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## Effects of a combined neuropsychological and cognitive behavioral group therapy on young adults with Fragile X Syndrome: An explorative study

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### ARTICLE INFO

#### Keywords:

Fragile X Syndrome  
Rare genetic syndromes  
Cognitive-behavioral therapy  
Intellectual disability  
Mental health  
Psychosocial treatment  
Young adult

### ABSTRACT

**Background:** Fragile X Syndrome (FXS) is an X-linked neurodevelopmental disorder that leads to intellectual disability (ID) along with cognitive-behavioral difficulties. Research on psychosocial treatments in individuals FXS and ID is still lacking. This study aimed to investigate the effectiveness of a combined neuropsychological and cognitive behavioral group therapy (nCBT) among young adults with FXS.

**Method:** Ten young adults diagnosed with FXS took part in the second stage intervention of "Corposa-Mente" (CoM II), a group nCBT program previously outlined by Montanaro and colleagues in an earlier study, with the participants being the same as in the previous research. This report details the outcomes of an additional twelve-month group sections aimed at enhancing the ability to manage emotions and the socio-communicative skills of these young adults. Caregivers completed measures of adaptive functioning, emotional and behavior problems, executive function, communication skills and family quality of life at pre-treatment (T0) and post-treatment (T1).

**Results:** CoM II showed a decrease in depressive and anxiety symptoms from T0 to T1, along with increased socio-pragmatic and communication skills from pre-test to post-test intervention. Additionally, our analysis revealed improvements in the adaptive behavior of participants and in the family quality of life.

*List of abbreviations:* ABAS II, Adaptive Behavior Assessment System, Second Edition; ADHD, Attention-Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; BRI, Behavior Regulation Index; BRIEF – 2, Behavior Rating Inventory of Executive Function – Second Edition; CA, Chronological Age; CBCL 6–18, Children Behavior Checklist 6–18; CCC-2, Children's Communication Checklist-Second Edition; CGG, Cytosine-Guanine-Guanine; CoM, CorposaMente; CRI, Cognitive Regulation Index; DAC, Conceptual Adaptive Domain; DAP, Practical Adaptive Domain; DAS, Social Adaptive Domain; EF, Executive Functioning; ERI, Emotional Regulation Index; FM, Full Mutation; FXAND, Fragile X-Associated Neuropsychiatric Disorders; FXPOL, Fragile X-Primary Ovarian Insufficiency; FXS, Fragile X Syndrome; FXTAS, fragile X-associated neuropsychiatric disorders; GAC, Global Adaptive Composite; GCC, General Communication Composite; GEC, Global Executive Composite; ID, Intellectual Disability; IQR, Interquartile Range; M, Mean; MA, Mental Age; MED, Median; nCBT, Neuropsychological and Cognitive Behavioral Group Therapy; PEDSQL FAMILY, Paediatric Quality of Life Inventory Family Impact Module; PEERS, Program for the Education and Enrichment of Relational Skills; PM, Permutation; QoL, Quality of Life; SD, Standard Deviation; SIDI, Social Interaction Deviance Index; WM, Working Memory.

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<https://doi.org/10.1016/j.ridd.2024.104839>

Received 29 March 2024; Received in revised form 2 August 2024; Accepted 13 September 2024

Available online 26 September 2024

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*Conclusions:* These preliminary findings suggest that young adults with FXS and ID experienced positive outcomes through participation in CoM II, a group nCBT. However, it is recommended to undertake additional methodologically rigorous studies, such as randomized controlled trials (RCTs), to substantiate these initially promising findings.

## 1. Introduction

### 1.1. Fragile X Syndrome phenotype

Fragile X Syndrome (FXS) is an X-linked neurodevelopmental disorder, officially classified as a rare condition since 2001 due to its prevalence in only 1 in 7000 males and 1 in 11000 females (Hunter et al., 2014). It stands as the primary hereditary cause of intellectual disability (ID) and autism spectrum disorder (ASD) linked to a single-gene mutation (Stone et al., 2023). FXS is caused by an unstable expansion of the CGG (cytosine-guanine-guanine) trinucleotide in the 5' untranslated region of the *FMR1* gene, which tends to change in size from one generation to the next (Hagerman & Hagerman, 2020). In fact, each X chromosome carries a *FMR1* gene with a distinct number of triplet repeats, classifying individuals into different categories. These include the normal range when the CGG repeat number is between 6 and 44, the grey zone when CGG repeats occur between 45 and 54 times, the premutation (PM) range when trinucleotide repeats fall between 55 and 200 times, and a full mutation (FM) when the CGG motif expands to more than 200 repeats (Monaghan et al., 2013). FM triggers a cascade of epigenetic events that result in the methylation of the promoter site, the silencing of the *FMR1* gene, the consequent reduction or absence of its product FMRP, thus resulting in the clinical manifestations of FXS. Effectively, FMRP plays a pivotal role in the cortical development, and is thus believed to significantly influence the cognitive and behavioral characteristics of FXS (Salcedo-Arellano et al., 2020).

It is worth to specify that FM is not the only clinical condition determined by the *FMR1* mutation. In fact, individuals with PM, who in the past were presumed to be unaffected because FMRP levels were usually normal, may exhibit other conditions such as fragile X-primary ovarian insufficiency (*FXPOI*), fragile X-associated neuropsychiatric disorders (*FXAND*) and fragile X-associated tremor/ataxia syndrome (*FXTAS*) (Tassone et al., 2023). Whilst PM description is beyond the scope of this work, it is important to acknowledge that parents, particularly mothers, of children with FXS typically carry a PM. Therefore, in the clinical care of individuals with FXS, it should be crucial to evaluate whether parents with PM exhibit clinical or sub-clinical symptoms and the possibility to conduct family-centred intervention. This consideration is based on previous studies highlighting a correlation between the severity of the phenotype of mothers with PM and the vulnerability of their children with FXS to develop further difficulties on the cognitive, linguistic, socio-pragmatic, and psychopathological levels (Bangert et al., 2021; Moser et al., 2021).

The cognitive-behavioural phenotype of FXS is variable and depends on age, sex and genetic and epigenetic factors (i.e. amount of the FMRP expression), even though some common features can be depicted (Schmitt et al., 2023). For instance, the 85 % of males and 25 % of females exhibit mild to moderate ID, with impairment in selective and sustained attention (Cornish et al., 2004), working memory (WM) (Schmitt et al., 2019), cognitive flexibility (Weber et al., 2019; Schmitt et al., 2023), sequential processing (Raspa et al., 2023) and executive functioning (EF) (Schmitt et al., 2019) and relative strengths in memory for meaningful information and long-term memory as well as in verbal processing and inductive reasoning (Klusek et al., 2014). In the area of language and communication, children with FXS show language development delay, which can be depictable since early stages of life (Kover et al., 2015). Expressive language is usually more impaired than receptive one, with particular difficulties in speech intelligibility and expressive grammar that are usually more pronounced in males. Deficits in pragmatic (social) language are also common. For instance, it has been observed that individuals with FXS struggle to maintain the focus of a conversation, having trouble in determining when to participate in a multi-person conversation and identifying information coherent with the conversational topic (Mazzocco et al., 2006), as well as to consider the informational needs of the listener, potentially failing to provide relevant information (Roberts et al., 2008). Furthermore, language of individuals with FXS tends to be repetitive, with repeated phonemes, words, or phrases during discourse with some authors suggesting that this linguistic characteristic may be considered a core-symptom of FXS phenotype and is more prevalent in males (Murphy & Abbeduto, 2007). Considering that usually individuals with FXS (without ASD) demonstrate good social drive, those linguistic difficulties represent a substantial hindrance across various facets of daily life (Fielding-Gebhardt & Warren, 2019). Therefore, a multimodal intervention involving speech and language therapy and social skills training should always be suggested.

