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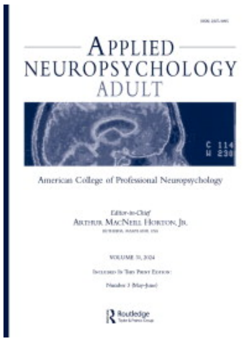

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Effectiveness of social management training on executive functions in males with Klinefelter syndrome (47, XXY)

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ABSTRACT

Men with an extra X chromosome are at risk for social difficulties in which executive functions are known to play an important role. The aim of this study was to examine the potential efficacy of a novel neurocognitive-behavioral treatment program tailored to the specific vulnerabilities of Klinefelter syndrome (47, XXY). Social Management Training (SMT) aimed to increase the ability of individuals to regulate their thoughts, emotions and behaviors in ways that are socially adaptive. 16 Adolescents and men with Klinefelter Syndrome participated in SMT. This novel group treatment program consists of 10 sessions and includes psychoeducation, cognitive-behavioral skills training, home-assignments, and relaxation exercises. There were pre- and posttest cognitive assessments (five months apart) of executive functioning including sustained attention, inhibition, cognitive flexibility and working memory, as well as self-evaluation of executive functioning in daily life. Significant pre- to posttest improvements in inhibitory control (performance test) and metacognition skills (self-report) were found, with effects sizes of 1.3 and 0.5, respectively. No effects of intervention were found on sustained attention, cognitive flexibility and working memory. These findings suggest that SMT, with a key focus on executive dysfunction and tailored to the behavioral and cognitive profile of males with Klinefelter syndrome, may be a promising and potentially efficacious treatment approach for improving self-control and social adaptation, although larger and randomized controlled studies are warranted.

KEYWORDS

Executive functioning; executive skills; inhibition; psychosocial treatment; sex chromosomal aneuploidy; social functioning; social adaptive behavior

Introduction

Klinefelter syndrome (KS or 47, XXY) is caused by the presence of a supernumerary X chromosome. With a prevalence of approximately 1 in 600 males it is the most common sex chromosomal aneuploidy (Boada et al., 2009; Groth et al., 2013 Visootsak & Graham, 2006). Men with Klinefelter syndrome are known to have physical and cognitive characteristics such as hypogonadism, fertility problems, tall stature, gynecomastia, language-based learning problems, cognitive impairments, and an increased risk of emotional and behavioral problems (Geschwind & Dykens, 2004; Groth et al., 2013).

In the domain of cognitive functioning, recent studies show increasing evidence for impairments in executive functioning, which may play an important role in emotional and behavioral problems and struggles in everyday life associated with Klinefelter syndrome (Boada et al., 2009; Lee et al., 2011, 2015; Van Rijn & Swaab, 2015, 2020). Executive functioning is an umbrella term for management of cognitive processes, information processing speed, selective and sustained attention, response inhibition, working memory, cognitive flexibility, attentional shift, conceptualization, initiating, planning and goal setting (Diamond, 2013; Lezak, 2012; Spreen et al., 1995; Stuss & Benson, 1986). These cognitive abilities are relied upon in complex situations, such as social interactions (Beauchamp & Anderson, 2010; Tuerk et al., 2021). In social interaction it is crucial to be able to perceive social information and subsequently hold this information in memory (working memory), to be able to adequately and rapidly react to changing situations (cognitive flexibility) and to be able to focus and sustain attention during social interaction (sustained attention). Furthermore, the ability to inhibit responses is important in everyday and social functioning. It enables a person to reflect on irrelevant thoughts and actions and to postpone impulsive behavior. Thus, executive functions enable us to regulate our thought, emotion and behavior and subsequently adapt to our social environment.

