Effectiveness of parent training in improving stress-coping capability, anxiety, and depression in mothers raising children with autism spectrum disorder

Naoko Iida1,2
Yoshihisa Wada1,3
Tatsuhisa Yamashita1,4
Michiko Aoyama5,6
Kiyoshi Hiraj5,6
Jin Narumoto1

1Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan;
2Department of Child Psychiatry, Kyoto Prefectural Child Development Support Center, Kyoto, Japan;
3Fuchu-mikumari Hospital, Hiroshima, Japan;
4Department of Child and Adolescent Psychiatry, Yamashita Mental Health Clinic, Kyoto, Japan;
5Department of Pediatrics, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan;
6Department of Pediatrics, Kyoto Prefectural Child Development Support Center, Kyoto, Japan

Purpose: Raising a child with autism spectrum disorder (ASD) can be a stressor, and mothers of ASD children often present with high levels of stress and depression. Interventional steps to enhance parental coping skills and resiliency are more important for parental mental health and the family-centered care of children with ASD than merely reducing parental stress. Although the importance of stress-coping skills is well established, only a few studies have investigated interventional steps to improve parental coping or resiliency. Parent training (PT) is known to improve a mother’s mental health. Here, we aimed to assess the effectiveness of PT in improving the stress-coping style of mothers raising children with ASD.

Patients and Methods: Thirty mothers of children with ASD aged 4–11 years participated in this study. The mothers underwent PT based on the Hizen Parenting Skills Training in Japan, which comprised seven sessions. Each session included education on behavior therapy, individual consultation, and workshops in small groups. Sixteen mothers completed psychological assessment, including the Stress Coping Inventory, the Beck Depression Inventory Second Edition, the State–Trait Anxiety Inventory, and the Child Behavior Checklist conducted before and after 2 months of PT.

Results: The outcomes before and after the PT program were compared using the paired t-test and Pearson’s correlation. After the PT program, the mothers’ stress-coping strategy “positive appraisal” significantly increased (P<0.01) and “escape/avoidance” significantly decreased (P<0.01). The Beck Depression Inventory Second Edition (P<0.05) and the trait anxiety scores (P<0.01) also significantly decreased. The change in the stress-coping strategy “distancing” had a significantly negative correlation with the change in the externalizing Child Behavior Checklist T-scores of children with ASD (Pearson r=−0.518, P<0.05).

Conclusion: PT may be effective for mothers of children with ASD to improve their stress-coping style and to decrease their depression and trait anxiety.

Keywords: parent training, autism spectrum disorder, parents’ stress coping, anxiety, depression

Introduction

Parents of children with autism spectrum disorder (ASD) reported significantly higher levels of aggravation than parents of children with developmental problems other than autism or of those with other special health care needs as reported in the National Survey of Children’s Health.1,2 A meta-analysis comparing the experience of parenting stress suggested that parents of children with ASD experience more parenting stress compared to those of typically developing children in a large effect size.3 Child behavior problems,
but not daily living skills, were positively associated with parenting stress for mothers of both children with ASD and children with developmental delay (DD). Parents of children with ASD use “active avoidance” and escape-coping strategies, such as passive appraisal, more frequently than parents of typically developing children; Lai et al pointed out the importance of coping needs of parents of children with ASD. Estes et al concluded that parents’ abilities to manage and reduce behavior problems are a critical target for interventions for young children with ASD to improve child functions and decrease parenting-related stress.

Family resilience has attracted more attention as a contributing factor to the better coping capability of parents of children with ASD. A specific resilience process was reported, such as looking at disability positively, mobilization of resources, and unifying and coming closer as a family. A higher use of emotional support, social support, positive reframing, planning, humor, acceptance, and religion was also reported than in parents of typically developing children. It was noted that as positive cognitions increased, caregivers’ resourcefulness increased. These findings suggested the need for developing interventional steps to strengthen positive thinking among caregivers of persons with ASD. Zablotsky et al mentioned that strong maternal coping skills, emotional social support, and neighborhood social support were associated with a decreased risk of high maternal stress levels. The methods of stress coping on subscales of escape/avoidance had a positive relationship with depression, and positive coping was negatively associated with depression. Several researchers have reported that parenting stress is significantly affected by the type of coping strategies utilized and the social support received by parents.

