OXFORD

International Journal of Neuropsychopharmacology (2022) 25(3): 215–225

https://doi.org/10.1093/ijnp/pyab057
Advance Access Publication: August 28, 2021
Regular Research Article

REGULAR RESEARCH ARTICLE

Selective Effects of Methylphenidate on Attention and Inhibition in 22q11.2 Deletion Syndrome: Results From a Clinical Trial

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Abstract

Background: Attention deficit and/or hyperactivity disorder (ADHD) is the most prevalent psychiatric disorder in children with 22q11.2 deletion syndrome (22q11DS) and frequently persists into adulthood. Although medication with stimulant has been demonstrated to be highly effective in idiopathic ADHD, evidence in 22q11DS is still scarce. Previous studies have shown safety and effectiveness of methylphenidate (MPH) on core symptoms of ADHD as well as improvement of associated cognitive deficits. However, only a limited number of cognitive domains have been explored.

Methods: Twenty-three participants with 22q11DS and attention difficulties, aged 8–24 years, entered a clinical trial aiming to specify the effects of MPH on clinical symptoms, cognition, and daily-life behavior. The effects of treatment were compared with/without medication in a within-subject design. The trial included both participants naïve to the molecule and chronic users.

Results: Benefit from the treatment was demonstrated through a decrease in core ADHD symptoms, specifically inattention symptoms, and improvement of cognitive measures of attention and inhibition. Conversely, no significant change was found for other executive functions (such as cognitive flexibility, working memory, initiation), learning, or memory. Moreover, no significant improvement on ecological measures of daily-life executive functioning was found, possibly because of the short treatment period. We replicated safety, and although very frequent, side effects were of mild intensity and comparable with previous findings.

Received: January 4, 2021; **Revised:** August 13, 2021; **Accepted:** August 20, 2021

Significance Statement

Although at high risk for various comorbid psychiatric diseases, research shows that the 22q11DS population is rather underdiagnosed and undertreated, particularly for ADHD. Additionally, despite high rates of ADHD and the common prescription of stimulant, there is a scarcity of clinical trials in this population. So far, only 2 studies have evaluated the effectiveness of methylphenidate in 22q11DS providing guidance for professionals and caregivers. This study adds evidence on safety and effectiveness of the treatment in an independent sample from previous work. Benefit of treatment is evaluated through multiple outcome measures: core ADHD symptoms, cognitive measures, and daily-life behaviors.

Conclusions: This study extends the current knowledge on the effects of MPH in patients with 22q11DS. Treatment was found to be effective for core ADHD symptoms and cognitive measures of attention and inhibition.

Keywords: 22q11.2 deletion syndrome, attention deficit, clinical trial, methylphenidate
Trial registry: ClinicalTrials.gov, ID: NCT04647500, https://www.clinicaltrials.gov

Introduction

Attention deficit and/or hyperactivity disorder (ADHD) is highly prevalent in neurodevelopmental disorders, including genetic syndromes (Lo-Castro et al., 2011; Reilly et al., 2015). Chromosome 22q11.2 deletion syndrome (22q11DS) is a genetic condition known for its increased risk for psychiatric disorders, including psychosis spectrum disorder (Rees et al., 2014; Schneider et al., 2014). A collaborative study assessing over 1400 patients found that ADHD is the most common diagnosis reported in children (37%) (Schneider et al., 2014). Furthermore, high rates of ADHD are also observed in adults (between 16% and 65%), confirming the persistence of this diagnosis with age (Antshel et al., 2013; Schneider et al., 2014). These rates largely exceed the worldwide prevalence of ADHD in the general population, with meta-analyses showing 5%–7% in children and adolescents and 2.5% in adults (Polanczyk et al., 2007; Simon et al., 2009; Faraone et al., 2015; Thomas et al., 2015).

The presentation of ADHD in 22q11DS is different from idiopathic ADHD, with higher rates of 22q11DS patients meeting the criteria for inattentive presentation (61%–79% in 22q11DS vs 38%–57% in idiopathic ADHD) (Antshel et al., 2007; Willcutt, 2012; Schneider et al., 2014; Niarchou et al., 2015). Because of its nature, inattentiveness is more difficult to recognize than hyperactivity and impulsivity. Additionally, even when symptoms are recognized, they are sometimes "over-shadowed" by the low intellectual functioning that characterizes 22q11DS, therefore delaying diagnostic and proper care (McDonald-McGinn et al., 2015; Reilly et al., 2015).

Treatment recommendation for ADHD for children from 5 years old includes medication with stimulants, with methylphenidate (MPH) being recommended in the first line (e.g., NICE Guideline, 2018). In idiopathic ADHD, extensive evidence shows that MPH medication significantly reduces core symptoms of ADHD compared with a placebo (Faraone and Buitelaar, 2010; Cortese et al., 2018). Additionally, cognitive domains (including attention and executive functions) consistently found to be impaired in ADHD also show improvement with medication (Willcutt et al., 2005; Swanson et al., 2011; Coghill et al., 2014). Results from a meta-analysis indicated that measures of non-executive functions, such as memory, are also significantly helped by MPH (Coghill et al., 2014).