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Evidence for compromised executive functioning in Klinefelter syndrome comes from studies showing behavioral symptoms such as attentional problems, hyperactivity and impulsivity (Green et al., 2022; Janusz et al., 2020; Kuiper et al., 2021; Tartaglia et al., 2012). A range of studies have shown that boys and men with Klinefelter syndrome experience difficulties in executive functioning such as deficits in working memory, inhibition, cognitive flexibility and attention (Bender, 1993, 2001; Boone, 2001; Fales, 2003; Janusz et al., 2020; Kompus et al., 2011; Lee et al., 2011, 2015; Ross, 2009; Urbanus et al., 2020; Van Rijn et al., 2009, 2012; van Rijn & Swaab, 2015).

Because executive functions are crucial for social functioning (Diamond, 2013), difficulties in EF may lead to social adaptive problems, which are often found in boys and men with Klinefelter syndrome. If present, the vulnerability in terms of social competence of boys and men with Klinefelter syndrome is expressed in reduced participation in social interaction and increased tension and stress in social situations (Cordeiro et al., 2012; van Rijn et al., 2006, 2008, 2014; Visootsak & Graham, 2009). Although the behavioral phenotype associated with Klinefelter syndrome is highly variable, boys and men with Klinefelter syndrome are at increased risk of developing psychopathology such as depression, social anxiety disorder, autism spectrum disorder and attention-deficit disorder (Boada et al., 2009; Boone et al., 2001; Bruining et al., 2009; Cederlöf et al., 2014; Leggett et al., 2010; Ross et al., 2012; Tartaglia et al., 2010; Van Rijn et al., 2009). The impact of these vulnerabilities on daily life functioning and social functioning calls for intervention targeted at improving the underlying mechanisms that contribute to social adaptive behaviors.

To meet this need, Social Management Training (SMT), a neurocognitive-behavioral self-management group treatment aimed at improving psychosocial problems and increasing social adaptive behavior in individuals with Klinefelter syndrome, was developed. To our knowledge this is the first treatment program for males with Klinefelter syndrome. SMT has been shown to reduce internalizing and externalizing behavior problems and to increase awareness of autism-like behaviors in men with Klinefelter syndrome (Martin et al., 2021).

Self-management, also referred as self-control or self-regulation, is defined as the ability to regulate one's emotions, thoughts, and behaviors adaptively in different situations. Self-regulation enable us to maintain optimal levels of emotional, motivational, and cognitive arousal and overlaps substantially with inhibitory control (Barkley, 2001).

Efficacious self-management of social adaptive behavior thus relies on executive functions and encompasses the ability to monitor one's condition and to change cognitive, behavioral, and emotional responses necessary to maintain a satisfactory quality of life. The goal of SMT for males with Klinefelter syndrome is to increase self-management of social adaptive behavior, by enhancing self-consciousness/awareness (insight), coping skills, self-confidence, and emotion regulation skills by focusing on EF as the neurocognitive building blocks of self-regulation and adaptive behavior (Figure 1).

SMT is a group training that includes a range of personalized goals that can be divided into four components: (1) pretreatment individual neuropsychological assessment of known cognitive vulnerabilities in Klinefelter syndrome to develop personalized goals and individual neurocognitive "ID-cards," (2) psycho education based both on the profile of strengths and weaknesses that is often seen in Klinefelter syndrome, and the personalized ID to enhance awareness of the social competence profile, (3) skills and strategy training, including role play and relaxation exercises in order to decrease social distress and to strengthen coping and emotion regulation skills, and (4) weekly exercises in a personalized workbook to increase transfer of social management skills to situations in daily life.

In a previous study we have reported on behavioral changes that resulted from this intervention (Martin et al., 2021). The participants and their significant others reported decreased scores on negative behaviors and improved scores on positive behaviors. Self-report showed a significant decrease in anxiety and depression and a trend for reduced social distress. Participants reported awareness of autism like behavior. They became more aware of their social challenges following intervention, which can be a first step in coping with limitation of social adaptive skills and starting to use learned regulation strategies. Informant reports showed a significant decrease in attention problems, rule breaking behavior and internalizing problems.

