Effect of calligraphy training on hyperarousal symptoms for childhood survivors of the 2008 China earthquakes

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
3 June 2014
Number of times this article has been viewed

Background: This study investigated the treatment effects of calligraphy therapy on childhood survivors of the 2008 Sichuan earthquakes in the People’s Republic of China.

Methods: In experiment 1, 129 children participated in a 30-day calligraphic training, and 81 children were controls. The Children’s Revised Impact of Event Scale was adopted to assess behavioral effects. Experiment 2 involved 41 treatment subjects and 39 controls, with the same procedure as in experiment 1 except that salivary cortisol level was also measured as a physiological indicator.

Results: After 30 days of calligraphy treatment, the arousal symptoms and salivary cortisol levels in the experimental group decreased from 5.72±0.31 and 13.34±2.88 to 4.98±0.31 and 9.99±2.81, respectively. In the control group, there was not a significant decrease from pretest to post-test. In addition, the arousal scores in posttest (4.98±4.39) were significantly lower than midtest (5.71±4.14) for girls; in contrast, for boys, posttest (4.90±4.24) showed little change compared with midtest (5.04±4.36), but both were significantly lower than pretest (6.42±4.59).

Conclusions: Calligraphy therapy was effective in reducing hyperarousal symptoms among child survivors.

Keywords: PTSD, calligraphy therapy, salivary cortisol, China earthquakes

Introduction

On May 12, 2008, an earthquake measuring 8.0 on the Richter scale hit Wenchuan, People’s Republic of China. The earthquake was considered the most devastating natural disaster in the People’s Republic of China since the 1976 Tangshan earthquake. According to official state statistics, the Wenchuan earthquake caused 69,277 deaths and 374,643 injuries and left 17,923 listed as missing and about 4.8 million homeless.1

Post-traumatic stress disorder (PTSD) is often considered the most frequently reported adverse psychological sequelae among survivors of natural disasters. PTSD is an anxiety disorder caused by exposure to a life-threatening situation or situations accompanied by feelings or fear, helplessness, or horror.2 The symptoms of PTSD listed in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, include intrusion and reexperience, avoidance and emotional numbing, and hyperarousal.3 Children, compared with adults, are a particularly vulnerable population4 because of their limited cognitive schema and behavioral repertoire.5 The prevalence of PTSD among child and adolescent survivors of earthquakes ranged from 4.5%–60%.6–10

Cortisol, a stress hormone secreted by the adrenal cortex, is considered an informative biomarker of PTSD.11 Psychological stress increases the synthesis and release of cortisol. Cortisol mobilizes and replenishes energy and contributes to increased arousal,
vigilance, focused attention, and memory formation. Acute exposure to stress leads to a rapid increase in cortisol level; a prolonged status of hypervigilance in PTSD may lead to dysregulation of cortisol. The relationship between cortisol level and PTSD is inconsistent, partly because of its comorbidity with major depression, severity of PTSD symptoms, time since the trauma, and duration of trauma exposure. Sex difference in cortisol level is also found among adults with PTSD, and the reactive change in cortisol level varies with age among dysphoric children, who exhibit age-related difference in cortisol changes in the face of a stressor.

Chinese calligraphic handwriting entails an integration of the mind, body, and character, interwoven in a dynamic process. It involves visual perception of the character, spatial structuring of the character, cognitive planning, and maneuvering of the brush to follow specific character configurations. Research in recent years has gradually established calligraphy therapy as an indigenous and complementary practice that is capable of improving aspects of people’s behavioral and psychosomatic conditions, enhancing their attention and concentration as well as facilitating their physical relaxation and emotional stabilization. The theoretical framework for calligraphy as a treatment is threefold: first, sensory and biomotional feedback: the individual receives sensory feedback from the graphic record while practicing calligraphy; second, biomotional feedback: the calligraphy involves the movement of the arms and the whole body as the individuals guide and regulate their movement; and finally, cognitive feedback: the subjective experiences of heightened attention, alertness, and quickened responses during the writing.

Via this feedback, calligraphy practice increases the ability of patients to self-monitor and may modify the cognitive deficits, as well as alter the arousal level. Brush writing in calligraphy requires intensive attention and concentration and involves highly controlled moves and well-coordinated movements. The writer has to reduce external and internal disturbances and focus on the present moment. This high level of attention is evidenced when the heart rate decelerates. Calligraphy therapy shares some fundamental elements with mindfulness practice: both involve paying attention to and being aware of the present experiences, and both have the same effect on attention regulation and relaxation.

