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**Research Articles** 

# Microdosing with psychedelics to self-medicate for ADHD symptoms in adults: A prospective naturalistic study



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#### ARTICLE INFO

Keywords:

Microdosing

Psychedelics

Well-being

Self-medication

Time perception

ADHD

#### ABSTRACT

ADHD in adulthood is often overlooked, which negatively affects the individual's well-being. First-line pharmacological interventions are effective in many ADHD patients, relieving symptoms rapidly. However, there seems to be a proportion of individuals who discontinue, or fail to respond to these treatments. For these individuals, alternative treatment options should be explored. A retrospective survey study reported that using classic psychedelics in low, repeated doses, so called microdosing (MD), was rated as being more effective than conventional treatments for ADHD. The current prospective study aimed to measure the effect of MD on ADHD symptoms, well-being and time perception. Adults with ADHD who had the intention to start MD on their own initiative to self-treat their symptoms were measured before MD and two- and four weeks later. It was expected that ADHD symptoms would decrease, well-being would increase, and performance on a time perception task would improve after MD. It was investigated if conventional medication use alongside MD and comorbidities alongside ADHD influenced the effect of MD. Sample sizes included N=233, N=66, and N=47, respectively. The results showed decreases and increases in ADHD symptoms and well-being, respectively. No improved performance on a time perception task was found. Conventional medication use and having comorbidities did not change the effect of MD on ADHD symptomatology and well-being after four weeks of MD. Placebo-controlled experimental studies are needed to explore further whether there is a beneficial effect of MD for ADHD, beyond the placebo-effect.

#### 1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common developmental disorders worldwide, with a prevalence rate of 5% in youths (Sayal et al., 2018). Increasing attention is paid to ADHD in adults, both in research and health care. Prevalence research indicates that 2.6% of the adult population has persistent ADHD, meaning that the symptoms had a childhood onset, and about 6.7% of adults diagnosed with ADHD have symptoms that started later than childhood (Song et al., 2021). ADHD in adults is often associated with financial distress, a higher risk of criminality and suicidality, resulting in serious detrimental consequences for an individual's quality of life and well-being (Beauchaine et al., 2020; Di Lorenzo et al., 2021). ADHD in adulthood has a high lifetime comorbidity rate of 60-80% (Kooij et al., 2019). Mood, anxiety, substance use, and behavioural disorders often co-occur with ADHD (Di Lorenzo et al., 2021; Ginsberg et al., 2014; Fayyad et al., 2017). ADHD in adults is often overlooked because of the high comorbidity rate and lack of knowledge about how ADHD is expressed in adulthood (Kooij et al.,

2019). Examples of age-appropriate ADHD symptoms include forgetfulness, chaotic presentation, difficulty in planning and time management, failing to meet deadlines, problems with finishing tasks in the workplace, inner restlessness, fidgeting, and emotional impulsivity (Butzbach et al., 2019; Hong et al., 2022; Marx et al., 2021; Ptacek et al., 2019). In addition, ADHD is associated with deficits in various domains of cognitive functioning. According to the triple pathway model, three dissociated domains may underlie ADHD symptomatology, including deficits in delay aversion, inhibition, and temporal processing. Twenty-five percent of ADHD cases suffered from ADHD symptoms purely because of deficiencies in temporal processing (Sonuga-Barke et al., 2010).

First-line ADHD treatments in adults mainly include pharmacological interventions to enhance dopaminergic and noradrenergic neurotransmission with stimulants, such as methylphenidate and amphetamine, and non-stimulant agents, such as atomoxetine (Cortese et al., 2018). Overall, they have been proven to work effectively in adults with ADHD (Asherson et al., 2016; Castells et al., 2011; Koesters et al., 2009), inducing fast symptom relief and thereby enhancing the person's quality of life. In the

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https://doi.org/10.1016/j.nsa.2022.101012

Received 8 April 2022; Received in revised form 25 August 2022; Accepted 14 October 2022 Available online 26 October 2022

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longer term, as shown by prospective studies, approximately twenty percent of ADHD patients discontinue their prescribed medication after six to nine months (Bejerot et al., 2010), thirty percent after one year (Fredriksen et al., 2014), and half of them after two years (Bejerot et al., 2010). Treatment discontinuation has been suggested to result from side effects that outweigh the therapeutic effects, such as insomnia, headaches, low appetite, weight loss, increased heart rate, and blood pressure (Khan and Aslani, 2021). Further, previous research has shown that many adults with ADHD fail to respond to prescribed medication. For instance, approximately half of the adult ADHD patients were considered non-responders (i.e., less than 30% reduction of ADHD symptoms) after ten weeks of treatment with atomoxetine, and 65% did not show a clinical response after 24 weeks (Bushe et al., 2016). Failing to respond to ADHD medication has been associated with a lower quality of life (Coghill et al., 2017; Mick et al., 2008). Alternative options need to be explored for the subset of adults with ADHD who do not benefit from or do not adhere to first-line pharmacological treatments.

The use of classical psychedelics like lysergic acid diethylamide (LSD) and psilocybin in small repeated doses, which is better known as microdosing (MD), has been suggested as a potential alternative in treating ADHD symptomatology. Previously, it was shown that one of the motives of people who microdose was to self-treat their ADHD, a practice they deemed more effective than taking conventional (first-line) pharmacological treatments (Hutten et al., 2019a). General claimed effects of MD include increased concentration, productivity, and enhanced positive mood (Hutten et al., 2019b). Placebo-controlled research in neurotypical volunteers has shown that a single small dose of LSD improved attention performance (20 µg LSD base, equivalent to 26 µg LSD tartrate) (Hutten et al., 2020) and increased positive mood (20 µg LSD base) (Hutten et al., 2020; Bershad et al., 2019). After repeated dosing in elder participants, changes in time perception were observed after the fourth dose (10  $\mu$ g LSD base, equivalent to 13 µg LSD tartrate) (Yanakieva et al., 2019). While the effect profile of a small dose of a psychedelic in healthy volunteers and the user claims about symptom relief in ADHD seem to point in the direction that MD can help in the treatment of ADHD, research is needed to show behavioural changes before and after MD in adults with ADHD. This approach will address the shortcomings of studies asking users retrospectively about their experience with MD.

