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ORIGINAL CONTRIBUTION

Cooperative parent-mediated therapy for Italian preschool children with autism spectrum disorder: a randomized controlled trial

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Abstract
Parent-mediated intervention is widely used for pre-schoolers with autism spectrum disorder (ASD). Previous studies indicate small-to-moderate effects on social communication skills, but with a wide heterogeneity that requires further research. In this randomized controlled trial (RCT), cooperative parent-mediated therapy (CPMT) an individual parent coaching program for young children with ASD was administered to preschool children with ASD. All children received the same low-intensity psychosocial intervention (LPI) delivered in community settings, to evaluate the potential additional benefit of CPMT. Thirty-four participants with ASD (7 females; 27 males; aged 2, 6, 11 years) and their parents were included in the trial. The primary blinded outcome was social communication skills, assessed using the ADOS-G social communication algorithm score (ADOS-G SC). Secondary outcomes included ASD symptom severity, parent-rated language abilities and emotional/behavioral problems, and self-reported caregiver stress. Evaluations were made at baseline and post-treatment (at 6 months) by an independent multidisciplinary team. Results documented that CPMT showed an additional benefit on LPI with significant improvements of the primary blinded outcome, socio-communication skills, and of some secondary outcomes such as ASD symptom severity, emotional problems and parental stress related to parent–child dysfunctional interaction. No additional benefit was found for language abilities. Findings of our RCT show that CPMT provide an additional significant short-term treatment benefit on ASD core symptoms, when compared with active control group receiving only LPI.

Keywords Autism spectrum disorder · Parent-mediated therapy · Preschool children · Additional therapeutic effect

Introduction

Autism spectrum disorder (ASD) is a set of heterogeneous neurodevelopmental disorders, characterized by early-onset difficulties in communication and reciprocal social interaction, associated with unusually restricted and repetitive behavior and interests [1]. ASD is a lifespan disorder, which affects about 1% of the world population and often determines reduced adaptive competencies [2].

Among the empirically validated treatments, psychosocial interventions, clinician or parent delivered, have been shown to improve some aspects of ASD, namely ASD core symptoms, emotional/behavioral disorders, and children's adaptive life skills [3–6]. Psychosocial interventions vary in a continuum, ranging from highly structured applied behavioral analysis (ABA) approaches, to naturalistic developmental behavioral interventions (NDBI) and developmental socio-pragmatic models [5, 7, 8]. Moreover, evidence-based psychosocial interventions also include structured teaching models, such as the treatment and education of autistic and communication related handicapped children TEACCH [9].

French and Kennedy's recent systematic review [6] of randomized controlled trials (RCTs) on psychosocial interventions for children with ASD up to 6 years of age documented significant improvements in both clinician- and parent-implemented interventions, with small effects and limited methodological quality of research. Furthermore, most studies have been conducted in a limited world geographical area since more than half the studies (34/48) were carried out in the United States.

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Concerning specifically the parent-mediated interventions (PMI), a recent meta-analysis of Nevill et al. [10] showed similar results to those reported in French and Kennedy's review. Indeed, the meta-analysis took into account 19 RCT on PMI for preschool children with ASD and confirmed that most outcomes in core symptoms of parent-delivered intervention were associated with small effects and low methodological quality of studies [10]. Regarding the overall efficacy of PMI, effect sizes were rated low for the outcome considered such as ASD symptom severity, socialization, communication-language, and cognition. The weighted Hedges' g varied from 0.18 (communication-language) to 0.27 (socialization) and averaged 0.23 across domains. However, results from the different studies included in the meta-analysis were heterogeneous. For example, concerning the socialization domain (socio-communicative skills) and ASD symptoms severity, Aldred's results [11] showed higher effect size ($g = 0.78$), than others [12–14]. Nevill et al. [10] have rated the methodological quality of research as moderate for ASD symptom severity, communication-language, and cognition, and very low for socialization. Furthermore, the meta-analysis [10] also documented that most of the studies had been conducted in a limited geographical area. More than half of them (10/19) took place in the United States and few studies are conducted in Europe.

Parent-mediated intervention (PMI) is widely used for pre-schoolers with autism spectrum disorder (ASD). Currently many guidelines [15–17] and intervention models, also in Italy [18, 19] recommend the inclusion of parents but, as mentioned above, recent systematic reviews and meta-analysis show general limited effectiveness and variability in results [10, 19, 20]. To better understand this heterogeneity in efficacy related to ASD core symptoms, scholars suggest a more detailed description of PMI features, taking into account the dose as well as theoretical model of reference, scope (comprehensive or targeted) and format [5, 21]. Additionally, some researchers suggest that studies should take into account methodological features such as the great variety in outcome measures, the use of Treatments As Usual as a control group, children and caregivers 'features, context characteristics, especially in early intervention programs for health and education [5, 22, 23].

The present study is the first RCT conducted in Italy in order to evaluate the potential benefits of a parent-mediated intervention taking into account dose and type of control group.