In addition to the cognitive and linguistic impairment, adaptive behaviour deficits have been reported, with a decline or plateau with age that is more prominent in males than females (Hartley et al., 2011; Seng et al., 2024). The greatest decline is observed in the domains of socialization and communication, consistent with the pragmatic, receptive and expressive language difficulties described in people with FXS (Abbeduto et al., 2016). In contrast, daily living skills appear to be a strength in people with FXS even when compared with people with other neurodevelopmental disorders (Abbeduto et al., 2016).

On a psychopathological level, the 30–60% of individuals with FXS exhibit ASD (Hagerman et al., 2017) while ADHD (attention-deficit/hyperactivity disorder) is present in the 70% of cases (Salcedo-Arellano et al., 2020). Concurrent psychiatric disorders may also be diagnosed, such as obsessive-compulsive disorder, depression, and anxiety. The latter, primarily diagnosed in the forms of generalized anxiety disorder and social anxiety disorder, appears to be a central feature in the FXS phenotype and represents one of the highest treatment priorities according to individuals with FXS, their parents and caregivers (Weber et al., 2019; Montanaro et al., 2024). Self-injury, aggression and oppositional defiant behaviour may also be depicted, with male individuals and with lower IQ being

more likely to engage in any type of behavioural problems (Hardiman & McGill, 2018). As psychiatric comorbidities enhance the severity of the presenting symptoms in FXS, weighing on the adaptive functioning and the quality of life (QoL) already compromised by ID (Tonge, 2009), a comprehensive evaluation of the cognitive-behavioural phenotype of FXS should always be pursued. This would help to tailor a multimodal, multidisciplinary intervention combining behavioural and, if needed, pharmacological treatment.

### 1.2. Behavioral treatments for Fragile X Syndrome

Whilst there is repeated evidence about the efficacy of behavioural intervention in ASD and ID (Hall et al., 2009) and a clear demand for structured interventions also in FXS (Weber et al., 2019), at present, studies about behavioural treatments specific to FXS are still missing (Protic & Hagerman, 2024). For instance, a systematic review of 2015 analysing 31 studies on non-pharmacological intervention in FXS showed that individuals with FXS may benefit from a behavioural analytic approach to intervention (Moskowitz & Jones, 2015). Nevertheless, these studies encompassed a range of strategies, complicating the generalization of the obtained results. Afterwards, Hessel and colleagues performed a randomized controlled trial (RCT) study with adolescents with FXS in order to evaluate the efficacy of Cogmed, a computer/tablet-based WM training program. The authors showed an amelioration in EF and WM after 6 weeks of treatment, indicating that neuropsychological treatment can be effective in people with FXS. On the other hand, the presence of different limitations (such as a clearly inactive control group) made it difficult to draw conclusions and pointed out the need to replicate results before providing guidelines for the treatment of cognitive symptomatology in FXS (Hessel et al., 2019). Another therapeutic approach that has shown some evidence of effectiveness in FXS is the parent management training. For instance, Alfieri and colleagues (Alfieri et al., 2021) conducted a RCT study demonstrating that cooperative parent-mediated therapy may be effective in the treatment of socio-communicative deficits of pre-schoolers with FXS. However, due to limitations (e.g. the small sample size) these results appeared still preliminary, thus not extendable to all the population with FXS.

In a prior study, we endeavoured to contribute to research examining the efficacy of psychosocial treatments in FXS by describing Corp-osa-Mente (CoM), a combined neuropsychological and cognitive behavioral group therapy (nCBT), targeting the different clinical manifestations of FXS through a unified approach (Montanaro et al., 2023). CoM aimed to: a) increase participants' knowledge of FXS through psychoeducation, b) help them to better manage negative emotions and dysfunctional thoughts through cognitive restructuring techniques, c) enhance cognitive skills through neuropsychological intervention and d) foster greater independence in daily life through occupational therapy techniques. A total of twenty sessions were conducted, most of which were performed through telehealth during the Covid-19 pandemic. Due to the lockdown, pre-treatment standardized data could not be collected; therefore, CoM results consisted mainly of clinical observations and a post-treatment survey. Together, these findings indicated an improvement in participants' psychopathological symptoms, cognitive abilities, and general adaptive behavior by the end of CoM, though limitations remained in their socio-pragmatic and communication skills. It is noteworthy that when CoM was initially developed, it lacked any research purpose; thus, the decision to share the program within the scientific community aimed to contribute to research in the field, providing further evidence that behavioral approaches are promising in the treatment of FXS symptomatology. However, the study faced strong methodological issues, the most significant being the absence of quantitative data.

### 1.3. Objectives of the present study

To address CoM limitations to some extent and to validate the results obtained by the previous study (Montanaro et al., 2023), we decided to conduct an additional year of nCBT (hereinafter CoM II) with the same participants from the first phase, collecting quantitative data from standardized evaluations pre-CoM II (T0) and post-CoM II (T1). Our aim was to explore if a combined nCBT specifically designed for people with FXS was effective in the treatment of the clinical manifestations associated to this condition. More specifically, considering the areas of improvements and weaknesses at the end of CoM, we carried out additional sessions aiming to:

1. Improve social skills knowledge and acquire more appropriate relationship skills.
2. Enhance the communication and socio-pragmatic skills.
3. Help participants to cope with dysfunctional thoughts and negative emotions especially in the social situations.
4. Run additional neuropsychological trainings with a particular focus on EF, which are essential in the everyday functioning.
5. Improve the adaptive functioning in order to make participants more independent from parents during daily life.

Based on the clinical experience of the intervention developers, the promising results of their previous research (Alfieri et al., 2021; Montanaro et al., 2023) and the literature review highlighting the efficacy of behavioural interventions in FXS (Moskowitz & Jones, 2015; Protic & Hagerman, 2024), it was expected that nCBT for young adults with FXS would be feasible and acceptable.

## 2. Methods

### 2.1. Study population

Ten Italian participants (M:F=7:3) with confirmed genetic diagnosis of FXS participated in the program. All the mothers of the participants carried a PM, but none of them had been diagnosed with a condition associated with PM at time of recruitment. Families involved in the study were middle-class with at least high-school education. All families were opposite gender parents and intact. Additional relevant demographic and diagnostic information for participants have been previously described (Montanaro et al., 2023).

The informed consent form to participate in the second phase of the program and for data publication was obtained in October 2022 and CoM II started in November 2022. As CoM II represented a feasibility trial and as the intervention had primarily clinical aims, no exclusion criteria were applied, and thus participants were not required to exhibit specific IQ levels or other main clinical manifestations to take part in the program. [Table 1](#) depicts participants' characteristics at T0.

## 2.2. Data measurements

Assessment was conducted by a team of trained and specialized medical doctors, psychologists and a speech and language therapist and consisted of clinical observations, cognitive evaluations and parent-reported questionnaires. Standardized evaluations as well as the intervention were performed at the Department of Educational Sciences, Psychology, and Communication - University of Studies of Bari, Italy.