The aim of this naturalistic, prospective study was to investigate the effectiveness of MD with psychedelics to self-medicate for ADHD symptoms in adults who had the intention to start MD on their own initiative. Additional measures focused on well-being and time perception, as the latter might be a key cognitive domain underlying ADHD symptoms (Sonuga-Barke et al., 2010). This approach provided the opportunity to collect data about this practice of self-medicating with psychedelics that is prevalent in this patient population (Hutten et al., 2019a) and to inform future controlled lab-based studies investigating this population. Based on previous findings, it was hypothesized that ADHD symptoms would decrease and self-rated well-being would increase after four weeks of MD compared to baseline. It was expected that changes in ADHD symptoms would be associated with changes in well-being. Further, it was hypothesized that performance on a time perception task would be enhanced. It was investigated if current first-line pharmacological treatment use alongside MD, and comorbid diagnoses alongside ADHD, influenced the change in ADHD symptoms, well-being, and time perception after MD. Lastly, it was investigated what type of individuals did not show an improvement in ADHD symptoms after four weeks of MD, to test whether this was related to using conventional medication alongside MD or having comorbid diagnoses alongside ADHD.

#### 2. Material and methods

#### 2.1. Study design and participants

The current study employed a prospective naturalistic design, assessing the performance and experiences of participants at baseline, before they start MD on their own initiative, and at two and four weeks after MD initiation. The target population included adults diagnosed with ADHD and individuals who experienced ADHD symptoms to the extent that these interfered with their daily lives and who had not been diagnosed with ADHD before. To be included in the analyses, participants needed to score above a cut-off point on at least one of the subscales of the Conner's Adult ADHD Rating Scale (CAARS-S:SV). According to the technical manual, this cut-off was indicative of clinically elevated symptoms (Conners et al., 1999) (see section 2.3). Furthermore, to be enrolled, participants needed to have the intention to start MD with psychedelics on their own initiative to relieve these symptoms.

# 2.2. Study procedure

An online advertisement was used to recruit participants. The online advertisement, including a link to the study, was placed on a website providing information about MD with psychedelics (www.microdo sing.nl). Interested participants clicking the link were redirected to the study information explaining the study rationale and procedure. After reading the information and being provided with the opportunity to contact the researchers regarding questions about the study, individuals could proceed to the informed consent sheet. Participants were asked to sign the informed consent sheet one to three days before they would start MD because after providing written consent participants were redirected to the first survey, which served as the baseline assessment. The baseline survey took about 20 min to complete. Once the baseline survey was completed, participants were enrolled in the emailing system, which generated links to the measurements two and four weeks after enrolment. If the survey had not been completed after 24 h, a reminder was sent, asking the participant to complete the survey as soon as possible. Each of the surveys at the two- and four-week time points took about 15 min to complete. Additionally, participants were asked to keep a diary of the substances and doses they administered during the study period. Participants were able to pause the surveys and complete them at another moment. Data collection occurred between November 2020 and July 2021. The study was approved by the Ethics Review Committee of Psychology and Neuroscience at Maastricht University (ERCPN-215\_05\_11\_2019\_A1).

# 2.3. Measures

#### 2.3.1. Demographic information and history of substance use

At baseline, demographic information and information about the history of substance use were collected. Demographics included the variables gender, continent of residence, educational level, and daily occupation. History of substance use assessed experience with psychedelics (i.e., ayahuasca, DMT, 5-MeO-DMT, LSD, novel lysergamides (e.g., 1P-LSD, ALD-52), psilocybin, salvia divinorum, ibogaine, and mescaline) in both full (psychedelic) doses and microdoses.

#### 2.3.2. Psychiatric and physiological diagnoses

At baseline, participants were asked whether they had a current diagnosis of a psychiatric, neurological, or physiological disorder. If the answer was yes, they were asked what diagnosis this was. Multiple answer options could be chosen: ADHD, depression, anxiety disorder, substance use disorder, dyslexia, autism/Asperger syndrome, obsessive-compulsive disorder, bipolar disorder, chronic pain, cluster headaches, epilepsy, migraines, post-traumatic stress disorder (PTSD), schizo-phrenia, "I do not want to mention", or the option to provide another answer in a textbox. These answer options were chosen because most of the listed diagnoses are often reported to co-occur with ADHD (Kooij et al., 2019), or because these diagnoses were reported to be common in people who microdose (Fadiman and Korb, 2019). Specific questions regarding ADHD diagnosis asked at what age the participant received this diagnosis, in case they were diagnosed, and a question about potential prescribed first-line pharmacological treatment: "Are you using, or have

you ever used, any prescribed medication for ADHD?" If it was indicated that individuals were using prescribed ADHD medication, it was asked what medication this was. Answer options consisted of six pre-set options: Adderall (amphetamine), Concerta (methylphenidate), Dexedrine (amphetamine), Focalin (dexmethylphenidate), Ritalin (methylphenidate), Strattera (atomoxetine hydrochloride), "I do not want to mention" or the option to enter text in a text box when the medication was not listed.

We constructed a variable Comorbidity alongside ADHD, differentiating respondents with and without a comorbid diagnosis alongside ADHD (0 = only ADHD or no ADHD diagnosis; 1 = ADHD and at least one other diagnosis). We constructed a variable Medication use alongside MD, differentiating respondents who were and were not using conventional ADHD medication alongside MD (0 = only MD; 1 = conventional medication use alongside MD).