The aim of the present study was to assess if SMT following changes on behavior (Martin et al., 2021) also influences cognitive skills, focusing in particular on executive functions as the neurocognitive building blocks of self-regulation and adaptive behavior. Effectiveness of the training was assessed in terms of changes in executive functions on a cognitive level in four domains: (1) sustained attention, (2) inhibition, (3) cognitive flexibility, and (4) working memory. In addition to these cognitive performance tests, self-reported daily life executive skills and metacognition in daily life were also evaluated. The research questions addressed in this study were: does SMT improve EF in daily life skills and does it improve EF in cognitive performance tests? Is there a specific effect on aspects of EF focusing on sustained attention, inhibition, cognitive flexibility and working memory?

Methods

Participants

The study population was equal to a previous publication in which we reported on a broad range of behavioral measures (Martin et al., 2021). Participants were individuals with Klinefelter syndrome referred to an academic outpatient department, seeking psychosocial support for problems in everyday or professional life. Sixteen males with Klinefelter syndrome agreed to participate in the SMT study. Upon registration at the outpatient clinic the referred clients reported clinical levels of the following problems on the Achenbach System of Empirically Based Assessment

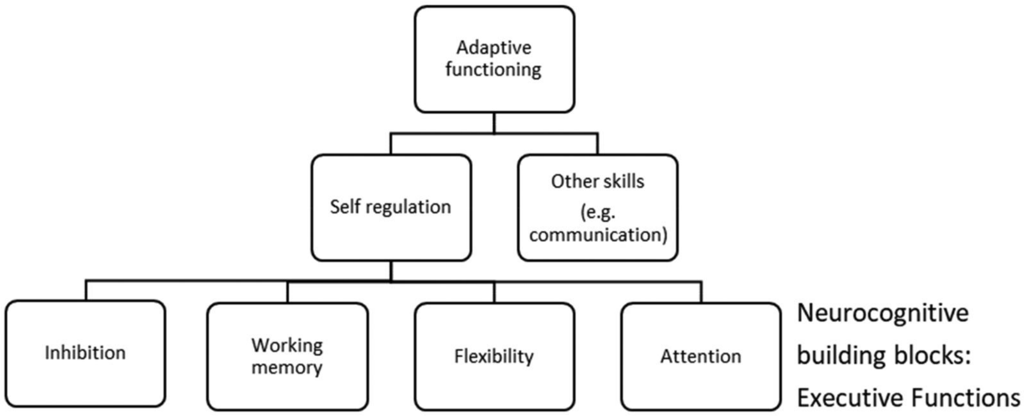

Figure 1. Neurocognitive building blocks. (*Based on Executive Functions (Diamond, 2013)*.).

Table 1. Percentage of participants in the clinical range on the ASEBA questionnaires ($N = 16$) at baseline of the study.

	ASEBA	
	Self-report (ASR)	Informant report (ABCL)
Total problems	20.1%	8.3%
Internalizing problems	46.2%	41.7%
Anxious/depressed	30.8%	25.0%
Withdrawn behavior	38.5%	33.0%
Somatic complaints	38.5%	25.0%
Externalizing problems	7.7%	8.3%
Intrusive behavior	0.0%	8.3%
Aggressive behavior	20.1%	8.3%
Rule-breaking behavior	0.0%	0.0%
Other problems		
Thought problems	15.4%	8.3%
Attention problems	46.2%	50.0%

(ASEBA) questionnaires (Achenbach & Rescorla, 2003): anxiety and feelings of depression, withdrawal, somatic complaints, thought problems, attention problems and aggressive behavior. For an overview of the clinical profile of the group, see Table 1 in which the percentage of participants with ASEBA scores in the clinical range according to self-report as well as informant report are presented.