The aim of the present RCT, conducted in Italy, is to evaluate the additional benefit of CPMT, a targeted PMI, based on NDBI approaches. We aim to evaluate whether the association of CPMT with LPI produces an additional benefit for ASD core symptoms, compared with an active control group (ACG) receiving only LPI. Previous longitudinal study of LPI compared with TAU, conducted by our research group [24], showed a significant reduction of emotional and behavioral problems but no significant improvement in ASD core symptoms was found.

The primary outcome was the socio-communicative domain of children with ASD. Secondary outcomes were ASD symptom severity, children's language abilities, emotional/behavioral problems, and parental stress in caregivers. We hypothesize that CPMT could provide additional benefit for the socio-communicative skills. In addition, we hypothesize that promoting the socio-communicative skills could also improve abilities which are not a direct target of therapy, for instance ASD symptom severity, language (lexicon), emotional/behavioral problems, and parental stress.

Methods

Study design

The study design is a rater-blinded RCT of two parallel groups: CPMT group (LPI plus CPMT) and ACG (only LPI). Evaluations were made at pre-randomization baseline and after 6 months of intervention, at the Child Neuropsychiatry Unit of the IRCCS Children's Hospital Bambino Gesù in Rome. The hospital's ethics committee approved the study and parents provided written informed consent. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

After completing primary and secondary outcome measures (baseline), families were randomly assigned to a CPMT group or to an ACG, stratified according to child's age and cognitive/developmental functioning. Treatment allocation was determined at the start of the study and revealed to coordinators, research assistants, and families only after completing the baseline assessment. All outcome measures were assessed at baseline (Time 0) and at 6 months post-treatment (Time 1) for both groups. All participants completed the intervention in 6 months.

Seventy preschool children with a clinical suspicion of ASD were recruited consecutively from June 1st 2011 to December 30th 2012 through the outpatient service of the Child Neuropsychiatry Unit of the Children' Hospital, and referred to the Specialist Unit for ASD of the Hospital. All children were assessed by a multi-professional team of neuropsychiatrists, psychologists and speech therapists. Out of the 70 children, 36 were excluded from the study, 29 children did not meet DSM-IV TR diagnostic criteria for autistic disorder or were below the autism spectrum cut-off on the ADI-R and ADOS-G; 7 children were excluded for epilepsy. Figure 1 shows the flowchart of study enrolment, treatment