# 2.3.3. ADHD symptoms

The self-report, short screening version of the Conner's Adult ADHD Rating Scale (CAARS-S:SV) (Conners et al., 1999) was used to assess ADHD symptoms at baseline, and the two and four-week time points. This questionnaire consists of 30 items assessing the core ADHD symptoms (i.e., inattention and hyperactivity/impulsivity) as well as related problem areas. Participants were instructed to indicate to what extent the items described them on a four-point Likert scale (0 = Not at all, never; 1 = Just a little, once in a while; 2 = Pretty much, often; 3 = Very much, very frequently). All 30 items of the CAARS-S:SV can be ascribed to one of three subscales: inattention, hyperactivity/impulsivity, and ADHD index. The inattention subscale captures problems experienced with attention and contains items such as 'I lose things necessary for tasks or activities (e.g., to-do lists, pencils, books, or tools)'. The hyperactivity/impulsivity subscale captures symptoms related to both hyperactivity and impulsivity and contains items such as 'I have trouble waiting in line or taking turns with others'. The technical manual states that the ADHD index subscale was created to identify adults who were likely to be diagnosed with ADHD. Items in this subscale were able to discriminate between individuals with ADHD and non-clinical individuals and capture features of ADHD that are not included in the DSM-IV diagnostic criteria, such as 'Sometimes my attention narrows so much that I am oblivious to everything else; other times it's so broad that everything distracts me'. A DSM-IV ADHD total symptom score can be calculated by summing the scores of the inattention and hyperactivity/impulsivity subscales. The CAARS-S:SV is known to have good internal consistency and inter-rater reliability and is sensitive to treatment outcomes (Adler et al., 2008).

For each subscale, T-scores were calculated to compare participants' scores to scores of the standardization sample mentioned in the technical manual consisting of non-clinical adults of the same age range and sex. The technical manual states as a guideline that if no subscale T-score is above 65, the CAARS-S:SV is not indicative of clinically elevated symptoms (Conners et al., 1999). Therefore, a cut-off T-score of 65 was used in this study to differentiate between individuals with and without elevated ADHD complaints. Only participants who scored above this cut-off point on at least one of the CAARS-S:SV subscales were included in the analyses.

#### 2.3.4. Well-being

The World Health Organisation-Five Well-Being Index (WHO-5) was included to measure the participants' well-being (World-Health-Organization, 1998). This scale consists of five statements that have to be rated on a six-point Likert scale (0 = At no time; 1 = Some of the time; 2 = Less than half of the time; 3 = More than half of the time; 4 = Most of the time; 5 = All the time). Participants had to indicate to what extent they have felt a certain way over the last two weeks. Scores of the five items were summed and multiplied by four to achieve a total well-being score ranging from 0 to 100. It was demonstrated that the WHO-5 has a high construct validity and that it can be used as an outcome measure

capturing changes in well-being resulting from pharmacological and non-pharmacological interventions and is applicable across study fields (Topp et al., 2015). The WHO-5 was included at baseline, and the two and four-week time points.

#### 2.3.5. Time perception

An auditory time reproduction task (TRT) was used to assess time perception (Wittmann et al., 2007) (www.millisecond.com). Participants were presented with a tone (tone 1: 300 Hz) with a duration of a certain time interval (i.e., 1000 ms, 1500 ms, 3200 ms, 3700 ms, 5500 ms, 6000 ms). Next, they were presented with a second tone (tone 2: 440 Hz). Participants were instructed to reproduce the time interval of tone 1, by pressing the spacebar at the moment when they felt the same time interval had passed for tone 2. As a measure of performance, the relative difference score was calculated by subtracting the estimated interval in ms (i.e., the interval between the start of tone 2 and the pressing of the spacebar) from the actual interval in ms (i.e., the duration of tone 1), divided by the actual interval in ms. A relative difference score of 0 indicated an exact reproduction of the time interval. A negative and positive relative difference score indicated an underestimation and overestimation of the time interval, respectively.

Before starting the task, instructions were provided and a small training took place. Participants were instructed to estimate the time interval based on when they felt the same duration of tone 1 had elapsed, explaining it was not the purpose of the task to count the seconds of the presented time interval of tone 1. Further, they were asked to sit in an environment without any distractions and use earphones to hear the tones more clearly if preferred. The task consisted of two practice trials and twelve test trials, each of the six time intervals was presented twice. It took 3 to 4 min to complete the task. The TRT was assessed at baseline, and the two and four-week time points.

## 2.4. Statistical analyses

All data was entered into the statistical program IBM SPSS Statistics version 26. Descriptive statistics were used to describe the demographic variables, information regarding psychiatric and physiological diagnoses, and drug types and doses that were used for MD during the study. Linear mixed model (LMM) analyses were used to assess changes in ADHD symptoms, well-being, and time perception after two and four weeks of MD compared to baseline. LMM analysis was chosen because of its ability to handle missing data in a repeated measures design and, as such, to use all existing data. The first LMMs contained the within-subject factor Time (three levels: baseline (0W), two (2W), and four-week (4W) time point). The fixed part of the models consisted of Time and the interaction terms between Time and Medication use (yes/no) and Time and Comorbidity alongside the ADHD diagnosis (yes/no).

To test whether MD decreased ADHD symptoms, the CAARS-S:SV DSM-IV total symptoms T-score was included as dependent variable. Additionally, T-scores of the CAARS-S:SV remaining subscales (i.e., ADHD index, inattention, and hyperactivity/impulsivity) were included as dependent variables in separate LMMs. Frequencies of non-responders (i.e., change in CAARS-S:SV DSM-IV total symptoms T-score (4W–0W and 2W–0W)  $\geq$  0) were calculated. To test whether MD increased wellbeing, the WHO-5 total score was included as dependent variable. To test the association between changes in ADHD symptoms and well-being, Pearson correlations were calculated between the difference scores (2W–0W and 4W–0W) of the CAARS-S:SV DSM-IV total symptoms T-score and the WHO-5 total score.

To test the effect of MD on time perception, an additional LMM was conducted containing Time (three levels: baseline (0W), two (2W), and four-week (4W) time point) and Interval (six levels: 1000 ms, 1500 ms, 3200 ms, 3700 ms, 5500 ms, 6000 ms) as within-subject factors. The fixed part of the model consisted of Time, Interval, and the interaction terms between Time and Interval, and the three-way interaction terms between Time, Interval, and Medication use (yes/no) and Time, Interval,

and Comorbidity alongside the ADHD diagnosis (yes/no). Medication use (yes/no) and Time and Comorbidity alongside the ADHD diagnosis (yes/ no) were included as covariates in all LMMs.