### 2.2.1. Cognitive assessment

Since CoM II did not aim to improve cognitive functioning and since IQ (intelligence quotient) levels have been reported not to be sensitive to fluctuations in very short time spans ([Jenni et al., 2015](#)), the intellectual assessment was performed only at T0. Cognitive profiles were assessed through the cognitive battery of Leiter International Performance Scale-Third Edition (Leiter-3) ([Roid et al., 2016](#)). The Leiter-3 scale consists of a non-verbal intelligence test that can be administered to people aged 3–75 through tests of fluid reasoning, visualization, and cognitive interference. This scale, being essentially administered through gestures, can be considered a culture-free test; furthermore, due to its structure, it allows to measuring IQ in individuals with language difficulties, reason for which we selected this scale among others. In fact, both considering the linguistic profile of people with FXS and the variability of our sample, Leiter-3 was considered the most suitable test for performing comparative investigations. Non-verbal IQ (hereinafter IQ) levels are presented in [Table 1](#).

### 2.2.2. Measures administered to parents

As shown in [Table 1](#), the mean IQ was  $46 \pm 6$  (M $\pm$ SD). The average chronological age (CA) was  $26 \pm 4.7$  years, with a difference of about 13 years between the youngest (19 years) and the oldest (32 years) individual. The average mental age (MA) was  $12 \pm 2.6$  years, which is more than half than CA, indicating that even though participants were young adults, their developmental profile corresponded to the one of a much younger age. This complicated the selection of assessment measures, as most standardized tests show floor effects when applied to people with ID, which means that because the abilities of many individuals with FXS often fall beneath this threshold, the minimum score might overstate their true capabilities. Furthermore, a person's performance in a specific area might experience improvement or decline without being detected by usual scores for CA that can remain at the same floor level in the follow-up. To partially address this difficulty, after Leiter-3 administration, we considered preferable to calculate MA and to select tools based on MA, rather than on CA. This enabled us to assess whether a behaviour fell in the normal or clinical range not by relying on the participant's CA, but by considering the developmental profile. This approach aimed to address the challenge posed by comparing individuals with ID to those of the same ages, since the former by definition cannot meet the environmental demands expected for their CA. It must be acknowledged that this methodology may lead to the opposite phenomenon (ceiling effect), whereby adults with ID may saturate items built for younger age groups, thereby being considered to exhibit "normal" behaviours. Nevertheless, knowing whether the behaviour of a person is appropriate in comparison to the MA group or not remain an important information to consider when structuring any intervention.

Considering the aforementioned considerations, given the risks associated with the various alternatives explained earlier, the high intra-group variability and the lack of material calibrated for ID, we decided to select questionnaires designed for paediatric ages, thus preferring the possibility of encountering a ceiling effect rather than a floor effect. The pre-test and post-test measures used to evaluate potential treatment effects are outlined in the following paragraphs.

**Table 1**

Demographic data in November 2023, at T0 prior to CoM II.

Participant's Number code	Gender	ID Level	nvIQ	Chronological Age (Years, Months)	Mental Age (Years, Months)
1	Female	Mild ID	41	29.4	12.0
2	Female	Severe ID	49	23.4	11.4
3	Female	Moderate ID	52	27.4	14.2
4	Male	Severe ID	41	32.8	13.4
5	Male	Moderate ID	45	20.4	9.2
6	Male	Severe ID	44	19	8.4
7	Male	Severe ID	41	24.2	9.9
8	Male	Severe ID	41	30.4	12.4
9	Male	Mild ID	54	23.1	12.4
10	Male	Mild ID	56	30.8	17.03
M $\pm$ SD	-	-	46 $\pm$ 6	26.1 $\pm$ 4.7	12.09 $\pm$ 2.6

Legend. ID level as confirmed by the clinical judgement reported by local medical doctors; nvIQ= non-verbal intelligence quotient; M=mean; SD= standard deviation.

### 2.2.3. Adaptive behavior assessment system, second edition (ABAS II), parent form

ABAS-II Adult parent/caregiver questionnaire provides a measure of adaptive behaviour skills for individuals aged 0–89 years (Harrison & Oakland, 2003). Parents/caregivers are asked to rate the individual's adaptive behaviour skills on a 4-point Likert scale. The tool yields three composite domains: Conceptual (DAC), Social (DAS) and Practical (DAP). The Conceptual composite consists of skills from communication, functional academics and self-direction. The Social composite comprises leisure and social skills areas. The Practical composite is comprised of skills including community use, home living, health and safety, self-care, plus an optional work skill area. Finally, from these three broad composite domains a Global Adaptive composite (GAC) that indicates the level of general adaptive functioning. GAC and the three composite domains have M of 100 and SD of 15, with scores under 85 falling in the clinical range. Since adaptive functioning together with cognitive functioning is essential for ID diagnosis, ABAS II has been the only test to be corrected for CA rather than MA. Finally, as the Italian version of ABAS II provides normative data for people aged between 0 and 18 years of age, results have been corrected based on USA standardization.

### 2.2.4. Children behavior checklist 6–18 (CBCL/ 6–18)

The behavioural and emotional profiles were assessed using the CBCL/ 6–18 scales that is a 113-item parent reported measures designed for children aged between 6 and 18 years (Achenbach, 2001). The questionnaires generate eight syndrome scores: Anxious/Depressed, Withdrawn/Depressed, Somatic Problems, Social Problems, Thought Problems, Attention Problems, Rule Breaking, and Aggressive Behavior. Additionally, Competence Scale, Internalizing, Externalizing and Other Problems Scales, DSM-Oriented Scales and 2007 Scales scores, are calculated too. According to the ASEBA Assessment Data Manager (ADM), t-scores of Syndrome Scales, DSM-Oriented Scale and 2007 Scales from 67 to 70 fall in the borderline range, while t-scores above 70 in the clinical range; concerning the Total Problem, Internalizing, and Externalizing Scale, t-scores of 60–63 delineate the borderline range, while t-scores above 63 delineate the clinical range.

### 2.2.5. Behavior rating inventory of executive function – second edition (BRIEF-2)

The BRIEF-2 measures behavioural manifestations of EF impairments in youth ages 5–18 years (Gioia et al., 2015) using a 3-point Likert-scale measuring problem frequency: 1=never; 2=sometimes; 3=often. The BRIEF-2 yields sex-adjusted and age-adjusted normative T scores (M=50, SD=10) for the nine scales (Inhibit, Self-Monitor, Shift, Emotional Control, Initiate, Working Memory, Plan/ Organize, Task Monitor, and Organization of Materials), three indexes (Behavior Regulation Index, BRI; Emotional Regulation Index, ERI; Cognitive Regulation Index, CRI) and the Global Executive Composite (GEC). Higher T scores denote greater executive function difficulties.

### 2.2.6. Children's communication checklist-second edition (CCC-2)

The CCC-2 is a 70-item questionnaire designed to assess communicative abilities and identify children with pragmatic deficits (Bishop, 2003). It is composed by 10 scales: (A) speech, (B) syntax, (C) semantics, (D) coherence, (E) inappropriate initiation, (F) stereotyped language, (G) use of context, (H) non-verbal communication, (I) social relations, and (J) interests. The first four scales (A-D) assess the areas of vocabulary, discourse, and language structure, while scales E, G, H, and I assess pragmatic language. Two composites, namely the General Communication Composite (GCC) and the Social Interaction Deviance Index (SIDI), serve to identify children facing clinically notable communication challenges and those who might necessitate additional evaluation for ASD. A scaled score of 6 or higher is considered a normal score for the A-J subscales. A GCC score of 55 or less is considered clinically significant and indicating a possible communication disorder. Conversely, negative overall SIDI means that there is significant discrepancy between language and social interaction abilities, with a more pronounced symptomatology in the latter. The Italian standardization provides normative data for individuals aged 4–11 years. Therefore, the results of participants 1, 2, 3, 4, 8, 9, and 10 have been corrected for MA based on the normative data of the oldest age group.