The participants all were motivated to participate in the group treatment program. Participants were aged 16 to 56 years old (mean age 37.5 years SD 11.7) and had intellectual abilities (IQ) ranging from 77 to 123 (mean IQ 96.7, SD 15.8). According to according to the Dutch Qualifications Framework (NLQF) 44 percent of the participants achieved level 2, 44 percent achieved level 3 and 12 percent achieved level 4. All but two men with XXY were using testosterone supplements which is the standard treatment for somatic problems associated with Klinefelter syndrome. Only two participants used other psychopharmacological medication (antidepressant and SSRI). Exclusion criteria were severe psychopathology preventing adaptability and participating in a group, and/or intellectual disability (IQ < 70). Treatment as usual e.g. individual cognitive behavioral therapy for anxiety or depressive symptoms was offered to patients who could not or did not want to participate. Approval for the study was obtained from the University Medical Center medical ethics committee and all patients gave written informed consent at the beginning of the study according to the Declaration of Helsinki.

Therapeutic setting

SMT was offered every other week over a period of five months, with each session lasting 90 minutes. The groups contained four to eight participants and were led by two experienced therapists. Each session followed a regular structure, starting with a summary and evaluation of the previous session, an introduction of the new topic, psychoeducation, cognitive-behavioral exercises, and finally instructions for the take-home assignment. Sessions ended with a relaxation exercise helpful to use in daily life to reduce stress and anxiety. Specific adjustments were made to meet language difficulties that men with Klinefelter syndrome may experience (Boada et al., 2009; Leggett et al., 2010). These adjustments consisted of: reducing psychological jargon, simplifying explanations and information, elaborately explaining and discussing the take-home assignments, ending each session with a summary, and starting each session with a summary of the previous session. During each session, verbal information and explanation included schematic visual support by means of a PowerPoint presentation. Written material and take-home exercises were distributed to the participants before and after each session and were compiled into a participant's workbook.

Attendance in the SMT was good. Of the sixteen participants, twelve attended all ten sessions and four participants missed one session each. One participant dropped out of the group treatment program after the first session because he preferred individual treatment.

Treatment protocol

The aim of the intervention was to train executive functions relevant for social functioning, through psychoeducation, practicing skills and feedback. Table 2 shows the session topics based on the executive functions relevant for self-management and social functioning according to the SOCIAL model of Beauchamp and Anderson (2010). This biopsychosocial SOcio-Cognitive Integration of Abilities modeL defines the core dimensions of social competence on a biological, psychological and social level. In this model social competence is dependent of the development of the

Table 2. Overview: Contents of the Social Management Training

Session number	Topics
1	Introduction and learning targets
2	Information process in a social context
3	Attention and emotions in a social context
4	Inhibition and emotions in a social context
5	Flexibility and planning in a social context
6	Working memory in a social context
7	Parent/partner session
8	Individual learning targets
9	Individual learning targets
10	Summary and integration

brain, cognitive functions and behavior in interaction with the environment. This model incorporates the biological underpinnings and socio-cognitive skills that underlie social function (attention/executive function, communication, socio-emotional skills), as well as the internal and external (environmental) factors that mediate these skills.

Based on these executive functions and on the profile of neuropsychological strengths and weaknesses in men with Klinefelter syndrome, the following session topics were selected: information processing, attention in a social environment, inhibition and emotion in a social environment, flexibility and planning in a social environment and working memory in a social environment.

To meet the variation in difficulties men with Klinefelter encounter neuropsychological assessment resulting in an individual neuropsychological profile was performed before the start of the intervention and evaluated by a clinical neuropsychologist. The individual neuropsychological profiles helped to formulate individual goals, home assignment and feedback. In addition, there was a parents or partner session, and two sessions in which all the previous information was integrated to fit the targets and individuals needs of the participants.

Study design

The participants in this study agreed to participate in a pretest cognition assessment, the training program and posttest cognition assessment. Computerized cognitive tests were used. Part of the computerized test assessment according to the standard administration prescribed by the test manual are extensive instruction and practice conditions to ensure optimal performance and to prevent learning effects from pretest to posttest. Pretest measurement occurred within a three-week period after referral to the academic outpatient department. After the intake session and the neuropsychological assessment, the participants were waitlisted for a period ranging from three weeks to three months before starting SMT. Posttest assessment was conducted within three weeks following the last SMT session.