Despite high rates of ADHD in 22q11DS and the common prescription of stimulant, this population is rather undertreated, with 31% of individuals diagnosed with ADHD receiving pharmacological treatment (Tang et al., 2014). Reluctance for treatment from clinicians might originate from multiple factors, one being the complex medical comorbidities of 22q11DS, including congenital heart defects (Green et al., 2011; McDonald-McGinn et al., 2015). Indeed, presence of congenital cardio-vascular anomalies can increase the risk for QT prolongation and requires surveillance (Kaltman and Berul, 2015). Another factor creating uncertainty in clinical practice is the use of stimulant in a population at high risk for developing psychosis such as 22q11DS, although a recent retrospective study found stimulant to be safe in terms of psychosis conversion and rates of side effects in 22q11DS patients (Basel et al., 2021).

All considered, the major shortcoming in the use of stimulants comes from the paucity of clinical trials conducted specifically in 22q11DS to guide clinicians in their decisions. So far, only 2 studies—to our knowledge—have investigated the safety and efficacy of MPH in this population (Gothelf et al., 2003; Green et al., 2011). In a first study, Gothelf et al. (2003) evaluated the effect of a low dose of MPH (0.3 mg/kg) in 12 children and adolescents with 22q11DS and ADHD. They demonstrated a significant decrease of ADHD symptoms as well as improvement of cognitive measures of attention. Overall, after 4 weeks, treatment was well tolerated with no significant change in cardiac measures. Because 22q11DS constitutes an increased risk for developing schizophrenia (Rees et al., 2014), patients were also screened for psychotic symptoms, but no change was reported at follow-up. Side effects were very common (92%) but never severe enough to warrant discontinuation of medication. Similar to other studies on idiopathic ADHD, the most commonly reported side effect was poor appetite, but other effects were also relatively frequent (irritability, sadness, stomachaches, reduced talking with others, and proneness to crying). Results are, however, limited by the small sample size (n=12) and the even smaller number of participants evaluated with cognitive measures of attention (n=6). In a second study, Green et al. (2011) extended previous findings by examining the effect and safety of MPH in 34 patients with 22q11DS and ADHD in a placebo vs MPH design (n=12 vs n=22, respectively). In addition to the larger sample size, the effectiveness of MPH was compared with a placebo group on several cognitive measures, including 3 tasks measuring prefrontal cognitive functioning. After a single dose of 0.5 mg/kg, the authors showed significant improvement in prefrontal task performance (2/3 tasks improved). Safety and good tolerance to MPH were replicated. Participants reported similar rates of side effects immediately after medication and at the follow-up (6 months). Only 15 participants continued the MPH treatment for the entire 6-month

period, but these participants showed a mean 40% reduction in severity of ADHD symptoms (reported by parents with questionnaires). Altogether, these 2 studies suggest effectiveness and safety of MPH in 22q11DS. However, they provide only limited knowledge on the effect of MPH on cognitive measures for this population, as a limited number of domains of attention and executive functions (EF) were explored. Therefore, the aim of this study was to investigate the benefit of a stimulant medication on a broader range of cognitive performance related to ADHD symptoms using a within-subject design (with/without MPH). Effects were evaluated during 13 days of treatment in participants with a regular prescription of MPH and naïve to the molecule. Because MPH has been shown to improve a broad range of attentional and EF domains in idiopathic ADHD (Nigg, 2005; Willcutt et al., 2005), we explored improvements of attention (selective and sustained), inhibition, cognitive flexibility, working memory, fluency, and planning. Change in broader cognitive domains, including learning and long-term memory, was also explored.

METHODS

This study aimed to investigate the effects of MPH on cognitive and clinical measures in 22q11DS patients. A within-subject design was employed to compare measures with/without MPH treatment. Depending on their medication history and current psychostimulant medication, participants were included in either the consumer group (participants with an ongoing treatment of MPH) or naïve group (participants naïve to the molecule).

Participants

Twenty-five participants (11 females) with 22q11DS, between 8 and 24 years old, were enrolled in this study (see flowchart in Figure 1). They were recruited from the longitudinal cohort of 22q11DS patients (Geneva cohort) from 01.08.2016 to 30.09.2020. The presence of the deletion was confirmed using quantitative fluorescent polymerase chain reaction prior to inclusion in the Geneva cohort. The study was approved by the Ethical Committee of the Canton of Geneva (Switzerland) as well as the Swiss Agency for Therapeutic Products: Swissmedic. Written informed consent was obtained for all participants and their parents (if participant were younger than 18 years).

For this study, inclusion criteria were the following:

1. Male or female with confirmed 22q11DS diagnosis.
2. Minimum age of 8 years or maximum age of 25 years and 11 months.
3. Attention difficulties pointed out by parents and/or the participant during the initial clinical interview.
4. Sufficient verbal expression and comprehension skills to understand and follow instructions based on initial interview.

Exclusion criteria for this study were:

1. Participants younger than 8 years and older than 25 years and 11 months.
2. Previous adverse experience with MPH, suggesting that the molecule is not well tolerated.
3. Cardio-vascular diseases listed as a contraindication to MPH, including rhythm disorders, severe hypertension, cardiac insufficiency, atherosclerotic heart disease, preexisting cerebrovascular affections, hemodynamically significant congenital heart defect, and channelopathies.
4. For naïve participants: corrected QT (QTc) distance at baseline electrocardiogram >460 milliseconds or elongation at control electrocardiogram (day 6 of treatment) superior to 30 milliseconds with functional complaint, both representing an increased risk for sudden heart failure.
5. Psychiatric affections for which use of MPH is contraindicated, including episodic paroxysmal anxiety, manic episode, marked psychotic symptoms, schizophrenia, borderline personality disorder, clinical depression (present or past), suicidal episode, diagnosis or family history of Tourette syndrome, and alcohol or drug abuse.
6. Other somatic affections, including hyperthyroid, glaucoma, and pheochromocytoma, all listed as contraindication to MPH.
7. Concurrent treatment with monoamine oxidase inhibitors or interruption less than 14 days before beginning of treatment because of the interaction that could lead to acute arterial hypertension.
8. Pregnancy or breastfeeding, due to the lack of data on safety of MPH during pregnancy in humans and analysis showing that traces of MPH can be found in breast milk.