### 2.2.7. Pediatric quality of life inventory family impact module (PedsQL family)

The PedsQL Family includes twenty-eight items measuring health-related quality of life of the caregiver of children ages 2–18 across six dimensions of health: Physical Functioning, Emotional Functioning, Social Functioning, Cognitive Functioning, Communication, and Worry (Varni et al., 1999). In addition, eight items measured the QoL of the caregiver's family as a result of the affected child's health across two dimensions: Daily Activities and Family Relationships. Subscale scores consist in the sum of the item scores divided by the number of items answered (to account for missing data). Higher scores indicate higher QoL/functioning. The PedsQL Family have been filled by mothers of participants.

## 2.3. Procedure

CoM II represents the second phase of CoM, a combined nCBT designed for ten young adults with FXS recruited via Fragile X Syndrome Italian Association–Apulian Region and carried out between March 2020 and September 2022 (Montanaro et al., 2023). Cognitive-behavioral, neuropsychological, occupational and behavioural techniques were merged and applied both during online and in person sections. At the end of CoM, qualitative results indicated that participants acquired new autonomies during daily life and were more capable to cope with negative emotions, although areas of weaknesses remained social engagement and socio-pragmatic skills. From the survey that was administered at the end of CoM, it was found that participants and their caregivers considered both the cognitive-behavioral strategies and the neuropsychological training to be particularly effective, which is why those techniques were repeated in the second phase of the intervention.



CoM II was conducted by the same psychologist that performed the first stage, who was a registered cognitive-behavioral therapist with previous experience in the assessment and treatment of the clinical manifestations of FXS and ID. It consisted in a total of eleven sessions, including one online session that was carried out only with caregivers (parents and one sibling in the case of participant n° 10) in October 2022, prior to start the second stage of CoM. The remaining ten sessions were held with the ten participants at the University of Bari (Puglia, Italy) from November 2022 to October 2023 and lasted about 5 hours with a 30-minute shared lunch break. A total of four educators who were directly trained by the therapist, took part in the face-to-face sessions. Additionally, the four educators directed the online sessions that were performed without the therapist with the aim to practice relevant skills and carry out group homework assignments. The video-calls lasted approximately 60–90 minutes, and similarly to CoM, participants were paired based on their cognitive strengths and weaknesses. The ten in-person meetings focused on improving socio-pragmatic and communicative skills, as well as cognitive abilities, emotional management and adaptive functioning. The treating psychotherapist maintained written records of the treatment sessions, documenting aspects such as the participants' understanding of the materials and comments of participants, parents and educators. Printed and video material were provided to each participant in each session.

#### 2.4. Intervention program

CoM II was conducted by combining cognitive-behavioral techniques and neuropsychological trainings, as extensively described in our previous work (Montanaro et al., 2023). Indeed, considering the promising qualitative results observed in the end of the first phase of the project, the use of an integrated and multidisciplinary intervention was deemed a strength of CoM. Additionally, the content of some sections of CoM-II was partially integrated with topics extracted from the UCLA Program for the Education and Enrichment of Relational Skills (*PEERS*) for young adults, originally developed to benefit individuals with ASD (Laugeson et al., 2009; Laugeson & Frankel, 2010; Laugeson, 2017) and later tested also in people with ID (Wyman & Claro, 2020). *PEERS* includes some applied behaviour analysis (ABA) techniques in a structured group-based social skills intervention delivered once a week over the course of 14 weeks. It is worth to specify that despite including some topics in our intervention, we found that *PEERS* was too rigid for our sample, and that the content needed to be integrated with other activities considered more specific to the FXS phenotype and to the broader objectives that we aimed to pursue. Refer to Table 2 for an overview of the activities and homework assignments for the ten CoM II sections.

Each session began with group psychological support, as we realized that it was important for our participants to share the most salient emotional events of the previous month with the therapist. Furthermore, each in-person meeting included psychoeducation, during which the therapist carried out didactic lessons by utilizing written and video materials specifically designed for the participants. For instance, in the session 1 the therapist provided a list of the most common socio-relational difficulties in FXS (i.e., excessive familiarity; tendency to ask overly personal questions or make inappropriate jokes), and participants were asked to identify those they believed characterized them. Young adults were also asked to provide examples, and different problem-solving strategies were hypothesized together. Furthermore, during sessions the therapist, in accordance with the caregivers' requests, carried out activities aimed at enhancing adaptive functioning and stimulating the youngsters to understand what they would do as adults (when parents would have passed away). The educators, who were directly trained by the therapist, participated to the face-to-face meetings, assisted with role-playing demonstrations a carried out the video-calls between sessions. Indeed, exactly as in the first stage of the intervention, CoM II included homework assignments that consisted of: a) socialization activities; b) cognitive-behavioral exercises with a particular focus on emotional management (some activities were extracted from Poppy, 2021); c) neuropsychological trainings combining material extracted from specific books (Gagliardini, 2015; Scitutto & Rolla, 2013) and exercises created by the therapist. It is worthwhile to clarify that books used in the homework assignments were selected based on the MA and on the linguistic profile, but contents were always adapted on the CA of participants.

#### 2.5. Data analysis

All statistical analyses were performed using JAMOVI software version 2.3.26.0. Continuous variables were presented as  $M \pm SD$ , median and IQR (interquartile range). For quantitative variables, normality of the data was assessed using the Shapiro-Wilk's test prior to statistical analysis. Changes in quantitative variables from baseline (T0) to follow-up (T1) were analyzed using paired t-test or Wilcoxon signed-rank test. Uncontrolled effect sizes (Cohen's  $d+$ ) were calculated on T0 to T1. We did not apply multiple-comparison correction to avoid the risk of type II errors, since the sample size is very small (VanderWeele & Mathur, 2019).  $P < 0.05$  was considered statistically significant.

### 3. Results

Results of comparative analyses are discussed separately for each measure. Additionally, given the number of subtests in each questionnaire, only statistically significant comparisons are presented (Table 3). The dataset with the all the comparative analyses is in [supplementary material](#).