Intellectual functioning

Intellectual capacities were assessed using the subtests Vocabulary and Block Design (V-BD short form) from the Wechsler Adult Intelligence Scale or the Wechsler Intelligence Scale for Children. Short forms of the WAIS and WISC are often used in research to estimate full scale intelligence (FSIQ) when assessment or testing time is limited. The V-BD short form correlates highly with FSIQ ($r = .88$) and the V-BD short form has been found valid for the estimation of intelligence (Denney et. al., 2015; Thompson et. al., 2004). The V-BD short form is calculated according to the algorithm (2.9 (sum of normed scores) +42).

Instruments

Executive functioning

The Amsterdam Neuropsychological Tasks (ANT) (De Sonneville, 1999) was used to evaluate different components of executive functioning (EF). The ANT has been proven to be a well validated and sensitive instrument to evaluate attentional processes and EF (Slaats-Willemse et al., 2007; Van Rijn et al., 2014). Test-retest reliability, construct-, criterion-, and discriminant validity of the ANT are satisfactory and have extensively been described and illustrated in several studies (De Sonneville, 2014; Huijbregts et al., 2002). In the subtests of the ANT, stimuli are presented on a computer screen and participants respond by pressing the mouse buttons with index fingers. To verify that participants understand the instructions and are able to meet task demands, each subtest is preceded by illustration trials and practice trials. The ANT automatically generates norm scores based on nonlinear regression functions capturing the norm data in the age range of 4–66 years, with the total sample size varying between 2500 and 6000 subjects, depending on type of task, with higher (positive) Z-scores representing more impaired performance. Different subtests of the ANT test battery were used to evaluate four components of executive functioning, including sustained attention, inhibition, cognitive flexibility and working memory.

ANT sustained attention

Sustained attention was assessed using the SA-Dots task (SAD), which measures the ability to maintain performance during a longer period of time. During a period of approximately 15 to 20 minutes, subjects are required to respond to targets (4-dots pattern) by pressing the "yes"-button on a computer mouse or non-targets (3 or 5-dots pattern) by pressing the "no"-button. 600 random patterns of 3, 4 or 5 dots are presented in 50 series of 12 trials. Outcome measures are standard deviation of reaction time (fluctuation of tempo reflecting attention regulation) and number of misses (inattention).

ANT Inhibition and cognitive flexibility

Inhibition and cognitive flexibility were assessed using the Shifting Attentional Set Visual task (SSV). During this task colored squares move randomly form right to left on a horizontal bar presented on a computer screen. The task consists of three parts. In part 1 the subject is asked to follow the movement of a green square by pressing the left button upon a left move of the square and the right button upon a right movement of the square (40 trials, green squares, fixed compatible condition).

In part 2 the subject is asked to perform an opposite reaction to the movement of a red square (40 trials, red squares, fixed incompatible condition). By pressing the left button upon a right move of the square and pressing the right button upon a left move inhibition of a prepotent response is required.

In part 3 the square changes color in a random way, asking the subject to follow the movement or to perform the opposite reaction depending on the color of the block (80 trials, green or red squares). In this part the subject needs to switch between response sets, to switch between execution of a prepotent response (variable compatible condition) and inhibition of a prepotent response (variable incompatible condition), which requires cognitive flexibility.

Inhibition is operationalized as the increase in errors/reaction times from part 1 (fixed compatible condition) to part 2 (fixed incompatible condition). Cognitive flexibility is operationalized as the increase in errors/reaction times from part 1 (fixed compatible condition) to part 3 (variable compatible condition). Both measures are relative measures in which baseline speed of responding and baseline accuracy are corrected for.

ANT working memory

Working memory was assessed using the Memory Search Letters task (MSL). In part 1 of this task the subject is asked to press the "yes"-button when a target letter (k) is detected on a display set of four letters. Memory load is increased to two letters in part 2 (k + r) and to three letters in part 3 (k + r + s). Incomplete target sets require a "no" response. Working memory search rate is operationalized as the contrast in accuracy of responses to target signals in part 1 (low load) and part three (high load).