Akaike's information criterion (AIC) was used to find the best fitting covariance structure for each LMM. Missing data were estimated using restricted maximum-likelihood estimation. Significant main effects were followed by pairwise comparisons between time points and were corrected for multiple comparisons using Bonferroni correction. An alpha of 0.05 was used. Partial eta squared ( $\eta_p^2$ ) was used to describe effect sizes, where 0.01, 0.09, and 0.25 were considered small, medium, and large, respectively (Richardson, 2011). Pearson correlation coefficients of 0.10, 0.30, and 0.50 were considered small, medium, and large, respectively (Cohen, 2013).

# 3. Results

# 3.1. Sample characteristics

Of the 356 participants who consented and started the survey, 247 individuals (69.4%) completed the baseline survey and received followup measurements (Fig. 1). The median completion time of the baseline survey was 26 min. When the total response time of the survey was less than 50% of the median response time, responses were visually checked to prevent non-serious responses (e.g., responses where only one answer option was chosen repeatedly throughout the survey leading to inconsistent responses) from being included in the analyses. This led to the exclusion of two respondents. Furthermore, we excluded 12 participants without an ADHD diagnosis who had T-scores below 65 on all CAARS-S:SV subscales, as these individuals were not among the target population. See Table 1 for demographic information of the remaining 233 respondents collected in the baseline survey.

Seventy-one percent of the sample had at least one current diagnosis of a psychiatric, neurological, and/or physical disorder. ADHD was the most prevalent diagnosis in the current sample, indicated by 159 participants of the complete sample (68%). More than half of the participants diagnosed with ADHD had a comorbid diagnosis (54%). Depression, anxiety disorder, PTSD, and dyslexia were the most common comorbid diagnoses alongside ADHD. Seven of the respondents without

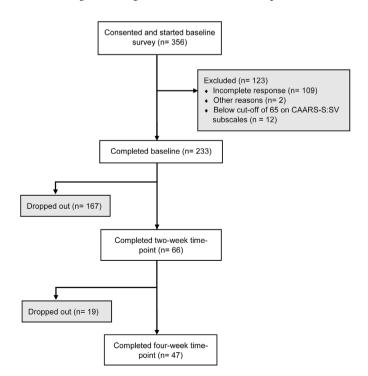


Fig. 1. Flowchart of included participants for each time point.

#### Table 1

Demographic information	from	respondents	at	baseline	and	the	two	and	four-
week time points.									

Time point		Baseline	Two week	Four week
N Age (mean $\pm$ standa	$\begin{array}{c} 233\\ 35.3 \ \pm \end{array}$	$\begin{array}{c} 66\\ 35.2 \ \pm \end{array}$	47 36.9 ±	
	10.7 N (%)	10.0 N (%)	9.5 N (%)	
Gender	Male	112	28	19
	Female	(48.1) 117 (50.2)	(42.4) 36 (54.5)	(40.4) 26 (55.3)
	Other	4 (1.7)	2 (3.0)	2 (4.3)
Continent of	Europe	193	2 (3.0) 62	2 (4.3) 46
current	Lutope	(82.8)	(93.9)	(97.9)
residence	America (North)	33 (14.2)	3 (4.5)	1 (2.1)
residence	America (South)	5 (2.1)	1 (1.5)	-
	Asia	2 (0.9)	-	_
	Africa	-	_	_
	Australia/Oceania	_	_	_
Highest level of	Tertiary (university,	107	- 50	_ 34
education	trade school, college)	(73.0)	(75.8)	(72.3)
education	Secondary (high school,	(73.0) 54 (23.2)	15	13
	academies, gymnasium, etc.)	34 (23.2)	(22.7)	(27.7)
	Primary (elementary)	9 (3.9)	1 (1.5)	_
Daily occupation	Computer/office work	57 (24.5)	17	13
Daily occupation	computer, onice work	0, (2110)	(25.8)	(27.7)
	Working with people	39 (16.7)	15	10
	froming that people	05 (1017)	(22.7)	(21.3)
	Studying	43 (18.5)	(22.7)	6
	bludying	10 (10.0)	(16.7)	(12.8)
	Creative work	31 (13.3)	10	8
	Greative work	51 (15.5)	(15.2)	(17.0)
	Physical work	13 (5.6)	4 (6.1)	4 (8.5)
	Other	50 (21.5)	9(13.6)	6
	other	50 (21.5)	) (10.0)	(12.8)
Currently	Yes	166	51	36
diagnosed <sup>a</sup>	105	(71.2)	(77.3)	(78.3)
diagnosed	No	67 (28.8)	15	10
Type of disorder b	ADHD	150	(22.7)	(21.7)
Type of disorder	ADHD	159	47	34
	Depression	(68.2) 44 (18.9)	(71.2) 8 (12.1)	(72.3) 5
	Anxiety disorder	39 (16.7)	9 (13.6)	(10.6) 6
				(12.8)
	PTSD	17 (7.3)	4 (6.1)	2 (4.3)
	Personality Disorder	11 (4.7)	3 (4.5)	-
	Dyslexia	12 (5.2)	2 (3.0)	2 (4.3)
	Migraines	8 (3.4)	4 (6.1)	3 (6.4)
	Chronic pain	7 (3.0)	2 (3.0)	2 (4.3)
	Cluster headaches	6 (2.6)	3 (4.5)	3 (6.4)
	Substance use disorder	4 (1.7)	2 (3.0)	-
	Autism/Asperger syndrome	4 (1.7)	1 (1.5)	-
	OCD	3 (1.3)	1 (1.5)	-
	Bipolar disorder	3 (1.3)	-	-
	Other	23 (9.9)	7 (10.6)	4 (8.5)
Experience with	Yes	191	51	37
psychedelic drug		(82.0)	(77.3)	(78.7)
c	No	42 (18.0)	15	10
			(22.7)	(21.3)

Absolute and relative frequencies are shown. Numbers in parentheses indicate the percentage corresponding to the absolute frequencies.