#### 3.1. ABAS II- parent form

Results highlight an overall low functioning both pre and post treatment. Comparative analyses show statistically significant improvements at T1 for General Adaptive Composite (GAC,  $W=0.87$ ;  $P=0.02$ ) and Conceptual domain (DAC,  $W=1.00$ ;  $P=0.01$ ). An

**Table 2**  
Overview of CoM-II program.

Session	Target	Aims	Activities	Homework assignments <sup>1</sup>
0	Caregivers (parents and one sibling)	<ul style="list-style-type: none"> <li>Giving information about CoM II content</li> </ul>	<ul style="list-style-type: none"> <li>Psychoeducation on socio-pragmatic skills in FXS: literature review</li> <li>Explanation of CoM II aims</li> <li>Delivery and explanation of the questionnaires to fill at T0 and T1</li> </ul>	-
1	Young adults with FXS	<ul style="list-style-type: none"> <li>Giving information about FXS</li> <li>Training socio-pragmatic skills</li> <li>Training cognitive functioning</li> </ul>	<ul style="list-style-type: none"> <li>Introduction to CoM II.</li> <li>Circle-time: "Tell us about your last summer" + group psychological support</li> <li>Psychoeducation: socio-pragmatic difficulties in FXS + delivery of a checklist of main social symptoms</li> <li>Starting and joining a conversation: having a two-way conversation with peers</li> <li>Role-playing</li> </ul>	<ul style="list-style-type: none"> <li>Videocall (4 young adults + 2 educators in each group): practice two-way conversation.</li> <li>Part 1 book "Sei Forte"<sup>a</sup></li> <li>Neuropsychological training: "Story Sequencing - Level 1" from the book "Abilità cognitive" Vol. 2. Esercizi di "problem solving"<sup>b</sup></li> </ul>
2	Young adults with FXS	<ul style="list-style-type: none"> <li>Training social adaptive functioning</li> <li>Training socio-pragmatic skills</li> <li>Training cognitive functioning</li> <li>Coping with negative emotions</li> </ul>	<ul style="list-style-type: none"> <li>Circle time: group psychological support</li> <li>Psychoeducation: list of the main conversational topics</li> <li>Psychoeducation: steps to join and maintain a conversation</li> <li>Psychoeducation: the difference between joking and teasing</li> <li>Assertiveness training: accept criticism<sup>2</sup></li> <li>Role playing</li> </ul>	<ul style="list-style-type: none"> <li>Videocall (4 young adults + 2 educators in each group): practice the difference between joking and teasing</li> <li>Part 2 book "Sei Forte"<sup>a</sup></li> <li>Neuropsychological training: Describe complex pictures (created by the therapist)</li> <li>Identify in your hometown potential social groups to join</li> </ul>
3	Young adults with FXS	<ul style="list-style-type: none"> <li>Training socio-pragmatic skills</li> <li>Training cognitive functioning</li> <li>Training conceptual adaptive functioning</li> </ul>	<ul style="list-style-type: none"> <li>Circle time: group psychological support</li> <li>Psychoeducation: the understanding of metaphors, jokes and idioms</li> <li>Problem solving activity: "What can I do when I cannot understand abstract language?"</li> <li>Role playing: "Let's tell a joke"</li> </ul>	<ul style="list-style-type: none"> <li>Videocall (4 young adults + 2 educators in each group): practice the understanding of metaphors, jokes and idioms</li> <li>Part 3 book "Sei Forte"<sup>a</sup></li> <li>Neuropsychological training: making inferences from complex images (created by the therapist)</li> </ul>
4	Young adults with FXS	<ul style="list-style-type: none"> <li>Cognitive restructuring</li> <li>Training socio-pragmatic skills</li> <li>Training cognitive functioning</li> <li>Coping with negative emotions</li> </ul>	<ul style="list-style-type: none"> <li>Circle time: group psychological support</li> <li>Assertiveness training: Assertive Rights<sup>2</sup></li> <li>Identifying and distinguishing between thoughts, feelings and behaviours (ABC model)<sup>2,3</sup></li> <li>Psychoeducation: join a conversation with strangers</li> <li>Role playing</li> </ul>	<ul style="list-style-type: none"> <li>Videocall (4 young adults + 2 educators in each group): practice ABC<sup>3</sup> and join conversations</li> <li>Part 4 book "Sei Forte"<sup>a</sup></li> <li>Neuropsychological training: "Story Sequencing – Level 2" from the book "Abilità cognitive" Vol. 2. Esercizi di problem solving<sup>b</sup></li> </ul>
5	Young adults with FXS	<ul style="list-style-type: none"> <li>Cognitive restructuring</li> <li>Training socio-pragmatic skills</li> <li>Training cognitive functioning</li> <li>Coping with negative emotions</li> </ul>	<ul style="list-style-type: none"> <li>Circle time: group psychological support</li> <li>Psychoeducation: the psychological and emotional profile of FXS. Delivery of a checklist to complete together</li> <li>Handling disagreements: strategies for resolving arguments</li> <li>Identifying irrational thoughts in social situations (ABC model)<sup>2,3</sup></li> <li>Role playing</li> </ul>	<ul style="list-style-type: none"> <li>Videocall (4 young adults + 2 educators in each group): practice ABC<sup>3</sup> and resolve arguments</li> <li>Part 5 book "Sei Forte"<sup>a</sup></li> <li>Activity: Invite a friend to go out</li> </ul>
6	Young adults with FXS	<ul style="list-style-type: none"> <li>Giving information about FXS</li> <li>Daily life problem solving</li> <li>Training conceptual adaptive functioning</li> <li>Improving social skills knowledge</li> </ul>	<ul style="list-style-type: none"> <li>Circle time: group psychological support.</li> <li>Psychoeducation: clinical manifestations associated with <i>FMR1</i> premutation</li> <li>Psychoeducation: independent life Adaptive functioning in FXS</li> <li>Electronic communication: how to use facebook, instagram and tik tok</li> <li>Role playing: dangers of internet</li> </ul>	<ul style="list-style-type: none"> <li>Videocall (4 young adults + 2 educators in each group): practice to identify dangers on internet</li> <li>Neuropsychological training: "What should I do when I grow up and my parents will be old?"</li> </ul>
7	Young adults with FXS	<ul style="list-style-type: none"> <li>Cognitive restructuring</li> <li>Coping with negative emotions</li> <li>Training social adaptive functioning</li> </ul>	<ul style="list-style-type: none"> <li>Circle time: group psychological support.</li> <li>Psychoeducation: physical, verbal and cyber bullying.</li> <li>Producing more helpful thoughts in social situations (ABC model)<sup>2,3</sup></li> <li>Role playing</li> </ul>	<ul style="list-style-type: none"> <li>Videocall (4 young adults + 2 educators in each group): practice handling bullying and arguments</li> <li>Practice identifying irrational thoughts in social situations and answer to the question "What changes may I do in my daily life to avoid irrelevant arguments with friends?"</li> </ul>
8	Young adults with FXS	<ul style="list-style-type: none"> <li>Giving information about FXS</li> <li>Training socio-pragmatic skills</li> </ul>	<ul style="list-style-type: none"> <li>Circle time: group psychological support</li> <li>Psychoeducation: socio-pragmatic difficulties in FXS + review of the checklist delivered in session 1</li> <li>Minimize rumours and gossip</li> </ul>	<ul style="list-style-type: none"> <li>Videocall (4 young adults + 2 educators in each group): practice strategies to handle with rumours</li> <li>Practice: "Identify social situation in which you have been aggressive with meaningful others"</li> </ul>

(continued on next page)