Of the 34 studies reviewed, Kuhaneck et al recommended measurement of parental and family functioning in all future studies of pediatric interventions. Interventions to improve stress, parental self-efficacy, and coping skills are critical aspects of family-centered care for families of children with ASD. However, these interventions are yet to be fully studied. Kuhaneck et al indicated that, despite the well-acknowledged importance of coping skills, only a few studies have investigated interventional steps to improve parental coping or resiliency and that it is more important to focus on positive outcomes such as coping and resiliency, hopefulness, or quality of life as opposed to merely reducing parental stress.

Systematic reviews and a randomized clinical trial demonstrated that various types of parent training (PT) programs for children with ASD and their parents are reported to improve children’s disruptive behaviors, mothers’ mental health (depression and stress), and parent–child interaction. Special recommendations for PT programs included the use of individual sessions along with a workshop and/or group approach with an emphasis on parental knowledge along with skill and inclusion of overall family support. Few studies have investigated the change in parental coping through PT. Samadi et al had reported on 37 parents of children with ASD who participated in seven family-centered, group-based sessions that emphasized families sharing their experiences and learning from one another and providing information about ASD. The parents acquired significantly more use of problem-focused coping strategies after sessions assessed by the Coping Style Questionnaire. In Japan, PT was conducted in various groups for parents of children with developmental disorders. Hizen Parenting Skills Training (HPST), the first systematic program in Japan, is based on social learning theory, principles of operant theory, and behavioral modification. HPST comprises learning theory with group lectures and training techniques individually in a small group (2–3 persons). Menta et al conducted HPST and assessed 26 mothers of children with DD in relation to stress, depression, the degree of child behavior achievement, and knowledge of behavioral principals at pre-HPST, post-HPST, follow-up 1 (2 months later), follow-up 2 (6 months later), and follow-up 3 (1 year later); these improved after HPST and were maintained or improved after 1 year. However, the effect of PT on parental coping skills remains unclear. The purpose of this study was to investigate the effect of PT on the coping skills and mental health of mothers of children with developmental disorders, and children’s behavior.

Methods
Subjects
PT was conducted on 30 mothers at the Kyoto Prefectural Child Development Support Center between April 2013 and February 2016. The inclusion criterion was that mothers should consent to attending all the programs. All mothers were provided with a questionnaire, but responses were received from only 19 mothers. Omitting the missing data, 16 mothers remained as the study subjects. Table 1 details demographic data of the study mothers. All mothers were living with a partner and had an average age of 40.3 years (SD, 4.6). Nine mothers were homemaker, four had part-time jobs, and one had full-time employment; relevant information on two mothers was unknown. Regarding education, 10 mothers did not hold a university degree, two had a
Characteristics of the children

Table 2 lists the clinical characteristics of the children of mothers involved in the study. The children were diagnosed with pervasive developmental disorder. The diagnosis was made clinically using the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria. The diagnostic procedure involved a comprehensive interview with the parents and observation of the child’s behavior under the clinical setting. The Kyoto Scale of Psychological Development 2001 or the Wechsler Intelligence Scale for Children (WISC) – third edition was used for evaluation of the developmental quotient (DQ) or the full intelligence quotient (FIQ). The mean DQ/FIQ was 101.9 (SD, 22.0). All children were aged 5–11 years (mean, 6.8 years; SD, 2.0 years) and were boys. Parents completed the Child Behavior Checklist (CBCL). The average of the T-score of the internalizing broadband, externalizing broadband, and total problems scales was 62.1 (SD, 7.6), 67.1 (SD, 10.7), and 68.1 (SD, 6.1), respectively.