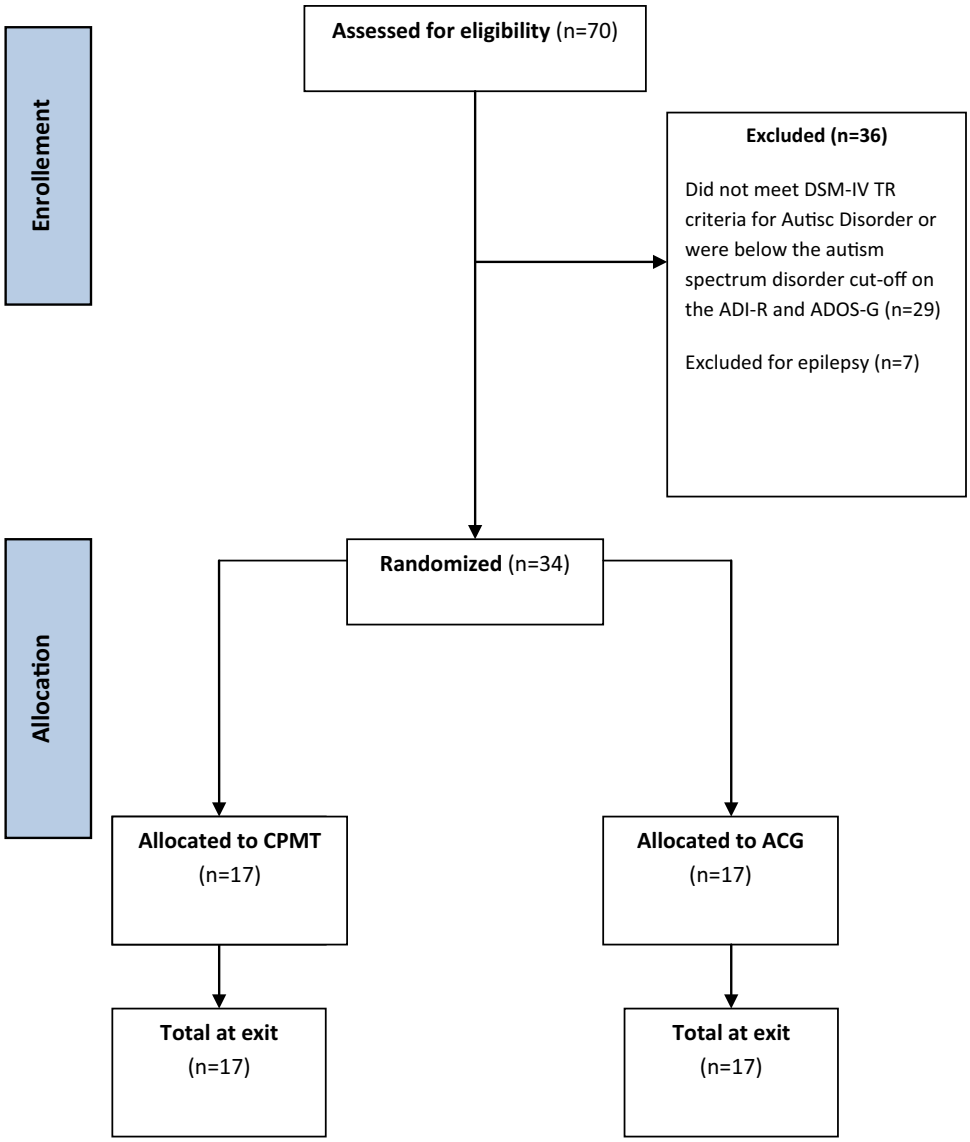

Fig. 1 Flow diagram

allocation. After consent and baseline assessment, family details were registered at hospital office and independent statistician assigned identification number to each family. Children were randomly assigned to either the CPMT group or to the ACG, stratified by age (2–4.5 years; 4.6–6.11 years) and cognitive level. The statistician informed the trial office and clinical teams of allocation. Assessments were made at pre-randomization baseline and after 6 months of treatment. Assessors and supervising research staff were independent from therapists and were unaware of treatment allocation and method of randomization. Families and therapists could not be blinded to treatment allocation.

Parents of the children gave informed consent. All families received an information sheet, which was read to participant's parents prior to asking their consent, with a copy handed to them to take home, and a separate sheet on which the consent was recorded. Explicit information about the project was given on the consent form, either as bullet points or extended text. The name and signature of the person taking the participants through the consent procedure was recorded. The privacy of participants was guaranteed according to the data protection law.

Thirty-four pre-schoolers (27 males, 7 females) were enrolled in the study on the basis of the following inclusion criteria: (a) age between 2 and 6.11 years; (b) clinical diagnosis of autistic disorder according to the criteria of the DSM-IV TR [25]; (c) scores above the autism spectrum cut-off on the Autism Diagnostic Observation Schedule Generic—ADOS-G [26] and the Autism Diagnostic Interview-Revised—ADI-R [27]; (d) no other major medical diagnosis (epilepsy, genetic syndromes); (e) children and their families received only LPI treatment and no other psychosocial treatment for the 6 months of the trial. The demographic characteristics (i.e., age, level of education and

occupation) of parents of CPMT group and ACG are shown in Table 1.

Measures

All participants were assessed at baseline (T0) and after 6 months (T1) at the end of the interventions. Specifically, ADOS-G [26], Italian version of MacArthur Communicative Development Inventories—MCDI [28], Child Behavior Checklist 1.5–5 CBCL 1.5–5 [29] and parental stress index—PSI [30] were administered at T0 and T1. ADI-R [27] was administered only at T0 to confirm clinical diagnosis. The cognitive or developmental level of participants was assessed only at baseline (T0) by the Brief-IQ from Leiter-R [31] or by the Global Developmental Quotient (GDQ) from GMDS-ER [32]. If the child failed to complete Leiter-R, due to his/her reduced attentional resources, the GMDS-ER was administered. The Leiter-R and GMDS-ER investigate cognitive abilities in a different and in a non-overlapping way, however the number of children evaluated with GMDS-ER was the same in both groups For both measures, a score was obtained on a scale calibrated with a mean of 100 and SD 15, thanks to the formula which allows to get scores on a common scale [33].

Children were considered with cognitive impairment if the Brief-IQ or GDQ was less than 70, and without cognitive impairment if the Brief-IQ or GDQ was equal to or higher than 70. A multidisciplinary team, including one neuropsychiatrist, two child psychologists and one speech therapist, conducted the evaluations. Raters were blind to the assigned treatment.

Primary outcome

The primary outcome measure was social communication domain assessed by *ADOS-G social communication algorithm score (ADOS-G SC),* a standardized diagnostic algorithm score on communication and reciprocal social interactions domains; this total algorithm score was used at screening to assist diagnosis and to measure change in autistic symptoms during treatment. The Autism Diagnostic Observation Schedule Generic—ADOS-G is a semi-structured, standardized assessment of social interaction, communication, play, and imaginative use of materials for individuals with autism spectrum disorder. Modules 1 or 2 were used for each child, and we used the same module at baseline and at the end of intervention and the number of children evaluated with mod.2 was very similar in the two groups, 3 out 17 in CPMT and 2 out 17 in ACG.

Inter-rater reliability was good, resulting in an intra-class-correlation of 0.8.

Secondary outcomes

Concerning the secondary outcomes measures, ASD symptom severity was assessed by the ADOS Calibrated Severity Scores—CSS for ADOS-G [34] that it is a metric useful in comparing assessments across modules and time. For detecting emotional and behavioral problems, the caregiver's report on the Child Behavior Checklist CBCL1.5–5 [29] was used. Scores on the internalizing subscale (CBCL-INT) and externalizing subscale (CBCL-EXT) were considered in the analysis. Different aspects of perceived stress in the parenting role were assessed by the Parental Stress-Index Short Form questionnaire—PSI [30], which gives a measure of parental distress (PSI-PD), Parent–Child Dysfunctional Interaction (PSI-PCDI), and Difficult Child (PSI-DC). The Receptive (REC) and Expressive (EXP) language abilities (lexicon) were assessed by the Italian version of the MacArthur Communicative Development Inventories—MCDI [28]. Parents completed the MCDI that includes word comprehension (maximum score = 370), word expression (maximum score = 370), and gestures (maximum score = 60). Raw data