**Table 2** (continued)

Session	Target	Aims	Activities	Homework assignments <sup>1</sup>
9	Young adults with FXS	<ul style="list-style-type: none"> <li>• Training cognitive functioning</li> <li>• Training social adaptive functioning</li> <li>• Training cognitive functioning</li> </ul>	<ul style="list-style-type: none"> <li>• Role playing</li> <li>• Circle time: group psychological support.</li> <li>• Psychoeducation: the difference between friendship and love + sharing personal events</li> <li>• Manage when and how to respond on social medias</li> <li>• Role playing</li> <li>• Circle time: "what I learnt during this year"</li> <li>• Psychoeducation: independent life when parents won't be here anymore. Available resources and local services.</li> <li>• Final review of topics</li> <li>• Future directions</li> </ul>	<ul style="list-style-type: none"> <li>• Neuropsychological training: "Incongruities – Part 4" from the book "Abilità cognitive Vol. 2. Esercizi di problem solving<sup>b</sup></li> <li>• Videocall (4 young adults + 2 educators in each group): practice the use of social media</li> <li>• Neuropsychological training: Book "Capire le metafore e i modi di dire. Attività di comprensione delle metafore dalla A alla Z"<sup>c</sup></li> </ul>
10	Young adults with FXS	<ul style="list-style-type: none"> <li>• Moving forward independent life</li> </ul>		<ul style="list-style-type: none"> <li>• Delivery of the questionnaires filled by parents</li> </ul>

Legend. FXS= Fragile Syndrome; 1 = some homework were repeated several times during the intervention and adapted to the abilities of the different participants. 2 = those topics were already presented in the first phase of CoM and addressed again during CoM-II; 3 = ABC model, antecedent-belief-consequence method aiming to modify dysfunctional behaviours and thoughts. <sup>a</sup>= Poppy, (2021); <sup>b</sup>= Gagliardini, (2015); <sup>c</sup>= Sciutto & Rolla, (2013)

**Table 3**

Changes from baseline to follow-up in Questionnaires scores.

Questionnaire	Baseline (T0)	Follow-up (T1)	P-value	Cohen's d+
ABAS II				
GAC	71.5 ± 18.9	77 ± 18.8	0.02	-0.87
Conceptual	72.7 ± 20.7	82.7 ± 17.9	0.01	-1.00
Social	74.6 ± 15	79.9 ± 16.3	0.08	-0.72
Social (Raw score)	11.3 ± 6 (10 (6.25))	13.1 ± 6.2 (13 (8))	0.03	-1.00
Practical (Raw score)	23.2 ± 12.9	28.1 ± 13.4	0.02	-0.91
CBCL 6–18				
Anx/Dep	58.8 ± 4.8	53.5 ± 4.5	0.02	1.00
BRIEF–2				
Emotional Control	60.1 ± 10.9	50.3 ± 10.2	0.04	0.78
CCC–2				
Syntax	7 ± 4 (6.5 (8))	9.9 ± 3.4 (12 (4.5))	0.03	-0.94
Semantics	6.7 ± 1.8 (7 (1.75))	9.8 ± 3.3 (10 (4))	0.03	-0.89
Stereotyped language	6.7 ± 3.3 (6 (4.2))	10.7 ± 4 (10 (6.7))	0.00	-1.00
NV communication	6.6 ± 2.2 (6.5 (2.7))	9.5 ± 3.4 (10 (5.7))	0.01	-0.95
Social Relations	6.6 ± 4 (6.5 (4.7))	9.10 ± 3.5 (7.5 (6))	0.02	-1.00
GCC (Raw)	54.4 ± 21.6 (49.5 (30))	69 ± 22 (65.5 (17))	0.01	-0.89
PedsQL Family Daily Activities	68 ± 15	86.7 ± 13.2	0.02	-0.89

**Legend.** P-value was obtained by Wilcoxon Signed-Rank test to test significance of change in scores from Baseline to Follow-up. For those non-normally distributed variables, summary statistics are reported as Mean ± SD and (Median (IQR, interquartile range)). Significant at P-value <.05. GAC= general adaptive composite; Anx/Dep= Anxious/Depressed. NV= nonverbal. GCC= General Communication Composite.

approaching tendency, but not reaching significance emerged for the standard scores of Social (DAS,  $W=0.72$ ;  $P=0.08$ , Table 2S) and Practical (DAP,  $W=0.73$ ;  $P=0.06$ , Table 2S) domains. However, when examining raw scores, a significant improvement was observed both in DAS ( $W=1.00$ ;  $P=0.03$ ) and in the DAP ( $W=0.91$ ;  $P=0.02$ ) as well. The decision to incorporate raw scores in the analysis stems from the recognition that standard scores may not always adequately capture changes over short periods, whereas raw scores can offer more clinically relevant information, particularly when there is a trend toward significance in standard scores.

### 3.2. CBCL/ 6–18

Participants averagely obtained scores in the non-clinical range both for the "Anxious/Depressed" and "Somatic problems"



subtests, while “Anxiety problems” subscale felt in the borderline range only at T0. The comparison between T0 and T1 for “Anxious/Depressed” subscale was the only one at eluding the conventional threshold of significance ( $W=0.77$ ,  $P=0.02$ ). In addition to this, it emerged that the difference between T0 and T1 in the subscales “Somatic problems” ( $W=1.00$ ;  $P=0.09$ , Table 2S) and “Anxiety problems” ( $W=0.77$ ;  $P=0.06$ , Table 2S) barely failed to attain statistical significance, with lower mean scores after treatment in both the subscales.

### 3.3. BRIEF-2

Participants attained mean scores within the non-clinical range both at baseline and follow-up. The Wilcoxon Signed-Rank test showed a significant improvement at T1 in the subscales “Emotional Control” ( $W=0.78$ ;  $P=0.04$ ), while the enhancement at T1 in working memory (WM,  $W=0.75$ ;  $P=0.05$ ), Emotional Regulation Index (ERI,  $W=0.67$ ;  $P=0.09$ ), Cognitive Regulation Index (CRI,  $W=0.73$ ;  $P=0.06$ ) and Global Executive Composite (GEC,  $W=0.75$ ;  $P=0.07$ ) approached but fell short of significance (Table 2S).

### 3.4. CCC-2

Participants' scores generally fell within the non-clinical range for their mental age both before and after CoM-II. The only exception was the General Communication Composite (GCC) score, which was low at T0. Significant improvements emerged at T1 in the subscales “Syntax” ( $W=0.95$ ;  $P=0.02$ ), “Semantics” ( $W=0.89$ ;  $P=0.03$ ), “Stereotyped language” ( $W=0.89$ ;  $P=0.00$ ), “NV communication” ( $W=1.00$ ;  $P=0.01$ ) and “Social Relations” ( $W=1.00$ ;  $P=0.01$ ). A statistical significance was reached also in the raw scores of the GCC (standard scores are not available for this index;  $W=0.89$ ;  $P=0.04$ ). A pronounced trend towards significance was observed also in the subscale “Coherence”, with higher scores at T1 ( $W=0.89$ ;  $P=0.07$ , Table 2S).

### 3.5. PedsQL family

Comparative analysis of the PedsQL Family revealed only one statistically significant difference. Specifically, at T1 caregivers reported significant reduced distress related to daily activities and thus less impact by participants' difficulties on their ability to manage family life (Daily activities,  $W=0.89$ ;  $P=0.03$ ).

## 4. Discussion

To our knowledge, the current study is the first published study to evaluate the feasibility and the effectiveness of an nCBT based intervention for young adults with FXS. More specifically, this paper presents CoM II, which is the second phase of the group intervention project described in our previous work (Montanaro et al., 2023). The main goal of CoM II was to enhance the socio-relational, pragmatic, and executive skills of the ten participants, as these remained significant weaknesses at the end of CoM. Additionally, considering the methodological limitations of the first phase of the project, both at T0 and at T1 of CoM II, structured evaluations were carried out through the administration of standardized evaluations and parent-report questionnaires.