Daily life executive skills (self-report)

The Dutch version of the Behavior Rating Inventory of Executive Function for Adults (BRIEF-A) (Scholte & Noens, 2014) was used to evaluate an adult's executive functioning or self-regulation in everyday environment by self-report. Based on the original BRIEF, the BRIEF-A is composed of 75 items within nine nonoverlapping theoretically and empirically derived clinical scales: Inhibit, Self-Monitor, Plan/Organize, Shift, Initiate, Task Monitor, Emotional Control, Working Memory, and Organization of Materials. Two broad indexes (Behavioral Regulation and Metacognition), an overall summary score, and three validity scales (Negativity, Inconsistency, and Infrequency) are included.

The BRIEF-A has demonstrated evidence of reliability, validity, and clinical utility as an ecologically sensitive measure of executive functioning in individuals with a range of conditions across a wide age range (Scholte & Noens, 2014). All validity scores were individually reviewed by a clinical neuropsychologist. If scores on the three validity scales were significantly elevated, data were excluded from the study. The two indexes Behavioral Regulation and Metacognition were used as measures of self-control. In case of an effect on one of the two main indexes, subscale interpretation was performed.

Missing data

Some participants were not able to participate in the posttest, for example due to inability to take leave from work or extensive travel distance. Some of the participants did not complete all ANT tests, due to various reasons such as premature ending of the test session due to fatigue or technical problems during testing or in converting the results. Four participants did not return the questionnaires.

Statistical analyses

Data were analyzed using SPSS (Statistical Package for the Social Sciences) version 23. For each outcome domain, multivariate repeated measure analyses were used to assess within subject differences between baseline (pretest T1) as compared to follow-up (post-test T2).

An effect size of .8 was able to be detected on this sample size of 16 participants according to statistical power calculation.

From the ANT computerized program we used optimized performance test data after extensive practice as part of the standardized administration prescribed by the test manual to prevent learning effects from pretest to posttest. The data on practice were not available for statistical analysis.

The subdomains were entered in the repeated measures analyses as within subjects variables, there were no between subjects factors. Univariate effects of specific subdomains were considered only when there were significant multivariate effects of intervention. Level of significance was set at $p = .05$.

T-tests were used to check if the subgroup of participants who did not participate in the post-test had significantly different EF scores at pretest than the subgroup of participants who did enter the pretest as well as the post-test.

Results

Sustained attention

On the SA-dots task for the assessment of sustained attention, repeated measures analysis revealed no significant main multivariate effect of intervention (pre, post), $F(2,13) = 0.19$, $p = .831$. In other words, there was no change in sustained attention as seen in standard deviation of reaction time (fluctuation of tempo) or number of misses between pretest and posttest.

Inhibition

On the SSV-task for the assessment of inhibition, repeated measures analysis revealed a significant multivariate effect of intervention (pre, post) $F(2,10) = 4{,}6$, $p = .037$. This was driven by a significant univariate effect seen as a decrease in

Table 3. Outcome measures (Raw scores) from pretest to posttest.

Outcome measure	Pretest M (SD)	Posttest M (SD)	Statistics	Cohen's d
ANT Sustained Attention (SAD)	*N* = 16	*N* = 13		
Fluctuation of tempo	0.8 (± 1.3)	0.9 (± 1.6)	*p* = .74	
Number of misses	17.0 (± 13.7)	15.5 (± 13.9)	*p* = .53	
ANT Inhibition (SSV)	*N* = 16	*N* = 15		
Reaction time	209.7 (± 130.5)	213.0 (± 163.5)	*p* = .91	
Errors	3.8 (± 4.4)	−.8 (± 1.8)	*p* = .009*	*d* = 1.3**
ANT Cognitive flexibility (SSV)	*N* = 16	*N* = 15		
Reaction time	474.0 (± 223.1)	494.4 (± 145.1)	*p* = .59	
Errors	3.9 (± 7.4)	1.0 (± 3.0)	*p* = .10	
ANT Working Memory (MSL)	*N* = 16	*N* = 14		
Errors	0.3 (± 1.3)	0.2 (± 1.0)	*p* = .79	
BRIEF-A	*N* = 16	*N* = 12		
Behavior Regulation	61.2 (± 14.8)	59.7 (± 14.5)	*p* = .41	
Metacognition	81.7 (± 12.3)	76.3 (± 11.5)	*p* = .007*	*d* = 0.5*