Table 1 Parent demographic characteristics of CPMT group and ACG

	CPMT group		ACG	
	Mothers ($n = 17$)	Fathers ($n = 17$)	Mothers ($n = 17$)	Fathers ($n = 17$)
Age (years), mean (SD)	31.2 (5.4)	36 (3.4)	31.5 (4.4)	34.6 (4.6)
Education (%)				
Middle/elementary school	12	18	12	24
High school	41	35	41	29
University	47	47	47	47
Occupation (%)				
Not employed	47	0	41	0
Technical, small employers, others	41	65	29	53
Managerial/professional [30]	12	35	29	47

CPMT group cooperative parent-mediated therapy group, *ACG* active control group

were used instead of standard scores because the children in the study were older than those in the normative groups.

Interventions

Low-intensity psychosocial intervention (LPI)

All 34 children received the same LPI, controlled for dose and type. The LPI is a community-based TEACCH inspired intervention described in a previous study [24]. The LPI was delivered at home and at school (4 h per week) by well-trained therapists supervised by a clinical psychologist with formal training in the TEACCH program.

Teachers were blinded to children's treatment group allocation (CPMT group or ACG). They were informed about the objectives of the LPI and supported the therapist in reaching the goals of the intervention. All children attended mainstream classes with support teachers in a one-to-one relationship for 12 h per week.

Cooperative parent-mediated therapy—CPMT

The CPMT is a parent coaching program that has already been adopted in the Children and Adolescent Mental Health Services of the Italian National Health System. More recently, CPMT has also been implemented at the Child Neuropsychiatry Units of the Bambino Gesù Children' Hospital. Following Bearss' Parent Training taxonomy [21], CPMT is a targeted parent-mediated intervention focused on the ASD core symptoms. CPMT is based on the most significant models of parent training for ASD [4], in the perspective of Naturalistic Developmental Behavioral Interventions—NDBI [8] with specific attention to the promotion of cooperative interactions [35–37].

The aim of CPMT was to improve parental skills, to enable parents to promote in their child the following seven target skills: socio-emotional engagement, emotional regulation, imitation, communication, joint attention, play and cognitive flexibility, and cooperative interaction. For each target skill an individualized treatment plan was designed for each child in order to determine his developmental level and treatment goals. To assess the current level of the child on each target skill and to program individualized short-term and long-term goals, therapist completes a checklist based on the 7 target skills at the beginning of the intervention CPMT strategies used were live active coaching in association with live modeling, live and video feedback.

The CPMT was performed in a dedicated playroom at the hospital; the setting was organized with toys suitable for each child's age range (toys different from those used for the assessment). As mentioned above, parents and their child followed the therapy for 6 months, for a total amount of 15 sessions of 60 min; twelve core sessions (one session per week) were delivered in the first 3 months, followed by 3 monthly booster sessions. Each weekly core session had a specific focus and specific intervention strategies based on active parent coaching during parent–child interaction, and included the parent–child dyad with the parent being actively coached by a trained therapist. Live active coaching increases parents' competence in implementing strategies to enhance child development, and at the same time increases their confidence that they are able to do so, following the caregiver capacity-building approach [38, 39]. Regarding the parent–child interaction, the therapist coached parents in order to develop specific strategies related to the main topics of the session and provided live modeling and specific live feedbacks on the parents' use of these strategies and the child's response, in order to promote and facilitate the child's acquisition of specific skills. Feedbacks were provided to the parents during parental–child interaction in each session and by video feedback in five specific sessions. At the end of each session, a memorandum on each specific topic was given to the parents and homeworks were assigned. Parents were required to work daily for at least 1 h with the child. All interactions between parent, child and therapist were video-taped. At the first and last session, parent–child spontaneous interactions were video-recorded for future video coding. Parents were required to play spontaneously with the child with a specific set of toys (different from those used in the sessions). Two clinical psychologists, specifically trained in intervention in ASD, administered the CPMT. The clinical psychologists were trained in CPMT through direct supervision and video analysis by the child neuropsychiatrist who had implemented the CPMT (GV).

Statistical analysis

On the basis of available information, ADOS-G SG showed a standard deviation between subjects (SD_b) of 4.5 points and the correlation between two measures 6 months apart was 0.7, indicating that about 50% of variance of the second assessment could be accounted for by the first. Thus, assuming homogeneity of variances at the two times, SD of changes was estimated to be $SD_b[2 \times (1 - r)] = 4.5 \times [2 \times (1 - 0.7)]$ 3.5. We considered that the minimal clinically important difference should be equal to 4 points. It is noteworthy that Green [13] documented that CPMT produced a decrease of such an extent (3.9). According to these assumptions and expectations, a sample size of $14 + 14 = 28$ subjects was defined in order to have a probability of at least 80% (power = 0.83) to detect the above effect as significant (at two-sided alpha level of 0.05). To be noted that the ratio between the minimal clinically important difference (4 points) and SD of changes (3.5) result in a standardized effect size (SES) of 1.14, which should be considered a

"very large effect size", given that SES = 0.8 is conventionally classified as "large".

