontrollgruppen. Trots att uppgifterna tidigare har visat sig ha hög känslighet i sin förmåga att skilja mellan barn med och utan ADHD framkom inte heller några generella signifikanta skillnader mellan ADHD- och kontrollgruppens prestationer på de olika uppgifterna utan brusstimulering.

Vidare visade resultaten att graden av ADHD-symtom inte hade någon signifikant påverkan på blinkfrekvens eller pupillstorlek, varken under brusstimulering eller utan stimulering. Detta tyder på att den fysiologiska responsen på vitt brus inte var direkt relaterad till barnens ADHD-symtom.

Intressant nog uppvisade pojkar generellt en större pupillstorlek än flickor utan brusstimulering. Detta resultat blev ännu mer uttalat under auditiv brusstimulering, där pojkarnas pupillstorlek ökade signifikant jämfört med utan brusstimulering. Pupillstorleken var konsekvent större under hela uppgiften som ett resultat av brusstimuleringen. Effekten av brusstimulering verkar därmed hålla i sig under den tidsperiod som den är aktiv.

Slutsatser

Stimulering med vitt brus verkar vara ineffektivt för att öka den kognitiva prestationen hos barn med ADHD i flera uppgifter relaterade till arbetsminne och exekutiv funktion. Detta innebär att vitt brus, oavsett om det är auditivt, visuellt eller vestibulärt, i denna avhandling inte visat sig ha samma positiva effekter på kognitiva förmågor hos barn med ADHD som tidigare studier funnit. Det finns flera möjliga förklaringar till att inga signifikanta skillnader observerades mellan ADHD-gruppen och kontrollgruppen utan brusstimulering samt till att inga effekter på kognitiv prestation framkom under brusstimulering. Dessa kommer diskuteras i avhandlingen.

Det verkar inte heller finnas något samband mellan blinkfrekvens eller pupillstorlek och ADHD-symtomens svårighetsgrad, eller att barn med olika nivå av ADHD-symtom påverkas olika av den auditiva brusstimuleringen. Att pojkar hade en större pupillstorlek än flickor samt att de fick signifikant större pupillstorlek under auditiv brusstimulering tyder dock på att vissa individer kan påverkas av brusstimulering. Om detta reflekterar förändringar i kognitiv prestation, och vilka de exakta karaktärsdrag personer som påverkas av brusstimulering har, kräver fortsatt forskning för att få svar på.

List of papers

I. **Effects of stochastic vestibular stimulation on cognitive performance in children with ADHD**

Jostrup, E., Nyström, M., Claesdotter-Knutsson, E., Tallberg, P., Gustafsson, P., Paulander, O., & Söderlund, G.
Experimental Brain Research 2023; 241(11-12), 2693-2703.
https://doi.org/10.1007/s00221-023-06713-7

II. **Effects of auditory and visual white noise on oculomotor inhibition in children with ADHD: Protocol for a crossover study**

Jostrup, E., Nyström, M., Tallberg, P., Söderlund, G., Gustafsson, P., & Claesdotter-Knutsson, E.
JMIR Research Protocols 2024; 13, e56388.
https://doi.org/10.2196/56388

III. **No effects of auditory and visual white noise on oculomotor control in children with ADHD**

Jostrup, E., Claesdotter-Knutsson, E., Tallberg, P., Söderlund, G., Gustafsson, P., & Nyström, M.
Journal of Attention Disorders 2024; 28(13), 1668-1683.
https://doi.org/10.1177/10870547241273249

IV. **Predicting blink rate and pupil dilation by ADHD symptoms: Effects of white noise stimulation in an experimental study.**

Jostrup, E., Claesdotter-Knutsson, E., Tallberg, P., Söderlund, G., Gustafsson, P., & Nyström, M.

[In review]

Abbreviations

ADHD	Attention-deficit/hyperactivity disorder
CPT	Continuos performance test
DA	Dopamine
DSM-5	The diagnostic manual of mental disorders, fifth edition
EF	Executive function
MBA model	Moderate brain arousal model
MGS	Memory guided saccade
NE	Norepinephrine/Noradrenaline
nGVS	Noisy galvanic vestibular stimulation
PF	Prolonged fixation
RD	Reading disability
RT	Reaction time
SNAP-IV	Swanson, Nolan and Pelham scale, fourth edition
SNR	Signal-to-noise ratio
SR	Stochastic resonance
SVS	Stochastic vestibular stimulation
TDC	Typically developing children
tRNS	Transcranial random noise stimulation

Introduction

ADHD

Symptoms, prevalence and diagnostics

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders, affecting approximately 5% of children worldwide (Faraone et al., 2024). It is predominantly a genetically based condition, but environmental factors interact with genetics through complex mechanisms (Faraone & Larsson, 2019; Larsson et al., 2014; Pettersson et al., 2019). ADHD is characterized by developmentally inappropriate and impairing levels of inattention and/or hyperactive-impulsive behavior (American Psychiatric Association, 2013). These symptoms significantly impact daily functioning and quality of life across various domains, including education, social interaction, and family life (Fleming et al., 2017; Lee et al., 2016; Ros & Graziano, 2018). Boys are often diagnosed earlier than girls (Staller & Faraone, 2006). Girls typically exhibit more inattentive behaviors while boys display more hyperactivity, which is more likely to disrupt classroom settings and lead to earlier diagnosis (Staller & Faraone, 2006).

The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), provides guidelines for diagnosing ADHD. The most common diagnostic tools include standardized and validated diagnostic interviews combined with rating scales that assess both specific and broad behavioral patterns (Faraone et al., 2021; Sharma & Couture, 2014). Diagnoses are typically based on self-reports (for adolescents), as well as reports from caregivers and teachers. In Sweden, commonly used rating scales include the ESSENCE-Q screening for symptoms, the BRIEF-2 that measures executive function, the Conners' Continuous performance test (CPT) that assesses ADHD symptoms, 5-15 for development and behavior, and SNAP-IV that assess ADHD and oppositional defiant disorder (SKR Uppdrag Psykisk Hälsa, 2024). These scales offer valuable insights into specific aspects of the disorder and are instrumental in assessing treatment response.

To diagnose ADHD, the DSM-5 requires the presence of at least six out of nine impairing symptoms of inattention and/or hyperactivity-impulsivity across multiple settings, normally in school and at home. The symptoms should have been present for a duration of at least 6 months and should have an onset before the age of 12. Additionally, these symptoms must not be better explained by another condition (American Psychiatric Association, 2013).

There have been reports of an increase in ADHD diagnoses over the last decades, where the use of medication has increased throughout Scandinavia, and most prominently in Sweden (Sørensen et al., 2023). Although, this rise appears largely attributable to cases involving subthreshold or milder symptom presentations (Rydell et al., 2018) and does not reflect any changes in the underlying etiology of the condition (Taylor et al., 2023). These trends may reflect changes in diagnostic practices, greater awareness of ADHD, improved access to healthcare, or potentially overdiagnosis due to evolving perceptions of impairments linked to ADHD symptomatology (Garcia-Argibay et al., 2024; Rydell et al., 2018).

Neurocognitive and executive functioning

Individuals with ADHD are at increased risk for poor school performance regardless of socioeconomic background (Jangmo et al., 2019). This can be attributed to the common display of some level of neurocognitive impairment associated with the condition (Faraone et al., 2021). When compared to neurotypical development, children with ADHD demonstrate a moderate degree of cognitive impairment, suggesting that all individuals with ADHD does not display any cognitive impairments (Pievsky & McGrath, 2018; Willcutt et al., 2005). Executive functions—which are mental processes essential for cognitive and physical health, academic success, and social interactions—are particularly impacted (Diamond, 2013). Specifically, executive functions such as working memory, focused and sustained attention, planning, response inhibition and reaction time (RT) variability have been demonstrated to be significantly affected in ADHD (Pievsky & McGrath, 2018; Willcutt et al., 2005).

Working memory

Working memory is one of the most affected executive functions in ADHD (Pievsky & McGrath, 2018). It involves the ability to hold and manipulate information that is no longer perceptually present (Diamond, 2013). Working memory is typically divided into three domains: visuospatial working memory, verbal (phonological) working memory, and episodic working memory (Baddeley, 1992), all of which have been shown to be impaired in individuals with ADHD (Kasper et al., 2012; Martinussen et al., 2005; Ramos et al., 2020). Several tasks are used to assess working memory performance, including the backward digit span task, spatial working memory task, the Corsi Block test and the automated working memory assessment (Diamond, 2013; Gau & Chiang, 2013).

Research by Gau and Chiang (2013) suggests that early symptoms of inattention are associated with greater working memory impairments during adolescence, with these impairments persisting throughout life (Alderson et al., 2013).

Inhibitory control

Inhibitory control, the ability to suppress nonproductive behaviors, encompasses a broad range of cognitive processes. Inhibitory control early in life has been found to predict lite outcome throughout life (Moffitt et al., 2011). Although, it is not a unitary construct, which complicates the interpretations of research results. Nigg (2000) has attempted to clarify distinctions between various types of inhibition, such as inference control, behavioral inhibition (or response inhibition), cognitive inhibition, and oculomotor inhibition, all of which have been shown to be affected in ADHD.

Consistent with the theory of Barkley (1997), which posits that response inhibition is a central deficit in ADHD, several meta-analyses have identified impairments in response inhibition as a defining characteristic of the disorder (Lijffijt et al., 2005; Lipszyc & Schachar, 2010; Oosterlaan et al., 1998; Wright et al., 2014). Response inhibition, defined as the ability to withhold a motor response, is commonly assessed using tasks such as the Stroop task, the Conners' CPT, the Stop Signal Task, and the go/no-go task (Roberts et al., 2011; Wright et al., 2014).

Diminished oculomotor inhibitory control, or the ability to suppress reflexive or impulsive eye movements, has recently been highlighted in meta-analyses as a key attribute of ADHD (Chamorro et al., 2022; Maron et al., 2021). It has thus been suggested that it may serve as a potential biomarker for the disorder. Roberts et al. (2011) suggest that oculomotor inhibitory control, rather than response inhibition, is more closely related to self-reported impulsivity in individuals with ADHD. Neuroimaging research further supports the idea that oculomotor performance is impaired in individuals with ADHD, revealing underactivation in the dorsolateral prefrontal cortex during attention and working memory tasks (Hart et al., 2013). The dorsolateral prefrontal cortex is not only critical for cognitive control but is also involved in the preparation of saccadic eye movements (Pierrot-Deseilligny et al., 1991).

Reaction time variability

RT variability, which refers to the inconsistency in an individual's speed of response, is commonly assessed using tasks like the Conners' CPT and the Stop Signal Task. It is a stable feature of ADHD (Kofler et al., 2013), with a meta-meta-analysis by Pievsky and McGrath (2018) finding that RT variability exhibited the largest differences among all executive functions when comparing ADHD individuals to healthy controls. This finding supports the default-mode network-model by Sonuga-Barke and Castellanos

(2007), which suggests that an inability to switch from a resting to an active cognitive state results in greater performance variability on attentional tasks.

Interconnectedness of executive functions

Although RT variability, working memory, and inhibitory control are discussed as distinct executive functions, they are not independent of each other. For instance, working memory and inhibitory control support one another and are rarely employed in isolation (Diamond, 2013). Executive functions have both overlapping and distinct neural structures and functionalities (Friedman & Miyake, 2017). Individual differences in these functions are largely genetically determined (Friedman et al., 2008) and collectively support the notion that ADHD is due to immature brain structure and atypical functional development (Faraone et al., 2024; Thissen et al., 2014).

Evaluation of executive function is often applied to clinically assess impairments in children and is used as a basis for a treatment plan. However, one factor that complicates the evaluation of performance on these tests are that the psychometric evaluations applied to study executive functions often are applied in a restricted environment, void of any influence from environmental factors that may affect performance. Thus, the experimental environment does not reflect the environment where the child normally displays ADHD symptoms and the results may not reflect the cognitive challenges experienced by the individual (Toplak et al., 2013).

It is also important to note that even though tests evaluating executive function have shown significant differences between children with ADHD and neurotypical controls, the differences are relatively small and many individuals with ADHD does not exhibit neurocognitive impairments (Pievsky & McGrath, 2018). Executive function tests are also not able to discriminate between ADHD and other developmental impairments (Kofler et al., 2013; Lipszyc & Schachar, 2010; Nichols & Waschbusch, 2004), since similar dysfunctions are prevalent across several psychiatric diagnoses (Bloemen et al., 2018; Chang et al., 2020; Martel et al., 2017).

Comorbidities

Co-occurring mental and physical conditions are common in ADHD, such as developmental coordination disorder, autism spectrum disorder, depression, anxiety, and dyslexia or reading disability (Arrondo et al., 2022; Biederman et al., 1991). For example, research suggests that approximately half of all children with ADHD exhibit motor impairments consistent with developmental coordination disorder (Piek et al., 1999; Pitcher et al., 2003), a condition closely associated with deficiencies in visuospatial processing (Wilson & McKenzie, 1998) and oculomotor control (Bucci et al., 2024). In addition, dyslexia in combination with ADHD have been suggested to be linked to more severe cognitive deficits, together with worse neuropsychological, academic, and behavioral outcome (Germanò et al., 2010). Another common comorbidity is autism spectrum disorder, with many similar symptoms that can make diagnosis challenging (Hours et al., 2022).

Besides the many common comorbidities in ADHD, the condition also exhibits considerable heterogeneity within itself (Faraone et al., 2024). This variability is reflected in the diverse presentation of symptoms and the varying levels of impairment experienced between individuals. Adding to heterogeneity is also the common experience of symptom and impairment fluctuations over time, within individuals (Vos et al., 2022). Deficits have also been seen in various domains of neurocognitive functioning (Gau & Chiang, 2013; Pievsky & McGrath, 2018), where research has identified numerous minor structural and functional brain differences associated with ADHD (Hoogman et al., 2017; Lukito et al., 2020; Norman et al., 2016; Parlatini et al., 2023; Reimann et al., 2024). Based on these differences other, neurophysiologically based biotypes of ADHD rather than symptomatic ones, have been suggested (Barth et al., 2018), which offers a promising alternative framework for understanding ADHD. This aligns with both the RDoC framework's emphasis on neural circuits and dimensional approaches (Cuthbert, 2020), as well as neurodiversity perspectives that recognize natural variations in brain function (Dwyer, 2022). These modern approaches may better capture the inherent complexity of ADHD and lead to more personalized understanding and support strategies that acknowledge both biological underpinnings and individual differences.

Dopamine and noradrenaline signaling in ADHD

Most research agrees that altered levels of the neurotransmitters dopamine (DA) and norepinephrine (NE) play an important role in ADHD. This is supported by findings showing that many brain regions and network patterns affected in ADHD are regulated by DA and NE (Faraone, 2018; Volkow et al., 2009). Additionally, pharmacological interventions for ADHD have been shown to restore the balance of the DA/NE system, further emphasizing the statement (Sharma & Couture, 2014).

DA and NE play essential roles in various executive functions. NE activity is regulated by the locus coeruleus, which governs several aspects of autonomic arousal, wakefulness, and mental activity (Samuels & Szabadi, 2008; Sara, 2009). DA, on the other hand, is particularly crucial for working memory, learning, goal-oriented behavior, and sustained attention (Westbrook & Braver, 2016). While DA is transmitted across multiple brain areas, its influence on cognitive performance is primarily observed in prefrontal areas (Ott & Nieder, 2019; Weber et al., 2022).

DA signaling in the brain is modulated along two time-scales, tonic (continuous) and phasic (stimulus dependent) levels of DA (Grace, 1995). Tonic levels refer to the baseline concentration of neurotransmitters in the system and are not affected by stimuli, while phasic responses are transient, constantly shifting, stimuli-evoked changes (Grace, 1995). Quickly increased phasic levels are seen as a response to a stimulus.

Cognitive performance follows an inverted U-shaped relationship with DA and NE levels where too high and too low levels leads to impaired performance (Weber et al., 2022). Thus, the balance between tonic and phasic neurotransmitter activity regulates performance (Robison et al., 2023). Impaired cognitive performance, commonly observed in conditions such as ADHD, is thought to result from an imbalance between tonic and phasic levels of DA and/or NA (Bellgrove et al., 2005; Swanson et al., 2011). When tonic levels are too low, phasic responses become up-regulated (Badgaiyan et al., 2015), leading to hypersensitivity to environmental stimuli (Sikström & Söderlund, 2007). Strong and salient stimuli that is irrelevant for the task at hand may thus disrupt concentration and lead to attentional problems.

Spontaneous blink rate and pupil diameter have been proposed as proxies for DA and NE signaling, respectively (Eckstein et al., 2017). Spontaneous blink rate, which refers to the frequency of eyelid closure and re-opening, is believed to be modulated by DA activity (Demiral et al., 2022). Evidence for this comes from research on Parkinson's disease, where reduced blink rates are observed due to the degeneration of dopaminergic neurons (Agostino et al., 2008), but increase with DA-enhancing medications (Bologna et al., 2012). Conversely, conditions characterized by elevated DA activity, such as schizophrenia and Tourette's syndrome, are associated with higher blink rates (Chan & Chen, 2004; Jacobsen et al., 1996; Tharp et al., 2015).

Even though several studies have suggested that DA and NE related changes in ADHD could be reflected in blink rate and pupil diameter in this group (Groen et al., 2017; Unsworth et al., 2019; Wainstein et al., 2017), the research within this area has found no clear consensus on whether there are any differences between individuals with and without ADHD. Regarding spontaneous blink rate, early research on children with ADHD revealed significantly lower blink rates during a verbal recall (Caplan et al., 1996). In contrast, a study by Jacobsen et al. (1996) that studied blink rate during a smooth pursuit task reported no significant differences in blink rates between children with ADHD and TDC. In more recent work, Fried et al. (2014) observed higher blink rates in individuals with ADHD relative to healthy controls during the Test of Variables of Attention. The higher blink rate in ADHD was found particularly at stimulus onset. Conversely, Groen et al. (2017) found no significant differences in blink rate between children with ADHD, both on and off medication, and TDC. The medication status of the ADHD group did not change the results. They reported no differences between the groups at rest, during tasks, or in transitions between rest and task. However, unmedicated children with ADHD exhibited reduced blink inhibition before stimulus onset.

Studies on pupil size in ADHD have primarily been made on adults and, as with blink rate, yield mixed results. Pupil diameter, in addition to adjusting to light, reflects attentional focus and mental effort (Eckstein et al., 2017). Baseline pupil diameter, that is the pupil size during rest, is linked to tonic arousal, while task-evoked pupil responses correspond to phasic arousal (Beatty, 1982a). An enlarged baseline pupil diameter suggests heightened tonic NE arousal, which may reflect suboptimal attentional allocation and an increased sensitivity to external stimuli. In contrast, enhanced phasic pupil responses during tasks indicate an enhanced allocation of attentional resources and effort to salient or task-relevant stimuli (Beatty, 1982b; Idrees et al., 2023).

When assessing whether there are any differences in baseline pupil diameter between individuals with ADHD and neurotypical controls, prolonged fixation tasks are often used. During a five-minute fixation task, Unsworth et al. (2019) found significant correlations between baseline pupil size, spontaneous blink rates, and self-reported ADHD traits in healthy adults. Similarly, during a two-minute fixation task, Nobukawa et al. (2021) reported that adults with ADHD exhibited significantly larger pupil diameters compared to neurotypical controls and Shirama et al. (2020) observed that non-medicated adults with ADHD had significantly larger tonic pupil diameter. On the other hand, during two five-minute rest periods, López-Hernández et al. (2024) found larger pupil diameters only in previously medicated individuals with ADHD, that were off their medication during the study. However, no such differences were found in previously unmedicated individuals or healthy controls. In contrast, Privitera et al. (2024) found smaller baseline pupil diameters in adults with ADHD.

When studying potential differences in phasic pupil diameter between individuals with and without ADHD, Shirama et al. (2020) reported smaller stimulus-evoked phasic pupil dilation compared to neurotypical controls whilst performing an auditory CPT. In children with ADHD, Wainstein et al. (2017) reported smaller pupil diameters during a visuospatial working memory task, compared to TDC, a difference that was eliminated with stimulant medication. Additionally, they found correlations between task performance, reaction time variability and pupil diameter. On the contrary, no differences in pupil diameter or variability in pupil diameter were found between children with and without ADHD during a visual CPT in a study by Redondo et al. (2020).

Overall, the existing research on blink rate and pupil diameter in ADHD shows inconsistent findings, making it difficult to draw definite conclusions regarding the presence and extent of oculomotor disruptions in the disorder. These inconsistencies may in part be due to the substantial heterogeneity within the ADHD population and new approaches to explore this potential relationship is needed.