A recent study has shown the appearance of theta waves in frontal midline during brush writing, which underlines the power of calligraphy training in contributing to facilitated attention, concentration, and focusing at the neurocognitive level. This reflects the relaxed and concentrated state evoked by the act of brush writing, with the brush writer’s body being in a relaxed state while his mind is in an apprehensive and intensive state. When long-term practitioners of meditation engage in mental training, it involves temporal integrative mechanisms, which may induce short-term and long-term neural changes through the generation of gamma waves. This is also what the act of calligraphy entails, showing both the fast gamma waves and the deep relaxing theta waves simultaneously. This indicates a sharing of similar neural cognitive experience between these two practices. In fact, some mindfulness practitioners have adapted calligraphy as a method of mindfulness meditation, as well as relaxation training.

Hypervigilance and concentration difficulty are two central characteristics of PTSD hyperarousal symptoms that play an important role in the maintenance of chronic PTSD. On the basis of previously reviewed clinical evidence of the enhanced attention and relaxation resulting from calligraphy treatment, we believed the treatment may also have the same benefits for PTSD, by reducing hyperarousal symptoms. Stress management intervention has long been adapted as a treatment for post-trauma adjustment, and a positive outcome includes reduced cortisol levels and increased relaxation. In addition, some behavioral treatment techniques (such as mind–body therapy) have shown moderating effects on salivary cortisol (SC). Although no study has accessed the effectiveness of calligraphy treatment for PTSD, mindfulness-based relaxation training has been recently used for treating PTSD and showed clinical effectiveness among military veterans, cancer patients, firefighters, and mental health workers after a natural disaster. Mindfulness-based therapy is suggested to be especially useful in reducing rumination symptoms, which are associated with increased basal cortisol levels. Mindful exercise enhanced the quality of life among women with breast cancer who exhibited a reduction in cortisol level after the treatment.

Of particular note is the therapeutic effectiveness of calligraphy treatment among children with behavioral and cognitive disorders. Calligraphy treatment has had an effect on enhanced attention, sensory-perceptual sharpness, cognitive and reasoning ability, emotional stability, and self-control among children with attention-deficit/hyperactivity disorder (ADHD) and autism. The results indicate that this training facilitates cognitive functioning, calms emotions, and improves some clinical and mental health conditions of children with ADHD. Significant improvement in all these areas of child behavior was seen after calligraphy training. In general, the results indicate that the practice has an especially...
positive effect on improving the attentiveness and emotional stability of ADHD children.

For autistic children, postcalligraphy training resulted in significant improvement in the measures of attention, social behavior, communication, volition, ability to adapt to the environment, and emotional and instinctual responses, as well as in a significant reduction in negative and group behaviors and in negative behavior in general and in family gatherings in particular, thus echoing the findings of similar reports on ADHD children. Both studies have offered evidence on the positive effects of calligraphy training on children with activity, conduct, and attention problems. This summary of our empirical research and of the clinical applications of calligraphy therapy, all involving children with various common disorders, serves as a summative review of the foundations and rationale that underlined the present study on PTSD intervention and treatment.

The current study aimed to investigate the effectiveness of calligraphy treatment among a sample of youth 1 year after exposure to natural disaster (ie, an earthquake). According to previous evidence revealing the psychological benefits (ie, enhanced attention, relaxation) of calligraphy treatment with regard to various mental health problems, we hypothesized that calligraphy treatment would reduce PTSD symptoms, especially hyperarousal symptoms, in the present sample. Second, on the basis of the theoretical and empirical evidence of the relationships between cortisol and stress reduction management, we hypothesized that calligraphy treatment would moderate the effect of calligraphy treatment. Caution was exercised with respect to balancing the geographic regions, age of the pupils, and assignment of treatment. For autistic children, postcalligraphy training resulted in a significant decline in cortisol level in the calligraphy treatment group compared with the control group. In addition, because sex is a moderator of both PTSD symptoms and cortisol reaction to stress, we expected that sex may moderate the effect of calligraphy treatment.