To assess the efficacy of CPMT on the primary endpoint, a repeated measures ANOVA (RM-ANOVA) was applied with ADOS-G SC as dependent variable, time (two levels: T0 and T1) as within-subjects factor and treatment (two levels: CPMT group and ACG) as between-subjects factor. Even if treatments were randomly assigned and no evidence of baseline differences were found between the two arms, in the statistical model the effect of potential confounders was taken into account. Thus, age, cognitive/developmental functioning and baseline ADOS-G SC were also entered as covariates (RM-ANCOVA). An additional reason to apply this procedure was the small sample size, since it is known that, in small size studies, slight baseline imbalance could result in inaccurate estimations. Findings with and without use of covariates are reported as sensitivity analysis. In case of significant treatment × time interaction, the two within-treatment T0–T1 comparisons were performed and a 0.05/2 = 0.025 two-sided alpha level was chosen as significant threshold. In addition, the difference between the two within-treatment changes was computed and reported as Cohen's delta as standardized effect size estimation.

The same approach was used also for the secondary outcomes: ASD symptom severity, children's language abilities, emotional/behavioral problems, and parental stress in caregivers.

Results

No evidence of baseline significant differences was found between the CPMT group and the ACG (Table 2).

Primary outcome results

Socio-communicative skills (ADOS-G SC)

According to RM-ANOVA, a significant group × time interaction was found [$F(1,32) = 4.149$; $p = 0.050$].

After adjusting for covariates (age, IQ/GDQ and ADOS-G SG baseline), the significance of the interaction was strengthened [$F(1,29) = 4.821$; $p = 0.036$), indicating that the decrease observed in CMPT group was larger than that found in ACG group. Bonferroni-adjusted post hoc comparisons indicated that T0–T1 change in CPMT group was significant (3.1; 95% CI 1.6, 4.7), while in ACG no evidence of change was found (+ 0.9; 95% CI − 0.7, 2.4).

Cohen's delta resulted equal to 0.58 (Tables 3, 4).

Table 2 Descriptive statistics of both groups at baseline

Sex, males (*n*, %)	CPMT group			ACG			*p* value
		n	%		*n*	%	
		14	82%		13	86%	0.671
	N	Mean	SD	*N*	Mean	SD	
Age (years)	17	4.4	1.3	17	4.2	0.9	0.653
IQ/DGQ	17	75.3	21.0	17	73.0	24.6	0.772
ADOS-G SC	17	13.1	4.1	17	13.0	4.8	0.97
CSS	15	5.7	1.2	16	6.3	1.6	0.262
MCDI-REC	12	59.9	66.9	10	64.2	34.3	0.262*
MCDI-EXP	12	23.6	41.1	11	16.7	17.3	0.615*
CBCL-INT	17	59.4	7.1	17	61.4	9.8	0.501
CBCL-EXT	17	53.9	6.5	17	58.0	8.7	0.134
PSI-PD	16	29.0	6.6	15	25.4	8.8	0.208
PSI-PCDI	16	26.6	5.5	15	25.3	6.1	0.541
PSI-DC	16	37.3	9.4	15	38.5	7.3	0.691

IQ Brief-IQ from Leiter–R, *GDQ* Global Developmental Quotient from GMDS-ER, *ADOS-G SC* ADOS-G social communication algorithm score of Autism Diagnostic Observation Schedule Generic, *CSS* ADOS Calibrated Severity Scores, *MCDI-REC* receptive language, *MCDI-EXP* expressive language of MacArthur Communicative Development Inventories, *CBCL-INT* CBCL1.5–5 internalizing subscale, *CBCL-EXT* CBCL1.5–5 externalizing subscale, *PSI-PD* Parental Distress, *PSI P-CDI* parent–child dysfunctional interaction, *PSI-DC* Difficult Child subscales of Parental Stress-Index (PSI), *CPMT group* cooperative parent-mediated therapy group, *ACG* active control group

**t* test after log-transformation

Table 3 Descriptive statistics of primary and secondary outcomes mean and standard deviation at 6 months post-treatment

	CPMT group			ACG		
	N	Mean	SD	*N*	Mean	SD
Primary outcome						
ADOS-G SC	17	9.9	4.0	17	12.2	4.8
Secondary outcomes						
CSS	15	4.9	1.2	15	6.0	1.5
MCDI-REC	12	103.3	104.2	7	79.7	25.9
MCDI-EXP	12	59.7	104.2	8	43.3	52.1
CBCL-INT	17	53.8	7.6	16	61.6	6.9
CBCL-EXT	17	51.2	7.3	16	57.1	8.0
PSI-PD	16	25.1	9.1	15	26.1	9.5
PSI-PCDI	16	22.5	5.3	15	25.9	6.9
PSI-DC	16	36.1	12.4	15	35.3	9.2