<sup>a</sup> "Are you currently diagnosed by a medical doctor or therapist with a psychiatric, neurological, or physical disorder?".

<sup>b</sup> Numbers do not add up to the sample size, because multiple answers were possible.

<sup>c</sup> "Do you have experience with at least one of the following psychedelics? Ayahuasca, DMT, 5-MeO-DMT, LSD, novel lysergamides (e.g., 1P-LSD, ALD-52), psilocybin/psilocin (magic mushrooms, truffles), salvia divinorum, ibogaine, mescaline (e.g., san pedro, peyote)." an ADHD diagnosis (9.5%) reported having a current diagnosis of a psychiatric, neurological, and/or physical disorder other than ADHD. Most participants diagnosed with ADHD received this diagnosis aged between 20 and 29 (45%), and about one-quarter were aged between 30 and 39 years old (24%) when diagnosed. More than half of the 159 participants who had been diagnosed with ADHD indicated to have used conventional ADHD medication but had stopped using it (53%), onethird were currently using conventional medication, and 14 percent had never used it. The two most common reasons for stopping conventional ADHD medication were because of physical and psychological side effects. Other reasons that were mentioned included "Feeling little emotions" and "Wanting to try microdosing". The participants who reported using conventional medication most often used amphetamines (Dextroamphetamine, Lisdexamfetamine, Adderall, Dexedrine) (50%) and methylphenidate (Mylan, Medikinet, Concerta) (40%). Eighty percent of the sample had at least one previous experience with a psychedelic.

Half of the participants at baseline (50%) reported through a diary what substance they used to microdose during the study. Of those, the majority indicated that they used psilocybin/psilocin (magic mushrooms, truffles) (78%), followed by novel lysergamides (e.g., 1P-LSD, ALD-52) (12%), LSD (9.5%), and one respondent used ayahuasca. Three respondents indicated that they had switched to another substance during the study: one participant used psilocybin/psilocin (magic mushrooms, truffles) after using novel lysergamides (e.g., 1P-LSD, ALD-52), one participant used psilocybin/psilocin (magic mushrooms, truffles) after using LSD and one participant used LSD after using psilocybin/psilocin (magic mushrooms, truffles). Averages of the self-reported doses were: 722 mg (SD: 485.5) of psilocybin/psilocin (magic mushrooms, truffles), 17.5  $\mu$ g (SD: 31.1) of novel lysergamides, 12  $\mu$ g (SD: 6.4) of LSD, and 5 mg of ayahuasca (1 person).

# 3.2. ADHD symptoms

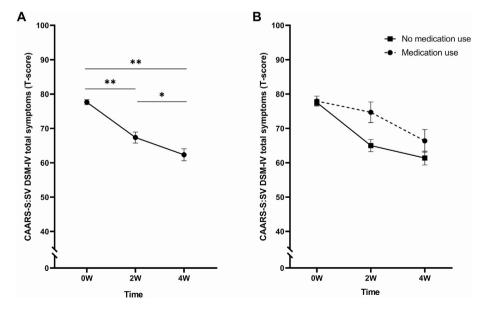
# 3.2.1. CAARS-S:SV DSM-IV total symptoms score

AR1 covariance structure was found to be the best fit for the model. The LMM showed a significant main effect of Time on the CAARS-S:SV DSM-IV total symptoms T-score ( $F_{(2, 154.2)} = 30.63$ , p < .001,  $\eta_p^2 = 0.284$ ), indicating a change in ADHD symptoms after MD. Bonferronicorrected pairwise comparisons showed that CAARS-S:SV DSM-IV total symptoms T-scores were significantly lower at two weeks ( $\Delta 2W$ –0W =

-10.17, p < .001) and four weeks ( $\Delta 4W-0W = -15.43, p < .001$ ) after MD compared to baseline, as expected (see Fig. 2A). CAARS-S:SV DSM-IV total symptoms T-scores were also significantly lower at the four-week time point compared to the two-week time point ( $\Delta 4W-2W = -5.26$ , p = .007). Further, a significant interaction effect between Time and Medication use was found ( $F_{(3, 241.4)} = 2.86, p = .038, \eta_p^2 = 0.034$ ). The evaluation of the estimates of fixed effects revealed a significant effect of Medication use on the CAARS-S:SV DSM-IV total symptoms T-score at 2W  $(\beta = 8.70, p = .006)$ , meaning that individuals who were using conventional ADHD medication alongside MD scored higher on the CAARS-S:SV at 2W, compared to individuals who were not using conventional medication. No effect of Medication use was found on the remaining two time points (OW and 4W). All respondents decreased in CAARS-S:SV scores from baseline to 2W and to 4W. Only respondents using conventional ADHD medication alongside MD showed less decrease in CAARS-S:SV DSM-IV total symptoms T-scores from baseline to 2W compared to those not using conventional medication alongside MD, leading to a significant difference between those respondents at 2W (see Fig. 2B). Lastly, the effect of the covariate consisting of the interaction term between Time and Comorbidity was not statistically significant ( $F_{(3, 223.4)}$ = 1.13, p = .338).