PT program

This study used the PT program fundamentally based on HPST, which requires mothers to actively acquire parenting skills and to learn coping skills against the problematic behaviors of their children with ASD. This PT had been conducted in community settings and clinical settings by the Study Group of Kyoto Parent Training. The PT program involved a small group of three to six mothers each and seven sessions of 2 hours each. The first half of each session (1-hour duration) was a lecture on behavior therapy that led children to behave in a socially appropriate manner. The latter half of each session (1-hour duration), when mothers were divided into two groups of two to three mothers in each group, was an individual consultation and a group workshop practicing real-time dealing. Each time, a homework sheet was handed out to record children’s behavior at home and mothers’ responses. We discussed, corrected, and praised the responses on the returned sheets. When we corrected, we gave lessons on a method, presented a model, and asked for role-play executions. Sessions 1–7 were held every 2 weeks for a total duration of 3 months. Follow-up was held 2 months after Session 7. This PT program was conducted by psychologists and doctors.

The contents and points of intervention in the seven sessions are listed in Table 3: Session 1, Orientation; Session 2, Observation and record of the behavior; Session 3, Structured teaching; Session 4, Reinforcement; Session 5, Help when your child cannot do; Session 6, How to decrease problematic behaviors; Session 7, Consideration of individual issues and summary.

1. Orientation: This session provided an introduction to ASD and behavior therapy.
2. Observation and record of the behavior: This session involved teaching one on how to observe, record, and analyze a behavior based on antecedent, behavior, and consequences.
3. Structured teaching: This session was about structured teaching via the treatment and education of autistic and communication-related handicapped children method involving physical structure, scheduling, work system, visual structure, and task organization.
4. Reinforcement: In this session, mothers were taught about positive reinforcement and the judicious use of reinforcements or a token economy system (reward) to increase appropriate behaviors. Mothers were also taught to focus

Table 1 Demographics of the study mothers

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>40.3 (4.6)</td>
</tr>
<tr>
<td>Level of education, n</td>
<td></td>
</tr>
<tr>
<td>University education</td>
<td>4</td>
</tr>
<tr>
<td>No university education</td>
<td>10</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>Working, n</td>
<td></td>
</tr>
<tr>
<td>Homemaker</td>
<td>9</td>
</tr>
<tr>
<td>Full-time job</td>
<td>1</td>
</tr>
<tr>
<td>Part-time job</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2 Characteristics of study children with ASD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>6.8 (2.0)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>DQ/IQ, mean (SD)</td>
<td>101.9 (22.0)</td>
</tr>
<tr>
<td>Siblings, n (%)</td>
<td></td>
</tr>
<tr>
<td>No siblings</td>
<td>3 (19)</td>
</tr>
<tr>
<td>With siblings</td>
<td>13 (81)</td>
</tr>
<tr>
<td>CBCL, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Total T-scores</td>
<td>68.1 (6.1)</td>
</tr>
<tr>
<td>Externalized T-scores</td>
<td>67.1 (10.7)</td>
</tr>
<tr>
<td>Internalized T-scores</td>
<td>62.1 (7.6)</td>
</tr>
</tbody>
</table>

Abbreviations: ASD, autism spectrum disorder; CBCL, Child Behavior Checklist; DQ, developmental quotient; IQ, intelligence quotient.
on a target behavior and to immediately reinforce action with an explanation and praise or a smile. In addition, they were taught about the effective use or timing of reinforcements.

5. Help when your child cannot do: This session taught about the ways in which the child should be aided when he or she could not adopt the target behavior. First, mothers were advised to reassess whether the behavior was appropriate for their children’s ability. Then, the behavior was divided into small steps, with careful observation of which was the difficult step for the child. Finally, mothers were taught about prompting and fading.

6. How to decrease problematic behaviors: This session was about the extinction procedure, planned ignoring, and time-out on the basis of applied behavior analysis methods.

7. Consideration of individual issues and summary. Mothers often had high expectations and complaints regarding their children’s behavior. First, facilitators helped mothers to change their ideal and abstract requirements for a realistic goal, encouraging mothers to observe behaviors objectively by asking in-depth questions. When mothers could identify the action that their children would take, or find triggers and positive reinforcement of the behavior, facilitators encouraged mothers with praise. Facilitators emphasized that in addition to a token economy system, a mother’s praises would be positive reinforcement for children. When mothers thought that their children could not achieve the target behavior, facilitators guided the mothers to find a small change and encouraged them to work together with their child.