ADOS-G SC ADOS-G social communication algorithm score of Autism Diagnostic Observation Schedule Generic, *CSS* ADOS Calibrated Severity Scores, *MCDI-REC* receptive language, *MCDI-EXP* expressive language of MacArthur Communicative Development Inventories, *CBCL-INT* CBCL1.5–5 internalizing subscale, *CBCL-EXT* CBCL1.5–5 externalizing subscale, *PSI-PD* parental distress, *PSI P-CDI* parent–child dysfunctional interaction, *PSI-DC* Difficult Child subscales of Parental Stress-Index (PSI), *CPMT group* cooperative parent-mediated therapy group, *ACG* active control group

Secondary outcome results

ASD symptoms severity (ADOS-CSS)

ASD symptom severity was assessed by ADOS-CSS. According to RM-ANOVA, group × time interaction was not significant [$F(1,28) = 2.800$; $p = 0.105$]. After adjusting for covariates (age, IQ/GDQ and ADOS-CSS baseline), the interaction became significant [$F(1,25) = 7.215$; $p = 0.013$], being the decrease observed in CPMT group larger than that found in ACG group. Bonferroni-adjusted post hoc comparisons indicated that T0–T1 change in CPMT group was significant (+ 0.9; 95% CI + 0.5, + 1.3), while in ACG no evidence of change was found (− 0.2; 95% CI − 0.3, 0.6). Cohen's delta resulted equal to 0.77 (Tables 3, 4).

Behavioral and emotional problems (CBCL)

Behavioral and emotional problems were assessed by CBCL1.5–5. Results documented a significant group × time effect for CBCL-INT [$F(1,31) = 8.257$, $p = 0.007$], but not for CBCL EXT [$F(1,31) = 0.829$, $p = 0.370$]. After adjusting for covariates (age, IQ/GDQ and CBCL-INT baseline), the significance of the interaction was strengthened [$F(1,28) = 13.601$; $p = 0.001$], with the decrease observed in CMPT group larger than that found in ACG group. Bonferroni-adjusted post hoc comparisons indicated that T0–T1 change in CPMT group was significant (+ 6.1; 95% CI + 3.6, + 8.5), while in ACG no evidence of change was found (+ 0.3; 95% CI − 2.2, 2.8). Cohen's delta resulted equal to 1. Regarding CBCL-EXT, even after covariates-adjustment, no significant group × time interaction was found [$F(1,28) = 2.980$; $p = 0.095$]. However, Bonferroni-adjusted post hoc comparisons showed a significant improvement in CPMT group (+ 3.6; 95% CI + 0.5, + 6.7), countered by a lack of change in ACG (− 0.2; 95% CI − 3.4, 3.0). Cohen's delta resulted equal to 0.47 (Tables 3, 4).

Parental stress (PSI)

Finally, for parental stress, assessed by PSI, ANOVA indicated a significant group × time effect for PSI-PCDI [$F(1,29) = 5.986$, $p = 0.021$] and for PSI-PD [$F(1,29) = 4.718$, $p = 0.038$] and not for PSI-DC [$F(1,26) = 0.274$, $p = 0.605$]. After adjusting for covariates (age, IQ/GDQ and PSI-PCDI baseline), the significance of the interaction for PSI-PCDI was strengthened [$F(1,26) = 6.355$; $p = 0.018$], indicating that the decrease observed in CMPT group was larger than that found in ACG group. Bonferroni-adjusted post hoc comparisons showed that T0–T1 change in CPMT group was significant (+ 4.0; 95% CI + 1.5, + 6.5), while in ACG no evidence of change was found (− 0.5; 95% CI − 3.0, 2.1). Cohen's delta resulted equal to 0.71. Taking into account covariates, the significance of group × time interaction was not confirmed for PSI-PD [$F(1,26) = 2.672$; $p = 0.114$]. To be noted that Bonferroni-adjusted post hoc comparisons showed a significant improvement in CPMT group (+ 3.4; 95% CI + 0.3, + 6.6) and no change in ACG (− 0.3; 95% CI − 3.5, + 3.0; Cohen's delta resulted equal to 0.46). Similarly, group × time interaction remained nonsignificant for PSI-DC [$F(1,26) = 0.099$; $p = 0.756$], without any significant change between T0 and T1 in both groups.

Table 4 *Primary* and *Secondary* Outcomes at 6 months post-treatment in both groups

Outcome measure	CPMT group				ACG				Treatment × time interaction		
	Change (T0–T1)	95% CI		*p* value	Change (T0–T1)	95% CI		*p* value	Statistical test	*p* value	Effect size (Cohen's delta)
Primary outcome											
ADOS-G SC	3.1	1.6	4.7	< 0.001	0.9	− 0.7	2.4	0.257	$F(1,29) = 4.821$	0.036	0.58
Secondary outcome											
CSS	0.9	0.5	1.3	< 0.001	0.2	− 0.3	0.6	0.452	$F(1,25) = 7.215$	0.013	0.77
MCDI-REC	− 44.5	− 68	− 21	0.001	− 12.3	− 43	18	0.401	$F(1,14) = 3.230$	0.094	0.69
MCDI-EXP	− 33.6	− 60	− 7	0.017	− 28.5	− 61	4.1	0.082	$F(1,14) = 0.066$	0.800	0.09
CBCL-INT	6.1	3.6	8.5	< 0.001	− 0.3	− 2.8	2.2	0.793	$F(1,28) = 13.601$	0.001	1
CBCL-EXT	3.6	0.5	6.7	0.023	− 0.2	− 3.4	3.0	0.892	$F(1,28) = 2.980$	0.095	0.47
PSI-PD	3.4	0.3	6.6	0.034	− 0.3	− 3.5	3.0	0.868	$F(1,26) = 2.672$	0.114	0.46
PSI P-CDI	4.0	1.5	6.5	0.003	− 0.5	− 3.0	2.1	0.720	$F(1,26) = 6.355$	0.018	0.71
PSI-DC	1.7	− 3.4	6.7	0.507	2.8	− 2.5	8.0	0.285	$F(1,26) = 0.099$	0.756	0.09