#### 3.2.2. CAARS-S:SV subscales

The effect of MD showed a similar pattern on the subscales of the CAARS-S:SV. A main effect of Time was found on all T-scores of the three subscales (see Table 2). A significant interaction between Time and Medication use was found on the ADHD index T-scores ( $F_{(3, 247.6)} = 3.65$ , p = .013,  $\eta_p^2 = 0.042$ ) and on the Inattention T-scores ( $F_{(3, 250.6)} = 3.45$ , p = .017,  $\eta_p^2 = 0.040$ ). Evaluation of the estimates of fixed effects showed a similar effect of Medication use alongside MD at 2W on the ADHD index  $(\beta = 8.04, p = .001)$  and Inattention  $(\beta = 10.92, p = .002)$  subscales, as was found on the DSM-IV total symptoms T-score. Namely, those using conventional medication alongside MD showed a smaller decrease in scores from baseline to 2W compared to those not using conventional medication alongside MD. No effect of Medication use alongside MD was found on the ADHD index and Inattention subscale at the remaining time points OW and 4W. Further, a significant interaction between Time and Comorbidity was found on the ADHD index subscale ( $F_{(3, 232.7)} = 2.73, p$ = .045,  $\eta_p^2$  = 0.034). Evaluation of the estimates of fixed effects showed a difference at 0W between those having a comorbid diagnosis alongside ADHD compared to those without comorbid diagnoses ( $\beta = 3.30$ , p =



**Fig. 2.** Mean scores of the CAARS-S:SV DSM-IV total symptoms T-scores at baseline (0W) and two (2W) and four weeks (4W) after MD (A) of the whole sample, and (B) per conventional ADHD medication use. Error bars represent mean  $\pm$  SEM. \*p < .05; \*\*p < .001.

#### Table 2

Mean raw- and T-scores (SEM) for each CAARS-S:SV subscale at baseline (0W), two-week (2W) and the four-week time points (4W). F-values, p-values and partial etasquared values are presented describing the main effect of Time on the corresponding subscale scores.

	Mean (SEM)			T-score (SEM)			F-value	<i>p</i> -value	$\eta_p^2$
	ow	2W	4W	0W	2W	4W			
ADHD index	22.70 (0.32)	18.02 (0.78)	15.32 (0.86)	70.69 (0.57)	63.02 (1.40)	58.53 (1.58)	30.87	.000	.281
Inattention	19.12 (0.27)	14.51 (0.68)	12.55 (0.73)	82.61 (0.73)	71.15 (1.89)	65.66 (1.86)	33.32	.000	.288
Hyperactivity/impulsivity	14.47 (0.32)	11.95 (0.56)	10.60 (0.64)	65.55 (0.78)	59.38 (1.32)	56.08 (1.50)	15.41	.000	.200
DSM-IV ADHD total symptom score	33.58 (0.49)	26.47 (1.10)	23.15 (1.26)	77.62 (0.73)	67.34 (1.60)	62.31 (1.75)	30.63	.000	.284

.011), meaning that respondents with comorbid diagnoses alongside ADHD scored higher on the ADHD index subscale at baseline compared to those without comorbid diagnoses. No effects were found on the ADHD index at 2W and 4W. Lastly, no interaction effects between Time and Medication use ( $F_{(3, 225.4)} = 1.63$ , p = .184) and Time and Comorbidity ( $F_{(3, 217.7)} = 0.54$ , p = .653) were found on the Hyperactivity/ impulsivity subscale.

#### 3.2.3. MD non-responders on CAARS-S:SV

Nine out of 47 respondents at 4W (19.1%) showed no change or an increase in the CAARS-S:SV DSM-IV total symptoms T-score. Three out of 9 non-responders at 4W (33.3%) used conventional medication alongside MD; none of these respondents had a comorbid diagnosis alongside ADHD.

Five of the 9 non-responders at 4W (55.6%) were already nonresponders at 2W, of which one individual was using conventional medication. The remaining 4 non-responders at 4W (44.4%) had shown improvements in CAARS-S:SV DSM-IV total symptoms scores at 2W compared to baseline, but worsened over time; 2 of these respondents (50%) were using conventional medication alongside MD.

## 3.3. Well-being

AR1 covariance structure was the best fit for this model. The LMM showed a significant main effect of Time on the WHO-5 score ( $F_{(2, 119.4)} = 31.50, p < .001, \eta_p^2 = 0.345$ ), indicating a change in well-being scores after MD (see Fig. 3A). Bonferroni-corrected pairwise comparisons showed that well-being scores were significantly higher two weeks ( $\Delta 2W$ –0W = 16.47, p < .001) and four weeks after MD ( $\Delta 4W$ –0W = 17.80, p < .001) compared to baseline, confirming the second

hypothesis. Well-being scores did not significantly differ between the two- and four-week time points ( $\Delta 4W-2W = 1.06$ , p > .999). Further, a significant interaction was found for Time and Comorbidity ( $F_{(3, 205.2)} = 2.85$ , p = .038,  $\eta_p^2 = 0.040$ ). Evaluation of the estimates of fixed effects indicated lower well-being scores at baseline for those having a comorbid diagnosis alongside ADHD compared to those without comorbid diagnoses ( $\beta = -6.61$ , p = .009). No interaction effect of Time and Comorbidity was present at the remaining two time points (2W and 4W). No significant interaction was found for Time and Medication use on the WHO-5 score ( $F_{(3, 210.4)} = 1.74$ , p = .160) (see Fig. 3B).

#### 3.4. Correlations between change in ADHD symptoms and well-being

A moderate negative correlation was found between the change scores of the CAARS-S:SV DSM-IV total symptoms T-scores and the WHO-5 total scores at the two-week time point (r = -0.367, p = .003). Furthermore, a moderate negative correlation was found between the change scores of the CAARS-S:SV DSM-IV total symptoms T-scores and the WHO-5 total scores at the four-week time point (r = -0.471, p = .001) (see Fig. 4).