Pharmacological and non-pharmacological interventions

When establishing the management of ADHD symptoms several factors need to be considered, such as the patient's age, symptom severity, comorbid conditions, and treatment preferences (Faraone et al., 2024). In Sweden, a multimodal approach is recommended, where medical interventions are neither the first nor the sole option. Management is tailored to symptom severity and the patient's individual circumstances, with interventions delivered in their everyday environment (SKR Uppdrag Psykisk Hälsa, 2024). The primary interventions include educational support in school, child and family psychoeducation, and parenting support programs with behavioral modifications (NICE, 2021). These interventions are continuously evaluated and modified to ensure best efficacy.

When non-pharmacological interventions prove insufficient, several pharmacological treatment options are available. Approved options include stimulants, such as methylphenidate and amphetamines, as well as non-stimulants like atomoxetine, guanfacine, and clonidine (Reddy, 2013). Stimulants are more commonly prescribed due to their greater effect sizes and fewer side effects (Biederman & Faraone, 2005). The stimulant pharmacological interventions restore the balance of the DA/NE system (Sharma & Couture, 2014) and are highly effective (Cortese et al., 2018). They have been shown to significantly reduce various ADHD-related symptoms and impairments, including the risk of developing other psychiatric disorders, substance use, accidents, injuries, and antisocial behavior (Boland et al., 2020; Franke et al., 2018).

In contrast, the effects of non-pharmacological interventions, such as cognitive and behavioral therapies, cognitive training, neurofeedback, physical activity, brain stimulation, and nutrient supplementation, tend to be smaller and more inconsistent. Among these, there is consensus only on the efficacy of cognitive and behavioral therapies, which have demonstrated a strong and consistent impact on executive functioning skills and ADHD symptoms (Sibley et al., 2023; Sibley et al., 2024). Based on this, a combination of pharmacological and behavioral treatments is recommended (Sibley et al., 2024). These approaches are complementary; while medication provides a consistent, day-to-day symptom reduction, behavioral therapies equip individuals with skills to manage impairments that medication alone cannot address.

Novel treatments, such as transcranial direct current stimulation, digital inventions, and supplementing with polysaturated fatty acids, have not demonstrated any consistent beneficial effects on ADHD symptoms or cognitive abilities, but are considered a promising area for further research (Sibley et al., 2024). Existing treatment methods are not problem free, and the development of new treatment methods are encouraged (Faraone et al., 2021).

Although medication significantly alleviates behavioral and functional symptoms in ADHD (Cortese et al., 2018), its long-term effects remain uncertain. On a group level, its efficacy tends to diminish after approximately three years (Molina et al., 2009; Swanson et al., 2017). While pharmacological treatments are reported to strongly reduce symptom severity, their effects on cognitive impairments are inconsistent (Sibley et al., 2024). Some studies have linked pharmacological use to improved school performance (Jangmo et al., 2019; Lu et al., 2017). However, children with ADHD remain over three times more likely to experience low educational achievement compared to neurotypical peers (Fleming et al., 2017). Moreover, there is limited evidence supporting the notion that medication improves learning processes or addresses the cognitive deficits frequently associated with ADHD (Franke et al., 2018; Hellwig-Brida et al., 2011; Molina et al., 2009; Tamminga et al., 2016). Notably, the optimal dosage for cognitive improvement may differ from that required for behavioral improvement (Hale et al., 2011).

Moreover, approximately 30% of patients do not respond to available pharmacological treatments, and some experience side effects such as sleep disturbance, decreased appetite, headaches, nausea, and mood changes (Boland et al., 2020; Franke et al., 2018; Solmi et al., 2020). Medication discontinuation is common, with only 40-50% of children and adolescents aged 4-17 remaining on medication one year after initiation (Brikell et al., 2024), leaving them unmedicated for the larger part of their school years.

These findings highlight the need for additional interventions that target areas where current treatments fall short. Enhancing cognitive performance through targeted interventions could help reduce the disparities in life outcomes frequently faced by individuals with ADHD. Sensory noise stimulation as a non-pharmacological intervention could offer multiple benefits in this case: it is noninvasive, affordable, widely accessible, and associated with minimal side effects.

Sensory noise

In signal processing, noise refers to unwanted and often unpredictable disturbances that alter a signal during capture, transmission, storage, processing, or conversion. These disturbances may degrade the signal's quality or interfere with its intended use. Noise can also refer to random signals devoid of meaningful information, even if they do not directly disrupt other signals. The latter is what is referred to in this thesis.

Noise is typically assumed to be detrimental to the quality of a signal (McDonnell & Abbott, 2009). However, an increasing number of research has found noise to be beneficial for non-linear systems. In non-linear systems, such as the nervous system, the activation of the system is dependent on whether a threshold is passed or not (Herrera-Murillo et al., 2022). Sensory noise has, for example, shown promising potential in enhancing cognitive performance among children with attention deficits and/or ADHD (Nigg et al., 2024; Pickens et al., 2019).

The specific 'color' of noise, categorized based on its spectral properties, defines how the noise is generated and perceived (Oppenheim, 1999). White noise, the most studied in this context (Nigg et al., 2024), is characterized by a flat power spectral density, meaning it has equal intensity across all frequencies within the human hearing range. This distribution is akin to the distribution of white light, which consists of all visible light frequencies (Oppenheim, 1999). Other types of noise, such as pink and brown noise, differ in their spectral characteristics. Pink noise follows a $1/f$ power spectrum, and brown noise follows a $1/f^2$ power spectrum, where f is the frequency. As a result, pink and brown noise sound 'duller' compared to white noise and are often considered to resemble the sound of a heavy rainfall or a waterfall (Lu et al., 2020; Warjri et al., 2022).

In addition to the color of the noise, the modality —or the sensory system through which noise is delivered to the nervous system—determines how it is received. While auditory noise has been the most extensively studied in relation to cognitive performance, other modalities, such as vestibular and visual noise, have recently garnered increasing research interest (Herrera-Murillo et al., 2022; Söderlund et al., 2021).

Auditory noise stimulation

In research settings, auditory noise is typically presented biannually, that is to both ears simultaneously, through a stereo-generated signal using a pair of headphones. Several studies have investigated the effects of auditory noise in different contexts, for example for relaxation and sleep improvement, with varying results (Capezuti et al., 2022; Warjri et al., 2022).

Two recent reviews have highlighted the potential of auditory white noise as an enhancer of cognitive performance for children with ADHD (Nigg et al., 2024; Pickens et al., 2019). White noise has been found to improve several executive functions such as visuospatial and verbal working memory, RT variability, and response inhibition (Baijot et al., 2016; Egeland et al., 2023; Helps et al., 2014; Söderlund et al., 2016). Increased reading and writing speed, reduced off-task behavior, and reduced hyperactive and/or impulsive behavior has also been demonstrated (Batho et al., 2020; Cook et al., 2014; Cook et al., 2015; Lin, 2022). Effective noise levels for improving cognitive performance in children with ADHD have been found in the range of 70-80dB, which is quite loud. Similarly, auditory white noise has shown improvements for healthy controls (Angwin et al., 2017; Angwin et al., 2018; Angwin et al., 2019; Awada et al., 2022; Lu et al., 2020; Othman et al., 2019). White noise at 70 dB has demonstrated immediate recognition accuracy for novel word meanings and superior recall accuracy over time in neurotypical adults (Angwin et al., 2017; Angwin et al., 2018; Angwin et al., 2019). In addition, white noise at 55 dB improved performance on an auditory working memory task in neurotypical adults (Othman et al., 2019).

Interestingly, when comparing the effects of different colors of noise on cognitive performance in neurotypical controls at 50 dB, Lu et al. (2020) found different effects of the color of the noise in different tasks. For example, they found that only the pink noise generated significantly beneficial effects on a CPT. However, all the different types of noise explored, both red, pink and white, produced better results on an executive functions test. When rating the comfort of the noise, the pink and the red noise was found to improve the environment and achieve better implementation than the white noise. In contrast, Metin et al. (2016) found no beneficial effects from pink noise stimulation at 80dB on impulsive choice in children with ADHD.

Moreover, different levels of noise have been demonstrated to produce different effects. For example, 45dB has shown improved accuracy, speed of performance, and sustained attention while 65dB improved working memory but also induced higher stress levels in neurotypical controls (Awada et al., 2022). In children with ADHD 75dB produced the largest improvement in performance on executive functioning tasks, compared to 65 and 85 dB. On non-executive functioning tasks 70dB had the largest effect, compared to 65 and 75 dB (Helps et al., 2014). These findings might suggest that different levels of noise are required to reach optimal performance in different tasks. However, not all studies have found effects from different levels of noise stimulation. In neurotypical adults, Sherman et al. (2023) were unable to identify any broad improvements in cognitive performance from white noise stimulation at levels 40, 55 or 70dB. On the other hand, they conclude that some individuals seem to be benefited by the noise stimulation. Similar findings are reported from Rufener et al. (2020), who found no general beneficial effects of noise stimulation in barely hearable auditory stimuli, only for certain subjects.

In line with findings that not all individuals seem to be beneficially affected by noise stimulation, Söderlund et al. (2024) suggest that individuals with high levels of inattention seem to be more affected by white noise stimulation. Additionally, Allen and Pammer (2018) only found beneficial effects on a visual search task in children with ADHD when white noise stimulation at "medium volume" was combined with medication and not for children with ADHD off-medication. These results are in opposition to results from Söderlund et al. (2016), who found auditory white noise stimulation to be even better than stimulant medication in children with ADHD.

In accordance with these varying results, Pickens et al. (2019) suggests that not all tasks or executive functions are beneficially affected by noise exposure and they encourages further research to establish best practice protocols to guide therapeutic use.

Visual noise stimulation

Visual noise stimulation is comparable to the static seen on old analog television screens when no broadcast signal was present. The term resembles the black-and-white flickering noise on the screen to ants in a chaotic battle. It is when each pixel value on the screen is randomly drawn from a distribution for each screen refresh.

Visual noise stimulation is much less studied than auditory noise stimulation. However, in a study of children with reading disability (RD) and phonological decoding difficulties Söderlund et al. (2021) found that visual white noise stimulation improved decoding (reading accuracy) and verbal memory. RD is a common comorbidity to ADHD, with 20-40% overlap between the conditions (Mueller & Tomblin, 2012), which motivated the study to look at children with RD compared to ADHD as in previous studies on white noise. A recent study on children with ADHD also explored the effects of visual white noise on performance on a visuospatial working memory task. In contrast to the study on participants with RD, they found no beneficial effects of the visual noise stimulation on performance (Söderlund et al., 2024).

Vestibular noise stimulation

There are several different techniques to apply noise stimulation targeting different brain regions. For example, transcranial random noise stimulation (tRNS) applies white electrical noise to the cortex. Noisy galvanic vestibular stimulation (nGVS), on the other hand, is random electrical noise applied to the vestibular system, through electrodes placed on the mastoid bones behind the ears (Herrera-Murillo et al., 2022).

tRNS as a method for improving cognitive performance has gained increased interest in the last decade. Applied to the visual cortex on neurotypical adults, it has been found to improve performance in a visual task (van der Groen & Wenderoth, 2016), and while applied to the ventrolateral prefrontal cortex to improve memory performance (Penton et al., 2018). It has also been demonstrated to reduce reaction times in Go/No-go tasks in neurotypical adults (Brevet-Aeby et al., 2019). When applied to children with ADHD, it has been shown to improve working memory, inhibition abilities and decision making (Nejati et al., 2024), and reduce clinical rating-scores of the condition (Berger et al., 2021; Dakwar-Kawar et al., 2023).

Most research on nGVS has centered around motor performance and spatial orientation, since the vestibular system detect linear and angular acceleration of the head and influence motoneuron and balance control (Dakin et al., 2007). As such, nGVS has been found to improve balance, gait, locomotor stability, and prevent falls in both healthy people and people with Parkinson's disease (Mulavara et al., 2011; Samoudi et al., 2015). However, research suggests that the vestibular system also plays a role in cognitive functions (Bigelow & Agrawal, 2015; Ferrè & Haggard, 2020; Hitier et al., 2014). For example, people with vestibular deficits also show memory impairments in several contexts (Bigelow & Agrawal, 2015). Moreover, several neurodevelopmental disorders, including ADHD, are associated with postural control and balance difficulties (Bucci et al., 2024; Lotfi et al., 2017b).

In fact, Lotfi et al. (2017a) showed improved cognitive performance in children with ADHD and vestibular impairment after a rehabilitation program comprising overall balance and gate, postural stability, and eye movement exercises. In neurotypical adults, nGVS has shown to enhance spatial learning, with greater effect on people with low spatial working memory (Hilliard et al., 2019). It has also demonstrated to improve sensorimotor performance (Kuatsjah et al., 2019), visual thresholds (Voros et al., 2021), and generate faster recall in a face imagery task (Wilkinson et al., 2008).

Why is noise efficient?

The precise mechanisms underlying the beneficial effects of noise stimulation on cognitive performance are not yet known. The basic assumption is that external environmental noise, introduced via the perceptual system, introduces internal neural noise. The generated internal neural noise activates sensory receptors and brain regions, thereby enhancing the performance of these systems (Herrera-Murillo et al., 2022).

One approach to investigating this phenomenon involves assessing event-related potentials (ERP), particularly the P300 component, that reflects several aspects of cognitive functioning. ERP studies employing Go/No-go tasks have previously demonstrated reduced P300 amplitudes in children with ADHD compared to TDC (Kaiser et al., 2020; Woltering et al., 2013). Intriguingly, auditory white noise stimulation has been shown to enhance both the P300 signal and task performance in children with ADHD during such a task (Baijot et al., 2016).

White noise stimulation has also been proposed to increase dopaminergic activity in the ventral tegmental area, enhancing connectivity (Rausch et al., 2014). However, despite finding a higher baseline blink rate (a proxy for dopamine levels) in children with ADHD, Baijot et al. (2016) did not observe any modulatory effect from white noise stimulation on blink rate.

While these findings are inconclusive, the moderate brain arousal (MBA) model proposes a more comprehensive theoretical explanation to why white noise stimulation appears to be beneficial for children with ADHD.

The moderate brain arousal model & stochastic resonance

The MBA model posits that noise improves attention and performance by compensating for the imbalance in the DA system in individuals with ADHD (Sikström & Söderlund, 2007). The model assumes that a dysfunctional DA system, characterized by low tonic DA levels, leads to increased levels of internal neural noise. This elevated noise results in random neuronal activation, which ultimately impairs attention (Badgaiyan et al., 2015; Bubl et al., 2015; Pertermann et al., 2019; Werner et al., 2020).

This relationship between neural noise and DA levels is described by the concept of "neural gain" (Hauser et al., 2016). Neural gain refers to the brain's ability to selectively amplify or suppress signals and is estimated through a sigmoidal function. High neural gain, associated with adequate DA and NE levels and a steeper sigmoidal function (cf. figure 1), promotes stable behavior, improves working memory and executive function. Low neural gain, on the other hand, is demonstrated by a less steep decision function. Low neural gain is common in ADHD, which is reflected in a reduced ability to discriminate between relevant and irrelevant signals and a greater variability in behavior.

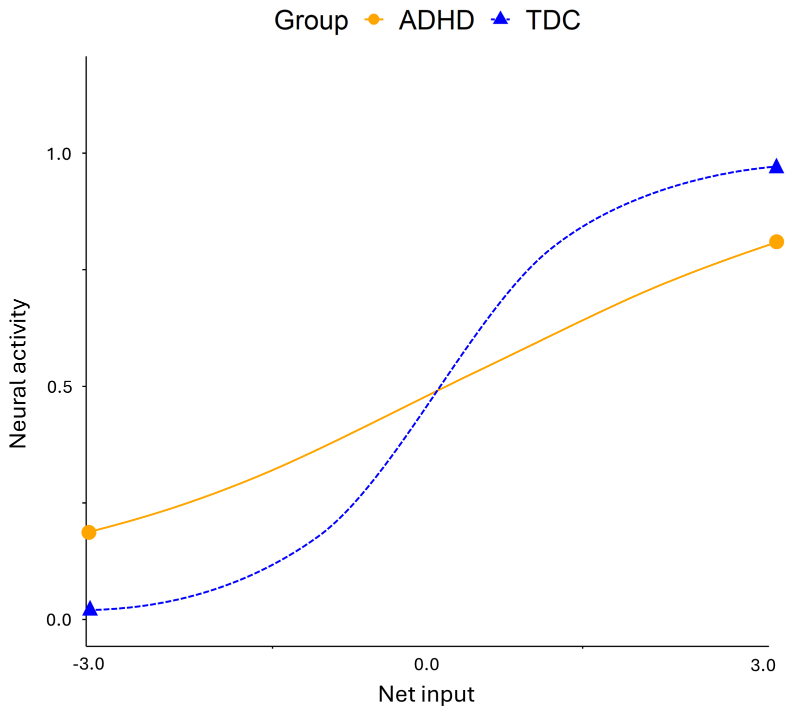

Figure 1. Neral gain.
The sigmoid activation function illustrates the differences in neural activity between children with ADHD (yellow line) and typically developing children (TDC; blue line) in a stimulus-impoverished environment. The y-axis represents neural activity, such as spike frequency, while the x-axis indicates net input. In ADHD systems, the sigmoid curve is shallower due to a low gain parameter, reflecting reduced dopamine (DA) levels compared to TDC systems. This indicates that reactions to external stimuli occurs more at random compared to TDC. In contrast, the steeper sigmoid curve in TDC systems is associated with a higher gain parameter, greater total DA availability and more stable behavior.

It is hypothesized that introducing external noise can increase neural gain in individuals with ADHD, enhancing both performance and stability (Sikström & Söderlund, 2007). This theory is supported by research showing that stimulant medication, that increases DA, reduces RT variability in ADHD, while non-stimulant treatments do not have this effect (Kofler et al., 2013).

The MBA model makes a distinction between absolute and relative levels of DA. Absolute DA levels are seen as the sum of the tonic and phasic response, where individuals with ADHD have lower absolute DA levels. Cognitive performance, however, is modeled based on the relative balance between tonic and phasic DA activity (Sikström & Söderlund, 2007). That is, since tonic DA levels are thought to be reduced due to DA transporter dysfunction in ADHD, the relative phasic level is hypothesized to be upregulated (Grace, 2000). This results in a higher relative phasic level in individuals with ADHD compared to neurotypical individuals (Badgaiyan et al., 2015), which leads to an increased sensitivity towards stimuli that competes with sustained attention towards tasks (Sikström & Söderlund, 2007). External noise is theorized to compensate for reduced tonic DA activity and enhance cognitive performance by improving neural signal processing (Sikström & Söderlund, 2007).

The relationship between DA levels and performance follows a reversed U-shaped curve, where both too high and too low levels of DA can impair performance (Sharma & Couture, 2014). Optimal performance occurs at moderate levels of brain arousal (Sharma & Couture, 2014). The MBA model posits that different people need different amounts of external noise to optimize cognitive performance (Sikström & Söderlund, 2007). While noise stimulation may help individuals with ADHD reach their optimal point on the U-curve, individuals with a balanced DA system may experience decreased performance when noise is added (cf. figure 2).

The relationship between performance and noise stimulation according to the reversed U has been found when applying tRNS (Pavan et al., 2019) and auditory white noise (Othman et al., 2019) to neurotypical adults. However, Rufener et al. (2020) did not find any effects of neither auditory- nor tRNS white noise on performance in neurotypical adults.

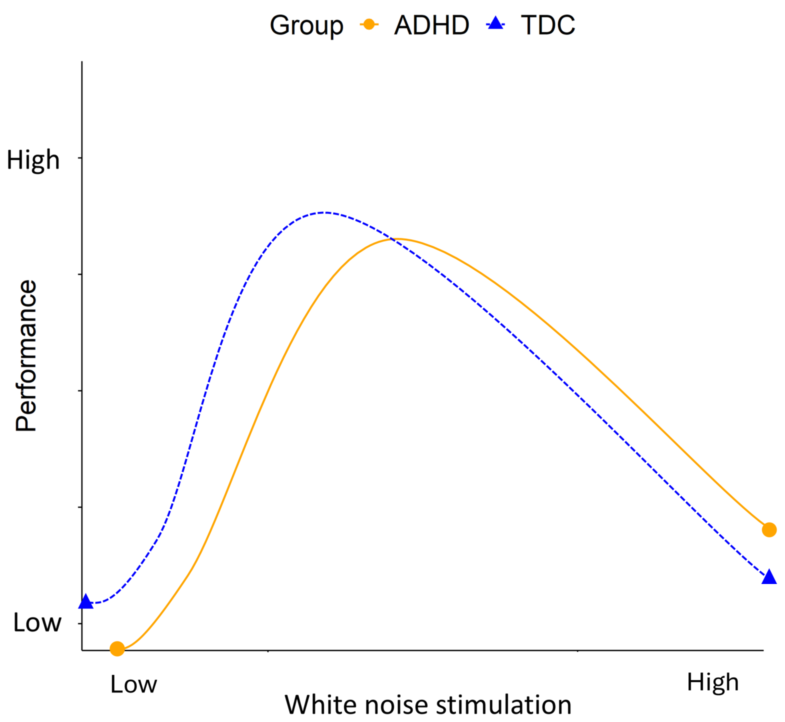

Figure 2. U-curve of noise stimulation and performance
In the moderate brain arousal model, performance is illustrated as a function of noise intensity. The reduced dopamine levels in individuals with ADHD (yellow line) shift the curve to the right, indicating that higher levels of noise are required to achieve optimal performance compared to typically developing controls (blue line).