ADOS-G SC ADOS-G social communication algorithm score of Autism Diagnostic Observation Schedule Generic, *CSS* ADOS Calibrated Severity Scores, *MCDI-REC* receptive language, *MCDI-EXP* expressive language of MacArthur Communicative Development Inventories, *CBCL-INT* CBCL1.5–5 internalizing subscale, *CBCL-EXT* CBCL1.5–5 externalizing subscale, *PSI-PD* parental distress, *PSI P-CDI* parent–child dysfunctional interaction, *PSI-DC* Difficult Child subscales of Parental Stress-Index (PSI), *CPMT group* cooperative parent-mediated therapy group, *ACG* active control group

Language abilities (MCDI)

Measures ANOVA on receptive and expressive MCDI (MCDI-REC and MCDI-EXP) did not document any significant difference in effect between groups neither for MCDI-REC [$F(1,17) = 1.904$, $p = 0.185$ nor for MCDI-EXP [$F(1,18) = 0.165$, $p = 0.690$]. After adjusting for covariates (age, IQ/GDQ and MCDI-REC baseline) no clear significant group × time interaction was found for MCDI-REC [$F(1,14) = 3.230$; $p = 0.094$]. However, according to Bonferroni-adjusted post hoc comparisons in CPMT group a significant increase of understood words was found (+ 44.5; 95% CI + 21.3, + 67.6), while no change in ACG (+ 12.2; 95% CI − 18.1, 42.6). Cohen's delta resulted equal to 0.69. Regarding MCDI-EXP, no significant group × time interaction was found after adjusting for covariates (age, IQ/GDQ and MCDI-EXP baseline) [$F(1,14) = 0.066$; $p = 0.800$]. Bonferroni-adjusted post hoc comparisons showed a significant increase of produced words in CPMT group (+ 33.6; 95% CI + 7.1, + 60.2) and a less evident increase in ACG (+ 28.5; 95% CI − 4.1, + 61.2). Cohen's delta resulted equal to 0.09 (Tables 3, 4).

Discussion

The present RCT was designed to assess the additional benefit of applying cooperative parent-mediated therapy (CPMT) associated with LPI for Italian preschool children with ASD compared to ACG. Both groups performed the same LPI controlled for dose and type, but the intervention group also underwent CPMT. The specific objective of the current study was to verify if the addition of CPMT could improve ASD core symptoms, in particular our primary outcome, the socio-communicative skills.

Our finding documented that CPMT showed an additional benefit with significant short-term improvement of socio-communication skills, ASD symptom severity, emotional problems and parental stress related to parent–child dysfunctional interaction. No additional benefit was found for parent-rated language abilities.

Regarding blinded primary outcome, social communication skills assessed by ADOS-G SC, was found a statistically significant difference in favor of the CPMT group (effect size 0.58). Specifically, only the CPMT group showed an ameliorative effect in socio-communication skills at T1, after 6 months of intervention, while ACG was stable (Tables 3, 4). This result is confirmed also by the significant improvement in ASD symptom severity (effect size 0.77) assessed by ADOS-CSS (Tab 4).

Our findings indicated a greater effect in ASD core symptoms than most RCT studies included in Neville's meta-analysis [10], where the average effect size in socialization skills was 0.27 and 0.30 in ASD symptom severity. Furthermore, the wide heterogeneity of results reported by Neville et al. [10], should be considered. Indeed, out of 19 RCT analyzed, 5 studies showed a medium effect size in socialization and ASD symptom severity [11, 14, 40–42]. Our results are consistent with those of Aldred's study [11], that showed short-term improvement of socio-communicative skills, assessed by ADOS-G (effect size $g = 0.78$). It should be emphasized that, in both studies a targeted PMI was delivered in a small but well-selected group of children with a diagnosis of autistic disorder. Our improvement in ASD core symptoms could be related to specific developmental and behavioral strategies centered on live active coaching, live modeling, live and video feedback to promote target skills adjusted to the child's developmental level.

Although CPMT did not directly focus on the associated emotional and behavioral problems, significant changes were observed in the CBCL-INT scale, a broad measure of emotional problems. Thus, only the CPMT group showed significant improvements in emotional problems (Table 3) and this significant result could be interpreted as the effect of the emotional regulation target skill, promoted by live active coaching. However, this correlation needs to be measured. Moreover, the reduction of internalizing problems is a further confirmation of the improvement of ASD symptoms, since different studies have described this cluster as a specific expression of autistic symptomatology [43].