### Psychological assessments

Intervention effects were assessed using the Lazarus-Type Stress Coping Inventory (SCI), the Beck Depression Inventory Second Edition (BDI-II), the State–Trait Anxiety Inventory (STAI), and CBCL. All mothers were asked to complete the aforementioned scales on two separate occasions: at starting PT Session 1 and at 2 months after the end of PT Session 7.

#### SCI

Lazarus and Folkman defined “coping” as constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that were appraised as taxing or exceeding the resources of the person. They constructed the Ways of Coping Questionnaire (WCQ). SCI is the Japanese version of WCQ. SCI is divided into eight factors: 1) planful problem solving (Pla: deliberate analytic efforts to alter or remedy the situation); 2) confrontive coping (Con: efforts to identify the cause of the problem and eliminate the source); 3) seeking social support (See: efforts to seek informational, tangible, and emotional support from others); 4) accepting responsibility (Acc: acknowledging one’s role in the problem with rectification); 5) self-control (Sel: efforts to control one’s feelings and actions); 6) escape/avoidance (Esc: wishful thinking to escape or avoid a problem); 7) distancing (Dis: efforts to detach oneself and to minimize the significance of the situation); and 8) positive reappraisal (Pos: efforts to create a positive meaning and personal growth).

#### BDI-II

BDI, created by Aaron T. Beck, is a 21-question, multiple-choice, self-report inventory. It is a psychometric test to measure the severity of depression. The Japanese version of this questionnaire is reported to possess good internal consistency and convergent validity for all subscales.

#### STAI form X

STAI was constructed by Spielberger et al. It purports to measure one’s conscious awareness at two extreme states of anxiety affect: labeled state anxiety (A-state) and trait anxiety (A-trait). A-state can be defined as fear nervousness,
discomfort, and arousal of the autonomic nervous system induced temporarily by situations perceived as dangerous. This type of anxiety refers to how a person is feeling at the moment. A-trait can be defined as a relatively enduring disposition to feel stress, worry, and discomfort. This type of anxiety refers to how a person feels on a regular basis. The Japanese version of this scale is reported to show good internal consistency and convergent validity for all subscales.

**CBCL**

CBCL is a scale designed to evaluate child behavioral problems. This scale takes the average of the T-score of the internalizing broadband, externalizing broadband, and total problems scales. Internalizing problems sum the anxious/depressed, withdrawn-depressed, and somatic complaints scores; externalizing problems combine rule breaking and aggressive behavior; and the total problems score is the sum of the scores of all of the problem items. Raw scores are converted to T-scores for the appropriate sex and age range with mean of 50 and SD of 10.

**Ethical considerations**

The research protocol was approved by the ethics committee of the Department of Medicine of Kyoto Prefectural University of Medicine and the Kyoto Prefectural Child Development Support Center. This study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The subjects were assured of the following: their participation was voluntary, they could withdraw at any time without facing any negative consequences, their anonymity would be protected, and the data obtained would not be used for purposes other than the present research. All participants provided their written informed consent.

The research purpose and guarantee to protect the privacy of the subjects were explained verbally as well as in written form to the participants by the doctor.

**Statistical analyses**

With reference to SCI, BDI-II, STAI, and CBCL scores, pretreatment and post-treatment data assessed by the Shapiro–Wilk test were distributed normally and compared using the paired t-test. The score changes of BDI-II, SCI, STAI, and CBCL between pre- and post-PT were analyzed by Pearson’s correlation analysis. For all the tests, a two-tailed $P \leq 0.05$ was considered to be statistically significant.

The data obtained were analyzed using SPSS version 23 for Mac.

### Results

After the PT program, the stress-coping strategy “positive appraisal” significantly increased from 4.6 (SD, 3.2) to 6.9 (SD, 4.1; $t(16) = -3.3, P<0.01$) and “escape/avoidance” significantly decreased from 5.9 (SD, 2.4) to 4.1 (SD, 2.2; $t(16) = 3.3, P<0.01$). The BDI-II score significantly decreased from 16.1 (SD, 8.4) to 11.9 (SD, 8.1; $t(16) = 2.8, P<0.05$) after PT. With reference to STAI, the trait anxiety significantly decreased from 53.3 (SD, 8.3) to 47.7 (SD, 9.5; $t(16) = 3.0, P<0.01$), whereas the decrease of state anxiety was not significant 50.6 (SD, 10.7) to 46.9 (SD, 12.7; $t(16) = 1.3, P=0.2$). The mean scores of CBCL at follow-up decreased in comparison with baseline although the differences were not significant (Table 4).