The MBA model incorporates the phenomenon of stochastic resonance (SR) to explain how noise reinforces weak signals and thus benefit performance (Sikström & Söderlund, 2007). SR is a phenomenon in which the addition of random noise to a weak, subthreshold, signal facilitates its detection, increasing the signal-to-noise ratio (SNR) (McDonnell & Abbott, 2009). Neural signaling involves noisy inputs and outputs, and the brain's challenge is to distinguish meaningful signals from irrelevant noise. Paradoxically, the brain can use noise to enhance signal differentiation, thereby improving the SNR (Söderlund & Sikström, 2012). SR exists in any threshold-based system with noise where a signal is required to pass a threshold to be registered (Moss et al., 2004). This process enables signals that are too weak to surpass a detection threshold to be amplified by added noise, allowing neurons to activate and boost performance in situations where cognitive demands would otherwise not be met. While applied to a signal below the detection threshold, SR is referred to subthreshold SR. Although, SR also occurs in suprathreshold signals, where the signal is above detection threshold and where adding moderate noise increases its discriminability (McDonnell et al., 2007).

McDonnell and Ward (2011) have suggested the term "stochastic facilitation" to describe biologically relevant noise in the nervous system, distinguishing it from SR as used in statistical physics. Stochastic facilitation has been demonstrated across various sensory modalities, including auditory, visual and tactile systems (Mendez-Balbuena et al., 2012; Treviño et al., 2016; Ward et al., 2010; Wells et al., 2005; Zeng et al., 2000), indicating that participants can be exposed to, and benefit from, noise in all modalities (auditory, visual, tactile, vestibular etc.).

Alternative explanations for noise benefit: Auditory masking and physical arousal

Other explanations propose that white noise improves cognitive performance through auditory masking or by increasing physical arousal.

Auditory masking, i.e., that auditory white noise masks surrounding distractors, allowing for improved focus by reducing external interference, has been proposed to explain white noise benefits (Cook et al., 2014). Apart from masking in the auditory modality, masking have been shown in tactile (Tan et al., 2003) and visual (Enns & Di Lollo, 2000) modalities as well. However, these types of masking do not exclude surrounding distractors and does not explain noise benefits in modalities other than the auditory.

Physical arousal, that can be measured through physiological markers like heart rate or galvanic skin response, has been suggested as another potential mechanism. Individuals with ADHD are suggested to be under-aroused, and hyperactivity is thought to be a homeostatic compensatory response to increase arousal levels (Sarver et al., 2015). It can be argued that auditory white noise may act as a "wake up signal", increasing arousal and thus improving performance. Recent findings are in line with this statement. In their study, Rijmen and Wiersema (2024) explored the effects of both 75 dB auditory pink noise and a pure 100 Hz tone on RT in a slow RT task designed to induce under-arousal. They found that both the pink noise and the pure tone improved RT for individuals with high levels of ADHD and questions the need for SR to achieve performance improvement from noise. However, they did not measure physical arousal specifically.

On the contrary, Rausch et al. (2014) performed a similar experiment while using fMRI. In their study they compared recognition memory after applying white noise or a 100 Hz sinus tone (or galloping horses) played at 70 dB during encoding. They found that only white noise, and not the pure tone, improved recognition memory. They also found that the performance enhancements from the white noise stimulation correlated with increased DA connectivity. Thus, one cannot exclude that noise benefits are due to a combination of these explanations.

Aims and hypotheses

The aim of this research has been to contribute to the understanding of the previously shown beneficial effects of white noise stimulation in children with ADHD. Two studies have been conducted for the scope of this thesis, assessing new noise modalities and assessment methods to evaluate the effects noise stimulation in children with ADHD.

Study I assessed the effects of subthreshold stochastic vestibular stimulation (SVS) on cognitive performance and reaction time variability in children with ADHD and typically developing children (TDC). The results were presented in Paper I.

Study II investigated the effects of auditory white noise stimulation and visual white pixel noise stimulation on oculomotor control in children with ADHD and TDC. The study was first described in a study protocol (Paper II) and results were presented in Paper III.

Study II also aimed at gaining a deeper understanding of the mechanisms behind white noise stimulation. This was investigated by assessing whether the level of ADHD symptoms could predict blink rate and pupil dilation, which are proxies for dopamine and noradrenaline, both with and without noise stimulation. Three main objectives were pursued and presented in Paper IV. First, to study whether there are any differences in baseline (without noise stimulation) blink rate and pupil diameter related to level of ADHD symptoms. Second, to investigate whether white noise stimulation affect these ocular measurements and whether the potential effect was related to the level of ADHD symptoms. Finally, to study how long the potential effect of noise stimulation lasted.

Hypotheses

Based on previous research on auditory white noise (Nigg et al., 2024; Pickens et al., 2019) and assumptions in the MBA model (Sikström & Söderlund, 2007) our hypotheses for Paper I, II and III were:

- H1: The ADHD group will be outperformed by the TDC group without any noise stimulation.
- H2: The white noise stimulation will remove any differences in cognitive performance between the groups.
- H3: The ADHD group will experience improved cognitive performance during white noise stimulation.
- H4: The TDC group will get impaired cognitive performance during white noise stimulation.

These are illustrated in figure 3 below.

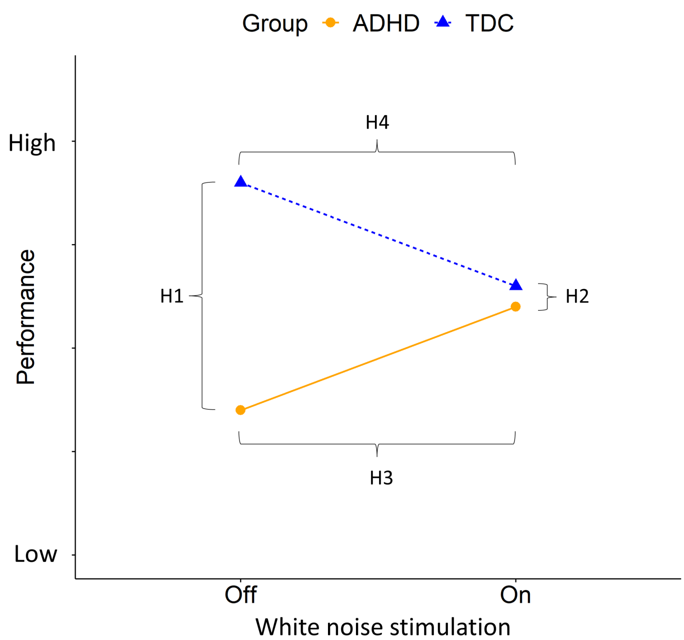

Figure 3. Hypotheses
H1: The TDC group (blue line) will outperform the ADHD group (yellow line) in the no-noise condition while, H2: the difference between the groups will disappear during white noise stimulation. H3: The ADHD group will experience increased performance from the white noise stimulation while, H4: the TDC group will experience impaired performance from the white noise stimulation.

Methods

Participants

Participants diagnosed with ADHD were recruited through the Child and Adolescent Outpatient Clinic in Skåne, Sweden, or via online advertisement. All diagnoses were confirmed by two senior consultants in child and adolescent psychiatry (Emma Claesdotter-Knutsson and Pia Tallberg).

To be eligible for the studies, all participants in the ADHD group had to be diagnosed with ADHD according to international guidelines, following the Diagnostic and Statistical Manual of Mental Disorder, fifth edition (DSM-5) (American Psychiatric Association, 2013). Children with both combined, predominantly inattentive, and predominantly hyperactive-impulsive type were included. Children in the ADHD group were either awaiting medication initiation or already on methylphenidate. Those on methylphenidate had to withdraw from their medication at least 24h prior to participation in the study. Exclusion criteria included failing to withdraw from methylphenidate medication, to be medicating with other substances than methylphenidate and being outside the age span of 7-17 years.

Typically developing children (TDC) were recruited from local schools in the district of Skåne. Exclusion criteria included having a psychiatric diagnosis and being outside the age span of 7-17 years.

All participants were rated either by their teacher (Study I) or legal guardians (Study I & Study II) regarding their level of ADHD symptoms, using the Swanson, Nolan and Pelham-IV (SNAP-IV) rating scale (Swanson et al., 2012). For Study II the five-to-fifteen, revised edition, (5-15R) (Kadesjö et al., 2017) and an assessment of participants reading and writing skills (Elwér et al., 2011) were also used.

SNAP-IV

SNAP-IV is one of the most extensively used parent and teacher rating scales for assessing ADHD symptoms (18 items, 9 for inattention and 9 for hyperactivity) and Oppositional Defiant Disorder (9 items), based on DSM-5 criteria. It is used for screening and evaluation of symptom severity over time (Bussing et al., 2008), and in treatment studies for ADHD (Hall et al., 2020). Each symptom item's severity is evaluated on a four-point scale: 0 (not at all), 1 (just a little), 2 (quite a bit), and 3 (very much). Only the items assessing ADHD symptoms were used in the studies. The maximum score for the inattention scale is 27, as it is for the hyperactivity scale.

5-15R

The 5-15R assessment comprises 181 statements related to everyday situations, comprising areas such as motor skills, executive functions, memory and perception. It is designed to assess skills and behavioral patterns in children aged 5 to 17 years. It is commonly used to evaluate behavioral issues and potential developmental disorders (Kadesjö et al., 2004). Respondents choose from four rating options—no, a little, a great deal, and very much—to answer each question.

Reading and writing

Reading and writing were assessed using a form from Elwér et al. (2011). The assessment consists of seven questions and inquiries on e.g. participants spelling performance, learning to read and learn letters, understanding of reading, and relationship to reading. The rating ranges from 0 (not at all) to 2 (very much) and the maximum number of points in the form is 12.

Study I: Paper I

Study design

A 3 × 2 × 2 repeated measures design was applied, consisting of a visuo-spatial working memory task (Spanboard), a verbal episodic memory task (Word recall) and a visuospatial N-back task. The Spanboard and Word recall tasks have previously shown to be affected by auditory white noise stimulation (Söderlund et al., 2016), while the N-back task has not been assessed in relation to white noise stimulation previously. The two groups (ADHD/TDC) performed the tasks during either SVS or in a no-noise condition (sham).

In the initial design, there was an intention to replicate previous findings on the impact of auditory noise on cognitive performance and to explore the effects of introducing noise in two modalities simultaneously. To this end, auditory noise was included in half of the Word recall tests. However, due to technical issues, the auditory noise was deemed unreliable and subsequently excluded from the analysis. A malfunction in the headphones was discovered, resulting in irregular and below-calibrated levels of speech. The data was thus not used for analysis.

Stochastic vestibular stimulation

Subthreshold nGVS is, from here on, referred to as (subthreshold) stochastic vestibular stimulation (SVS) (Lajoie et al., 2021). Electrodes placed bilaterally on the mastoid bones behind the ears were used to deliver the SVS. The electrodes were connected to a portable, programmable stochastic vestibular stimulator designed to deliver a precisely controlled weak current. The device (see Fig. 4) has been previously used in vestibular stimulation research (Samoudi et al., 2015) and is based on a NASA prototype (Mulavara et al., 2015).

Figure 4. The Stochasic vestibular stimulator
A developed version of Mulavara et al. (2015) Stochastic Vestibular Stimulator, developed by Nigul Ilves, Ilves Engineering

Since there are no standard stimulation parameters for SVS (Lajoie et al., 2021), the stimulation protocol for the pre-generated stochastic current for this study was similar to the SVS protocol described by Forbes et al. (2014), consisting of Gaussian white noise low-pass filtered with a fourth-order Butterworth filter and a cutoff frequency of 25 Hz. However, two modifications were made to Forbes et al.'s (2014) original protocol to ensure compatibility with our device: (1) time-scaling and (2) limiting the current amplitude to ±500 μA. The time-scaling preserved the original protocol's attributes (e.g., frequency distribution). The current limit was determined through an in-house pilot study to identify the maximum undetectable current, essential for maintaining the double-blinded design.

The SVS was delivered at 100 Hz with a three-second ramp-up period for participant comfort and to conceal the stimulation's activation. All participants received the same electrical stimulation, starting simultaneously with the first task.

Test battery

Spanboard task

The visuospatial working memory task, hereon referred to as the Spanboard task, has been found to be able to distinguish between children with and without ADHD with large effect sizes (Westerberg et al., 2004). In the task, participants were presented with a 4 × 4 grid containing 16 squares (cf. Figure 5). They were instructed to remember the location and order of a series of red dots, which appeared one by one, and to recall the sequence using a computer mouse. The task aimed to assess the highest possible level of memory performance, requiring participants to remember as many dots in sequence as possible. No feedback was provided on the accuracy of their responses.

Each dot was displayed for 2250 ms, followed by a 750 ms pause before the next dot appeared, resulting in an interstimulus interval (ISI) of 3 seconds. The task began with two dots to remember, and an additional dot was added every two successful trials until the participant made two consecutive errors at the same level. Reaction times were recorded as the interval between two mouse clicks. The task took approximately 5 minutes to complete.

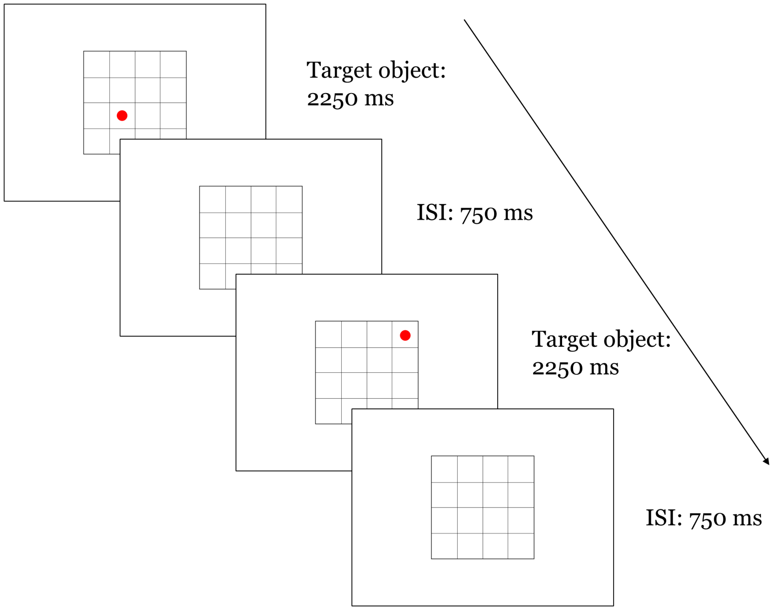

Figure 5. The spanboard task
The task consisted of a 4 × 4 grid of 16 squares. Participants were tasked with remembering the positions and sequence of red dots that appeared one at a time in the grid. Using a computer mouse, they then had to recall and recreate the sequence in the correct order.

Word Recall task

The word recall task is a verbal working memory task, in which participants were instructed to orally recall as many words as possible after listening to prerecorded words played through a pair of earphones. The task consisted of four repetitions (or lists) for each session, though two lists with auditory noise from each session were excluded from the analysis due to the previously mentioned technical issues. Overall, the assessment comprised eight lists of 12 unrelated Swedish nouns each, with a total of 96 words selected from a pool of 157 words previously used in Flodin et al. (2012). The words were matched based on (i) frequency of use in the Swedish language according to the Swedish Kelly-list (Volodina, 2019; Volodina & Kokkinakis, 2012), (ii) word length, and (iii) the number of syllables. Each list included a mix of both high-frequency and low-frequency words. A balanced Latin-square design was used to control the order of list presentation, based on participant ID.

Both written and oral instructions were provided to participants before the task began. While listening to the lists, a fixation cross was displayed at the center of the screen, which participants were instructed to focus on. After each list, participants were asked to orally recall as many words as possible in any order. Responses in plural form were accepted as correct.

The words were approximately 1 second long, and presented in random order, with a four-second pause between each word, resulting in an interstimulus interval (ISI) of 5 seconds. The task took approximately 8 minutes to complete, including the two excluded lists.

The speech signals were presented through Sennheiser HDA 300 earphones at 81 dB. The calibration of the speech signals and equipment followed ISO 389-8 (2004) and IEC 60318-2 (1998) standards, with the calibration performed using a Brüel & Kjaer Impulse Precision Sound Level Meter Type 2209, equipped with a 4134 microphone in a 4153 ear-simulator.

Visuospatial N-back task

The visuospatial N-back task requires the activation of working memory and response inhibition (Diamond, 2013). It comprised three levels of difficulty: 0-back, 1-back, and 2-back. The stimuli consisted of twenty three-dimensional figures constructed from identically sized cubes. In this task, participants were required to recall a specific figure, termed the target, and identify it n steps (0, 1, or 2) back in a sequence of figures.

During the 0-back condition, participants were instructed to press the left arrow key whenever the predetermined target was displayed, while pressing the right arrow key for all other stimuli. In the 1-back condition, participants were required to press the left arrow key whenever they saw the same figure appear consecutively (see Figure 6). The 2-back condition prompted participants to determine whether the third image in the sequence matched the first image, responding to all subsequent figures by identifying them as either matching or mismatching with the figure presented two steps earlier. The participants' response rates governed the pace of the task, with a few exceptions: the initial target(s) in the 1-back (one target) and 2-back tasks (two targets) were displayed for 2 seconds. Each figure was followed by a fixation cross for 1 second before the next figure was presented.

Participants first completed a baseline assessment for each level, consisting of 10 trials, accompanied by both written and oral instructions. The assessments were conducted in the sequence of increasing difficulty: 0-back, followed by 1-back and finally 2-back. Each level in the experimental session included 30 trials, with a distribution of 1/3 target figures and 2/3 non-target figures. The stimuli sequence was randomized for each trial, level, participant, and testing occasion. Reaction times were recorded from the moment a new figure appeared until the participant selected whether the figure was the same or different by pressing either the left or right arrow key. The entire task lasted approximately 10 minutes.

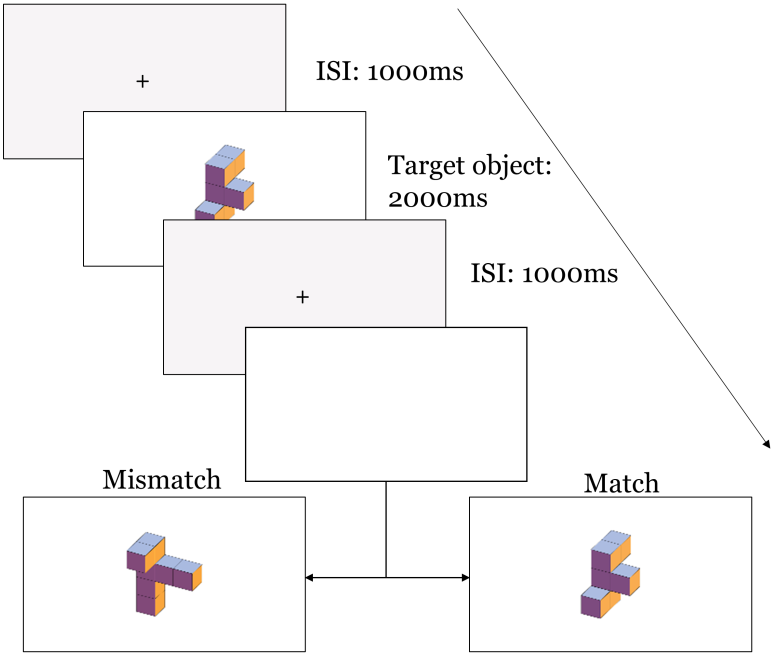

Figure 6. The N-back task
In the 1-back condition, participants were instructed to respond with different keys to wether the same figure appeared consecutively and thus was a match or a mismatch with the image previously displayed.

Procedure

Participants were assessed individually while seated approximately 40 cm from the screen of a 15-inch Dell XPS 15 9560 laptop running Windows 10. The skin behind each participant's ears was thoroughly cleaned with 70% alcohol, and Cefar Dura-Stick Plus electrodes (5 × 5 cm) were affixed using a generous application of Cefar blågel. The electrodes were secured in place with a custom-made headband worn by the participant. The order of electrical stimulation (first or second) was randomly assigned and counterbalanced across participants, ensuring a double-blind design; neither the participant nor the experimenter knew whether the protocol being applied was a sham or the stimulation protocol. Participants were instructed to report any sensations experienced from the electrodes.