The total sample was composed of 16 naïve participants (6 females) and 9 consumer participants (4 females). Due to the inability to travel during the Coronavirus pandemic, 2 consumer participants (1 female) did not complete the second visit and were therefore excluded from the analyses. The final sample included 23 participants with at least 2 visits. Mean age at study inclusion was 14.46 (SD = 5.22) years for the naïve group and 13.88 (SD = 4.09) years for the consumer group.

Procedure

The evaluation was carried out by a trained psychologist and took place in person with some additional follow-up via videoconference the next day and 1 week later. All consumer participants had a prescription of Concerta, although this study was intended as open-label. Concerta is rapidly absorbed and reaches a first maximum in plasmatic concentration after 1 to 2 hours after oral administration (https://compendium.ch; Banaschewski et al., 2006). The plasmatic peak is reported to be between 6 and 8 hours after oral administration. Considering this, all evaluations done with MPH were conducted between 1.5 and 8 hours after oral administration to ensure coverage of the treatment. In the naïve group, the first visit served as baseline (without MPH) and the second assessed changes with treatment. In the consumer group, first visit was randomly assigned with/without treatment (3 participants started by visit with MPH) and second visit was planned accordingly. To limit learning effects of the cognitive measures, parallel task version with comparable difficulty were used for learning and memory assessments. Additionally, a period of at least 1 month was required between visits with/without MPH. Mean interval between visits was 65.17 days (SD = 32.07; minimum = 35; maximum = 134).

Treatment in the Naïve Group—Naïve participants were prescribed 13 days of Concerta at a weight-adjusted dose of 0.7 mg/kg, following 5 weight categories (see supplementary Table 1). Except for participants lighter than 30 kg (n = 2), the treatment phase began with a lower introduction dose for 5 days before increasing to the weight-adjusted dose.

Effect of treatment on cognitive measures was evaluated on day 6 with a follow-up on memory on day 7 and 13. Effect of treatment assessed with clinical measures and questionnaires was

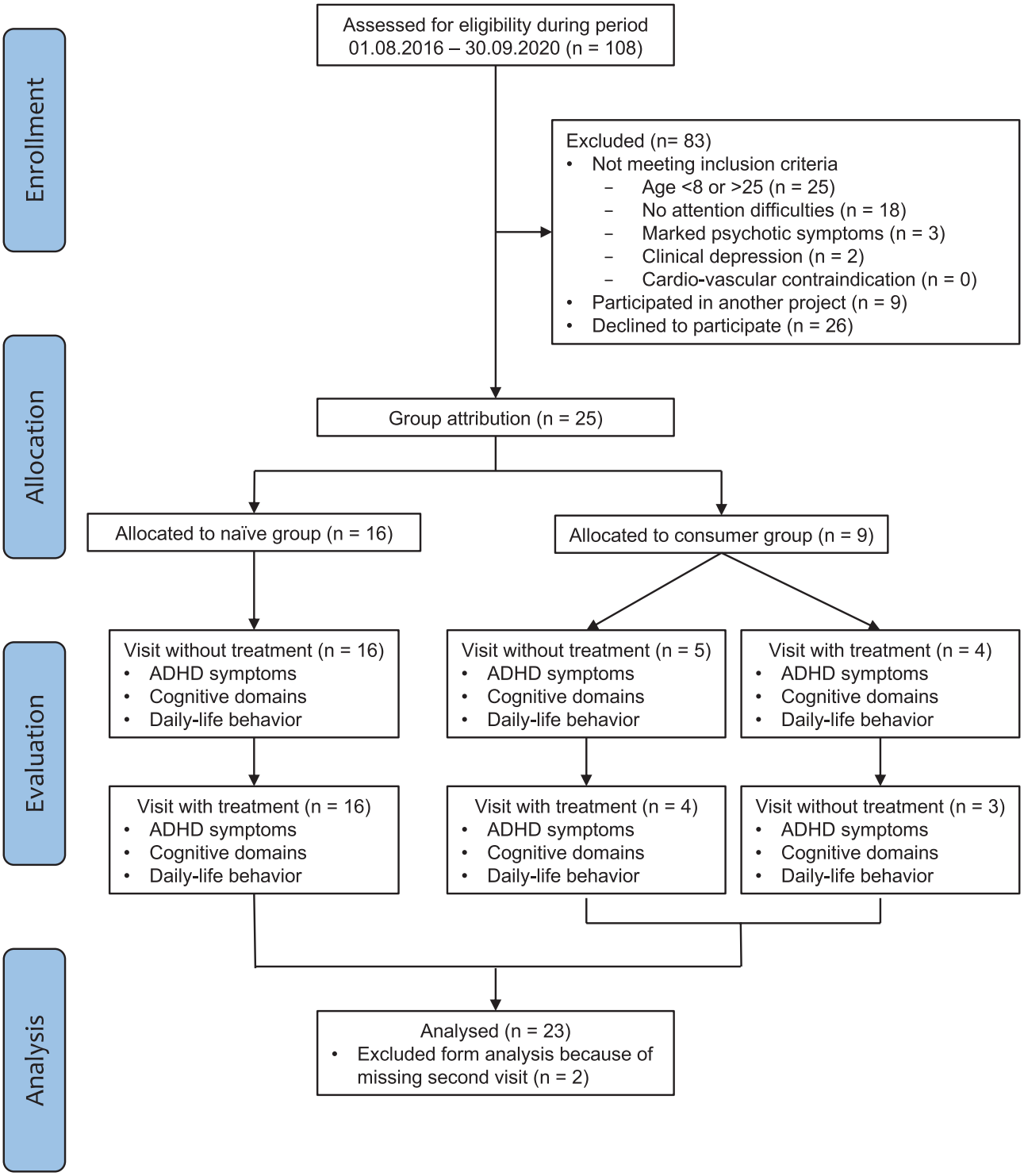

Figure 1. Flowchart of participant selection, group attribution and data analysis.