The ABAS-II results revealed an overall improvement in adaptive functioning at the end of CoM II. More specifically, a significant amelioration was highlighted both in the General Adaptive Composite (GAC) and in the Conceptual domain (DAC). A significant increase was also observed when analyzing the raw scores of the Practical domain (DAP) and the Social domain (DAS), indicating that although the latter were not of such magnitude if compared to the general population, changes in practical and social skills emerged by comparing the participants' abilities at the end of CoM II with those they had at the beginning. The results are of extreme clinical relevance since several studies in the literature have highlighted a reduction in adaptive functioning in individuals with FXS with growth (Fisch et al., 1999a; Fisch, Simensen, & Schroer, 2002; Freund, Peebles, Aylward, & Reiss, 1995; Klaiman et al., 2014; Hahn et al., 2015). The fact that this did not occur in CoM II participants would suggest that targeted interventions can significantly influence the ability of individuals with ID to adapt to their daily living environments, thus counteracting the decline/plateau typically observed in individuals with FXS with growth. A possible explanation is that CoM II, even though aiming primarily at enhancing the socio-relational and emotional skills of participants, encouraged them to communicate more assertively to better control their reactions, and to face various daily challenges, consequently leading to an improvement in adaptive abilities in the different life contexts. Effectively, the DAC is calculated by summing three subscales, namely “Communication,” “Self-Control,” and “School Skills,” which include skills that CoM II specifically targeted (i.e., some items: “speaks clearly and distinctly,” “waits for his turn during a conversation”, “works independently and asks for help only when necessary”, “controls himself when things don't go his way”). It's also probable that the neurocognitive stimulation activities, indirectly led to the acquisition of additional skills in the academic field and to generalize them to various daily life situations (i.e., some items of DAC-Academic Skills: “takes notes”, “reads a menu”).

The raw scores of the DAP have also shown changes, despite involving skills that were not directly addressed by CoM II. This could be attributed to the heightened awareness and self-efficacy perceived by participants following the intervention, which may have empowered them to cope with situations not directly encountered within the structured program. In this regard, we believe that the presence of trained educators, who helped participants to generalize to daily life what they were learning during sessions, represented a strength of the study. Indeed, in this way the young adults had the chance to consolidate the acquired skills during the video-calls but also to use the new strategies in more ecologic settings. At the end of CoM II, there was a notable rise in the raw scores of the DAS, though not in the standard scores. One potential explanation is that, despite the overall enhancement in socio-communicative skills, this improvement does not appear to have translated into the establishment of a more robust social network. Indeed, some skills

belonging to the DAS, such as "has a stable group of friends," "invites others over", or "participates in group activities", remained unacquired at T1. In this regard, it's not to exclude that the absence of substantial change is at least partially due to the environment and social opportunities; indeed, it's more complex for adults to engage in new friendships, especially in small towns and for people with ID. Therefore, despite the acquisition of new socio-relational skills, participants may not have found fertile ground in their living environments, which remained unchanged from T0. On the other hand, at T1 participants exhibited greater social confidence, social motivation and responsiveness, as confirmed by the fact that the young adults started to consider CoM a "group of friends" and to organize small outings among themselves and without caregivers (taking public transportation independently or asking parents to accompany them). This means that certain skills were learnt but unfortunately did not find space in the person's social network, providing indications of what the future directions of an intervention like CoM should be (i.e. peer psychoeducation during high school, etc.).

CBCL 6–18 results also demonstrated significant reduction in the scores of the scale "Anxiety/Depression", while trends to significance were observed in the scales "Anxiety Problems" and "Somatic Problems". However, it should be specified that neither at T0 nor at T1 any of the scores fell within the clinical range, which should be interpreted not in terms of "absence of pathology" but of "in line with people of similar MA" (approximately 12 years old). Comparative analyses of the CBCL 6–8 highlight a further decrease in anxiety and depressive problems in the group of participants at the end of CoM II. It's possible that the improvement in communication skills and the increased sense of self-efficacy acquired through the assertiveness training and the cognitive restructuring included in CoM II led participants to better control their emotions and manage daily challenges.

These data were supported by clinical interviews with parents and direct observations of participants by the psychologist. Over time, participants learnt to face unexpected/new situations more appropriately and to approach with less anxiety some social challenges, such as reconnecting with an old friend, asking someone out, etc. (i.e., one mother reported that once her son, before phoning a friend to solve a misunderstanding, took his workbook in order to review specific conversational passages - "Handling disagreement", session 5). These improvements seem to confirm the few data in the literature (i.e., Wyman & Claro, 2020; Blakeley-Smith et al., 2021), which indicate that young adults with ID, if subjected to specific trainings, can generalize their learnings to less structured contexts and manage their emotions (i.e., social anxiety) more appropriately outside the setting.

BRIEF-2 results, even though clinical scores were observed neither pre- nor post-intervention, revealed a significant improvement in "Emotional control", while a favorable statistical trend was observed in working memory (WM), Global Executive Composite (GEC), Emotional Regulation Index (ERI) and Cognitive Regulation Index (CRI). It's possible that the nCBT intervention provided by CoM II increased some cognitive skills, such as WM and self-monitoring. Simultaneously, the intervention may have facilitated better emotional regulation among participants, as also pointed out by CBCL 6–18 results. Neurocognitive trainings, in combination with cognitive-behavioral therapy, may have helped participants to strengthen their cognitive abilities (both general domains such as memory, planning, executive functions and specific domains such as writing, reading, comprehension), and to self-regulate and accept mistakes and contingencies without excessive anxiety or anger.

CCC-2 comparative analyses showed an overall improvement after the intervention in almost all the subscales. This demonstrates that targeted interventions on socio-communicative skills can lead also to a broader amelioration in various language abilities. For instance, despite no structured interventions addressing "syntax" and "semantics", it is plausible that performing neuropsychological exercises, and practicing conversational techniques induced changes in these language levels as well. Conversely, the presence of significant changes in non-verbal communication is not surprising, since CoM II specifically worked on the ability to communicate with others also through gestures. Additionally, it is possible that the psychoeducational intervention on communication, along with role-playing and exercises conducted during video-calls, induced improvement also in the "stereotyped language", promoting the development of a personal way of communicating and thus the use of fewer clichés/linguistic formulas. Moreover, the increase in CCC-2 scores is consistent with the improvement in DAC; therefore, it could be speculated that CoM II facilitated the development of greater linguistic, socio-relational, and executive skills, which in turn would have improved the young adults' communication abilities even outside the setting, resulting in greater adaptation in various life contexts.

Finally, from the analysis of the Peds-QL - family impact module, it emerged that at T1, daily activities such as those related to family or household chores were less affected by participants' symptomatology. It's possible that the reduction in anxiety problems, the increased socio-relational abilities, and the greater autonomy in performing daily tasks may have all contributed to a greater QoL of the families involved.

Analysing the data all together, CoM II demonstrated effectiveness in reducing anxious symptomatology, enhancing EF, and acquiring new socio-relational skills, ultimately resulting in an improvement in adaptive functioning and family QoL. These results align with previous qualitative findings of CoM (Montanaro et al., 2023), suggesting that the combination of cognitive, behavioral, psychosocial, and occupational techniques may be effective in improving FXS symptomatology.