All tasks were developed using PsychoPy, version 3.1.0, standalone software (Peirce et al., 2019) and were administered in a consistent sequence: Spanboard, Word Recall, and N-back task, utilizing a Logitech G203 Prodigy mouse. Each testing session lasted approximately 45 minutes.

Setting

All tasks were conducted in a quiet environment, either at the child and adolescent psychiatry unit or at the participants' schools, over two separate sessions. During the assessments at school, only the participant and the experimenter were present in the room, while parents were able to accompany their child during the assessments at the child and adolescent psychiatry unit.

Study II: Paper II-IV

Study design

A 2 × 2 × 4 repeated measures design was used for the data collection procedure. The two study groups (ADHD/TDC) performed two tasks, a memory guided saccade (MGS) task and a prolonged fixation (PF) task, that in two meta-analyses had the largest effect size in differentiating between the groups (Chamorro et al., 2022; Maron et al., 2021). The tasks were performed in four different noise conditions: a no-noise condition, an auditory white noise condition, and in two conditions with different levels of visual white pixel noise. PsychoPy code to run the experiment is publicly available on GitHub: https://github.com/marcus-nystrom/white-noise-exp.

Auditory white noise stimulation

The auditory white noise was generated from a uniform distribution (U[0, 255]), and presented as a stereo signal, with separate arrays drawn for each channel. The audio was sampled at 48,000 Hz, digitized to 16 bits, and saved in uncompressed .wav format. Before each experimental session, the noise level was calibrated to 78 dB using a UNI-T UT351/352 sound level meter. Calibration was performed separately for each computer setup and pair of earphones to ensure consistency across assessments.

Visual white pixel noise stimulation

Visual white noise was added to each pixel of the stimulus image by blending it with a transparent noise image of the same size, with noise values drawn from a uniform distribution, U[0, 255]. In the distribution 0 represents black and 255 represents white. The level of noise was controlled by the transparency of the noise image. A transparency of 100% would result in only noise, obscuring the stimulus, while 0% would add no noise to the stimulus image. In this study, noise levels of 25% and 50% were used (cf.

Figure 7). The noise image was updated every screen refresh, at 60 Hz, to maintain dynamic noise across the stimuli.

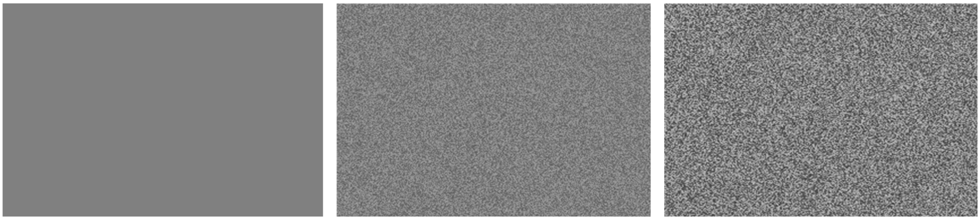

Figure 7. Visual white pixel noise
The visual white pixel noise at 0% (no noise), 25%, and 50%.

Eye tracking

An eye tracker is a device that records eye movements relative to the head or gaze direction (Holmqvist et al., 2011). Most modern eye trackers are video-based, tracking the pupil's position and corneal reflections in each video frame. They typically provide gaze position (x, y coordinates) in the screen's coordinate system and pupil size, collected at sampling rates ranging from 50 to 1000 Hz, enabling detailed analysis of the gaze behavior.

The Humanities Lab at Lund University is equipped with 16 Tobii Pro Spectrum eye trackers that were used to collect data for the study. The eye trackers record eye positions at 600 Hz for both horizontal and vertical gaze directions, with (0,0) representing the top-left of the screen and (1,1) representing the bottom-right. Eye openness and pupil diameter in mm was also recorded.

Calibration and validation were performed with Titta version 2.0.2 (Niehorster et al., 2020), while TittaPy (version 1.0.0) facilitated communication between PsychoPy and the eye tracker. The default calibration settings in Titta were applied, consisting of five calibration points and four validation points. Recalibration was performed if the accuracy was above 1°. If accuracy below 1° was not achieved after three calibration attempts, the calibration with the best accuracy was selected.

In Paper III and IV eye tracking data quality was presented in terms of precision, accuracy, and data loss, following the minimal reporting guideline for research involving eye tracking from Dunn et al. (2023). According to this guideline, precision is an estimate of uncertainty regarding the gaze position while accuracy is the offset between the estimation and true gaze position. Accuracy and precision were computed from validation data (Niehorster et al., 2020). Data loss refers to the proportion of invalid eye tracking data, due to e.g. blinks or the participant looking outside the tracking range of the eye tracker (Dunn et al., 2023). Data loss was computed from the data collected during the actual tasks.

Averaged across participants, precision in terms of sample-to-sample root mean square (RMS) distance was 0.07° (SD = 0.07°) for both right and left eye. Accuracy for left eye was 0.62° (SD = 0.24°) and 0.60° (SD = 0.27°) for right eye.

In Paper III mean data loss was 4.67% (SD = 9.17%) for participants right eye and 4.92% (SD = 10.15%) for left eye. There were no significant differences between the groups in terms of accuracy and precision. However, a significant difference in data loss was observed, see table 3.

Table 3. Precision, accuracy, and mean data loss in the ADHD and TDC group from paper III

Measure/eye	**ADHD**	**TDC**	**ADHD vs. TDC**
Precision			
Right eye	0.08° (0.08°)	0.06° (0.04°)	$t(73) = -1.48$, $p = 0.14$
Left eye	0.08° (0.09°)	0.07° (0.03°)	$t(60) = -1.03$, $p = 0.31$
Accuracy			
Right eye	0.62° (0.29°)	0.58° (0.24°)	$t(95) = -0.84$, $p = 0.41$
Left eye	0.64° (0.27°)	0.60° (0.21°)	$t(94) = -0.96$, $p = 0.34$
Mean data loss			
Right eye	5.36% (10.19%)	3.87% (7.76%)	$t(12482) = -9.4$, $p < 0.001$***
Left eye	5.22% (9.82%)	4.57% (10.50%)	$t(12171) = -3.6$, $p < 0.001$***

Mean (standard deviation), ***p < 0.001

In Paper IV mean data loss from the eye openness signal was 0.22% (*SD* = 1.10%) for participants right eye and 0.13% (*SD* = 0.48%) for left eye. Mean data loss from the pupil diameter signal was 5.41% (*SD* = 6.53%) for participants right eye and 5.83% (*SD* = 7.06%) for left eye.

Test battery

Prolonged fixation task

The PF task requires participants to exhibit sustained attention and inhibitory control. During the task, participants are asked to fixate on a central fixation point presented on a screen, consisting of a red disc (diameter 0.2°) within a blue disc (diameter 1°), for 60 seconds (Figure 8). The fixation point was presented on a mid-gray background (gray value 128, where 0 is black and 255 white). Participants were instructed to return their gaze to the fixation point as soon as possible if they found themselves deviating from the fixation point. The task was performed once in each noise condition.

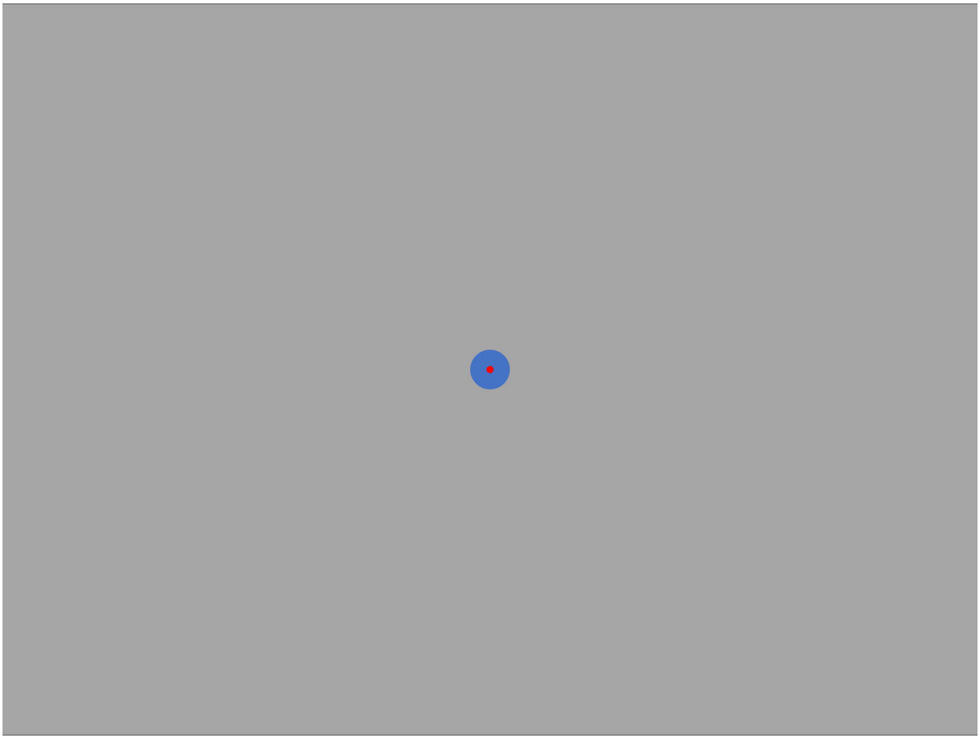

Figure 8. Prolonged fixation task
In the prolonged fixation task, participants are instructed to maintain their gaze on a central fixation point continuously for one minute.

Memory guided saccade task

The MGS task requires visuospatial working memory and inhibitory control (Nigg, 2000). During the task participants were instructed to fixate on a central fixation point, consisting of a red disc (diameter 0.2°) within a blue disc (diameter 1°), for as long as it was visible. During that time a white disc (diameter 1°) would appear in one of four different directions. The participant was instructed to not look at it, but remember the location of the disc. When the central fixation point disappeared, the participant should move their gaze, as quickly as possible, to the remembered location of the white disc. The disc reappeared at the same location, enabling the participant to make a corrective saccade to it. In accordance with previous studies on MGS (Caldani et al., 2023; Mahone et al., 2009), the central fixation point was visible for a random time interval (2,000–3,500 ms before disc onset, 2,000–3,500 ms after disc offset). The white disc randomly appeared in one of four directions (45°, 135°, 225°, or 315°) 10° away from the central fixation point and was visible for 300 ms. The white disc reappeared 1,000 ms after central fixation point offset and was visible for 1,000 ms (see Figure 9). Each participant completed 30 MGS-trials for each noise condition.

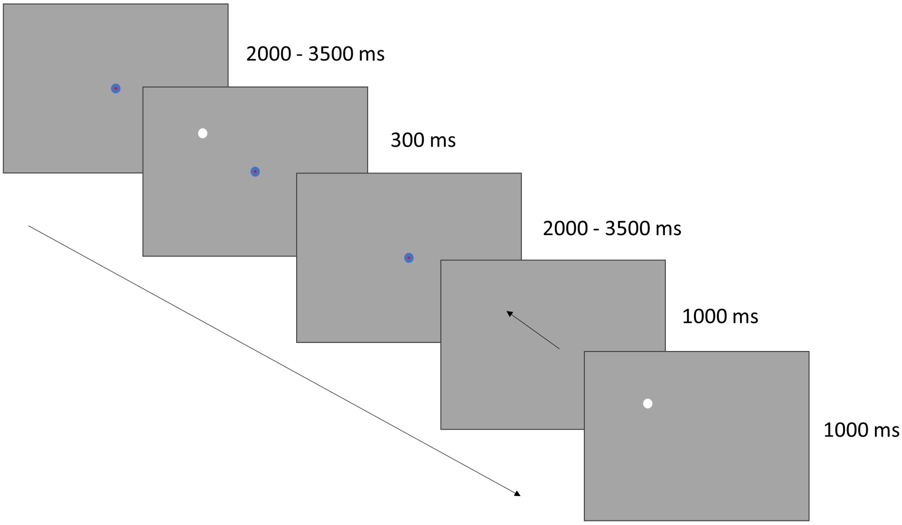

Figure 9. Memory guided saccade task
In the memory-guided saccade task, participants are instructed to focus on a central fixation point while avoiding looking directly at a briefly displayed white disc, instead memorizing its location. Once the fixation point disappears, they should quickly direct their gaze to the remembered position of the disc and maintain their focus there until it reappears.

Procedure

Before the experiment began, participants were introduced to the various types of noise and instructed on how to perform the MGS task, following guidelines similar to those of Mahone et al. (2009). They were told: "As long as the center fixation point is visible, look only at the center point. Do not look at the flash when it occurs but remember its location. When the center point disappears, immediately move your gaze to the place where you saw the flash." To ensure understanding, participants completed a training session for the MGS task. The training evaluated correct versus incorrect trials, and participants were only allowed to proceed to the experimental session after achieving at least three correct trials out of five. A correct trial was defined as maintaining gaze within a 6° area from the central fixation point until it disappeared and then shifting gaze to within 6° of where the white disc had appeared. The training was conducted without noise stimulation.

After successfully completing the training, participants performed two MGS tasks, followed by four PF tasks, and then two final MGS tasks. The four noise conditions—no-noise, auditory white noise, visual white pixel noise at 25%, and visual white pixel noise at 50%—were randomly assigned across the tasks so that each participant completed all tasks under all noise conditions. Between the initial MGS tasks and the following PF tasks, participants were given a planned break during which they received instructions on the PF task. A second break, between the PF tasks and the final MGS tasks, allowed participants to rest and have refreshments (see figure 10 for timeline of the experiment). The entire training and experimental session lasted approximately 50 minutes.

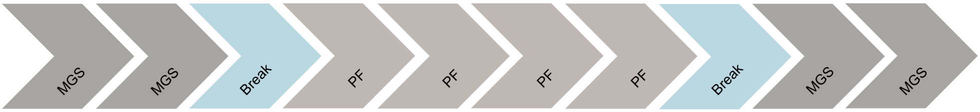

Figure 10. Timeline of the experimental session.
Participants completed two Memory Guided Saccade (MGS) tasks, followed by four Prolonged Fixation (PF) tasks, and then two additional MGS tasks. A scheduled break was provided between the initial MGS tasks and the PF tasks, and a second break was given between the PF tasks and the final MGS tasks.

After the experimental session, participants were asked to provide individual objective assessments of their experience with the tasks and noise interventions by completing a form. The form included five questions, rated on a 10cm visual analogue scale. The first two questions assessed whether participants found the tasks easier or harder when exposed to auditory or visual noise. The third and fourth questions evaluated the comfort level of the noise, determining whether participants experienced it as uncomfortable or pleasant. The final question gauged whether participants found the tasks fun or boring.

Setting

The study was conducted in a windowless room at the Humanities Lab at Lund University. Participants were seated 63 cm in front of an Eizo Flexscan EV2451 screen, using a chin, and forehead-rest for stability, and wore RØDE NTH-100M earphones connected to a desktop computer running Windows 10. The stimuli were presented using PsychoPy standalone version 2022.1.3 (Peirce et al., 2019), running on Python version 3.8.10.

Ethical considerations

Admitting patients to a study is a sensitive issue that must be considered. Patients may fear negative consequences related to their present or future health care if they decline to participate. Therefore, information about the study was provided by the research leader when meeting the family at the Child and Adolescent outpatient clinic but follow up and collection of approvals as well as testing was performed by me, a person with no clinical or personal relationship with the participants.

Since the studies include children, consideration to information material has been thoroughly taken. All information has been adapted to the age of the child informed about the study and more in-depth information provided to the legal guardians. All potential questions were thoroughly answered before participants responded to whether they wanted to participate in the study or not.

Legal guardians provided a written consent for all participating children. Verbal approval was obtained from children under the age of 15 while written approval was obtained from children aged 15 or above. All participants were informed that they could discontinue participation at any time without providing a specific reason and without facing any consequences. Participants received compensation for their participation in the form of a gift certificate.

Although all assessment methods used in the papers have been used prior to our studies, considerations regarding applying white noise stimulation on children is essential. Auditory white noise has previously been assessed in several studies. However, the noise levels found to be effective in improving cognitive performance (70-80dB) are quite loud and should not be applied for an extended period of time. To ensure that the noise stimulation was not harmful, only short time-periods of auditory noise were assigned. The visual white noise has been less studied, but adverse experiences were considered unexpected. A potential risk could be to elicit migraine. The vestibular stimulation had been designed to be below sensation threshold, to ensure a blinded study. Although, during the experimental procedure, some of the participants reported a tingling feeling from the stimulation. Only one participant chose to withdraw from participating due to their experience from the noise stimulation (SVS).

All data collected in the studies have been anonymized, kept confidential, and handled in accordance with the Data Protection Act, General Data Protection Regulation (GDPR) policies, and the Swedish Act concerning the Ethical Review of Research Involving Humans (SFS 2003:460). Data is securely stored both physically and electronically, and access has been restricted to the study team.

The results have been reported on a group basis and no individual information regarding participants have been reported.

The studies were granted ethical permission from the Swedish Ethical Review Authority (Study I: EPN 2021-04444, Study II: EPN 2023-02476-01) and were registered at clinicaltrials.gov (Study I: NCT03425669, Study II: NCT06057441).

Analytical and statistical methods

The statistical models used in the dissertation work will shortly be presented, followed by a description of the analyses performed in each paper.

Comparison of means were done using either an independent-samples t-test or chi-square test. An *independent-samples t-test* is used to assess the means of two independent groups, to determine whether there is a significant difference between them or not. The *chi-square test* is a non-parametric statistical test used to examine the association between two categorical variables. It compares the observed frequencies in different categories with the frequencies expected under the null hypothesis of no association.

An examination of the relationship between the outcome variable and predictors can be done using linear regression analysis. *Multiple linear regression analysis* is applied to predict a dependent variable based on its association with several (multiple) independent variables. *Linear mixed-effects analysis* is similar to multiple linear regression analysis but allows for the modeling of both fixed and random effects in data. This approach is applicable when there are repeated measures from the same individuals. The fixed effects capture the average effect of predictors on the outcome, while random effects account for variations across subjects or groups.

Visual *inspection of residual plots* has been performed for all regression analyses, which is a diagnostic step used to assess the validity of model assumptions and fit of the model. The inspections help determine if the assumptions of linearity, homoscedasticity, and normality are reasonably met. If deviations were found, these were adjusted for each model.

Post hoc pairwise comparisons of estimated marginal means provide a detailed follow-up analysis to determine which specific group differences drive the overall significance in a statistical model, while adjusting for multiple comparisons. These analyses were done on significant main or interaction effects from the regression analyses, using the emmeans-function (Lenth, 2022), with Bonferroni correction.

All statistical analyses were performed in R (R Core Team, 2022). In both Study I and II, participants' characteristics have been compared between the ADHD group and TDC group using independent-samples t-tests and chi-square tests. The regression analyses were done separately for each noise condition and dependent variable(s) for each task. Statistical significance was considered at $p = .05$.

Study I: Paper I

In Paper I, linear mixed-effects analyses were used to investigate predictions in the data. Independent variables were noise condition, group and the interaction between noise condition and group. Age and sex were added as covariates in all regression models, since there was a significant difference between the groups regarding these variables (see table 1). Random effects were set to the intercept for each subject.

Spanboard task

The dependent variables for this task were: (1) the total number of correctly recalled dots, and (2) the standard deviation of reaction time (RT) values, hereon referred to as RT variability.

All RT values above or equal to 3 SD were removed. The remaining reaction times were then used to compute a RT variability variable for each participant. The RT variability variable was not normally distributed and thus transformed to normality using square-root transformation.

Word Recall task

The dependent variable for this task was the number of correctly recalled words.

N-back task

The dependent variables for this assessment included (1) the number of incorrect responses and (2) RT variability.

The data from the three levels of the N-back task (0-, 1- and 2-back) were merged into one "N-back" analysis. All RT values above or equal to 3 SD were removed. The remaining reaction times were then used to compute a RT variability variable for each participant. The RT variability variable was not normally distributed and thus transformed to normality using square-root transformation. Performance (number of incorrect responses) on the N-back task was transformed to normality with log-transformation after adding 1 to each subject, since the log(0) is undefined.

Sample size

The power calculations for the required number of participants were based on prior research on auditory noise stimulation (Söderlund et al., 2016), indicating that a minimum of 26 participants per group would be necessary for the study.

Study II: Paper III

Preprocessing of data from the eye trackers was performed in Python. Fixations and saccades were used for analysis. Fixations were detected with the I2MC algorithm (Hessels et al., 2017), with default settings where both eyes were used as input. Saccades were defined as distances between two consecutive fixations. Trials with >20% data loss from both eyes were excluded from the analyses.