Our findings on parental stress showed that parents who delivered intervention did not increase general parental stress [44, 45] and that the intervention specifically improves the stress associated with the perception of parent–child dysfunctional interaction (see PSI-PCDI subscale, Table 3). This specific improvement could be due to the use of live active coaching associated with strategies to promote caregiver capacity building, however his association needs to be proved.

Despite these appreciable questionnaires' results, should be taken with prudence as the informant was not blind.

Finally, no significant improvement in parent-rated language abilities (lexicon) was observed (Table 3). This result may be due to the fact that both interventions (CPMT group and ACG) were not specifically intended to increase children's lexical abilities; also, the duration of the intervention may have been too short to determine significant change in the lexicon and longer interventions would perhaps be more effective. The apparent contradiction between the lack of significant improvement in lexicon and enhancement in social-communication skills could also be due to the specific work of the CPMT to promote specifically non-verbal communication skills.

Several limitations of this study should be considered. First, our group was relatively small which could limit the generalizability of our findings; larger groups should be used

in future studies. Second, no follow-up assessment was performed, and this may question the stability of the results obtained. So, our results should be confirmed in larger independent groups with follow-up measures that also take into account generalization in other settings. Third, effective changes in parent–child interaction, a possible moderator [46, 47] were not quantitatively evaluated and only indirect observations were collected [20, 22].

Despite these limitations, our study clearly shows that a specific targeted PMI, CPMT, can lead to improvement after 6 months in ASD core symptoms, which are generally considered poorly modifiable, at least in the short term [10, 20]. We suppose that specifical aspects of the CPMT may explain our findings, for instance the use of developmental and behavioral strategies, following the NDBI approach [8], and the use of live active coaching to promote caregiver capacity building [38, 39]. CPMT attempts to improve a caregiver's ability to generate learning opportunities in everyday activities in order to promote the target skills based on the child's developmental level.

Another interesting feature of our study is that it was carried out, for the first time, in Italy. Indeed, of the 19 RCTs examined in the Nevill meta-analysis [10], 10 studies were conducted in the US [12, 14, 40–42, 48–51], three in Australia [52–54], three studies in the UK [11, 13, 55], one in Canada [56], one in Netherlands [57] and one in Thailand [58].Therefore, our study may contribute to expand the knowledge of the effectiveness of the therapy in children with ASD through the inclusion of a new geographical area with different social and cultural features [59–62].

Many guidelines [16, 17, 63] and intervention models, also in Italy [17, 18], recommend the inclusion of parents in the intervention but recent systematic reviews and meta-analyses show general limited effectiveness and great variability in results [10, 19, 20]. In order to increase our knowledge on this topic, it is probably necessary to better characterize the parent training features of interventions [21] taking into account the dose as well as the theoretical model of reference, the scope (comprehensive or targeted) and the format [5, 22]. Regarding ASD core symptoms, recent PMI studies show a generally low effect size but with significant heterogeneity, probably related to methodological features such as the great heterogeneity of outcome measures, the specific features of child, caregiver and context; in particular early intervention programs for health and education [23, 64].

In our study, we tried to control for some of these methodological features. Concerning the heterogeneity of outcome measures for the core symptoms of ASD, scholars recommend the use of standardized tests of social interaction which are reliable, can be blindly coded and are administered by researchers [65]. Following this recommendation, we used ADOS, one of the most validated tests, in order to evaluate the primary outcome [20]. Since ADOS captures the social communication of the child with an unfamiliar adult in a context which is different from the parent–child dyad or treatment setting, it provides a partial assessment for the generalization of behaviors in different contexts and with different partners.

Regarding children's characteristics, in Neville's meta-analysis [10], we found studies with considerable differences in the inclusion criteria. For example, in Roberts' study [53], all 84 children were included with a clinical diagnosis of pervasive developmental disorders—PDD, and ten children were outside the autism spectrum according to ADOS assessment. Other studies, such as Aldred's [11], included only children with a diagnosis of autistic disorder, confirmed in all clinical areas by ADI, but not by ADOS-G. Our study design was characterized by the choice of more restrictive inclusion criteria, a clinical diagnosis of autistic disorder confirmed by ADI and ADOS in all areas, in order to identify a more homogeneous and clinically significant sample.

Regarding the context, several studies have reported considerable geographical variability in early health and education intervention programs. Indeed, both in Europe and in the US it is possible to find significant differences among states [50, 66]. With this geographical variability in early intervention programs, the use of treatments as usual as a control group becomes questionable. Our study took these aspects into account by choosing an active control group, with the same dose and type of intervention in both groups. In addition, we also controlled the dose of special educational interventions: all children were included in mainstream classes with a support teacher for 12 h per week.

In conclusion, our RCT in Italian pre-schoolers with ASD shows that CPMT, a targeted PMI, based on NDBI approaches and on a caregiver capacity building model, is feasible and gives short-term benefit on ASD core symptoms when compared with ACG. We need further trials on larger and independent groups built on the current RCT, and long-term follow-up studies that also take into account generalization in other settings.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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