*Significant effect.
Cohen's *d*: *Medium effect. **Large effect.
Note. ANT: Amsterdam Neuropsychological Tasks; BRIEF-A: Behavior Rating Inventory of Executive Function for Adults.

the number of errors between pretest and posttest $F(1,11) = 9.8$, $p = .009$. The effect size was large, with a Cohen's d of 1.31. There was no significant univariate effect on reaction time pretest to posttest $F(1,11) = 0.01$, $p = .91$). Scores are presented in Table 3.

Cognitive flexibility

On the SSV-task for the assessment of cognitive flexibility, repeated measures analysis revealed no main multivariate effect of intervention (pre, post), $F(2,11) = 1.7$, $p = .234$. There was no change in cognitive flexibility as seen in reaction time and accuracy (number of errors) between pretest and posttest.

Working memory

On the MSL-task for the assessment of working memory, repeated measures analysis revealed no main multivariate effect of intervention (pre, post), $F(2,12) = 0.34$, $p = .716$. There was no change in working memory as seen in reaction time and accuracy (number of errors) between pretest and posttest.

Daily life executive skills (self-report)

On the BRIEF-A self-report to evaluate executive functions and self-regulation, repeated measures analysis revealed a significant main multivariate effect of intervention (pre, post) $F(2,12) = 4.8$, $p = .029$. This effect was driven by a significant univariate effect on the subscales Metacognition between pretest and posttest $F(1,13) = 10.4$, $p = .007$. The effect size was medium, with a Cohen's d of 0.5. There was no significant univariate effect on the subscale Behavior Regulation between pretest and posttest $F(1,13) = 0.72$, $p = .412$.

Discussion

The aim of the present pilot study was to evaluate the effect of a novel treatment program for individuals with Klinefelter syndrome on executive functioning. This newly developed Social Management Training focuses on executive domains that are needed for adequate self-regulation and resulting social adaptation, which is often compromised in individuals with Klinefelter syndrome. Overall, our findings indicate specific improvements in cognitive tests of executive functioning and daily life executive skills following SMT. Although cognitive assessments of working memory, attention and cognitive flexibility showed no improvement following intervention, there was a significant improvement of 1.3 standard deviations in inhibitory performance, which refers to the ability to suppress and postpone thoughts or actions. In addition to this cognitive performance test, self-report measures on daily life executive dysfunction also indicated significant improvement in metacognition (with an effect size of 0.5), which refers to the ability of problem-solving and setting goals through planning, monitoring and organization. However no behavioral improvement in inhibition according to self-report was yet recognized or experienced. This may suggest improvement in inhibition is more sensitive registered though performance testing than through self-evaluation of everyday behavior. This emphasizes the importance of extensive neuropsychological assessment using different types of tests e.g. performance tests and self-report next to informant report questionnaires.

These results are promising and an important first step toward further developing and tailoring evidence-based psychosocial treatment programs for males with Klinefelter syndrome. Several studies on executive functioning deficits in boys and men with Klinefelter syndrome have found that executive function is compromised in many individuals with an extra X chromosome, impacting self-control in daily life and thereby influencing social adaption in relationships, and academic and professional settings (van Rijn & Swaab, 2020). This study suggests that we might be able to improve inhibitory control, a function that is crucial for regulation of thinking, emotion and behavior and related to risk for psychopathology (Kompus et al., 2011; van Rijn et al., 2013). The ability to inhibit responses is important because it enables a person to reflect on irrelevant thoughts and actions and to postpone impulsive behavior. In communication with other people, response inhibition is important for adequate turn taking in conversation and preventing oneself from inadequate, impulsive, or emotional responses. Improving inhibitory control might therefore lead to improved self-control. In this study, the men with Klinefelter syndrome experienced improvements in problem-solving skills and goal setting in daily life, in which the observed findings of inhibitory performance may play an important role. Being better able to prevent or override unwanted thoughts and emotions makes it easier to create and evaluate options, to tackle problems or assess difficult situations and select a suitable solution, all of which are crucial for social adaptation.