#### 3.5. Time perception

The first-order ante-dependence covariance structure was the best fit for the model. No main effect of Time was found ( $F_{(2, 59.2)} = 0.63$ , p =.534) (see Fig. 5A). A significant main effect of Interval was found on the relative difference score ( $F_{(5, 182.2)} = 24.66$ , p = .000,  $\eta_p^2 = 0.403$ ), indicating differences in relative difference scores per time interval. Bonferroni-corrected pairwise comparisons showed that the relative difference scores of all pairs differed significantly from each other, apart

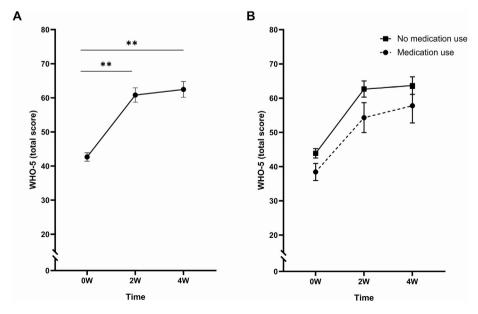
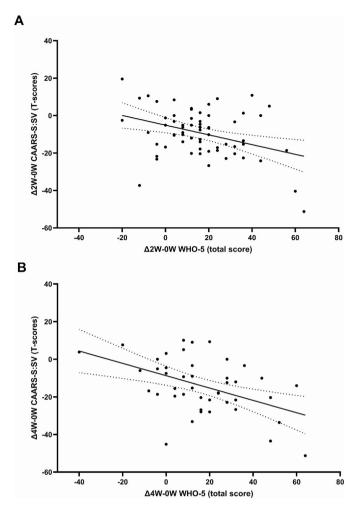


Fig. 3. Mean total scores of the WHO-5 at baseline (0W) and two (2W) and four weeks (4W) after MD (A) of the whole sample, and (B) per conventional ADHD medication use. Error bars represent mean  $\pm$  SEM. \*p < .05; \*\*p < .001.



**Fig. 4.** Correlations between changes in ADHD symptoms and well-being. Decreases in CAARS-S:SV DSM-IV total symptom T-scores were negatively related to increases in WHO-5 total scores at (A) two weeks and (B) four weeks after MD compared to baseline. The best-fit line is shown including the 95% confidence bands (dotted lines).

from two pairs (1000 ms vs 1500 ms and 5500 ms vs 6000 ms). In general, the longer the time interval, the more likely it was that the interval was underestimated (see Fig. 5B). No significant interaction was found between Time and Interval ( $F_{(10, 176.7)} = 1.01, p = .441$ ) (see Fig. 5B). The LMM showed a significant three-way interaction between Time, Interval, and Medication use ( $F_{(18, 97.8)} = 2.52, p = .002, \eta_p^2 =$ 0.317). Evaluation of the estimates of fixed effects showed a significant effect of Medication use at 2W ( $\beta = 0.19$ , p = .038) and 4W ( $\beta = 0.35$ , p =.004) for the 1000 ms interval. This finding indicated that individuals who were using conventional ADHD medication alongside MD had higher relative difference scores when estimating the 1000 ms interval at time points 2W and 4W, compared to individuals not using conventional medication alongside MD (see Fig. 5C). There was no effect of Medication use on any of the other intervals. No significant interaction effect between Time, Tone and Comorbidity was found  $(F_{(18, 100.2)} = 1.31, p =$ .201).

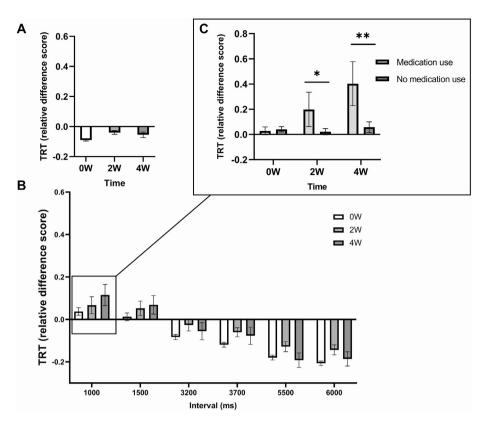
#### 4. Discussion

This online prospective naturalistic survey study aimed to assess changes in ADHD symptoms, well-being, and time perception using validated questionnaires and a time reproduction task in individuals with an ADHD diagnosis or severe ADHD complaints, who started MD on their own initiative. The primary hypothesis that MD would reduce ADHD symptoms was confirmed, as findings showed decreased (self-report) ADHD symptoms after two weeks of MD, with additional decrements two weeks later. Using conventional ADHD medication seemed to delay the decrease in ADHD symptoms after MD. In line with expectations, increased well-being was reported at two and four weeks after MD. Additionally, MD-related changes in well-being and ADHD symptoms were negatively associated. Using conventional medication alongside MD, or having comorbidities alongside ADHD, did not change the effect of MD on ADHD symptoms and well-being after four weeks of MD in the current study. Lastly, time perception seemed to be altered after MD for individuals using conventional medication, illustrated by an overreproduction of the shortest (1000 ms) time interval used in a time reproduction task. The results do not find support for the hypothesis that performance on a time perception task would be improved after MD in individuals with an ADHD diagnosis or severe ADHD complaints.

The decrease in ADHD symptoms after MD was in line with earlier findings showing that MD as self-medication used by people diagnosed with ADHD was rated as being more effective than conventional treatments and increasing their quality of life (Hutten et al., 2019a). Also, the findings were in line with anecdotes of individuals who microdosed to self-treat their ADHD (Andersson and Kjellgren, 2019). The strength of the present study over retrospective reports is that the current design allows causal inferences to be made about MD and the observed and self-rated effects. Based on this, it can be said with more certainty that MD could be beneficial and of therapeutic value for individuals diagnosed with ADHD or having severe ADHD complaints, even in addition to first-line pharmacological interventions. After four weeks of MD, mean CAARS-S:SV T-scores were below the used cut-off of 65 for three out of four subscales. The current study sample showed similar changes in the CAARS-S:SV DSM-IV total symptoms scores compared to studies investigating the effects of several weeks of mindfulness-based cognitive therapy (Hepark et al., 2019; Janssen et al., 2019) and treatment with methylphenidate (Takahashi et al., 2014) in adults diagnosed with ADHD. Almost twenty percent of the sample at the four-week time point did not show improvements in ADHD symptoms. This lack of improvement did not seem related to using conventional medication alongside MD or having comorbidities alongside ADHD. Other aspects most likely underlay the lack of improvement in the non-responding participants. A potential explanation might be that individuals had difficulties determining the right dose, a question that future controlled dose-titration studies could investigate.