Our findings are consistent with prior research exploring the efficacy of group CBT in addressing anxiety among adults with ID. Studies such as those by Douglass et al. (2007) and by Marwood and Hewitt (Marwood & Hewitt, 2012) have reported post-treatment improvements in anxiety management and emotional understanding among participants. Similarly, Hartley et al. (2015) observed a reduction in depressive symptoms and behavioral issues, as well as enhanced coping with maladaptive cognitive patterns, following a ten-week group CBT program for adults with mild ID.

Moreover, CBT has demonstrated effectiveness not only in managing psychological concerns in individuals with ID but also in those with chronic mental health conditions. For instance, Ballesteros et al. (2023) found that psychotherapy sessions led to improvements in overall symptomatology and anger management among one hundred-eighty-four psychotic patients. Additionally, CBT has shown promise in treating neurodevelopmental disorders such as autism spectrum disorder (ASD). Kuroda et al. (2022) reported enhancements in emotion regulation, including improved adaptive strategies and emotion control, among autistic adults who underwent group

CBT.

The convergence of our findings with existing literature on individuals with various neurodevelopmental disorders and chronic conditions underscores the potential efficacy of CBT in addressing the needs of individuals with FXS. These results advocate for further investigation into the effectiveness of CBT tailored specifically for FXS, highlighting its potential as a therapeutic approach in this population.

At least in Italy, CoM represents the first nCBT group intervention performed with young adults with FXS. In this context, the results become even more relevant, given that the interventions available in local services are still scarce.

#### 4.1. Limitations and strengths of the current study

Despite the overwhelmingly positive results reported here, some limitations warrant discussion: (1) The small sample size, which limits results' generalization and data interpretation. On the other hand, it is worthy considering that it is not easy to find people with the same syndrome and of the same age living in the same

Region. Thus, while statistically limited, the number of participants becomes more representative within the context of FXS being a rare genetic condition and a strength in our study. (2) The fact that CoM II represents a second stage-group intervention means that the possible influence of prior learning during CoM on the results of CoM II cannot be ruled out; on the other side, there is a need to point out that initially the intervention did not have any research purpose and that the choice to share findings with the scientific community reflects a commitment to bridge the gap between research and clinical practice. Indeed, since clinicians often do not engage in research, failing to share findings publicly not allow them to monitor the effectiveness of certain interventions. (3) The lack of blinded behavioral observation of targeted behaviors is a notable limitation. Since CoM was not initially designed for research purposes, blinded and/or single-case designs were not implemented. Consequently, the potential influence of caregiver expectations on parent-report ratings cannot be excluded. However, while blinded studies are generally superior, they pose significant challenges in clinical practice regarding cost and ethics. Additionally, it is important to consider that the intervention was directly requested by the Italian Association of Fragile X Syndrome – Apulian Region, and thus CoM was implemented to respond to the specific needs of participants and their caregivers. Therefore, the results of the current study should be generalized cautiously. (4) The absence of more representative measures, specifically tailored for adults with ID, posed significant challenges. Indeed, the lack of standardized tests for this population, particularly in Italian language, made material selection difficult. (5) The absence of a secondary comparison group, which prevents results' generalization and the formulation of more consistent conclusions. Future research undertaking additional methodologically rigorous studies, such as RCTs, is necessary to substantiate these findings.

Notwithstanding these limitations, the present study has different main strengths: (1) The strong positive therapeutic relationship, which is known to be a critical element in both adult and youth psychotherapies in promoting a receptive attitude toward change, engagement, and the ability to cope with the sense of helplessness experienced by many patients (Labouliere, Reyes, Shirk, & Karver, 2017). The therapeutic alliance not only enabled the young adults with FXS to feel understood and supported but also emphasized that disability is a limitation only if we choose to define it as such. (2) An additional strength lies in the application of standardized pre- and post-treatment assessments, addressing the limitations of CoM, allowing to validate previous qualitative data and to quantify effective changes following CoM II intervention. (3). The inclusion of distinct aims achieved in specific sessions within a structured intervention constitutes a significant strength. Indeed, this methodology enhances the study's replicability across different groups (such as individuals with ID in FXS or similar cognitive-behavioral phenotypes) and geographical locations, facilitating comparisons and collaborations among clinical researchers. (4) The relationship formed between CoM members, some of whom became real friends and started to go out together during their free time (two of them even started a romantic relationship during the intervention). Effectively, participants in group interventions usually have the chance to develop relationships with other members, appreciating the opportunity for social interaction, which suggests that group CBT may be particularly appropriate for people with ID, who often face social isolation. In our study, the shared genetic condition among participants may have further facilitated the clinical improvement. This observation aligns with the broader literature emphasizing the importance of social connections in therapeutic settings (Smith et al., 2020).

## 5. Conclusions

Notwithstanding these limitations and although more research in the area is required, the current study underscores the feasibility of a group intervention that integrates cognitive-behavioral and neuropsychological techniques to target the diverse clinical manifestations of FXS in a unified method. This approach holds promise for this population and should be further pursued, mostly with growth when life becomes more demanding and there is a documented cognitive/adaptive decline in FXS phenotype. Furthermore, considering the current problems of the public mental health services in meeting the needs of people with ID (Kroese et al., 2013; Pouls et al., 2022), a multi-integrated approach represents an encouraging advancement in delivering care to vulnerable individuals who might otherwise lack access to treatment. Finally, based on the results of this and the previous study (Montanaro et al., 2023) and on the experience of the intervention developers, future directions in the assistance of young adults with FXS (and in general with ID) should include: 1) orientation programs to new professionals who want to work in the Fragile X field, incorporating opportunities for shadowing and mentorship under experienced colleagues; 2) the implementation of assessment and treatment materials specifically tailored for adults with ID, in order to avoid the ceiling and floor effects during the evaluation and to present more engaging rehabilitation exercises to patients; 3) a more robust liaison with employment centres, local universities and social inclusion services, with the aim to enhance the adaptive functioning of adults with ID, who may no longer have real opportunities for integration after finishing

high school.

In conclusion, considering that CBT is already established as a first-line treatment for anxiety and depression disorders (American Psychiatric Association, 2010; National Institute for Health and Clinical Excellence, NICE, 2011), and with emerging evidence supporting its effectiveness for emotional disorders among individuals with ID, we suggest the incorporation of cognitive and neuropsychological interventions in the treatment of clinical manifestations associated with FXS.

## Funding

This research received no external funding.

## CRedit authorship contribution statement

**Giuseppina Spano:** Formal analysis, Data curation. **Andrea Bosco:** Investigation, Formal analysis, Data curation. **Stefano Vicari:** Supervision. **Paolo Alfieri:** Writing – review & editing, Validation, Supervision, Conceptualization. **Cristina Caciolo:** Writing – review & editing, Writing – original draft, Data curation. **Federica Alice Maria Montanaro:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

## Data Availability

Data will be made available on request.

## Acknowledgments

We wish to thank “Associazione Italiana Sindrome X Fragile” and “Associazione Italiana Sindrome X Fragile—Sezione Puglia” for their support. We also thank the participants IM, LG, ST, PG, MM, AT, SC, BG, FB and MM, for their enthusiasm and motivation. Finally, we thank the educators/care assistants Simona Maria Muraglia, Simona Tiriolo, Elio Mastrofilippo, Stefania Luggeri and Rosa Garzilli for the participation to the project. This work was supported also by the Italian Ministry of Health with "Current Research" funds".

## Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Department of Education, Psychology, and Communication, University of Bari ‘Aldo Moro’. ET-23-15

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ridd.2024.104839](https://doi.org/10.1016/j.ridd.2024.104839).

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