The results of this study fit with earlier observations that SMT results in improved self-control as evidenced by reduced problems in attention, aggression and offensive behavior reported by informants (Martin et al., 2021). These results indicate an improvement on both cognitive and behavioral aspects of inhibitory control in adolescents and adults with Klinefelter syndrome following SMT, which is promising considering the neurodevelopmental course of inhibitory control. Berkman et al. (2012) illustrate that inhibitory control develops gradually over time, beginning in early childhood and continuing to late adolescence and even into early adulthood. This extended developmental course for inhibitory control suggests an extended window of opportunity for intervention during periods of plasticity associated with ongoing development. Because inhibition is an important element of self-control and its relation to successful navigation in daily life and future success in life (Barkley, 2001; Bedard et al., 2002; Muraven et al., 1999), further development of such intervention programs for younger individuals with Klinefelter syndrome is warranted.

Being a pilot study, there were several limitations which need to be addressed. First, we did not find significant improvements in other domains of executive functioning, including sustained attention, working memory and mental flexibility, which are also important for adapting to social situations. This could indicate that inhibitory control may be more sensitive for improvement than other executive functions. However, we also cannot exclude that methodological limitations played a role. This pilot study with a small sample size resulted in limited statistical power. In a larger sample size it will be possible due to increased statistical power to describe stronger reliable statements on effects on a group level. In a following study it will be interesting to determine changes on an individual level as well and subsequently cluster those individuals with similar change effects in order to take a closer look at different subgroups of participants. This may lead to an opportunity to determine which subgroups benefit from the intervention and which subgroups do not benefit. In light of this it is also important to identify possible intervening factors such as additional or alternative ongoing therapies or use of psychopharmacological medication. Although in this study only two participants used other psychopharmacological medication which would not have systematic effects on the statistical analyses, this is worth mentioning as a factor that has to be considered when psychotherapy is pursued.

Another limitation is that there was no waiting list or control condition, which would be needed to assess if effects are driven merely by attention of a professional, or by learning effects on the cognitive tasks. However, extensive practice of the cognitive tasks directly preceding testing was executed according to the manual to prevent learning effects. Indeed, several of the EF tasks did not show improved performance over time, which argues against a learning effect in this test battery.

Furthermore the current study only examined post-treatment outcome, and did not have a follow-up period to investigate if lasting effects in daily life behavior are possible. Generalizability of training effects are small over time. Prevention of drop-out at post-test or long-term follow-up deserves attention to prevent specific effects caused by a possible selection in participation of relative stronger functioning participants. In this study we concluded that there were no significant differences in EF scores at baseline between the subgroup of participants who did not participate in the follow up and the subgroup of participants who did enter the baseline as well as the follow-up. We concluded that the drop-out was therefore not attributable to differences in group characteristics.

Finally, the training comprised a variety of potentially effective intervention techniques, which makes it difficult to identify which specific aspects of the training contributed to the observed effects. Thus, although promising, this study requires replication in studies with larger sample sizes and more conditions.

The promising findings of this explorative and preliminary effectiveness study suggest that SMT treatment program for individuals with Klinefelter syndrome may be an effective way of intervening to enhance self-management and related social adaptation through improving inhibitory self-control of behavior, emotion and increased organization and planning skills. Until now, interventions have primarily focused on the potential positive effects of physical treatment such as testosterone supplements. However, the efficacy of other types of treatments such as cognitive behavior therapy need to be further investigated, given such interventions have shown positive effects in other vulnerable populations. This study is an important step toward expanding the field of research into interventions for Klinefelter patients, and improving clinical care for this vulnerable population.

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