conducted at the end of the treatment phase to guarantee several observation opportunities for the participant and the caregivers.

Treatment in the Consumer Group—For the visits with MPH, participants were asked to take their usual prescription. Mean dosage of MPH for the consumer group was 0.67 mg/kg (SD = 0.20; minimum = 0.34; maximum = 0.93), roughly comparable with the naïve group.

To follow the naïve group procedure as closely as possible, for visits without MPH, consumer participants were asked to interrupt their usual prescription for 13 days. Because many participants usually have a break in treatment during weekends or holidays, compliance was high. For visits without MPH, a washout period of 5 days prior to evaluation with cognitive measures was asked of each participant. Again, to guarantee several observation opportunities for the participant and the caregivers,

assessments with clinical measures and questionnaires were done at the end of the interruption (day 13).

Materials

Outcome measures were chosen to evaluate ADHD through different aspects: clinical symptoms; cognitive tests of attention, EF, learning, and long-term memory; and questionnaires on daily-life behavior. For the naïve group, tolerance to treatment was examined though the report of side effects (quality, quantity, severity).

Clinical Symptomatology—To appreciate the intensity of ADHD symptomatology and change with/without MPH, caregivers were interviewed on the 18 symptoms from the ADHD section, criteria A, of the DSM-V (American Psychiatric Association, 2013). Each symptom was evaluated with the following scale: 1 = not present; 2 = subclinical, behavior occurs sometimes with minimal impact on global functioning; and 3 = clinical, behavior occurs frequently with moderate to severe impact on global functioning. A global sum of symptoms intensity was computed as well as a sum of inattention symptoms severity and a sum of hyperactivity/impulsivity symptoms severity. Assessment was available for 20 participants (16 naïve and 4 consumer).

Cognitive Measures—A large selection of cognitive measures was chosen to evaluate the following domains: attention (Conners' Continuous Performance Test 3rd edition, CPT3, Conners and MHS Staff, 2014), inhibition (Stroop task, Albaret and Migliore, 1999; stop-signal task, Cambridge Cognition Ltd., 2013), cognitive flexibility (color trails test, D'Elia and Satz, 1989; Williams et al., 1995; intra-/extra-dimensional shift task Cambridge Cognition Ltd., 2013), updating (digit span and letter-number sequencing, Wechsler, 2004, 2011); spatial working memory task Cambridge Cognition Ltd., 2013), initiation (verbal and non-verbal fluency task, Sevino, 1998), planning (Tower of London, Culbertson and Zillmer, 1999), processing speed (coding and symbol search, Wechsler, 2004, 2011), learning and long-term memory (modified 15 words and 15 signs, Maeder et al., 2020). For details, see supplementary Table 2.

Different types of tools were used (paper/pencil, computerized tasks) in different modalities (verbal and non-verbal). Three computerized tasks came from the computer-interfaced Cambridge Neuropsychological Test Automated Battery. Due to an update, 2 different systems were used: Research suit and Connect. To ensure continuity, each participant was examined with the same system throughout all visits. For 21 participants (91.3%), tests were administered in the Research suit system using the Cambridge Neuropsychological Test Automated Battery eclipse version 6 on a portable touch-screen tablet running on a Windows-based PC system. For the remaining 2 participants, tests were administered with an IPad via the Connect web-based platform.

Questionnaires—Daily-life behaviors were assessed with the Behavior Rating Inventory of Executive Function (BRIEF), children and adult version (Gioia et al., 2000; Roth et al., 2002). This questionnaire provides an ecological assessment of EF, with a Global Executive Composite score derived from the Behavioral Regulation Index (BRI) and Metacognitive Index. The BRI includes subscales of inhibition, shifting, emotional regulation, and, only in the adult-form, self-monitoring. The Metacognitive Index includes subscales of initiation, working memory, planning, organization, and monitoring. Observations are reported using standardized scores (T-scores). A T-score ≥65 is considered as pathological. To increase the sample for paired comparisons, the children and adult versions were combined by using T-scores only. As a result, the self-monitoring subscale from the adult version was not included in the analyses. Analyses were based on the assessment from caregivers (other-reported) available for 23 participants. Five adult 22q11DS participants also completed the self-reported version of the questionnaire, built on the same structure. This information was used in a complementary qualitative analysis.

Safety and Tolerance to Treatment (Only Naïve Group)—An electrocardiogram was performed prior to the beginning of treatment (<3 months) to check QTc at baseline and repeated on day 6 of treatment to evaluate possible change due to the treatment.