**Experiment 1: behavioral changes in Children's Revised Impact of Event Scale**

**Method**

**Participants**

A total of 210 children in the fourth and fifth grades, 105 boys and 105 girls, participated in our study. They were selected randomly from the five classrooms of two farm villages and township schools in the disaster areas. Three of the classes were randomly selected as treatment groups, and the other two were control groups. The treatment group consisted of 129 pupils, 65 boys and 64 girls, and had a mean age of 10.51±1.13 years. They were given calligraphy training for 1 hour a day for 30 consecutive days. The control group had 81 children (41 boys and 40 girls) and a mean age of 10.52±1.13 years. These children were similarly assessed before and after the same period as the treatment group, but without calligraphy training. The demographic characteristics of experiment 1 and experiment 2 are outlined in Table 1.

**Instruments**

The Children's Revised Impact of Event Scale (CRIES-13) was adopted to assess the behavioral effects of the participants before and after training. This scale was validated for use in the disaster areas by the Institute of Psychology, Chinese Academy of Sciences. It had three subscales: Intrusion, Avoidance, and Arousal.

**Procedure**

The experiment procedure followed a validated system of treatment protocols. The participants in the experimental group were each required to brush write 40 medium-sized characters from five copybook pages by the tracing mode of writing. The copybook, ink, and writing brush were allocated to these children by the experimenters. The treatment took 1 hour a day, 5 days a week, for a total of 30 days under the supervision of a teacher while the child was in the school or a parent if the child was at home. The controls carried on their regular school activities throughout the study duration, without any writing tasks. The study was conducted a year after the Sichuan earthquakes.

The Chinese version of CRIES-13 was administered to all subjects once before the experiment, again at the halfway point after 15 days, and one more time after 30 days of treatment. Caution was exercised with respect to balancing the geographic regions, age of the pupils, and assignment of groups, as well as potential intervening variables.

**Results**

Data were submitted to a 3×2×2 repeated measures analysis of variance in which test (three levels: pretest, midtest, and post-test) served as the within-subjects variable and group

| Characteristic | Experiment 1 | Experiment 2 |
|----------------|--------------|--------------|
|                | Treatment    | Control      | Treatment | Control  |
| Boys           | 65           | 41           | 21        | 17       |
| Girls          | 64           | 40           | 20        | 22       |
| Age, years     | 10.51±1.15   | 10.52±1.13   | 10.52±1.16| 10.54±1.15|
| Total          | 129          | 81           | 41        | 39       |
(two levels: experimental group and control group) and sex (two levels: boys and girls) was the between-subjects variable.

Intrusion and avoidance as dependent variable
The main effect of test \([F(2,412)=8.10; P=0.000; \eta^2=0.053]\) reached a significant level \((P<0.05)\). Further analysis showed that compared with the pretest (mean \(=5.37,\) standard deviation \(=4.05)\) and midtest (mean \(=5.28,\) standard deviation \(=4.15)\), there was a significant decrease in Intrusion scores in post-test (mean \(=4.35,\) standard deviation \(=3.71)\). For Avoidance, neither main effects nor interaction effect reached a significant level (Table 2).

Arousal as a dependent variable
When Arousal scores were analyzed, the main effect of test \([F(2,410)=3.44; P=0.033; \eta^2=0.016]\) reached a significant level \((P<0.05)\). After further multiple comparisons, it was found that the Arousal scores at post-test (mean \(=4.98,\) standard deviation \(=0.31)\) were significantly lower than at pretest (mean \(=5.72,\) standard deviation \(=0.31)\; Table 2). More important, there was a significant interaction between test and group \([F(2,410)=3.29; P=0.038; \eta^2=0.016]\). Further analysis showed that compared with the pretest (mean \(=6.30,\) standard deviation \(=4.78)\) and midtest (mean \(=5.64,\) standard deviation \(=4.38)\) results, there was a significant decrease in Arousal scores in post-test (mean \(=4.84,\) standard deviation \(=4.25)\) for the experimental group, whereas the control group showed no significant change (Figure 1).

Similarly, a significant interaction between test and sex was found \([F(2,410)=6.13; P=0.002; \eta^2=0.019]\), and the Arousal scores in post-test (mean \(=4.98,\) standard deviation \(=4.39)\) were significantly lower than in midtest (mean \(=5.71,\) standard deviation \(=4.14)\) for girls, whereas for boys, post-test (mean \(=4.90,\) standard deviation \(=4.24)\) showed little change compared with midtest (mean \(=5.04,\) standard deviation \(=4.36)\); both were significantly lower than pretest (mean \(=6.42,\) standard deviation \(=4.59)\) in boys (Figure 2).