The change of SCI Esc positively correlated with the change of STAI trait anxiety (A-trait; $r=0.6, P<0.05$; Table 5).

SCI Dis change in mothers demonstrated a significant negative correlation with the change in externalizing CBCL T-scores of their children with ASD (Pearson $r=-0.518, P=0.04$; Table 6). No other change in SCI subscales exhibited...
Table 5 Correlation between the change of SCI and the change of STAI anxiety trait

<table>
<thead>
<tr>
<th>STAI A-trait</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCI Pla</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>SCI Con</td>
<td>0.5</td>
<td>0.05</td>
</tr>
<tr>
<td>SCI See</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>SCI Acc</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>SCI Sel</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>SCI Esc</td>
<td>0.6</td>
<td>0.01*</td>
</tr>
<tr>
<td>SCI Dis</td>
<td>−0.01</td>
<td>1.0</td>
</tr>
<tr>
<td>SCI Pos</td>
<td>−0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Notes: *P < 0.05. Pla indicates deliberate analytic efforts to alter or remedy the situation; Con indicates efforts to identify the cause of the problem and eliminate the source; See indicates efforts to seek informational, tangible, and emotional support from others; Acc indicates acknowledging one’s role in the problem with rectification; Sel indicates efforts to control one’s feelings and actions; Esc indicates wishful thinking to escape or avoid a problem; Dis indicates efforts to detach oneself and to minimize the significance of the situation; Pos indicates efforts to create a positive meaning and personal growth.

Abbreviations: r, Pearson correlation coefficient; SCI, Stress Coping Inventory; STAI, State–Trait Anxiety Inventory.

any significant correlation with the change in the CBCL T-scores.

Discussion

Our results suggested that the PT program may be effective in improving mothers’ coping skills. After PT, the escape/avoidance coping skills decreased and the positive appraisal coping increased. In addition, trait anxiety and depression among the mothers decreased. The results also suggested that as the distancing coping skill of mothers increased, their children’s externalizing problems decreased through PT.

Table 6 Correlation between the change of the externalized CBCL T-scores and SCI subscales

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCI Pla</td>
<td>0.243</td>
<td>0.365</td>
</tr>
<tr>
<td>SCI Con</td>
<td>0.416</td>
<td>0.109</td>
</tr>
<tr>
<td>SCI See</td>
<td>0.089</td>
<td>0.742</td>
</tr>
<tr>
<td>SCI Acc</td>
<td>0.432</td>
<td>0.095</td>
</tr>
<tr>
<td>SCI Sel</td>
<td>−0.291</td>
<td>0.274</td>
</tr>
<tr>
<td>SCI Esc</td>
<td>0.268</td>
<td>0.315</td>
</tr>
<tr>
<td>SCI Dis</td>
<td>−0.518</td>
<td>0.04*</td>
</tr>
<tr>
<td>SCI Pos</td>
<td>0.117</td>
<td>0.667</td>
</tr>
</tbody>
</table>

Notes: *P < 0.05. Pla indicates deliberate analytic efforts to alter or remedy the situation; Con indicates efforts to identify the cause of the problem and eliminate the source; See indicates efforts to seek informational, tangible, and emotional support from others; Acc indicates acknowledging one’s role in the problem with rectification; Sel indicates efforts to control one’s feelings and actions; Esc indicates wishful thinking to escape or avoid a problem; Dis indicates efforts to detach oneself and to minimize the significance of the situation; Pos indicates efforts to create a positive meaning and personal growth.

Abbreviations: r, Pearson correlation coefficient; CBCL, Child Behavior Checklist; SCI, Stress Coping Inventory.