Linear mixed effects analyses were fit and analyzed with the anova-function to produce a type III Analysis of variance (ANOVA) table. Noise condition, group and the interaction between the two were independent variables. Random effects were set to the intercept for each subject.

Prolonged fixation task

Two measures were computed from data collected during the PF task: (1) fixation ratio and (2) the number of intrusive saccades.

Fixation ratio for each trial was calculated as the duration of correct fixations divided by the duration of all fixations. To be classified as correct, the fixation had to be within a range of <2° from the central fixation point. The variable was transformed to normality using rank-based transformation.

Saccades with amplitudes larger than ≥2° were taken as intrusive saccades. Saccades made in the beginning of the PF task to move the gaze to the central fixation point, were not included. The variable was transformed to normality using rank-based transformation.

Memory guided saccade task

The MGS task was analyzed on four different measures, (1) the number of anticipatory saccades, (2) the latency for correct trials, (3) the gain of correct trials and, (4) the ratio of correct trials.

Anticipatory saccades were defined as saccades initiated before the extinction of the central fixation point and include saccades made <80 ms after the extinction of the central fixation point, since it takes at least 80 ms to react to the fact that the point has disappeared. The number of anticipatory saccades were counted as the number of saccades with amplitudes ≥2°. The variable was transformed to normality with log-transformation after adding 1 to each trial, since the log(0) is undefined.

Latency for each correct trial was calculated, that is, the time between the offset of the target and the onset of the next saccade ≥2°. The latency variable was transformed to normality using log-transformation.

Gain, that is, the accuracy of saccades, was computed as the saccade amplitude divided by the target amplitude. The variable was transformed to normality using square-root transformation.

The number of correct trials were defined based on several analysis-steps. To be classified as correct there had to (i) be at least one fixation between flash onset and target offset, (ii) the fixation(s) that were between flash onset and target offset had to be within a range of <2° from the central fixation point, (iii) there had to be at least an 80 ms latency after target offset, and no longer than 1,000 ms, until there was a new fixation. Additionally, (iv) the new fixation after target offset had to be ≥2° from the central fixation point, and (v) the fixation had to be in the same quartile as the flash. The proportion between correct and incorrect trials were calculated. Fixations before flash onset were not analyzed.

Sample size

The power calculations performed were based on previous studies examining the effects of auditory noise (Söderlund et al., 2021; Söderlund et al., 2016), along with a review on oculomotor inhibition during MGS and PF tasks (Chamorro et al., 2022). To detect an improvement in performance with sensory noise equivalent to half a standard deviation in intrusive saccades during the PF task, approximately 15 participants per group were needed to achieve a statistical power of 0.80 at a significance level of p = .05.

Study II: Paper IV

Blink rate and pupil size were analyzed from the prolonged fixation task. Only data from the auditory white noise condition and the no-noise condition was analyzed. Blink rate is the number of blinks made during one minute. Pupil size was analyzed both as the mean pupil size during one minute and as mean pupil size during 6 ten-second periods of the task.

Pupil diameter data were extracted from the pupil diameter signal from when the gaze remained within a 2-degree radius of the central fixation point. Blink rate was calculated from eye-openness data using a blink detection algorithm (Nyström et al., 2024). Trials with more than 20% data loss from both eyes were excluded to ensure data quality.

To examine mean blink rate and pupil diameter in the no-noise condition, multiple linear regression models were employed, using SNAP-IV ratings (separately for hyperactivity and inattention) as predictors. For the auditory white noise condition, condition (no-noise vs. noise) was included in the model as an interaction with the SNAP-IV ratings. Sex and age were added as covariates in the analyses.

The duration of noise effects on pupil diameter was analyzed using a linear mixed-effects model. Condition, timeframe, and the interaction between the two, together with SNAP ratings (hyperactivity/impulsivity), age and sex, was used to predict the mean pupil diameter from six ten-second time periods. Participant-specific random intercepts were included.

Results

Participant characteristics from both studies will first be presented, followed by findings regarding the effects of white noise stimulation from each study, divided into the different papers (I, III and IV).

Participants

For Study I 71 participants aged 8-17, 43 children with an ADHD diagnosis and 28 typically developing children (TDC), were recruited. The groups exhibited significant differences in sex and age, as well as level of hyperactivity, inattention and total SNAP-IV score levels, see table 1.

Table 1. Participants' characteristics, parent SNAP-IV ratings on hyperactivity/impulsivity and inattention and parents assessment on reading and writing skills in the ADHD and TDC groups.

	ADHD	TDC	ADHD vs TDC
Paper I			
Boy/Girl	28/15	12/16	$X^2(1, N = 70) = 5.42, p = .020$*
Age	12.4 (2.1)	11.2 (0.4)	$t(91) = -5.18, p < .001$***
Hyperactivity/Impulsivity	14.9 (6.8) [a]	0.3 (0.9) [b]	$t(85) = -19.18, p < .001$***
Inattention	17.6 (4.8) [a]	1.9 (2.7) [b]	$t(132) = -24.34, p < .001$***
Total (H+I)	32.5 (10.3) [a]	2.2 (3.2) [b]	$t(102) = -24.84, p < .001$***
Paper III & IV			
Boy/Girl	31/21	20/25	$X^2(1, N = 97) = 1.66, p = .20$
Age	11.7 (1.7)	11.7 (2.4)	$t(79) = -0.00, p = .99$
Hyperactivity/Impulsivity	14.4 (6.3) [a]	2.3 (3.3) [a]	$t(79) = -12.13, p < .001$***
Inattention	18.4 (4.8) [a]	3.7 (3.7) [a]	$t(94) = -17.02, p < .001$***
Total (H+I)	32.4 (8.8) [a]	6.0 (6.0) [a]	$t(91) = -17.74, p < .001$***
Reading & writing	5.7 (4.2) [a]	1.5 (2.8) [a]	$t(90) = -5.59, p < .001$***

Mean (standard deviation), Age: years, H: Hyperactivity/impulsivity, I: Inattention, [a]Parent rated scores, [b]Teacher rated scores, * $p \leq .05$, *** $p \leq .001$

For Study II 97 participants aged 7-16, 52 children with an ADHD diagnosis and 45 TDC, were recruited. The groups did not differ significantly according to age or sex. However, they exhibited significant differences in hyperactivity, inattention and total SNAP-IV score levels. There was also a significant difference between the ADHD and TDC group regarding the reading and writing assessment, see table 1.

5-15R

Study II included the collection of developmental characteristics. These have not yet been analyzed in relation to noise stimulation, but descriptive statistics are presented in table 2. The groups displayed significant differences in all assessment criteria, although the difference in executive functioning was profoundly large.

Table 2. Participants' ratings on the 5-15R assessment in the ADHD and TDC groups.

	ADHD	TDC	ADHD vs TDC
Motor skills	0.49 (0.36)	0.06 (0.12)	$t(62) = -8.13$, $p < .001$***
Executive functions	1.25 (0.33)	0.17 (0.19)	$t(84) = -19.78$, $p < .001$***
Perception	0.39 (0.27)	0.06 (0.08)	$t(62) = -8.38$, $p < .001$***
Memory	0.70 (0.42)	0.09 (0.15)	$t(66) = -9.80$, $p < .001$***
Language and communication	0.43 (0.37)	0.04 (0.07)	$t(55) = -7.56$, $p < .001$***
Learning skills	0.99 (0.47)	0.17 (0.25)	$t(79) = -10.61$, $p < .001$***
Social skills	0.53 (0.38)	0.05 (0.11)	$t(60) = -8.78$, $p < .001$***
Mental health problems	0.53 (0.36)	0.07 (0.09)	$t(58) = -8.92$, $p < .001$***

Mean (standard deviation), *** $p \leq .001$

Study I: Paper I

Spanboard task

The Spanboard task was evaluated in relation to both performance (the number of correctly recalled items) and reaction time (RT) variability.

Performance

There was no difference in task performance between SVS on (ADHD: M = 35.2, SD = 16.4; TDC: M = 35.8, SD = 16.3) and SVS off (ADHD: M = 33.5, SD = 15.0; TDC: M = 35.9, SD = 12.7). Neither group nor noise condition could predict performance, and there was no interaction between group and noise condition (cf. Table 3 and Fig. 11A). However, age could significantly predict performance. The number of correctly recalled items increased with age.

RT variability

When assessing RT variability in the Spanboard task, neither the noise condition, nor the interaction between noise condition and group, could significantly predict RT variability. However, group could significantly predict RT variability, the ADHD group had a larger RT variability than the TDC group (cf. Table 3).

Post hoc analyses of group (ADHD/TDC) and noise condition (SVS on/off) revealed a significant difference in RT variability between the groups when SVS was off but not on (see Fig. 11B). The RT variability was significantly higher for the ADHD group with the SVS off, compared to the TDC group (ADHD: M = 0.53s, SD = 0.21s; TDC: M = 0.44s, SD = 0.13s). When the SVS was on the significant difference between the groups was no longer present (ADHD: M = 0.56s, SD = 0.21s; TDC: M = 0.48s, SD = 0.14s).

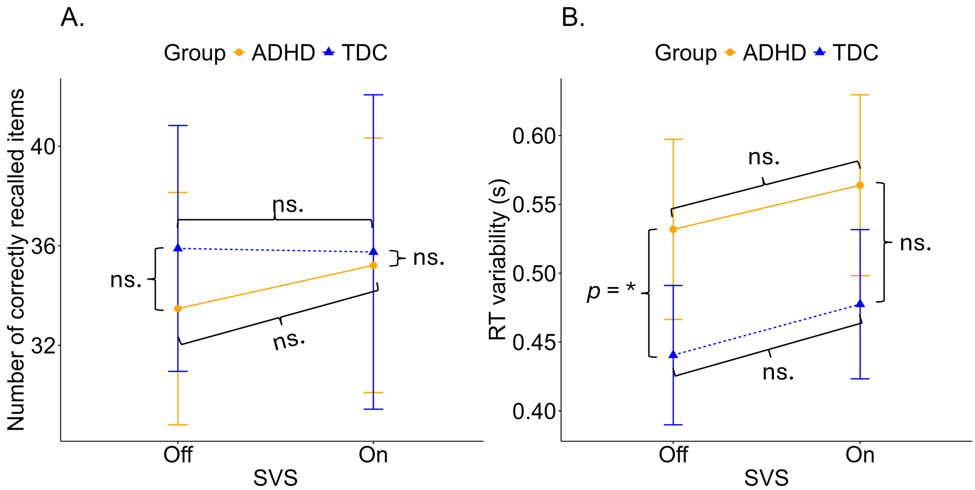

Figure 11. (A) Number of correctly recalled items in the Spanboard task and (B) Spanboard RT variability, as a function of SVS on/off, in two groups: ADHD (yellow line) and TDC (blue line). Error bars represent 95% CI. *p < .05.

Word Recall task

The word recall task was assessed regarding performance, i.e. the number of correctly recalled nouns in free recall. Neither noise condition, group nor the interaction between noise condition and group could significantly predict performance in the word recall task. The participants recalled about an equal number of words with SVS off (ADHD: M = 9.1, SD = 3.1; TDC: M = 8.6, SD = 2.6) as with SVS on (ADHD: M = 8.7, SD = 3.4; TDC: M = 9.0, SD = 2.0). See Table 3 for exact figures.

N-back task

In the N-back task, task performance (the number of errors on the 0-, 1- and 2-back task summarized) and RT variability was assessed.

Performance

Neither noise condition nor the interaction between noise condition and group could significantly predict the number of errors on the N-back task. However, group was able to significantly predict the number of errors. The ADHD group made significantly more errors than the TDC group, see Table 3.

Post hoc analyses revealed a significant difference between the groups with SVS off, see Fig. 12A. When SVS was on the difference between groups disappeared. This effect was most likely due to both groups having a larger SD with the SVS on (ADHD: M = 11.2, SD = 8.2; TDC: M = 8.9, SD = 5.4) compared to off (ADHD: M = 11.2, SD = 5.8; TDC: M=8.4, SD = 4.0).

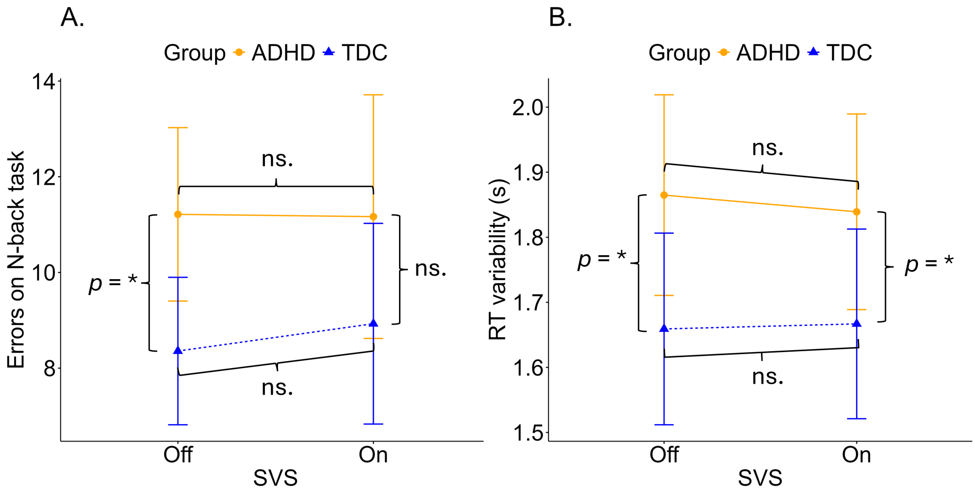

Figure 12. (A) Total number of errors on the N-back task (0-, 1-, and 2-back summarized), and (B) N-back RT variability, as a function of SVS on/off, in two groups: ADHD (yellow line) and TDC (blue line). Error bars represent 95% CI. *p < .05.

RT variability

Both the variables group and age were able to significantly predict RT variability on the N-back task (cf. Table 3). The ADHD group had a larger RT variability than the TDC group and the RT variability significantly decreased as age increased. Noise condition, sex, or the interaction between noise condition and group, could not significantly predict RT variability.

Post hoc comparisons of noise condition (SVS on/off) and group (ADHD/TDC) revealed a significant difference between groups both with SVS off and SVS on, see Fig. 12B. That is, the groups differed significantly in their RT variability during both test occasions. When SVS was off the ADHD group had a significantly larger RT variability than the TDC group (ADHD: M = 1.87s, SD = 0.50s; TDC: M = 1.66s, SD = 0.38s), which was also the case when SVS was on (ADHD: M = 1.84s, SD = 0.48s; TDC: M = 1.67s, SD = 0.38s).

Table 3. Results of linear mixed effect analyses for the Spanboard, Word Recall and N-back task during stochastic vestibular stimulation.

Dependent variable	*Predictors*	*β*	*95% CI*	*p*
Correct answers on Spanboard task	Group [ADHD]	-5.16	-13.07 – 2.75	0.200
	Age	2.02	0.02 – 4.03	**0.050**
	Sex [Boy]	1.21	-5.54 – 7.96	0.723
	Noise condition [SVS on]	-0.14	-4.95 – 4.66	0.953
	Noise condition [SVS on] * group [ADHD]	1.93	-4.27 – 8.13	0.540
RT variability (s)on Spanboard task	Group [ADHD]	0.07	0.00 – 0.13	**0.047**
	Age	-0.01	-0.02 – 0.01	0.427
	Sex [Boy]	-0.01	-0.06 – 0.05	0.770
	Noise condition [SVS on]	0.03	-0.02 – 0.08	0.295
	Noise condition [SVS on] * group [ADHD]	-0.01	-0.07 – 0.06	0.880
Correctly recalled words on Word Recall task	Group [ADHD]	0.13	-1.37 – 1.63	0.866
	Age	0.32	-0.06 – 0.70	0.097
	Sex [Boy]	-0.32	-1.59 – 0.95	0.619
	Noise condition [SVS on]	0.32	-0.65 – 1.29	0.513
	Noise condition [SVS on] * group [ADHD]	-0.74	-2.00 – 0.52	0.247
Performance (errors) on N-back task	Group [ADHD]	0.30	0.01 – 0.58	**0.042**
	Age	-0.03	-0.09 – 0.04	0.458
	Sex [Boy]	-0.16	-0.39 – 0.06	0.154
	Noise condition [SVS on]	0.00	-0.23 – 0.24	0.987
	Noise condition [SVS on] * Group [ADHD]	-0.07	-0.38 – 0.23	0.636
RT variability (s) on N-back task	Group [ADHD]	0.11	0.02 – 0.19	**0.018**
	Age	-0.02	-0.04 – -0.00	**0.031**
	Sex [Boy]	-0.02	-0.09 – 0.05	0.667
	Noise condition [SVS on]	0.00	-0.06 – 0.07	0.922
	Noise condition [SVS on] * Group [ADHD]	-0.01	-0.10 – 0.07	0.771

RT: Reaction time, *β*: estimate, CI: Confidence interval

Prolonged fixation task

The prolonged fixation task was assessed in relation to both fixation ratio and the number of intrusive saccades during the no-noise, auditory white noise and two levels of visual white pixel noise conditions. Performance during auditory noise was compared to the no-noise condition separately from the visual noise conditions. Similarly, the visual noise conditions were assessed against the no-noise condition and not the auditory condition.

Fixation ratio

When assessing the *auditory white noise* stimulation, no main effect of noise was revealed ($F(1, 95) = 3.01$, $p = 0.086$). However, a significant main effect of group was observed ($F(1, 95) = 4.26$, $p = 0.042$). There was no interaction between noise condition and group ($F(1, 95) = 0.20$, $p = 0.655$), see figure 13A.

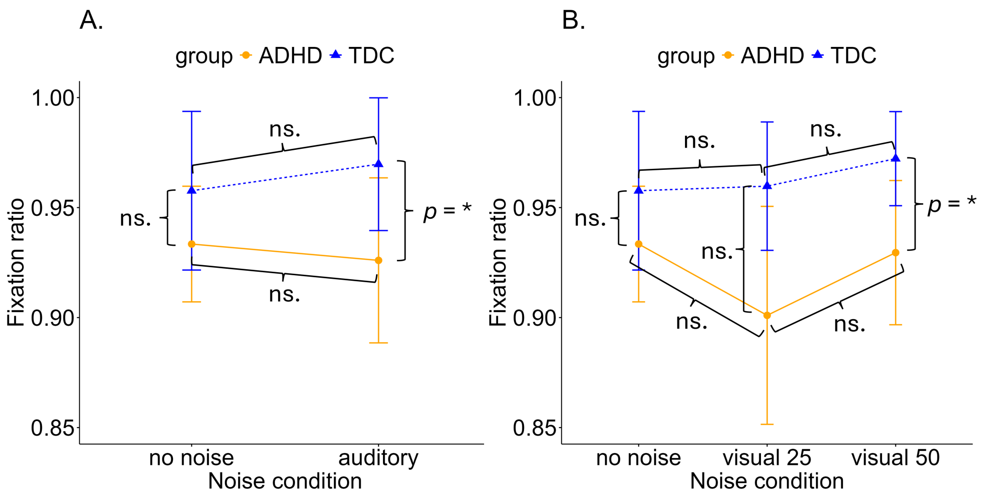

Figure 13. Fixation ratio on the prolonged fixation task in the (A) no-noise and auditory white noise condition, and (B) no-noise and two levels of visual white pixel noise (25% and 50%) conditions, for the ADHD (yellow line) and TDC (blue line) group. Error bars represent 95% confidence intervals. *p < .05.

A post hoc analysis of group differences found no difference between the ADHD group (ADHD: M = 0.93, SD = 0.09) and TDC group (TDC: M = 0.96, SD = 0.12) in the no-noise condition ($p = 0.113$). However, a significant difference between the groups in the auditory noise condition was found ($p = 0.045$). The ADHD group had a significantly lower fixation ratio (M = 0.93, SD = 0.13) compared to the TDC group (M = 0.97, SD = 0.10).

When assessing fixation ratio during the *visual white noise* stimulation no main effect of noise was found (F(2, 190) = 1.90, p = 0.153). However, a significant main effect of group was observed (F(1, 95) = 4.70, p = 0.033). There was no interaction between noise condition and group (F(2, 190) = 0.13, p = 0.880), see figure 13B.

A post hoc analysis found no differences between the ADHD and the TDC group in the no-noise condition (p = 0.113), the groups did not differ in their fixation ratio (ADHD: M = 0.93, SD = 0.09; TDC: M = 0.96, SD = 0.12). In the visual noise condition at level 25% no difference between the groups was found (p = 0.071), the ADHD group did not differ in their fixation ratio (M = 0.90, SD = 0.17) compared to the TDC group (M = 0.96, SD = 0.10). In the noise condition at level 50%, a significant difference between the groups was revealed (p = 0.040). The ADHD group had a significantly smaller fixation ratio (M = 0.93, SD = 0.12) compared to the TDC group (M = 0.97, SD = 0.07).