Summary
It is noted therefore that after 30 days of calligraphy treatment, the experimental group’s stress reduction was highly

### Table 2 Average (standard deviation) scores on intrusion, avoidance, and arousal by condition

| Variables | Experimental group (N=129) | Control group (N=81) |
|-----------|---------------------------|----------------------|
|           | Pretest | Midtest | Posttest | Pretest | Midtest | Posttest |
| Intrusion |         |         |         |         |         |         |
| Boys      | 5.61 (4.56) | 4.98 (4.29) | 4.50 (3.94) | 4.27 (3.39) | 5.45 (3.93) | 4.85 (3.69) |
| Girls     | 5.78 (3.92) | 5.98 (4.61) | 4.26 (3.75) | 4.39 (3.05) | 5.52 (4.03) | 4.95 (3.59) |
| Total     | 5.70 (4.24) | 5.49 (4.47) | 4.38 (3.84) | 3.68 (2.62) | 4.93 (4.20) | 4.30 (3.52) |
| Avoidance |         |         |         |         |         |         |
| Boys      | 6.58 (4.43) | 6.30 (5.02) | 5.80 (5.52) | 6.12 (4.18) | 5.66 (4.55) | 5.85 (4.62) |
| Girls     | 5.82 (4.13) | 6.02 (4.81) | 4.69 (4.25) | 6.10 (4.99) | 6.77 (5.51) | 6.35 (5.72) |
| Total     | 6.19 (4.29) | 6.16 (4.90) | 5.24 (4.93) | 6.11 (4.57) | 6.21 (5.05) | 6.10 (5.17) |
| Arousal   |         |         |         |         |         |         |
| Boys      | 6.95 (4.96) | 5.56 (4.41) | 5.16 (4.40) | 5.61 (3.88) | 4.24 (4.20) | 4.51 (4.02) |
| Girls     | 5.68 (4.55) | 5.72 (4.38) | 4.54 (4.11) | 4.65 (3.71) | 5.70 (3.76) | 5.70 (4.78) |
| Total     | 6.30 (4.78) | 5.64 (4.38) | 4.84 (4.25) | 5.14 (3.80) | 4.96 (4.03) | 5.10 (4.43) |

![Figure 1](https://example.com/figure1.png)

**Figure 1** Arousal scores of posttraumatic stress disorder change with the course of test across group.

![Figure 2](https://example.com/figure2.png)

**Figure 2** Arousal scores of posttraumatic stress disorder change with the course of test across sex.
significantly different from that of the control group, bringing these children’s Intrusion and Arousal scores much lower than their baseline measures. The control group showed some decrease as well, possibly because of a natural mental readjustment of the participants in the aftermath of the tragic event. We also found that among the Arousal scores, which is an important symptom of PTSD, there was significant interaction between test and sex, indicating that sex differences may exist for calligraphy treatment.

In sum, this experiment has provided the first evidence of the promising application of calligraphy therapy as an indigenous and effective means of alleviating PTSD symptoms and behavioral conditions of earthquake victims.

Experiment 2: SC and a second CRIES-13 assessment

Method

Participants

Eighty fourth- and fifth-grade primary children participated in the second experiment. They were screened and selected from an initial pool of 700 children in two district primary schools in the earthquake regions. The participants were balanced for age, sex, and random assignment of groups. The experimental group had 41 children with a mean age of 10.52±1.16 years and was given calligraphy training 1 hour a day for a consecutive 30 days. CRIES-13 (r=0.79; P<0.001) was adopted to assess the treatment effects before, at halfway through, and after the training course. The control group had 39 children with a mean age of 10.54±1.15 years and was similarly assessed, but without calligraphy training. Both groups also had Salivary Collection assessment. The instrument, the CRIES-13, and other experimental conditions were the same as in experiment 1. The description of the participants is presented in Table 1.