There may be some elements in PT that may affect the coping skills of mothers. Attending PT itself may be a sign of improving the coping style by seeking some form of social support. Through PT, therapists empower and support parents in observing their children’s behavior in an objective way, understanding the characteristics of ASD, learning Antecedent Behavior Consequence analysis, and positively interpreting the small changes among children. Through the PT process, mothers can learn to understand and raise their children with ASD, and it may also support the mother’s psychological acceptance and the mother–child relationship. Objective observation could sometimes lead to behavior recognition and modification in mothers, which might improve the mother–child relationship. As a result of PT, mothers of children with ASD made meaning out of their parenting experience. Although some problematic behaviors, which were stressful for mothers, were seen in children with ASD, mothers could learn how to observe and deal with them rather than escape or avoid them; they could lead their children, experience the behavioral changes in their children, and find positive meaning in raising their children as responsible mothers. The difference between pre- and post-CBCL scores was not significant possibly because some mothers often discussed daily behaviors and not trouble behaviors at the individual consultation. The finding that the change in SCI Dis was significantly negatively correlated with the change in the externalizing CBCL T-scores suggests that as mothers tend to separate themselves from problems (Dis), they may be inclined to believe that their children have less-troubled behaviors. Before PT, mothers of children with ASD might have been overwhelmed and anxious by their children’s behavior. It is likely that mothers can learn to separate and analyze behavior based on the multiple objective elements and to correspond strategically through PT, and as a result, their children can change behaviors. The PT program encourages mothers to reinforce that they are capable of raising children with ASD. Pakenham et al.\textsuperscript{10} stated that the ability of parents of children with ASD to make meaning out of their parenting experience has improved their ability to cope in an adaptive manner. Making meaning out of their parenting experience may be the key to improving their coping skills. Dunn et al.\textsuperscript{11} showed that escape correlated significantly with social isolation. The PT program in groups may also ease the isolation of mothers, and mothers feel the support not only from experts but also from other mothers in the same position. Mothers share the hardships of raising children with ASD with each other. Group PT may have the attributes of group therapy, which includes a peer counseling element.\textsuperscript{21} As a result, mothers may be encouraged not to escape or avoid...
problems, but rather to think about these problems and consult with others. They can thus retain a positive attitude.

Coping skills are reported to influence both illness-related behaviors and the outcome of disorders with psychological or physical symptoms such as somatoform disorder and panic disorder. The change in SCI “escape/avoidance” stress coping positively correlated with the change of STAI “trait anxiety,” suggesting that the decrease in stress-coping style “escape-avoidance” correlates with the decrease in trait anxiety. Through PT, mothers learned to not avoid stressors, to feel less anxious and depressed in their everyday life, and to find a positive meaning in raising their children with ASD. PT can also improve a mother’s resilience.

It has been suggested that PT may be an effective intervention in changing stress coping, namely, to decrease “escape/avoidance coping” and increase “positive appraisal coping”, as well as to decrease the trait anxiety and depression of mothers who raise children with ASD.

Limitations

The present study has several limitations. First, because there was no control group, it was impossible to determine whether the observed changes between pre- and post-PT were specific to PT effectiveness. Theoretically, it would be better to make the mothers of patients coming to our hospital as the control group, and it was difficult clinically to conduct psychological scales on them without a special intervention. Second, because all the dependent measurements were based on self-reports, there is the possibility of bias. Third, the sample size was smaller than the expected sample size calculated from power analysis. We administered PT on 30 mothers in our clinical setting during the study period, but only 16 mothers answered the questionnaire completely. A future study with a large number of participants and a control group is necessary to confirm the present results. Fourth, we did not assess another family function. It will be useful to measure aspects of family functional analysis to examine the relationship with stress coping.

Conclusion

PT may be effective for mothers of children with ASD in improving their stress-coping skills and decreasing their trait anxiety and depression.

Acknowledgments

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Author contributions

Naoko Iida, Yoshihisa Wada, and Tatsuhisa Yamashita designed the study. Naoko Iida wrote the initial draft of the manuscript. Yoshihisa Wada and Tatsuhisa Yamashita contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

The authors report no conflicts of interest in this work.

References