Intrusive saccades

When assessing the effects of *auditory white noise* stimulation on the number of intrusive saccades, no main effect of noise (F(1, 95) = 1.52, p = .221) or group (F(1, 95) = 3.11, p = .081) was revealed. No interaction between noise and group was found (F(1, 95) = 0.03, p = .856), see Figure 14A. The groups did not differ in the number of intrusive saccades made during the prolonged fixation task in the no-noise condition (ADHD: M = 15.35, SD = 17.33; TDC: M = 9.46, SD = 15.22) and the auditory noise condition (ADHD: M = 13.68, SD = 17.01; TDC: M = 9.02, SD = 15.71).

When assessing the number of intrusive saccades during *visual white noise* stimulation, no main effect of noise was observed (F(2, 190) = 2.67, p = .072). However, we found a trend toward a significant main effect of group (F(1, 95) = 3.90, p = .051). No interaction between noise and group was revealed (F(2, 190) = 0.24, p = .788), see Figure 14B. The groups did not statistically differ in the number of intrusive saccades in the no-noise condition (ADHD: M = 15.35, SD = 17.33; TDC: M = 9.46, SD = 15.22), the visual noise at level 25% condition (ADHD: M = 12.06, SD = 13.11; TDC: M = 8.61, SD = 15.99), or the visual noise at level 50% condition (ADHD: M = 11.92, SD = 14.02; TDC: M = 7.05, SD = 13.35). Overall, the noise stimulation did not significantly impact the performance of either group in terms of the number of intrusive saccades.

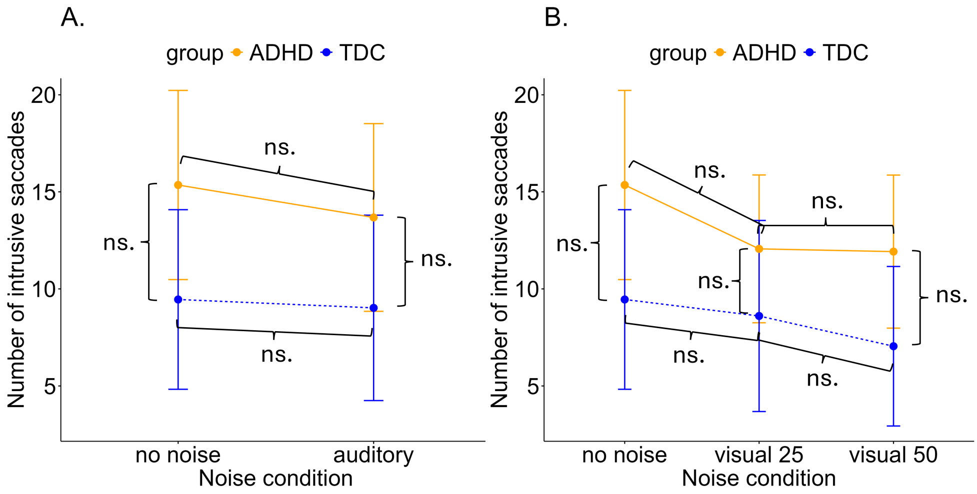

Figure 14. Number of intrusive saccades for the ADHD (yellow line) and TDC (blue line) group in the prolonged fixation task in (A) no-noise and auditory noise, and (B) no-noise, visual noise at 25% and visual noise at 50%. Error bars represent 95% confidence intervals.

Memory guided saccade task

The memory guided saccade task was assessed in relation to the number of anticipatory saccades, latency, gain, and the number of correctly performed trials.

Anticipatory saccades

When assessing the effects of *auditory white noise* stimulation on the number of anticipatory saccades, no overall effect of noise was found ($F(1, 5{,}570) = 1.23$, $p = .268$). However, we observed a significant main effect of group ($F(1, 95) = 8.11$, $p = .005$). No interaction between noise and group was revealed ($F(1, 5{,}570) = 0.89$, $p = .346$), see Figure 15A.

A post hoc analysis indicated a significant difference between the groups in both the auditory noise condition ($p = .003$) and the no-noise condition ($p = .013$). The ADHD group made significantly more anticipatory saccades in both the no-noise condition (ADHD: $M = 0.69$, $SD = 1.28$; TDC: $M = 0.43$, $SD = 0.97$) and the auditory noise condition (ADHD: $M = 0.70$, $SD = 1.28$; TDC: $M = 0.39$, $SD = 0.96$) compared to the TDC group.

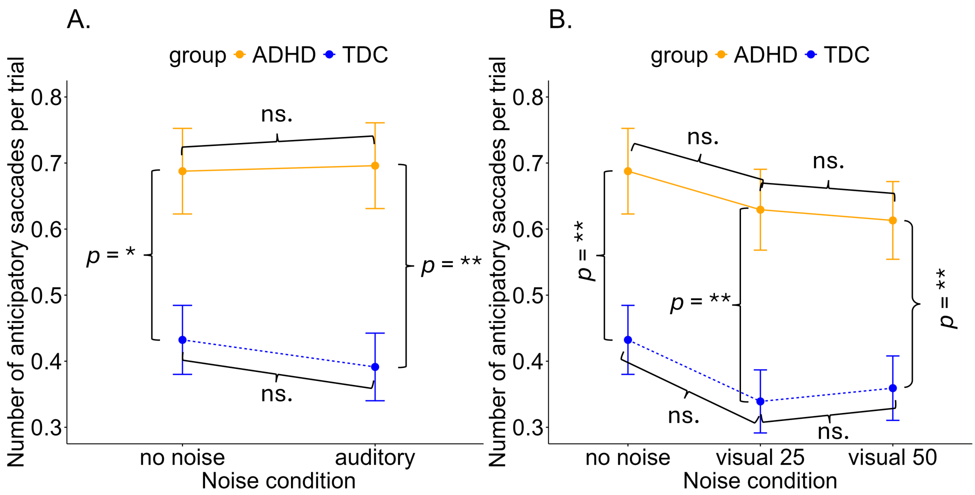

Figure 15. Number of anticipatory saccades per trial in the ADHD (yellow line) and TDC (blue line) group during (A) no-noise and auditory white noise, and (B) no-noise, visual white pixel noise at 25% and visual white pixel noise at 50%. Error bars represent 95% confidence intervals. *p < .05. **p < .01.

When assessing the number of anticipatory saccades during the *visual white noise* stimulation, a significant main effect of noise (F(2, 8,357) = 4.16, p = .016) and a significant main effect of group (F(1, 93) = 8.31, p = .005) was revealed. No interaction between noise and group was observed (F(2, 8,357) = 0.10, p = .907), see Figure 15B.

A post hoc analysis found a significant difference between the groups across all noise conditions, both the no-noise condition (p = .007), the visual noise condition at level 25% (p = .004) and visual noise condition at level 50% (p = .009). The ADHD group made significantly more anticipatory saccades in both the no-noise condition (ADHD: M = 0.69, SD = 1.28; TDC: M = 0.43, SD = 0.97), the visual noise condition at level 25% (ADHD: M = 0.63, SD = 1.21; TDC: M = 0.34, SD = 0.88), and the visual noise condition at level 50% (ADHD: M = 0.61, SD = 1.16; TDC: M = 0.36, SD = 0.90) compared to the TDC group. However, post hoc tests did not detect any significant differences between the noise conditions within groups (all p > .05). This discrepancy, from the significant main effect found in the ANOVA, suggests that factors other than specific pairwise comparisons may drive the observed overall differences among the noise conditions.

Latency

When assessing latency in the *auditory white noise* condition, no main effect of noise (F(1, 3,067) = 0.09, p = .771) or group (F(1, 95) = 0.33, p = .566) and no interaction between noise and group (F(1, 3067) = 0.86, p = 0.354) was observed, see Figure16A.

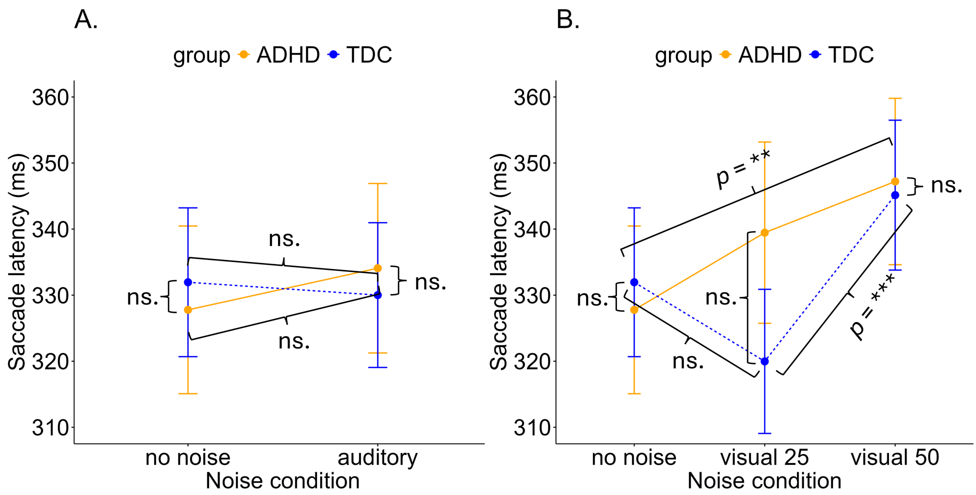

Figure 16. Saccade latency for correct trials for the ADHD (yellow line) and TDC (blue line) group in (A) no-noise and auditory white noise, and (B) no-noise, visual white pixel noise at 25% and visual white pixel noise at 50%. Error bars represent 95% confidence intervals. **p < .01, ***p < .001.

In the *visual white noise* condition, a significant main effect of noise was observed ($F(2, 4457) = 7.52$, $p < .001$). No main effect of group was found ($F(1, 93) = 0.09$, $p = .770$). However, a significant curve-linear interaction between noise and group was revealed ($F(2, 4{,}457) = 3.79$, $p = .023$), see Figure 16B.

A post hoc analysis revealed specific effects of noise condition on latency for both the ADHD and TDC groups. The ADHD group exhibited a significant increase in latency in the visual noise condition at 50% (M = 347.2 ms, SD = 170.5 ms) compared to the no-noise condition (M = 327.8 ms, SD = 174.5 ms; $p = .006$). There was no significant difference in latency between the visual noise condition at level 25% (M = 339.5 ms, SD = 178.0 ms) and the other noise conditions for the ADHD group. Similarly, the TDC group demonstrated a significant increase in latency in the visual noise condition at 50% (M = 345.1 ms, SD = 164.4 ms) compared to the visual white noise condition at level 25% (M = 320.0 ms, SD = 159.1 ms; $p < .001$). There was no significant difference between the no-noise condition (M = 332.0 ms, SD = 163 ms) and the other noise conditions for the TDC group.

Gain

In the analysis the effects of *auditory white noise* on gain, a significant main effect of noise was found ($F(1, 3{,}060) = 9.82$, $p = .002$). No main effect of group ($F(1, 84) = 2.54$, $p = .115$) and no interaction between noise and group ($F(1, 3{,}060) = 1.48$, $p = .225$) was observed, see Figure 17A.

A post hoc analysis indicated a significant decline in gain between the no-noise condition (M = 0.84, SD = 0.21) and the auditory noise condition (M = 0.81, SD = 0.20; p = .003) in the ADHD group. No effect of noise was found in the TDC group, they did not differ in gain between the no-noise condition (M = 0.86, SD = 0.20) and the auditory noise condition (M = 0.85, SD = 0.21).

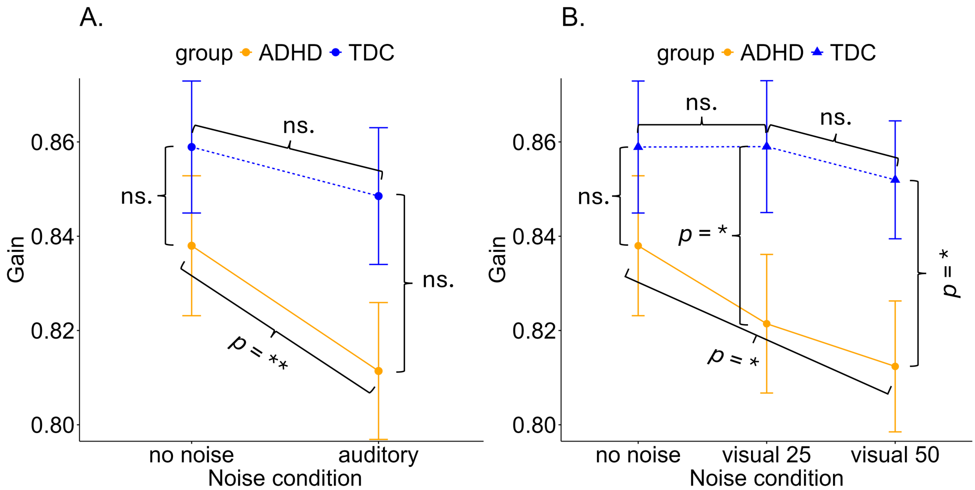

Figure 17. Gain of memory guided saccades for the ADHD (yellow line) and TDC (blue line) group in the (A) no-noise and auditory noise condition, and (B) no-noise, visual white pixel noise at 25% and visual white pixel noise at 50% conditions. Error bars represent 95% confidence intervals. *p < .05, **p < .01.

When assessing the *visual white noise* stimulation, a significant main effect of noise (F(2, 4,459) = 3.79, p = .023) and a significant main effect of group (F(1, 93) = 4.24, p = .042) was revealed. No interaction between noise and group was found (F(2, 4,459) = 1.45, p = .236), see Figure 17B.

Post hoc analyses revealed significant effects of noise within the ADHD group, there was a significant decrease in gain between the no-noise condition and the visual noise at level 50% condition (p = .011). Furthermore, significant differences were observed between the ADHD and TDC groups during visual white noise at level 25% (ADHD: M = 0.82, SD = 0.19; TDC: M = 0.86, SD = 0.20; p = .029) and visual white noise at level 50% (ADHD: M = 0.81, SD = 0.19; TDC: M = 0.85, SD = 0.18; p = .025), but not in the no-noise condition (ADHD: M = 0.84, SD = 0.21; TDC: M = 0.86, SD = 0.20; p = .255).

Correctly performed trials

In the analysis of the effects of *auditory white noise* on proportion of correctly performed MGS trials, no main effect of noise was found (F(1, 5,570) = 2.68, p = .102). However, we observed a significant main effect of group (F(1, 95) = 7.06, p = .009). No interaction between noise and group was revealed (F(1, 5,570) = 0.36, p = .551), see Figure 18A.

A post hoc analysis showed a significant difference between the groups in both the no-noise condition (p = .015) and the auditory noise condition (p = .007). The ADHD group had a significantly smaller proportion of correctly performed trials, compared to the TDC group, in both the no-noise (ADHD: M = 0.49, SD = 0.50; TDC: M = 0.61, SD = 0.49) and the auditory noise condition (ADHD: M = 0.50, SD = 0.50; TDC: M = 0.63, SD = 0.48).

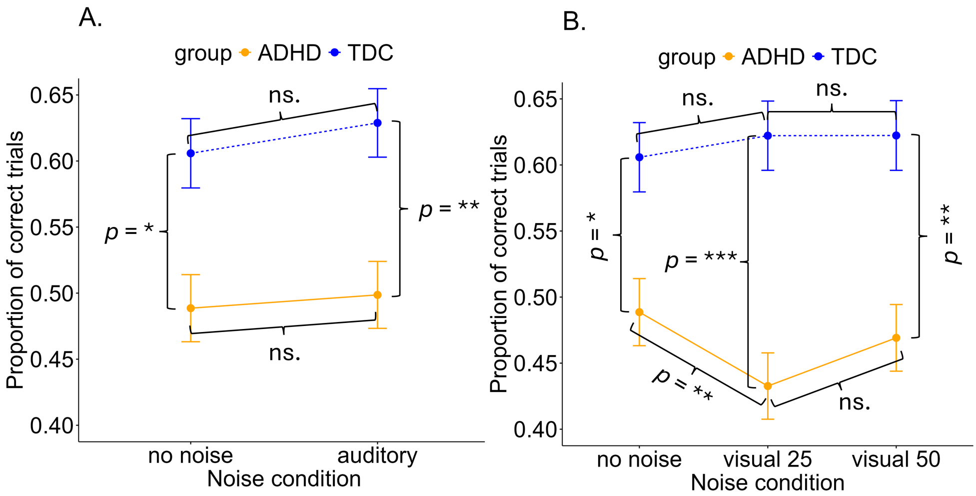

Figure 18. Proportion of correct trials for the ADHD (yellow line) and TDC (blue line) group in the (A) no-noise and auditory noise condition and, (B) no-noise, visual noise at 25% and visual noise at 50% conditions. Error bars represent 95% confidence intervals. *p < .05. **p < .01. ***p < .001.

When assessing the proportion of correct trials during *visual white noise* stimulation, no main effect of noise was observed (F(2, 8,357) = 2.07, p = .127). However, a significant main effect of group (F(1, 95) = 10.30, p = .002) and a significant interaction between noise and group (F(2, 8,357) = 3.40, p = .034) was found, see Figure 18B.

A post hoc analysis indicated a significant difference between the groups in the no-noise condition (p = .014), the visual noise condition at level 25% (p < .001) as well as the visual noise condition at level 50% (p = .002). The ADHD group had a significantly smaller proportion of correct trials in both no-noise (ADHD: M = 0.49, SD = 0.50; TDC: M = 0.61, SD = 0.49), visual noise at level 25% (ADHD: M = 0.43, SD = 0.50;

TDC: M = 0.62, SD = 0.49), and visual noise at level 50% (ADHD: M = 0.47, SD = 0.50; TDC: M = 0.62, SD = 0.49). Additionally, within the ADHD group, significantly lower proportion of correct trials was observed in the visual noise condition at 25% compared to the no-noise condition ($p = .003$), the ADHD group performed worse in the visual noise condition at 25%.

Noise rating

When assessing the participants experience of the *auditory white noise* there was no difference between the groups in how they rated the noise ($t(95) = -0.76$, $p = .447$, ADHD: M = 6.0, SD = 2.8, TDC: M = 5.6, SD = 2.3) or the level of discomfort experienced from the noise ($t(93) = -0.06$, $p = .953$, ADHD: M = 6.1, SD = 3.4, TDC: M = 6.1, SD = 3.3).

Similarly, no difference was found between the groups in how they rated the *visual white noise* ($t(92) = -0.49$, $p = .645$, ADHD: M = 5.8, SD = 2.8, TDC: M = 5.5, SD = 2.9) or the level of discomfort experienced from the noise ($t(94) = 0.30$, $p = .765$, ADHD: M = 4.8, SD = 3.3, TDC: M = 5.0, SD = 3.2).

Task assessment

Participants were asked to rate how they experienced both the PF and MGS tasks, which was reported in Paper III. A welch two sample t-test revealed a significant difference between the ADHD and TDC group ($t(95) = -3.40$, $p = .001$, ADHD: M = 5.5, SD = 2.7, TDC: M = 3.8, SD = 2.4). The ADHD group rated the tasks as significantly less fun than the TDC group. A medium to large effect was found ($d = -0.69$, 95% CI [−1.1, −0.27]).

Study II: Paper IV

In Paper IV mean baseline (in the no-noise condition) blink rate and pupil diameter were assessed in relation to the level of ADHD symptoms, to evaluate whether either level of hyperactivity/impulsivity or inattention could predict these variables. A similar analysis was performed during auditory white noise stimulation, with the addition of condition (no-noise/auditory white noise) as an interaction variable.

Additionally, the effects of noise stimulation on pupil diameter during one minute, divided into six ten-second timeframes of mean pupil diameter, were analyzed. The data was derived from the no-noise and auditory white noise condition during the prolonged fixation task.

Baseline blink rate and pupil diameter

Blink rate

None of the predictors could significantly predict baseline blink rate in the participants, neither level of hyperactivity, level of inattention, sex or age (cf. Table 4). Blink rate for boys (M = 11.49, SD = 9.66) did not significantly differ from girls (M = 12.41, SD = 7.79).

Pupil diameter

When assessing predictors for pupil diameter, only sex could significantly predict pupil diameter. Boys had a larger mean pupil diameter (M = 3.71, SD = 0.51) than girls (M = 3.37, SD = 0.48), see figure 19. Level of hyperactivity, level of inattention and age did not significantly predict pupil diameter (cf. Table 4).

Table 4. Result of linear regression analyses for baseline blink rate and pupil diameter.