Well-being was increased after two weeks of MD compared to baseline and remained elevated two weeks later. These scores were put into context by comparing them to normative data collected during the COVID-19 pandemic because the current data was collected within the same period. Compared to the normative dataset collected from almost 15 thousand respondents from 14 countries, the current study sample reported low well-being scores at baseline (mean WHO-5: 42.7) (Wilke et al., 2021). After two and four weeks of MD, the current sample showed well-being scores (mean WHO-5 (2W): 59, mean WHO-5 (4W): 60) that were more in line with the average well-being scores of West-European countries during the COVID-19 pandemic. This shows that, during MD, the sample evolved from below-average to average well-being scores.

No support was found for improved performance on a time perception task after MD. However, a decrease in performance was found after MD compared to baseline in individuals using conventional medication. The hypothesis was based on previous research showing that individuals diagnosed with ADHD tended to underestimate presented time intervals (Marx et al., 2021) and a study showing that microdoses of LSD led to an over-reproduction of 2000–4000 ms time intervals (Yanakieva et al., 2019). The only effect of MD on time perception found here included an overestimation of the 1000 ms interval for individuals using conventional ADHD medication next to MD, after two- and four weeks of MD. This finding should be interpreted with caution, given the small number of respondents using conventional ADHD medication at the two- (n = 16; 25% of respondents at 2W) and four-week time points (n = 9; 20% of



**Fig. 5.** Means of the relative difference scores of the time reproduction task (TRT) (A) for each time point, (B) for each interval per time point, and (C) for the 1000 ms interval for each time point per Medication use. Error bars represent mean  $\pm$  SEM. \*p < .05; \*\*p < .001.

respondents at 4W). Furthermore, the large variability in the accuracy of time estimations suggests that two trials per time interval were potentially not enough to capture a potential main effect of MD. The effect found in some of the respondents in the current study provides enough reason to further investigate the possible impact of MD on time perception in this population in a controlled environment and using more trials in the time perception task.

Strengths of the current study included using a naturalistic, prospective design. This allowed drawing causal inferences with less uncertainty compared to asking retrospectively about individuals' MD experiences. Widely used, validated questionnaires were used to assess ADHD symptoms and well-being, which allowed comparison across studies investigating conventional treatments and comparison to normative non-clinical data. In addition, the inclusion of a cognitive task combined with the subjective self-report questionnaires provided the opportunity to assess the effects of MD in adults diagnosed with ADHD or having serious ADHD complaints on a clinical, psychological, and cognitive level.

Although the current study design provided an easy way to collect data and observe the effects of MD in an ADHD population without manipulating MD practices, it comes, of course, with its limitations. Due to lacking a placebo-control group, the design could not test whether the MD group behaved differently than a group receiving a placebo. In the current study, participants were recruited via a MD website and respondents had the intention to microdose to self-treat their ADHD symptoms. It can only be expected that individuals who choose MD as self-treatment are positively oriented towards the practice of MD, which might enhance a potential placebo effect (Geers and Rose, 2011; Rose et al., 2014). Future research could instruct participants on how to blind themselves, including a placebo-control group, as has been done recently by Szigeti and colleagues (Szigeti et al., 2021). When comparing the effectiveness of MD for ADHD to other interventions for ADHD, it should be noted that the participants of the current study chose MD to self-treat

their ADHD complaints on their own initiative, while in controlled, experimental studies participants are assigned to a treatment. In both cases, participants choose to be enrolled in research, however, it can be suggested that choosing a treatment may increase the positivity about the treatment and the treatment's efficacy (Rose et al., 2012, 2014). Furthermore, participants enrolling themselves in the study might have led to self-selection bias. Perhaps only individuals who were willing to adhere to completing several questionnaires participated in the study, resulting in a study sample that may not be representative of the general ADHD population. Further, the study suffered from a large dropout rate, with only 20% of the sample at baseline completing the four-week time point, which is common in prospective survey studies (Hübner et al., 2021). Perhaps only those with a positive MD experience continued in the study, biasing the findings. Future studies could follow up and ask participants about their reason to drop out. Furthermore, participants were requested to report in a diary what substance they had used to microdose. About half of the respondents at baseline did not fill in the diary, leading to a large amount of missing data about the substances and doses that were used during the study. No additional information about the substances was collected, such as the formulation, storage conditions, and route of administration, which may be important factors influencing experienced effects. Lastly, the CAARS-S:SV originates from 1999, therefore the change from DSM-IV to DSM-5 has not been taken into account by using this scale. The DSM-5 devotes more attention to ADHD in adulthood, by including more examples of how ADHD is expressed in adults and by raising the age of symptom onset. Also, the normative data of the CAARS-S:SV could be considered outdated. Future research should include a more up-to-date ADHD scale taking into account the changes from DSM-IV to DSM-5 and more recent norm scores.

Future placebo-controlled studies are needed to assess the possible therapeutic value of MD in adults diagnosed with ADHD. In this context, it would be interesting to compare another type of practice/therapy as self-treatment to MD, to assess if MD potentially has effects superior to the effect of treatment choice and placebo in adults self-treating their ADHD symptoms. Further, a more standardized test administration should be used to assess the effects of MD on time perception in adults with ADHD. Other cognitive domains that are impaired in ADHD, such as working memory, attention, and executive functioning, should also be investigated in future studies investigating the effects of MD in adults with ADHD, to assess in what domain MD might exert beneficial effects. Lastly, since inattention, hyperactivity, and impulsivity symptoms may occur in other disorders (Grant et al., 2005), such as substance use disorder (Karlsson et al., 2021), bipolar (Strakowski et al., 2010) and borderline personality disorder (Paris, 2005; Eskander et al., 2020), future studies should investigate the effects of MD in these populations.

To conclude, the present study provides the first evidence that MD may have therapeutic value in adults diagnosed with ADHD or experiencing severe ADHD complaints. Given the limitations of the current study design, studies including placebo-treated and/or other control groups could confirm the magnitude of the therapeutic effect of MD in ADHD.

### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

#### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: KPC Kuypers reports a relationship with Mind Medicine Inc. that includes: funding grants. KPC Kuypers reports a relationship with The Beckley Foundation that includes: funding grants.

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