Regarding tolerance, observations from the participant and caregivers were compiled during the treatment phase through a homemade questionnaire sent by email or filled out with the examiner. Information was collected about the time at which treatment was taken, eventual missed treatment, side effects, and intensity of eventual side effects to the treatment. The questionnaire was completed on 3 occasions: end of day 1 of treatment, day 6 of treatment (when the dosage was increased for participants heavier than 31 kg), and end of the last treatment day (day 13).

Evaluation of side effects was inspired by the Barkley Side Effect Rating Scale (Barkley et al., 1988). Side effects were regrouped in 7 different categories: gastro-intestinal (including stomachache, nausea, decreased appetite), sleep disturbances (including difficulties falling asleep, insomnia, tiredness), neurologic (including headache, tremors, tics or nervous movements), cardio-vascular (including heart palpitations, dyspnea), mood (including sadness, withdrawal), other psychiatric (including restlessness, increased anxiety, nervousness), and other side effects for unexpected observations. Severity of each side effect was rated 0 = absent, 1 = mild, 2 = significant and 3 = discontinued medication because of the side effects.

Statistical Analyses

Given the broad age range of the recruited participants and protracted maturation of certain cognitive measures, particularly executive functions (Anderson, 2002; Best and Miller, 2010), relationship with age was explored using Spearman correlations. As significant correlations were found for several but not all cognitive measures, differently without and with MPH medication (see supplementary Table 3), the effect of age was regressed out from the variable of interest before group comparison with a homemade script in MATLAB R2018b (Mathworks, USA). Assumptions for normality and homoscedasticity were checked. Accordingly, paired sample Student's *t* test or Wilcoxon signed rank test (when normality assumption was not satisfied) was performed. Results were corrected for multiple comparison using the Benjamini-Hochberg method (B-H; Thissen et al., 2002).

Results

Clinical Symptomatology

At baseline, without MPH treatment, the sum of inattentive symptoms intensity (M = 21.95, SD = 3.44) was significantly higher than the sum of hyperactivity/impulsivity symptoms intensity [M = 14.3, SD = 5.48; $t(19) = 8.99$, $P < .001$, $d = 2.01$].

As summarized in Table 1, the sum of ADHD symptom intensity without treatment was significantly higher than with treatment, after B-H correction (adjusted $P = .013$). Reduction of symptom severity was observed both for the sum of inattentive symptoms and the sum of hyperactivity/impulsivity symptoms.

Comparing changes on single symptoms (supplementary Table 4), almost all inattentive symptoms decreased in intensity with MPH treatment, except for the "avoids mental effort" symptom, where the decrease did not survive B-H correction, and the "loses things" symptom, where change with MPH treatment was not significant. For hyperactivity/impulsivity symptoms, again several symptoms decreased significantly in intensity with MPH treatment. However, only the "interrupts or intrudes" symptom survived the B-H correction (adjusted $P = .010$).

Cognitive Measures

***Attention*—**Without medication, mean group performance was in the clinical range (T-score ≥ 60) for measures of inattentiveness and impulsivity on the CPT task (see Figure 2). More specifically, elevated mean T-scores were observed for detectability ($M = 60$; $SD = 7.24$), perseverations ($M = 68.32$; $SD = 13.73$), hit reaction time (HRT) SD ($M = 66.86$; $SD = 15.10$), and variability ($M = 64.85$; $SD = 11.39$).

As summarized in Table 1 and displayed in detail in supplementary Table 5, after B-H correction (adjusted $P = .007$), a majority of measures of inattentiveness, impulsivity, and vigilance significantly improved with medication. Commissions errors and HRT block change also showed significant improvement ($P = .025$ and $P = .033$, respectively) but did not survive the B-H correction.

Looking closer at measures of sustained attention, a supplementary analysis block by block showed evidence for improvement of sustained attention with MPH (see supplementary Table 6). Indeed, after B-H correction (adjusted $P = .009$), there was a significant decrease in HRT with MPH at the end of the task for block 4 to 6. HRT SD was significantly lower with medication in blocks 2, 5, and 6. Omission errors were significantly lower with MPH medication at block 1, 4, and 6, indicating a lot a fluctuation. Finally, changes in commission errors across block did not survive B-H correction.

***EFs*—**As summarized in Table 1, significant improvement of performance with MPH was only visible on measures of inhibition and processing speed (see details in supplementary Table 5). However, only stop-signal reaction time and coding survived the B-H correction for multiple comparisons ($P < .007$). No other comparison of cognitive flexibility, updating, verbal and non-verbal initiation, or planning reached statistical significance.

***Learning and Long-Term Memory*—**No significant improvement with MPH was found for acquisition or retention of information over time in verbal or non-verbal modalities (see Table 1; supplementary Table 5).

Daily-Life Observations

As resumed in Table 1 (for details, see supplementary Table 7), without medication, caregivers reported clinically significant executive dysfunctions in daily-life using the BRIEF questionnaire (mean T-scores for Global Executive Composite, BRI, and MI ≥ 65). More specifically, domains of inhibition, flexibility, emotional control, initiation, working memory, and planning were reported as problematic.

With medication, only the emotional control subscale showed significant improvement. However, this result did not survive the B-H correction (adjusted $P = .002$).

In a complementary qualitative analysis based on 5 participants who completed the BRIEF self-report, without medication, participants reported no problems in any of the daily-life EF examined (mean T-score < 65). Change with medication could not be assessed due to insufficient sample size.

Safety and Tolerance to Treatment

Changes in QTc values did not exceed the cut-off of 30 milliseconds on the electrocardiogram done on day 6 after beginning of treatment.