Dependent variable	*Predictors*	*β*	*95% CI*	*p*
Baseline blink rate	Hyperactivity	0.04	-0.04 – 0.11	.306
	Inattention	-0.03	-0.09 – 0.04	.469
	Sex [Boy]	-0.31	-1.06 – 0.45	.423
	Age	-0.04	-0.23 – 0.14	.645
Baseline pupil diameter	Hyperactivity	0.00	-0.00 – 0.01	.081
	Inattention	-0.00	-0.01 – 0.00	.565
	Sex [Boy]	0.07	0.03 – 0.11	**.002**
	Age	-0.01	-0.02 – 0.00	.255

β = estimate; CI = confidence interval

Blink rate and pupil diameter during auditory white noise stimulation

Blink rate

The amount of ADHD symptoms could not predict mean blink rate during the prolonged fixation task. Neither the auditory noise stimulation nor level of hyperactivity or level of inattention was able to significantly predict blink rate (cf. Table 5). The interaction between noise condition and level of hyperactivity or noise condition and level of inattention could not predict blink rate either. There were no effect of sex or age.

Pupil diameter

The linear mixed effects model found the auditory noise stimulation to significantly predict mean pupil diameter and a tendency towards a predictive effect from the level of hyperactivity, while no effect of level of inattention was found. There was no interaction between noise condition and level of hyperactivity or noise condition and level of inattention. There was also a significant effect of sex. Age did not contribute to the model. See Table 5 for exact figures.

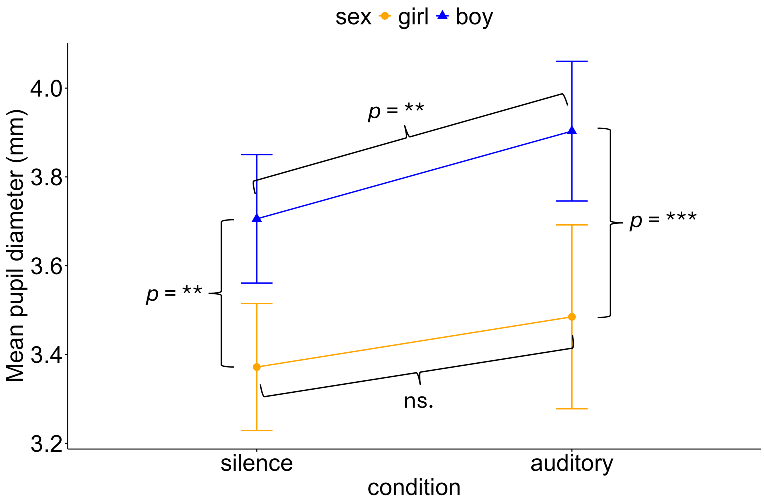

Figure 19. Difference in mean pupil diameter between the no-noise and auditory noise condition in boys (blue line) and girls (yellow line). Error bars represent 95% confidence intervals. $^{**}p < .01$, $^{***}p < 0.001$

Post hoc comparisons of estimated marginal means investigating condition and sex revealed a significant difference in mean pupil diameter between girls and boys in both the no-noise (p = .001) and the auditory noise condition (p < .001). However, there was no significant difference in pupil diameter between the no-noise and the auditory noise condition for girls (p = .108), but for boys (p = .003). Only the pupil diameter in boys were affected by the auditory white noise stimulation (see figure 19).

Pupil diameter as an effect of noise over time

The timeframe was able to significantly predict pupil diameter during timeframes 30-40s, 40-50s and 50-60s, but not timeframe 10-20s and timeframe 20-30s (cf. Table 5). Again, there was a significant predictive effect of condition and sex, a marginally predictive effect of level of hyperactivity and no effect of level of inattention or age. There was a significant interaction between all timeframes and noise condition.

Post hoc comparisons of estimated marginal means of timeframe and condition revealed a significant difference in mean pupil diameter between the no-noise and the auditory noise condition across all timeframes but the one between 40-50s (cf. Figure 20), with results averaged over the factor of sex. There was a larger pupil diameter in auditory noise compared to the no-noise condition at all timeframes but the second last one. There was also a significant decline in pupil diameter in the auditory white noise condition, from the first timeframe (0-10) to the second one (10-20), but not between the following timeframes in either the noise or no-noise condition.

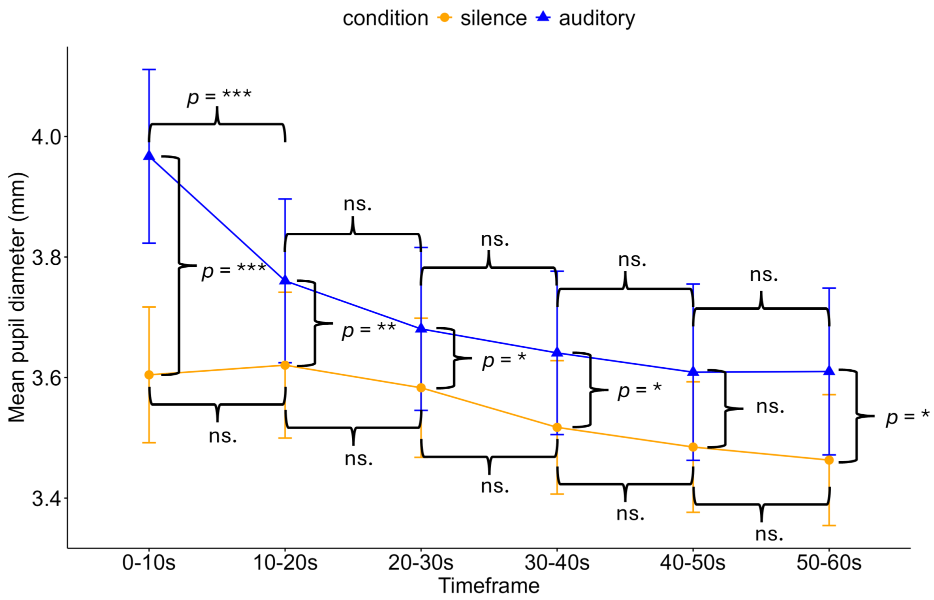

Figure 20. Mean pupil diameter in the no-noise (yellow line) and the auditory noise (blue line) condition during the 60 second PF task, divided into six timeframes of 10 seconds each. Error bars represent 95% confidence intervals. *$p < .05$, **$p < .01$, ***$p < .001$

Table 5. Result of linear mixed effect analyses for blink rate and pupil diameter.

Dependent variable	*Predictors*	*β*	*95% CI*	*p*
Blink rate during auditory white noise stimulation	Condition [auditory]	0.14	-0.34 – 0.62	.566
	Hyperactivity	0.03	-0.04 – 0.10	.435
	Inattention	-0.02	-0.08 – 0.05	.633
	Sex [Boy]	-0.55	-1.23 – 0.13	.122
	Age	-0.10	-0.26 – 0.07	.272
	Condition [auditory] * Hyperactivity	-0.01	-0.06 – 0.05	.856
	Condition [auditory] * Inattention	0.06	-0.04 – 0.06	.622
Pupil diameter during auditory white noise stimulation	Condition [auditory]	0.02	0.01 – 0.04	**.015**
	Hyperactivity	0.00	-0.00 – 0.01	.058
	Inattention	-0.00	-0.00 – 0.00	.408
	Sex [Boy]	0.05	0.03 – 0.08	**<.001**
	Age	-0.00	-0.01 – 0.00	.393
	Condition [auditory] * Hyperactivity	0.00	-0.00 – 0.00	.675
	Condition [auditory] * Inattention	-0.00	-0.00 – 0.00	.941
Pupil diameter as an effect of noise over time	Condition [auditory]	-0.05	0.04 – 0.06	**<.001**
	Timeframe 10-20s	0.00	-0.01 – 0.01	.913
	Timeframe 20-30s	-0.01	-0.02 – 0.01	.349
	Timeframe 30-40s	-0.02	-0.03 – -0.00	**.019**
	Timeframe 40-50s	-0.02	-0.03 – -0.01	**.004**
	Timeframe 50-60s	-0.02	-0.03 – -0.01	**.001**
	Hyperactivity	0.00	-0.00 – 0.01	.069
	Inattention	-0.00	-0.00 – 0.00	.370
	Age	-0.00	-0.01 – 0.00	.350
	Sex [Boy]	0.06	0.03 – 0.09	**<.001**
	Condition [auditory] * Timeframe 10-20s	-0.03	-0.05 – -0.01	**.003**
	Condition [auditory] * Timeframe 10-20s	-0.03	-0.05 – -0.02	**<.001**
	Condition [auditory] * Timeframe 10-20s	-0.03	-0.05 – -0.01	**<.001**
	Condition [auditory] * Timeframe 10-20s	-0.04	-0.06 – -0.02	**<.001**
	Condition [auditory] * Timeframe 10-20s	-0.03	-0.05 – -0.01	**<.001**

β = estimate; CI = confidence interval

Discussion

The studies included in this thesis have investigated the effects of sensory noise stimulation (in different modalities) on cognitive performance, pupil diameter, and blink rate in children with ADHD and typically developing children (TDC).

The hypotheses in Paper I, II, and III were based on previous research on white noise stimulation (Nigg et al., 2024; Pickens et al., 2019) in combination with the Moderate brain arousal (MBA) model (Sikström & Söderlund, 2007). The hypotheses were: H1: The TDC group will have better cognitive performance than the ADHD group without noise stimulation while H2: the difference in cognitive performance between the groups will disappear during white noise stimulation. H3: The ADHD group will experience improved cognitive performance during white noise stimulation while H4: the TDC group will get impaired cognitive performance during white noise stimulation.

Taken together, no beneficial effects of white noise stimulation on cognitive performance were found in children with ADHD. As such, none of the hypotheses were supported, irrespective of modality or task. However, some indications were given that auditory white noise stimulation may affect noradrenaline (NE) levels, for which pupil diameter is a proxy, in certain participants. The differences between our findings and previous research lead to the question of why others find effects from noise while we do not. There are several possible reasons for these discrepancies. One is publication bias, that studies that did not find any beneficial effect from white noise stimulation in ADHD have not been published. This would create an imbalance in the publications that could lead to an over-estimation of the effects from the white noise stimulation reported in the meta-analyses from Pickens et al. (2019) and Nigg et al. (2024). Additional explanations relate to the specific aspects investigated in relation to the studies in this thesis, including noise modality, type of tasks, and assessment methods used to explore the mechanisms behind the effects of white noise stimulation.

Questions related to these aspects will be discussed, one at the time, in the following paragraphs. These are: Do methodological differences, such as the modality in which the noise is applied, the noise level, or the color of the noise, affect the outcome? Are noise benefits task specific? What characterizes an individual who benefits from white noise stimulation? And finally, how do our results inform the MBA model?

Do methodological differences affect the outcome?

There are several different methodological approaches and difficulties to consider when studying the effects of noise stimulation. The modality and noise level at which the noise is delivered may affect the outcome, as well as the color of the noise. This will be discussed below. However, most notably is the limited information previous studies provide on how the noise was generated, and the experiments were conducted. This is a vital aspect to consider when discussing white noise effects. To assess the stability of the beneficial effects of white noise stimulation and ensure reproducibility of those effects, the methodological approaches need to be described in detail. Improving methodological rigor is critical for advancing research on noise stimulation.

Noise modality

Most research on white noise stimulation has previously been done on auditory white noise (Nigg et al., 2024). Because of this, one aim of this thesis was to study white noise stimulation in different modalities, with the presumption that modality is irrelevant in relation to the noise benefits (Moss et al., 2004).

In Study II both auditory and visual white noise were assessed and compared against the no-noise condition. However, none of the noise modalities generated any effects on cognitive performance in accordance with our hypotheses, in any of the groups. To our knowledge, this was the third study investigating visual white noise in relation to cognitive performance (see Söderlund et al., 2021 and Söderlund et al., 2024), and the second one studying it in relation to children with ADHD. In Söderlund et al. (2024) the effects of both auditory and visual white noise were assessed in children with varying levels of ADHD. They found no beneficial effects on performance from either the auditory or the visual white noise stimulation during a Spanboard task. These results are in line with the results from our study and adds to the uncertainty of whether there is a general beneficial effect of white noise stimulation.

However interestingly, Söderlund et al. (2021) found different effects of auditory white noise and visual white noise in children with reading disorders. They evaluated a single word reading task during both a no-noise condition, three visual white pixel noise conditions (noise level 50, 75 and 100), and one auditory white noise condition. Three groups of children participated: one with phonological reading difficulties, one with orthographical reading difficulties and one control group. While the visual white noise (at level 50 and 75) removed the differences between the group with phonological reading difficulties and the control group, the auditory white noise had no such effect. These results bring into question whether different types of noise modalities activate different cortical areas in the brain. Noise modality could in this case be related to stimuli modality, where greater benefits could be experienced if the noise and stimuli are presented in the same modality. For instance, auditory stimuli and auditory white noise stimulation, or visual stimuli and visual white noise stimulation.

In Study I, data from the auditory white noise stimulation was excluded from the analysis due to technical issues. This limited our ability to assess the combined effects of different noise modalities or to compare auditory white noise with stochastic vestibular stimulation (SVS). However, when investigating cognitive performance in neurotypical adults during auditory white noise, noisy galvanic vestibular stimulation (nGVS), and both simultaneously, Sherman et al. (2023) found no broad cognitive improvements in any condition. The simultaneous application of different noise modalities did not affect cognitive performance, neither did the different noise stimulation modalities alone. Although, some participants showed cognitive changes during noise stimulation, and the authors suggest that individual noise preferences may indicate whether cognitive benefits are experienced.

In a similar manner, we collected information on how the participants experienced the visual and auditory white noise stimulation in Study II. While no differences were found between the groups in how they rated the level of discomfort experienced from the noise, neither the auditory nor the visual, it is possible that individual judgements could be related to the effects generated by the noise, as demonstrated in Sherman et al. (2023).

Noise level

When determining appropriate noise levels for different modalities, previous research and theoretical models serve as important guides. In this thesis, auditory white noise (sound) levels were based on previous research involving children with ADHD, these sound levels are generally between 65-80 dB. Our research focused on the higher end (78 dB), but did not find any beneficial effects from the auditory white noise stimulation.

Theoretical models suggest that different individuals have their own optimal noise levels for enhanced cognitive performance. As stated in the MBA model, higher noise levels are required for individuals with ADHD (Sikström & Söderlund, 2007). The level of noise that is optimal for each individual can be described as a reversed U-curve, where too much or too little noise is detrimental for performance (Sikström & Söderlund, 2007). Indeed, when investigating three different levels of auditory white noise (65, 75 and 85 dB) in relation to cognitive performance in sub-, normal- and super-attentive children, Helps et al. (2014) found that the effects of white noise on performance varied across the three groups. White noise at 75 dB decreased performance for super-attentive children, while it improved executive function in sub-attentive children. The normal-attentive group showed no change in performance due to white noise exposure. Increasing the noise level from 75 dB to 85 dB had little additional impact on any group's performance. Even though finding differential effects from noise in the different groups, Helps et al. (2014) did not find support for the reversed U-curve. The participants did not experience any detrimental effects from the 85 dB white noise stimulation. They suggest that the response from white noise stimulation may be binary, that is, either present or not. The fact that we did not find any beneficial effects from the white noise stimulation may be due to the noise levels not being optimal for all individuals in the ADHD group. Some individuals may have experienced beneficial effects while others detrimental effects; when analyzed on a group level, the effects may cancel each other out. Another possible explanation is that the noise level might not be adapted to the task at hand. Awada et al. (2022) suggest that different noise levels may be beneficial for different cognitive functions. They studied cognitive performance and stress levels during two levels of auditory white noise stimulation, 45 dB and 65 dB, in neurotypical adults. The results from the study demonstrated that the lower noise level improved speed, accuracy and sustained attention, as well as lower stress levels and enhanced creativity. The noise at 65 dB improved working memory, but also increased stress levels.

Research on visual white noise, on the other hand, remains limited. As described above, Söderlund et al. (2021) evaluated the effects of three levels of visual white pixel noise (noise level 50, 75 and 100) during a single word reading task. Three groups of children participated: one with phonological reading difficulties, one with orthographical reading difficulties and one control group. The visual white noise (at level 50 and 75) removed the differences between the group with phonological reading difficulties and the control group, but the noise level at 100% impaired performance. In our study, we investigated two levels of visual white pixel noise (25% and 50%), since we were not interested in finding support for the reversed U but rather study potential beneficial effects from the noise. The visual noise did not produce any beneficial effects in study II, at either noise level. On the contrary, the ADHD group experienced significantly worse performance during visual noise compared to the no-noise condition for both saccadic gain and the proportion of correct trials in the MGS task. Thus, no differentiating effects between the different noise levels were found.

Most studies on auditory and visual white noise examine suprathreshold levels—significantly above the detection threshold—when assessing its impact on cognitive performance. In contrast, subthreshold noise, generated below the detection threshold, is typically used in electrical stimulation studies due to the discomfort associated with higher levels of electrical stimulation. Subthreshold stimulation is also essential for maintaining blinding in experiments, as masking suprathreshold noise is challenging. The absence of masking in studies using suprathreshold noise may influence participant performance, potentially reflecting their assumptions about the experiment. Only

Study I was a blinded study while the results from Study II could be influenced by participants' expectations from the study.

One challenge with subthreshold SVS is accurately quantifying and validating the noise level. Studies aim to deliver electrical stimuli that maximize cognitive enhancement while remaining below the detection threshold. However, it is difficult to measure the actual noise level delivered by the stimulator and determine what intensity is sufficient to enhance cognitive performance. The lack of observed effects in Study I may be due to insufficient noise intensity to target relevant brain areas. Individual perception thresholds, as used by Samoudi et al. (2015), could help achieve optimal stimulation below the detection threshold. For Study I, different protocols were assessed in an in-house pilot study to identify the best vestibular stimulation protocol below detection threshold.

This difficulty in quantifying and standardizing stimulation levels is compounded when comparing protocols across studies. A large variety of simulation protocols are applied across different studies but limited details on procedures and protocols are common (Bigelow & Agrawal, 2015). Despite this, previous studies have demonstrated beneficial effects of vestibular stimulation on cognitive performance (Hilliard et al., 2019; Kuatsjah et al., 2019; Voros et al., 2021; Wilkinson et al., 2008), suggesting that alternative stimulation protocols may yield beneficial effects in children with ADHD.

One important aspect to consider when assessing the effects of electrical noise stimulation is the placement of the electrodes on the head. Different placements target different areas in the brain. It is possible that other areas on the head, besides the mastoid bone behind the ears, are more effective in enhancing cognitive performance through electrical stimulation. For example, transcranial random noise stimulation (tRNS), which is placed on the forehead, may yield different effects. Additionally, the distribution of electrodes could influence their efficacy. Chenot et al. (2022) demonstrated that using four electrodes produced better cognitive performance outcomes with tRNS compared to two electrodes, which may be due to a different distribution of the current flow.

Future studies cloud explore whether individualized noise levels are necessary to achieve cognitive benefits from noise stimulation. Mapping the full U-curve for each participant could provide insights into the optimal noise intensity for enhanced performance. Such personalized approaches could refine our understanding of noise effects and clarify its broader potential as a cognitive intervention.

Color of the noise

In addition to modality and noise level, the color of the noise can be discussed in relation to the effects of noise stimulation. As stated in the introduction, pink noise have a ‘softer’ sound compared to white noise and is often considered to resemble the sound of a heavy rainfall or a waterfall (Warjri et al., 2022). Because of this it can be experienced as more pleasant to listen to (Lu et al., 2020). There is not much research on pink noise in relation to ADHD, and only white noise stimulation has been studied in the scope of this thesis. Still, the color of the noise is a relevant aspect to consider when discussing the effects of noise stimulation. For example, Aghababaiyan (2020) suggests that pink noise has a wider range of optimum values that can amplify a signal through stochastic resonance compared to white noise, and therefore is better suited for enhancing the performance in the nervous system.

Interestingly, when comparing the effects of different noise colors on cognitive performance in neurotypical individuals at 50 dB, Lu et al. (2020) observed task-specific variations. For instance, only pink noise significantly enhanced performance on a Continuous Performance Test (CPT). Conversely, all noise types—red, pink, and white—improved outcomes in an executive functions test. Additionally, when assessing noise comfort, pink and red noise were rated as more favorable than white noise, as they improved the perceived environment and facilitated better implementation.

In relation to ADHD, Metin et al. (2016) investigated whether pink noise could reduce impulsive choice in children with ADHD. The two groups of children, ADHD and TDC, had to choose between a smaller reward sooner or a larger reward later during two noise conditions: no-noise or auditory pink noise at 80dB. The ADHD group made more impulsive choices, and the noise stimulation did not reduce their impulsiveness. In a second study, Rijmen and Wiersema (2024) studied reaction time (RT) and RT variability in healthy adults with varying levels of ADHD traits. The test was performed both in a no-noise condition, a pink noise condition at 75dB, and a pure 100 Hz tone condition at 75dB. They found a significant interaction between noise condition and ADHD traits; both the pink noise stimulation and the pure tone condition improved (decreased) RT and RT variability in those with high levels of ADHD symptoms while those with low levels of ADHD symptoms got higher RT and RT variability.