Salivary collection

The salivary cortical measurement was taken for both the experimental and control groups as a new dependent variable. The procedure entailed inserting a cotton ball under the subject’s tongue for 5 minutes, followed by taking a 2 mL saliva sample by syringe and storing it in a −20°C refrigerator. The sample was refrozen for 24 hours and centrifuged at 3,000 rpm for final collection of the specimen. The specimen was analyzed with a Gamma Coat™ Cortisol RIA Kit (R&D Systems, Minneapolis, MN, USA) at the State Key Laboratory of Brain and Cognitive Science, Chinese Academy of Sciences, Beijing, People’s Republic of China. The treatment duration was 30 consecutive days, with the SC sample taken 3 times: before the experiment for the pretest, 2 weeks later for midtest, and within 3 days after the treatment for the posttest. The timing of SC sample collection was set at 4 pm on Fridays. The CRIES-13 was administered before the treatment and 3 days after the conclusion of the treatment for both groups. The children in the control group participated in the regular calligraphy class.

Results

Data were submitted to a 3×2×2 repeated measures analysis of variance, in which the test (three levels: pretest, midtest, and post-test) served as the within-subjects variable, whereas the group (two levels: experimental group and control group) and sex (two levels: boys and girls) were the between-subjects variables.

When SC measures were analyzed, we observed that SC measures revealed a significant main effect of test [F(2,196)=17.76; P=0.000] as well as group [F(1, 98)=14.17; P=0.000; η²=0.153]. Further analysis showed that the SC level in post-test (mean =10.99, standard deviation =2.53) is much lower than in pretest (mean =11.99, standard deviation =2.48) and midtest (mean =13.29, standard deviation =2.90) and that the SC level in the experimental group (mean =11.64, standard deviation =0.21) is significantly lower than in the control group (mean =12.97, standard deviation =0.28; Table 3). This main effect is qualified by a significant test × group interaction [F(2,196)=8.47; P=0.029; η²=0.080]. In comparison with pretest (mean =13.34, standard deviation =2.88) and midtest (mean =11.61, standard deviation =2.17), there was a significant decrease of total

Table 3 Average (standard deviation) measures on salivary cortisol by condition

| Variables | Experimental group (N=64) | Control group (N=38) |
|-----------|---------------------------|----------------------|
|           | Pretest                  | Midtest              | Posttest                        | Pretest                  | Midtest              | Posttest                        |
| SC        |                          |                      |                                 |                          |                      |                                 |
| Boys      | 13.52 (3.01)             | 11.32 (2.46)         | 9.89 (1.39)                     | 14.17 (3.30)             | 13.57 (3.19)         | 13.14 (2.30)                     |
| Girls     | 13.18 (2.80)             | 11.86 (1.88)         | 10.08 (2.12)                    | 12.55 (2.62)             | 12.01 (2.49)         | 12.36 (2.94)                     |
| Total     | 13.34 (2.88)             | 11.61 (2.17)         | 9.99 (1.81)                     | 13.19 (2.97)             | 12.63 (2.85)         | 12.67 (2.70)                     |

Abbreviation: SC, salivary cortisol.
scores in post-test (mean = 9.99, standard deviation = 1.81) for the experimental group, whereas the control group showed no significant change (Figure 3).

Summary
The results from this experiment have not only lent support and confirmed the validity of the treatment effect of calligraphy practice in the area of CRIES-13 behaviors in children but have also broken new ground in its therapeutic application at a deeper level (ie, the SC changes as an index of severe stress disorder because of the earthquake experiences). These double, simultaneous outcomes mark a significant new step for calligraphy treatment as a complementary approach of clinical and rehabilitative psychology. The SC findings are most welcoming in showing the progressive nature of this graphonomic treatment as a function of the progress of the training. This observation adds to the rigor and scientific strength of the treatment. Some discussion of the theoretical and empirical foundations of calligraphy treatment deserves closer attention and analysis.

Discussion
The findings of these two experiments are highly illuminating, showing the effectiveness of calligraphy treatment for the PTSD hyperarousal symptoms of the trauma-exposed children from China’s major 2008 earthquakes. A significant decrease in both the CRIES-13 scores, and the SC as a result, has been disclosed. The significance of this result lies in observing, for the first time, the positive effect of calligraphy training in reducing the PTSD symptoms of natural disaster child survivors.