A large majority of naïve participants (15/16) reported at least 1 side effect during the study. However, treatment was never discontinued due to adverse side effects. Following the first MPH dose at day 1, 9 participants (56.25%) reported some side effect. After increasing the dosage at day 6, 13 participants (81.25%) reported some side effect. At the end of the treatment phase on day 13, 11 participants (68.75%) reported some side effect. As displayed in Table 2, gastro-intestinal and sleep disturbances were mostly represented. More specifically, a qualitative

Table 1. Summary of Changes Observed With MPH Medication (Compared With Without) in Core ADHD Symptoms, Cognitive, and Daily-Life Behavioral Measures

Type of measure		Improvement with treatment	Effect size
Core ADHD Symptoms	Total	Yes	Very large
	Inattentive symptoms	Yes	Very large
	Hyperactivity symptoms	Yes	Large
Cognitive domains	Attention	Yes	Medium to very large
	Inhibition	Yes	Medium
	Cognitive flexibility	No change	
	Updating	No change	
	Initiation	No change	
	Planning	No change	
	Processing speed	Yes	Medium
	Learning	No change	
	Memory	No change	
Daily-life behavior	BRIEF Global Executive Composite (GEC)	No change	
	BRIEF Behavioral Regulation Index (BRI)	No change	
	BRIEF Metacognitive Index (MI)	No change	

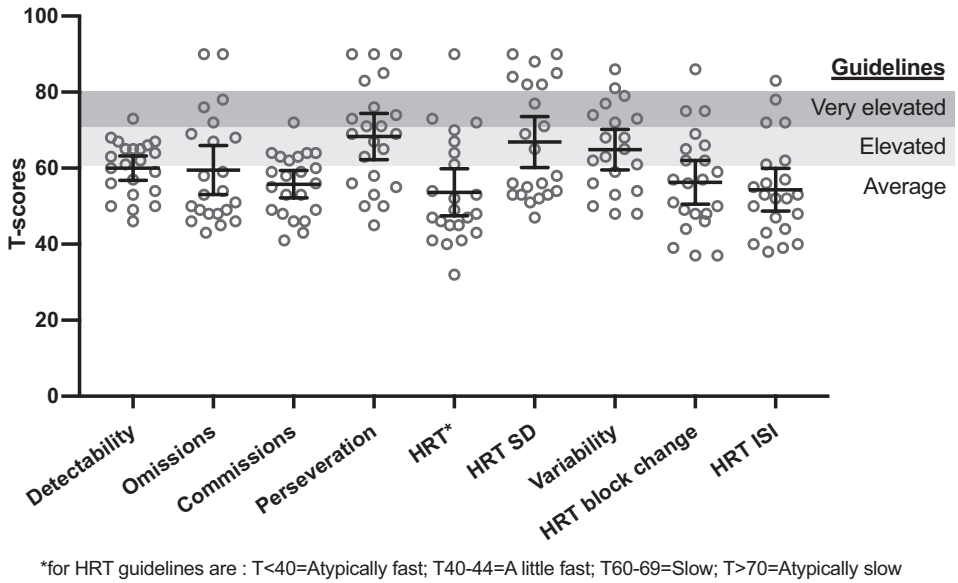

Figure 2. Standardized group performance (T-scores) on measures of attention from Conners' Continuous Performance Test 3rd edition. Scores in the grey area are considered to be within the clinical range (qualified as elevated or very elevated).

Table 2. Frequency and Intensity of Side Effects at Day 1, 6, and 13 of Methylphenidate Treatment

	Mild, n (%)			Significant, n (%)			Total, n (%)		
Side effect category	Day 1	Day 6	Day 13	Day 1	Day 6	Day 13	Day 1	Day 6	Day 13
Gastro-intestinal	5 (55.56)	11 (84.62)	6 (54.55)	0	0	0	5 (55.56)	11 (84.62)	6 (54.55)
Sleep disturbances	3 (3.33)	5 (38.46)	7 (63.64)	2 (22.22)	2 (15.38)	2 (18.18)	5 (55.56)	7 (53.85)	9 (81.82)
Neurologic	0	0	2 (18.18)	0	0	0	0	0	2 (18.18)
Cardio-vascular	0	1 (7.69)	0	0	0	0	0	1 (7.69)	0
Mood	0	0	1 (9.09)	0	0	1 (9.09)	0	0	2 (18.18)
Other psychiatric	0	0	1 (9.09)	2 (22.22)	2 (15.38)	0	2 (22.22)	2 (15.38)	1 (9.09)
Other	0	0	0	1 (11.11)	0	0	1 (11.11)	0	0

analysis showed that decreased appetite and difficulties falling asleep were the most common side effects reported.

Gastro-intestinal side effects tended to be more frequent after dosage increase (84.62%) but slightly less frequent at the end of the treatment phase (54.55%). On the contrary, frequency of sleep disturbances tended to increase from the beginning of treatment (first dose = 44.44%; dosage increase = 53.85%) and were most frequent at the end of the treatment phase (81.81%).

Regarding intensity, the majority of reported side effects were mild, and significant sleep disturbances were reported across all stages of treatment.

Discussion

The general aim of this study was to bring additional knowledge on the effectiveness of a stimulant medication (methylphenidate) in patients with 22q11DS. To fully grasp the observed changes, the outcome was measured at different levels (core ADHD symptoms, cognitive measures, and daily-life behavior). Finally, tolerance to treatment was investigated in a sub-group of patients naïve to the molecule.