The studies on pink noise generate contradictory results, much like previous research on white noise stimulation. However, future studies might consider comparing the effects of white and pink noise stimulation to determine whether they produce distinct or similar outcomes in enhancing cognitive performance. If one type of noise is perceived as more pleasant while offering comparable cognitive benefits, individuals could achieve the desired enhancements while also enjoying a more comfortable and enjoyable experience. This approach could improve adherence and satisfaction with noise-based interventions, particularly in long-term applications.

Are noise benefits task specific?

While Pickens et al. (2019) conclude that auditory white noise stimulation could be beneficial for cognitive performance in children with ADHD, they also conclude that children with ADHD seem to benefit more from white noise stimulation only for certain tasks. White noise appears to enhance language recognition, reading and writing speed, vigilance, and some working memory tasks. On the other hand, its effect on reaction time remains inconclusive. Moreover, white noise does not seem to improve the ability to choose larger long-term rewards over smaller short-term ones, nor does it enhance reading and writing accuracy or word order recall (Pickens et al., 2019). These tasks cover a wide range of cognitive and executive functions and do not give any confirmation on which types of functions are benefited by white noise stimulation.

In the studies included in this thesis, tasks that previously have shown to be effective in differentiating between children with and without ADHD were used (Chamorro et al., 2022; Cubillo et al., 2014; Helps et al., 2014; Maron et al., 2021; Söderlund et al., 2016; Westerberg et al., 2004). However, the results from our studies suggest that these tasks may not be as reliable for differentiating between children with and without ADHD as previously suggested. Few differences in performance were observed between the ADHD and TDC group in the no-noise condition in both studies and no support for hypothesis H1 was found. In fact, it has been discussed whether the MGS and PF tasks applied in Study II are effective in distinguishing between children with and without ADHD. While Bucci et al. (2024) suggest that oculomotor measurements can be used as phenotype biomarkers for children with neurodevelopmental disorders, and both Chamorro et al. (2022) and Maron et al. (2021) conclude in their meta-analyses that children with ADHD perform more oculomotor inhibition errors than TDC, others oppose this. For example, in their review Sherigar et al. (2023) found no significant differences in ocular performance between children with and without ADHD.

Moreover, the Spanboard and Word Recall tasks used in Study I have been employed in previous research where white noise stimulation significantly improved task performance in children with ADHD (Helps et al., 2014; Söderlund et al., 2016; Söderlund & Sikström, 2012). White noise stimulation has shown to induce medium effect sizes (Cohen's d: 0.41-0.46) in the word recall task (Söderlund et al., 2010; Söderlund et al., 2007) while large effect sizes (Cohen's d: >0.80) have been found in the Spanboard task (Helps et al., 2014; Söderlund et al., 2016). Even though previous studies have found beneficial effects from white noise stimulation in children with ADHD during these tasks, we found very little support for this in our studies. Only in two cases did the white noise stimulation remove significant differences in performance between children with ADHD and TDC. This was during stochastic vestibular stimulation (SVS) where performance in the N-back task and in RT variability in the

Spanboard task was affected by the noise stimulation. Even though the significant difference in performance between the groups in the no-noise condition was removed by the white noise stimulation in these cases, we found no support for either improved performance in the ADHD group or impaired performance in the TDC group. In addition, even though there was a significant difference in performance between the ADHD and TDC group during the no-noise condition in the N-back task, that disappeared during noise stimulation, this effect was due to an increased SD in both groups during vestibular stimulation.

In some cases, the noise stimulation even led to worse performance for the ADHD group. For example, as reported in Paper III, the ADHD group displayed a significantly lower (worse) saccadic gain during both auditory white noise stimulation and visual white noise stimulation at 50% compared to the no-noise condition. Moreover, the visual white noise at 50% produced a significant difference in performance between the groups, that was not present in the no-noise condition.

It has been suggested that tasks eliciting under-arousal, a state where low tonic levels of DA are assumed, might be better suited for studying the effects of noise stimulation (Rijmen & Wiersema, 2024). Since individuals with ADHD are sensitive to under-arousal, these types of tasks could benefit more from noise stimulation (Rijmen & Wiersema, 2024). This would imply that the prolonged fixation (PF) task assessed in Study II would be a good task to test the effectiveness of white noise stimulation. Our results do not support this assumption; we found no differences in performance between the groups in the no-noise condition and the white noise stimulation either had no effect or caused a significant difference in performance between the groups. On the contrary, our results might even suggest otherwise, that children who already exert a certain amount of effort are the ones that are affected by the noise stimulation.

A different perspective, suggested by Söderlund et al. (2021) is that a task must be experienced as difficult, that is, induce a high cognitive load, for white noise stimulation to produce beneficial effects on cognitive performance. The necessary DA levels for optimal cognitive performance have been proposed to vary depending on the type of task (Angwin et al., 2017), where mentally demanding tasks require higher levels of DA (Cools & D'Esposito, 2011). This suggestion would be in line with research on effects of stimulant medication, where participants with poorer baseline cognitive abilities experience greater improvement from the medication (Fosco et al., 2021). When assessing tRNS, Tokikuni et al. (2024) indeed found greater benefits in individuals with lower working memory performance. Tailoring tasks to individual difficulties could potentially provide stronger effects from the white noise stimulation.

What characterizes an individual who benefits from white noise stimulation?

The majority of studies on white noise stimulation have investigated noise stimulation in relation to the presence of an ADHD diagnosis or not. However, ADHD is a largely heterogenous condition, with a wide span of symptom representations, impairments experienced, as well as co-occurring mental and physical conditions (Faraone et al., 2024). As such, there are several characteristics that may differ between the individuals in the groups included in the different studies. Notably, even within individuals, symptoms and impairments are reported to fluctuate over time (Vos et al., 2022). It is thus not known how other variables may interact with the effects of white noise stimulation. For example, Gau and Chiang (2013), who assessed symptom representation during early childhood in relation to short-term memory in late childhood found that only early symptoms of inattention were associated with verbal and visuo-spatial short-term memory later in childhood. This is interesting, since both the Spanboard task and the Word Recall tasks used in several white noise studies assess these abilities. Additionally, Bubl et al. (2015) found that elevated neural background noise was associated with symptoms of inattention in ADHD. Based on this, they suggested interventions that may reduce that noise and, consequently distraction, in this group. Hence, there is a possibility that different symptom presentations, i.e. primarily inattentive, primarily hyperactive or a combination of both, could interact with performance and noise stimulation.

In relation to the studies performed in the scope of this thesis, there are a few studies that are highly relevant. First is a study by Falck-Ytter et al. (2020) where they explored the association between the ability to perform a PF task and ADHD traits. They found a correlation between decreased performance and increased levels of ADHD symptoms. Second, Herweg and Bunzeck (2015) hypothesized that the beneficial effects from white noise stimulation would correlate with personality dimensions related to individual differences in dopamine (DA), but could not fully confirm that assumption. Another recent study explored the effects of visual and auditory white noise on cognitive performance in children with different levels of ADHD symptoms. Even though they did not find any significant effect from either of the noise modalities, they found that the level of inattention and hyperactivity could predict the level of noise benefit (Söderlund et al., 2024).

For Paper IV, we adopted a similar approach to the one by Falck-Ytter et al. (2020) and Söderlund et al. (2024), where the level of ADHD symptomology was investigated in relation to the white noise stimulation on a continuous scale rather than binary diagnosis (ADHD or not ADHD). Pupil diameter and blink rate were used as proxies for norepinephrine (NE) and dopamine (DA) signaling, based on presumptions of lower levels of DA and/or NE in ADHD (Faraone et al., 2024). In Paper IV we thus hypothesized that there would be a relationship between pupil diameter or blink rate and level of ADHD symptoms within the no-noise condition. We also hypothesized that the noise stimulation would remove the differences in blink rate and pupil diameter associated with the level of ADHD symptoms.

Our results showed that neither noise stimulation nor the level of ADHD symptoms was significantly able to predict blink rate or pupil diameter. However, the auditory white noise stimulation does seem to have some effect on pupil diameter in boys. Boys also displayed a significantly larger pupil diameter in the no-noise condition compared to girls. This was quite an unexpected finding, since no previous research have reported any differences in pupil diameter in relation to sex, neither during a free-viewing task involving faces and landscape images (Cascone et al., 2020) nor under varying light conditions, whether in a controlled experimental setup (López-Hernández et al., 2024) or a real-world environment (Lazar et al., 2024). The larger pupil diameter in the no-noise condition was thus interpreted to stem from the group exerting larger effort towards the task, something previously displayed by van der Wel and van Steenbergen (2018). NE governs autonomic arousal, wakefulness, and mental activity (Samuels & Szabadi, 2008; Sara, 2009), which are important processes involved in executive functioning. On the other hand, we interpret the significant effect from the white noise stimulation as noise-induced norepinephrine (NE) activation, since it is unlikely that the group exerted an even larger amount of effort during the white noise stimulation.

Whether the increased pupil diameter, and assumed increase in NE, is reflected in the performance in the prolonged fixation (PF) task is not known, since pupil diameter and blink rate have not been analyzed in relation to performance on the PF and MGS task. Neither have sex and age been included as covariates in the analysis of performance in the PF task.

Although neither the interaction between the degree of ADHD symptoms and noise condition (on/off) nor the variables alone did not significantly predict pupil diameter in Paper IV, there are several other factors that may be better in predicting the effects of white noise stimulation. We have, for example, collected data on development and behavior with the 5-15R assessment and, as suggested by Söderlund et al. (2021), reading and writing performance might also affect whether beneficial effects of white noise are found. In addition, there are many other suggested ADHD subgroups that are not based on clinical symptom representations. One of them is from Barth et al. (2018), who propose three neurophysiological based biotypes in ADHD: one with above-average functioning in attention allocation, one with difficulties in attention allocation and inhibitory control and one with functional impairments in state regulation. These subtypes resonate with a statement from Pievsky and McGrath (2018), that not all individuals with ADHD have neurocognitive deficits or that the neurocognitive deficits of many individuals with ADHD are comparatively small.

Investigating noise stimulation in relation to subgroups which experience poor executive functioning abilities may generate a different result than the ones in our studies.

One important factor to consider when comparing our results from noise stimulation with the previous literature is that we, in many cases, were unable to find differences between the ADHD and TDC group even in the no-noise condition. Even though the groups did significantly differ in respect to SNAP-IV ratings in all studies, that does not seem to be reflected in differences in cognitive performance and working memory. One explanation to the lacking differences in performance between the groups may be the increased number of ADHD diagnoses that have primarily been concentrated on the lower scale of symptomatology (Rydell et al., 2018). This might contribute to the fact that we did not find any significant differences in performance between the groups although there was one on the symptomatic scale (SNAP-IV).

How do our results inform the MBA model?

As initially described, the hypotheses for the papers included in this thesis are rooted in the MBA model. The MBA model is based on the presumption that people with ADHD have low tonic dopamine levels (Sharma & Couture, 2014). The model proposes that low dopamine levels are related to reduced internal neural noise and a low signal-to-noise ratio, which leads to attenuated cognitive performance. To improve cognitive performance individuals with ADHD need more external random noise, which will increase their signal-to-noise ratio – a process that is believed to happen through stochastic resonance (SR) (Sikström & Söderlund, 2007).

This model was recently challenged by Rijmen and Wiersema (2024). As described above, they studied the impact of both pink noise and a pure 100 Hz tone in relation to RT on a slow reaction test. Their results showed that the tone and the noise generated similar beneficial effects on RT in individuals with high levels of ADHD. They interpret their findings as contradicting the MBA model, since the MBA model is based on the phenomenon of SR and the pure tone does not induce SR. This is not the first study examining other types of auditory noise in relation to performance in ADHD. Rausch et al. (2014) also compared the effects of a pure 100 Hz tone with (white) noise stimulation. Contrary to Rijmen and Wiersema (2024), they found no beneficial effects from the pure tone, only the white noise improved recognition memory. From fMRI scanning, they also found that the beneficial effects of white noise stimulation were due to increased activation in dopaminergic areas. Moreover, Awada et al. (2022) compared the effects of ambient noise and white noise stimulation. They only found beneficial effects on sustained attention and working memory from the white noise stimulation and not from the ambient noise. On the other hand, Söderlund and Sikström (2012) compared the effects of white noise at 78 dB and speech at a similar dB, either alone or in combination with white noise, during a Spanboard task. They found that both the white noise stimulation and the speech improved performance for inattentive children. Reports of beneficial effects from music in individuals with ADHD have also been made (Martin-Moratinos et al., 2023).

Whether noise stimulation does indeed work though the phenomenon of SR or through other mechanisms is thus still unclear. Cook et al. (2014) proposed that auditory masking could be the reason for beneficial effects of white noise. Masking have been shown in tactile (Tan et al., 2003) and visual (Enns & Di Lollo, 2000) modalities as well. However, this theory seems less plausible due to evidence showing that the white noise stimulation affects dopamine pathways in the brain (Baijot et al., 2016; Rausch et al., 2014).

Another alternative reason for the beneficial effects found by different types of sound and noise in different types of modalities could be increased arousal. This explanation is in line with the state regulation model of ADHD (Sonuga-Barke et al., 2010) which states that individuals with ADHD have difficulties adjusting their arousal to optimal levels, which leads to either under- or over-arousal. In highly stimulating situations, they may become over-aroused and impulsive, while in low-stimulation situations, they may become under-aroused, leading to inattention or boredom. Some of our results can be interpreted in relation to this notion. In Paper IV we found a significantly increased baseline pupil diameter in boys (in the no-noise condition) compared to girls. The pupil diameter in boys was also the one significantly increasing during auditory white noise stimulation. This can be interpreted in different ways. First, the boys may have been over-aroused and noise stimulation increased their arousal even further while the girls experienced a moderate arousal level and were unaffected by the noise stimulation. Second, the girls may have been under-aroused, and the noise stimulation was unable to up-regulate their arousal levels, while the boys were moderately aroused and the noise up-regulated their arousal. Either way, some baseline level of arousal might be needed to enable an effect of increased arousal from the white noise stimulation.

Whether the effects of white noise stimulation are attributable to stochastic resonance or increased arousal remains unclear; it is possible that both mechanisms play a role. While our findings suggest that auditory white noise stimulation increases NE levels in some individuals and that this effect persists during active noise exposure, further research is necessary to clarify the underlying mechanisms driving these effects and to better understand how white noise stimulation influences cognitive and physiological processes.

General limitations

As discussed throughout the thesis, there is a large heterogeneity in ADHD. This means that there are several potential confounding variables, for instance subtypes of ADHD, that were not explored in the different studies. Another limitation is that different comorbidities were not addressed in any of the studies. Similarly, gender and age were not added as covariates throughout the studies since hypotheses on any effects from these variables were not generated. Only in instances where hypotheses regarding these variables were made, or significant differences were found between the groups, were gender and age included in the analyses. In retrospect, with results from Study IV, gender and age were probably suitable covariates for all analyses.

Generally, generalizability of the results from noise studies are difficult. Information on sample characteristics in relation to other variables than group (ADHD vs TDC) is sparse, and even in our studies few investigations in relation to other variables have been made. Additionally, the effects from noise stimulation on the different tasks assessed in the studies seem to be diverse. Even though the same assessments have been used in previous studies and the ones here, different outcomes have been found, making general conclusions and guidelines hard to establish.

On a similar note, data for the studies were collected from a single site and may contain potential sampling biases which limit the generalizability of the results. The participants who agreed to participate in the study may be different from those who declined to participate. However, we cannot know in what way. Additionally, the fact that data from the same sample was analyzed in both study III and study IV, means that potential errors from this sample are present in both studies.

In studies of suprathreshold noise stimulation, blinding between the experimental and control condition is hard to acquire since the stimuli is always above detection threshold. Thus, only Study I had a double blinded design. In the other study (Study II), a Hawthorne-effect cannot be ruled out. That is, participants may have adapted their behavior based on their presumptions of what the experiment was studying.

Power calculations of the studies are based on previous research on noise and the applied assessment methods. The statistical power was found to be adequate to detect medium-sized effect sizes, but not to detect small effect sizes. If previous effect sizes are not representative of the research in this thesis but are in fact smaller, it would be more difficult to find differences in our data. However, our studies included a larger sample than was suggested by the power calculations (52 calculated vs 71 included and 30 calculated vs 97 included) and should thus be representative. Moreover, our studies have a larger sample size than most other studies on white noise stimulation in children with ADHD.

Conclusions

The studies conducted within the scope of this thesis did not yield evidence supporting the efficacy of white noise stimulation in enhancing cognitive performance in children with ADHD. Regardless of modality and task, the white noise stimulation did not improve working memory performance, reduce reaction time variability or enhance inhibitory control. Effects of noise stimulation does not appear to be related to the level of ADHD symptoms. However, auditory white noise appeared to influence noradrenaline (NE) levels in certain individuals, as indicated by the increased pupil diameter observed in boys in Paper IV. The exact characteristics of the affected group are not known and whether the increased NE levels affect cognitive performance is still unexplored.

Notably, the reviews by Pickens et al. (2019) and Nigg et al. (2024) include a much larger number of studies compared to the limited scope of this thesis. While these reviews report modest beneficial effects of white noise stimulation, comparable to other complementary ADHD interventions but smaller than medication effects (Nigg et al., 2024), our results contribute to the ongoing discussion on white noise. They highlight the uncertainty surrounding which individuals benefit from noise, the specific tasks or executive functions impacted, which modalities are effective, and the underlying mechanisms behind these potential effects.

Clinical relevance

Child- and adolescent psychiatry clinics in Sweden face mounting pressures as ADHD diagnoses among children rise (Sørensen et al., 2023). Much of this increase appears to stem from milder ADHD cases (Rydell et al., 2018), highlighting the need for effective non-pharmacological interventions (Faraone et al., 2021). White noise stimulation presents several advantages: it is noninvasive, accessible, cost-effective, and has minimal side effects. Its ease of implementation and compatibility with other treatments make it a promising adjunct. Particularly auditory and visual white noise, which can be integrated inexpensively into home and school environments.

However, mixed findings on the efficacy of white noise raise questions about its viability as a clinical tool. The lacking effects of white noise stimulation found in the studies in this thesis suggest a limited applicability in practice. Effective interventions might require targeting narrow subgroups, using specific cognitive tasks, and employing noise at high dB—constraints that diminish clinical feasibility. Moreover, excessive noise may in fact impair cognitive performance (Stansfeld et al., 2005) and auditory white noise should not be applied at high decibels during extended periods of time, necessitating caution in its use. Prior to widespread implementation, clinical guidelines must be developed to ensure safety and efficacy.

For the future

Both clinical and neurobiological research is progressing, with the potential to develop personalized diagnostic and therapeutic approaches for ADHD (Faraone et al., 2024). While this thesis did not find support for any beneficial effects on cognitive performance from white noise stimulation, prior reviews suggest it could still emerge as a viable non-pharmacological intervention for children with ADHD. To achieve this potential, several questions must be addressed.

First, in the light of the knowledge brought forward by this thesis, strategies to identify "noise benefiters" must evolve. Individual differences and covariates influencing response to noise stimulation should be systematically explored to isolate subgroups that might derive the most benefit. This could also shed light on the underlying neural mechanisms affected by white noise.

Second, greater clarity is needed on the characteristics of tasks impacted by white noise stimulation. Identifying which cognitive or executive functions are most sensitive to noise—and how these functions align with individual impairments—could help refine its applications. Additionally, the noise levels required to achieve benefits need further investigation. Current evidence indicates that 70-80 dB yield benefits, but prolonged exposure to such intensities could harm hearing. Research on whether lower, personalized noise levels can produce comparable effects are welcome, such as the 45 dB benefit observed in neurotypical individuals by Awada et al. (2022). Future studies should also include studying other types of noise, for example pink noise, that may be experienced as more pleasurable to listen to.

Most prominently, studies replicating previous findings are needed. The mixed findings from studies on white noise stimulation underscore the need for replication to confirm the effects and assess the reliability of the results. However, many previous studies lack transparency in how noise was generated and applied, and exactly how the experiments were conducted, limiting reproducibility. With regard to stochastic vestibular stimulation, even more parameters are needed to take into consideration, something Hurley and Machado (2018) have highlighted in order to improve protocols in the future. We aimed at remedying this by making our code for noise generation and assessments from Study II available online (https://github.com/marcus-nystrom/white-noise-exp).

Future research may generate a better understanding of the magnitude of the effect sizes provided from white noise stimulation. Research also needs to aid in the development of clinical best-practices and safety limitations as well as age-appropriate levels of use, before noise stimulation can be used as a non-pharmacological treatment method for children with ADHD.

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