Findings from both self-reported PTSD symptoms and physiological data indicate a consistent lowering of physical arousal conditions as a result of brush writing. We attribute these observed states of emotional stabilization, relaxed alertness, and mindful quiescence to the fundamental changes embedded in the act of brush writing. The physical changes reported are similar to those obtained in studies on meditation.46 Because of this, we regard calligraphic writing as a graphic form of meditation involving rich cognitive and linguistic processing, which is not part of other forms of meditation practice. The latest confirmation of this effect is the Heart Rate Variability study, showing a progressive coherence of the subject’s heart rate with respiration through calligraphy training.47 The finding of a reduction in hyperarousal symptoms among trauma-exposed children echoed past results of calligraphy treatment for facilitating visual attention, as well as a reduced state of hyperactivity among ADHD and autistic children.20,48 In examining the physiological effects of calligraphy training, we have found that the practitioner’s heart rate, blood, blood pressure, and respiration are generally reduced as a result of this practice in various practitioner categories. The associated emotional stability and relaxation have been observed with patients of mental disorders, hypertension and diabetes students, executives and administrators, and children with autism and ADHD.49 The studies presented here have highlighted an alternative model of behavioral treatment of children with various mental problems.

No sex difference was found in either pre- or post-training self-report PTSD symptoms, which suggests the calligraphy treatment has an equivalent effect on boys and girls. This finding is consistent with the result from a meta-analysis on sex differences in treatment effectiveness for PTSD patients.51 However, the studies in the meta-analysis were primarily focused on adult patients, and the trauma type and treatments were heterogeneous. Much remained unknown for childhood victims of natural disaster. In the present study, a significant sex–time interaction was found at the second measurement: a significant decline in symptom severity was reported in boys but not girls during the treatment. This indicated a sex difference in the trajectory of recovering from PTSD symptoms, suggesting that girls would benefit from treatment more slowly than boys but that they would reach the same outcome if the treatment persists. Although no study has reported sex difference in treatment trajectory among children, some researchers found a slower decline in posttraumatic stress symptoms associated with physical injury in girls than in boys in the natural recovery,52 and a lower rate of resilience in girls than boys.53 However, that no sex difference was found in the cortisol changes over time suggests a consistent decline of stress level accompanying the course of calligraphy treatment. This inconsistency between self-report...
data and physiological data may suggest that factors other than stress-related hormonal changes may contribute to the sex difference in resilience to trauma.

The calligraphy treatment showed no effect on Intrusion and Avoidance symptoms, which reflect the cognitive aspects of PTSD. According to cognitive theories, intrusion is the result of trauma memory that has not been integrated into the cognitive schema. In contrast, trauma-exposed individuals are hypervigilant to threat and trauma-related cues in the environment but strategically avoid the cues as a coping mechanism. However, persistently avoiding trauma-related triggers may prevent the trauma memory from integrating into the schema, which leads to maintenance of PTSD symptoms. Thus, one of the main purposes of cognitive treatments of PTSD is to integrate the fragments of trauma memory into the cognitive schema. Because the emphasis of calligraphy treatment is attention and relaxation, the traumatic memory and cognitive modification have not been processed. To make the most of calligraphy treatment, a combined cognitive therapy is recommended.

In a summary, our past research has been conducted in the context of a general system of perceptual motor control behavior, as well as a cybernetic theory of handwriting and feedback regulation. This body of work, along with our recent principles of character geometric specificity for calligraphy production, has given credence to calligraphy therapy as an evidence-based system of treatment and rehabilitation. In addition, this body of work offers valid support to the theoretical, empirical, and treatment foundations of calligraphy therapy. This research, as a whole, predicted positive and effective treatment benefits for trauma-exposed pupils, in the case of the present study, in reducing hyperarousal symptoms. The results arising from this study have indeed supported our stated predictions. The demonstration of changes in SC as a direct effect of calligraphy training makes its first contribution toward the relief of the children’s symptoms in a neurochemical level of analysis.

The overall results of this study have lent convincing support to the predictions of calligraphy treatment in improving and changing the common post-traumatic hyperarousal symptoms in a sample of trauma-exposed children. This global outcome is further backed and confirmed by the measure of the progressive change and reduction of SC throughout the treatment. This main finding indicates a strengthening and enhancement of the participants’ immunity system as a positive response to calligraphy treatment. Overall, we recognize successful calligraphy treatment as an effective, validated, and culturally congruent system of intervention.

Acknowledgment
Our work was supported by the Knowledge Innovation Program of the Chinese Academy of Sciences (KSCX2-EW-J-8-j).

Disclosure
The authors report no conflicts of interest in this work.

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