Firstly, the results showed a significant diminution of core ADHD symptoms (reported by the parents) with medication. These results replicate findings from idiopathic ADHD and extend specific findings from the 22q11DS population (Gothelf et al., 2003; Green et al., 2011; Cortese et al., 2018). Improvement was shown for both symptoms of inattentiveness and hyperactivity/impulsivity, although the latter were on average significantly less severe in our sample. This observation is coherent with the predominant inattentive type consistently found in 22q11DS (Niarchou et al., 2015). On the symptom level, not surprisingly, symptoms with the highest ratings without MPH, such as "careless mistakes" or "sustaining attention," were the ones that improved the most with medication, while less frequent symptoms or symptoms staying in the subclinical range, such as "fidgets or squirms," "difficulty for quiet activities," or "talks excessively," showed no significant change.

Secondly, regarding cognitive measures, a wide range of domains was assessed. However, in this sample, a selectivity in the effects of MPH was observed, with only measures of attention and inhibition robustly improving with medication. Some measures of processing speed also significantly improved but could also be tainted by a learning effect on that specific task (coding) and would need to be confirmed with other measures. Regarding attention, we replicated previous findings of a significant decrease of measures of inattentiveness with MPH (Gothelf et al., 2003). By including more indicators in our analyses, we extend findings to measures of sustained attention, which also improved with medication. Overall, with MPH, participants were able to stay more attentive to the task and for longer delays with less fluctuation of attention. For EF, improvement of

prefrontal cognitive functioning with MPH has previously been demonstrated in 22q11DS; however, selectivity of different subdomains improving was difficult to disentangle (Green et al., 2011). Nonetheless, the authors showed that performance on the cognitive task only taxing working memory was not affected by MPH, while tasks taxing both working memory and inhibition improved significantly with medication, which hints to a certain selectivity. Our findings confirm that mostly inhibition and not all EF are improved with medication in 22q11DS. This is in contrast with findings from idiopathic ADHD, where performance on multiple EF domains are reported to be ameliorated with MPH (Nigg, 2005; Coghill et al., 2014). One explanation could come from the higher dosage of MPH used (individual dose from 18 to 90 mg in Coghill et al., 2014) or even the use of titration to find the optimal clinical response before evaluating effects on cognition (e.g., Yang et al., 2012). Another important point to consider is that EF deficit is part of the 22q11DS neuropsychological profile independently of low intellectual functioning and ADHD comorbidity (Shapiro et al., 2014; Maeder et al., 2016; Moberg et al., 2018). This suggests that poor performance on EF in 22q11DS is not necessarily related to ADHD symptomatology and therefore might not respond as well to ADHD medication.

In the same way for long-term memory, no previous study, to our knowledge, has investigated the effect of MPH in 22q11DS, although in idiopathic ADHD, results from a review and meta-analysis showed that effects of MPH were significantly superior to a placebo (Coghill et al., 2014). Nonetheless, deficits in non-verbal learning and both verbal and non-verbal memory retention over time have been demonstrated independently of ADHD comorbidity in 22q11DS (Lajiness-O'Neill et al., 2005; Lepach and Petermann, 2011; Maeder et al., 2020). This suggests that mechanisms leading to inefficient learning and memory retention are different from those observed in the context of idiopathic ADHD and might not be as sensitive to MPH medication. To summarize, the results of the present study show a selective improvement of inhibition while other cognitive domains stayed relatively unchanged with medication.

Thirdly, daily-life behavior was assessed by the parents with a specific focus on executive dysfunction with the BRIEF questionnaire, providing an ecological assessment tool. Although participants displayed executive dysfunction on several subscales, including inhibition, flexibility, emotional control, initiation, working memory, and planning, no significant change was reported with medication. This is in contrast to findings from idiopathic ADHD, where improvement of daily-life EF with stimulants (including slow-release MPH) has been shown using the BRIEF questionnaire (Turgay et al., 2010; Yang et al., 2012; Taş Torun et al., 2020). Again, higher dosage and dosage optimization should be considered in the interpretation of this comparison. Additionally, in this situation, as a majority of participants were naïve to MPH and were medicated for only a short period (13 days), lack of results could come from insufficient observations possibilities. Unfortunately, our sample of consumer participant (n = 7) was too small to run any comparison. Future studies should consider longer treatment periods when this type of questionnaire is used or used with more chronic MPH users.

Results from the qualitative additional analysis on self-reported executive dysfunction in daily life revealed that while caregivers reported important impairments in several domains, young adults did not identify any difficulties. While coming from a limited sample, this observation suggests that young adults with 22q11DS experience difficulties in assessing their own strength and weaknesses. This observation is in line with previous results comparing patients' and parents' answers on the BRIEF questionnaire (Taylor et al., 2018). The authors found evidence that young adults with 22q11DS do not perceive themselves as experiencing difficulties in every-day life. Additional research is needed to confirm our preliminary findings and explore if difficulty to assess one's own behaviors is restricted to executive dysfunction (possibly coming from a type of anosognosia) or if it is a more general phenomenon for all types of self-assessment (related to the low intellectual functioning that characterizes this population).

Finally, safety and tolerance to MPH medication were assessed in the naïve group, replicating previous findings in 22q11DS (Gothelf et al., 2003; Green et al., 2011). Although a different form was used with respect to prior studies (0.7 mg/kg long acting instead of 0.3 mg/kg or 0.5 mg/kg short acting), treatment was well tolerated with no change in cardiac measures and no adverse effect resulting in interruption of treatment. Similarly, in both previous studies, side effects were present in a majority of participants but were mostly of mild intensity. The most common side effects reported were from the gastrointestinal category and sleep disturbances, matching general observations from idiopathic ADHD (Banaschewski et al., 2006). Interestingly, in this study, higher rates of sleep disturbances were reported. Indeed, while sleep disturbances are a common side effect of MPH, no side effects related to trouble sleeping were found in the study from Gothelf et al. (2003). The absence of insomnia was explained by the fact that the medication was given once in the morning at a very low dosage. As for Green's study (2011), trouble sleeping was present in almost one-half of the participants and tended to be persistent after the 6-month follow-up. However, the dosage was still quite low and could explain some difference with the findings from our study. It is worth mentioning also that sleep disturbances in 22q11DS are very frequent (60%) and related not only to the presence of ADHD (Moulding et al., 2020).

Limitations

Findings from this study are limited by the sample size (n = 23). Indeed, as a rare genetic condition, prevalence of 22q11DS is approximately 1:4000 live births (Botto et al., 2003). Furthermore, the high comorbidity of psychiatric conditions reported in this syndrome, particularly psychosis spectrum disorder, creates difficulties in finding suitable participants for a clinical trial with stimulants (Rees et al., 2014; Schneider et al., 2014). Interestingly, naïve participants were much easier to find compared with participants who already had a prescription of MPH, although a comparison between our sample (n = 25) and participants from the Geneva cohort who met inclusion criteria but declined participation (n = 26) showed similar rates of treated vs not treated participants (approximately one-third in each group). These rates are comparable with another study reporting 31% of 22q11DS individuals with ADHD receiving pharmacological treatment (Tang et al., 2014) and might explain the imbalance of the groups. However, in the group who declined participation, 14 individuals (53.85%) met the criteria for ADHD and 7 of those (50%) were taking an MPH treatment. In sum, in the complete sample of eligible participants (n = 51), approxiately one-half of the treated participants declined taking part in the study. One possible explanation is a recruitment bias caused by satisfaction with MPH treatment. Indeed, 22q11DS patients with treatment are possibly satisfied with their current care and do not seek additional help through clinics or clinical research projects, while participants from the naïve group did.

Related to the small sample, no formal ADHD diagnosis was required for inclusion in the study, only attention difficulties pointed out by parents and/or the participant. However, all participants presented with at least ADHD traits and confounding origins of attention difficulties (e.g., severe insomnia, psychosis spectrum disorder) were ruled out by a trained psychiatrist (S.E.) prior to inclusion in the study.

Another shortcoming from this design is the low dosage (0.7 mg/kg) and short treatment phase in the naïve group. Originally, a short period of time was chosen to maximize participation to the study. However, treatment duration was often insufficient for patients and caregivers to really appreciate change. It also prevented further increase and adaptation of the dosage for each participant, which could have led to different results. Related to the issue of treatment optimization, the fixed dosage depending on weight prevented a more individual approach, as response to treatment varies significantly between individuals (Huss et al., 2017). Future studies should consider introducing dosage titration to optimize response to treatment. Indeed, because of gastrointestinal problems affecting 30% of individuals with 22q11DS (McDonald-McGinn et al., 2015), blood dosage could be even more variable.

A final limitation from this study is the lack of information from school/work environment. Indeed, contrary to the majority of studies in idiopathic ADHD and the studies on 22q11DS, only parents were asked to assess change with medication. Because of fear of stigmatization, some parents chose not to share the specific diagnosis outside the family environment. Additionally, some young adults were between occupations during the study. For these reasons, third-party observations were not included.

Clinical Implications

Results from this study provide important information for clinicians and caregivers involved in management and care of individuals with 22q11DS. First of all, safety and tolerance to treatment were replicated in an independent sample, providing additional evidence for using MPH in this genetic condition. Secondly, MPH was found to significantly reduce core ADHD symptoms reported by the parents as well as improve attention and inhibition measures. Finally, results from the self-report questionnaire highlighted difficulties for young adults with 22q11DS to identify their limits. This suggests that multiple informants are required to get a representative overview of an individual's functioning.

Conclusions

In sum, this study shows effectiveness of a short treatment of MPH in 22q11DS patients. Benefit from the treatment was demonstrated by diminished core ADHD symptoms, specifically inattention symptoms, and improvement of cognitive measures. Results showed a selectivity of improvement on cognitive measures, with attention and inhibition being robustly ameliorated by MPH while other measures of EF, learning, and memory remained relatively unchanged. Conversely, no significant improvement on ecological measures of daily-life EF was found, possibly because of the short treatment period.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

Acknowledgments

The authors are grateful to all the families for their participation and their commitment to the study. We thank Léa Chambaz, Virginie Pouillard, and Eva Micol for their help in recruitment and study organization. We thank our colleagues who participated in data collection and processing: Laura Abdili, Lucia-Manuela Cantonas, Charlène Bernard, Giulia Binarelli, Farnaz Delavari, Marina Goncalves, Marc Jeanneret, Léa Moreau, Justine Quiblier, and Vincent Rochas. Finally, we thank Clémence Feller for her help in proof-reading the manuscript and Karin Bortolin for her guidance in data analysis.

This study was supported by grants from the Swiss National Science Foundation (SNSF) to Prof. Stephan Eliez (#324730_144260 and #320030_179404) and The National Center of Competence in Research (NCCR) "Synapsy - The Synaptic Bases of Mental Diseases" (#51NF40-158776 and #51NF40-185897). Maude Schneider is supported by a personal grant from the SNSF (grant number: PZ00P1_174206).

Interest Statement

The authors declare that they have no conflict of interest.

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