



Commentary

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Oxytocin and arginine vasopressin: a bridge between acupuncture and autism spectrum disorder

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The status of autism spectrum disorder

In the Sui Dynasty (581–618) of China, Chao's "On the Etiology of Diseases" described the "hun se" (muddle-headed) and "yu chi" (language delay) phenotypes, which are clinically manifested as a lack of speech and neurodevelopmental retardation in children (Figure 1).

Since the first report of early infantile autism by Kanner in 1943 [1], the diagnosis of autism has undergone several revisions, and this broader group of disorders was renamed autism spectrum disorder (ASD) in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* in 2013 [2]. The phenotypes of ASD extend beyond the classic form of autism described by Dr. Leo Kanner, as evidenced by the observation that an increasing number of people with some autistic traits, including social and communication deficits and stereotyped repetitive

behaviors, have normal intelligence. In recent years, the prevalence of ASD has reached 1 in 44 8-year-old children in the United States [3] and 1 in 143 6–12-year-old children in China [4]. As rapid advances in genetic research and neuroscience have clarified this disorder more than 200 highly plausible ASD-risk genes or copy number variants and environmental risk factors have been identified. These complex etiologies cause structural and functional brain-wide alterations, resulting in abnormal cortical development, synaptic dysfunction, circuit-level brain dysfunction, and neuroinflammation, which can, in turn, lead to behavioral phenotypes in ASD.

However, there is currently no true medication available for effectively treating ASD, and early behavior modification has long been regarded as the only effective treatment technique. There is still a long way to go in terms of new drug development, with aripiprazole and risperidone being the only FDA-approved medications for treating severe symptoms of ASD. Several other new drugs have failed in phase two or three clinical trials.

ASD, oxytocin, and arginine vasopressin

Oxytocin (OXT) and arginine vasopressin (AVP) are closely related nonapeptides that differ in only two amino acids. These nonapeptides are mainly synthesized in the paraventricular and supraoptic nuclei, are processed along axonal projections to the posterior lobe of the pituitary, and released from dendrites and somata within the brain [5]. OXT and AVP neurons project directly to other brain regions, including the amygdala, striatum, hippocampus, bed nucleus of the stria terminalis, and supra-chiasmatic nucleus. OXT and AVP have been investigated for their potential to promote the ability to interpret social cues correctly. These two peptides also play important roles in facilitating parturition and lactation, and regulating the salt and water balance, respectively, when released from the pituitary into peripheral circulation. While OXT was first

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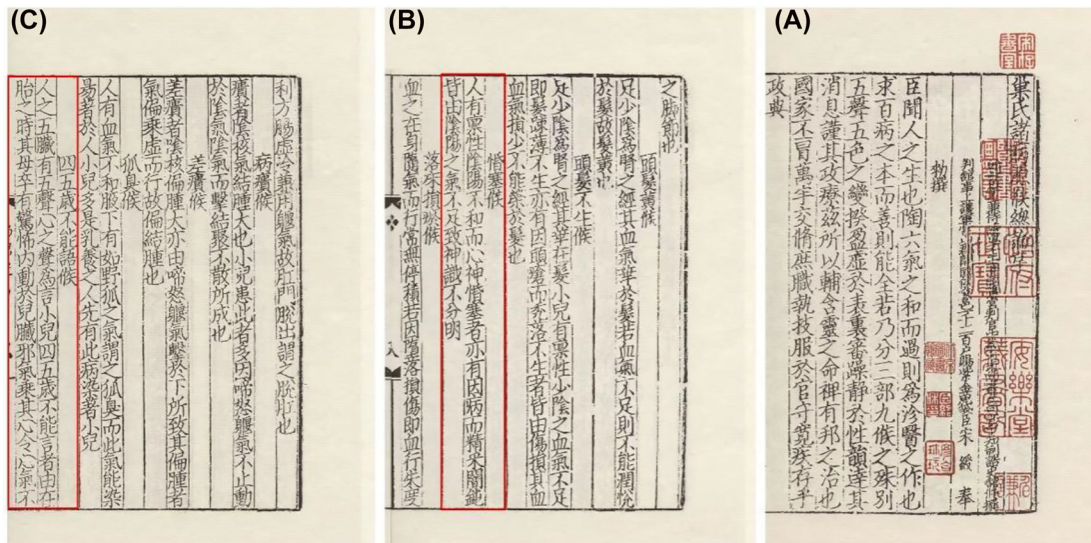


Figure 1: During China’s Sui Dynasty (581–618), Chao Yuanfang, in “Zhubing Yuanhou Lun” (“on the Etiology of diseases”) (A, cover of the book) volume 48, described a phenotype called “hun se.” Children with this phenotype exhibit an unclear and obstructed mind because of a natural discordance between Yin and Yang, while other children exhibit mental retardation caused by postnatal diseases. According to Chao Yuanfang, this condition occurs because the Qi of Yin and Yang is not sufficient, causing the mind and spirit to be muddled. (B, red box). In volume 50, Chao Yuanfang wrote of “yu chi,” specifying that the five internal organs correspond to five sounds, and that the heart (in ancient China, the heart refers to the brain) corresponds to language ability. For example, a child aged 4–5 years may be unable to speak because their mother was frightened during pregnancy when the child’s organs were forming, causing evil Qi to oppress the child’s heart and preventing them from being energetic. (C, red box). This is the earliest recorded description of autism-like behaviors in Chinese medical history. The image is from a carving copy of a book produced in the Yuan Dynasty (1271–1368). Copyright © National Library of China.

reported to be involved in maternal behavior and mother-infant bonds in sheep by Kendrick in 1987 [6], OXT and AVP have subsequently been reported to be involved in enhancing socially relevant recognition, cognition, memory, reward, empathy, trust, and attachment behaviors by acting on its receptors distributed in many different brain regions involved in controlling social behavior [7]. In this way, OXT and AVP may enable individuals to focus on social information both by increasing the salience of social cues and facilitating the accurate interpretation of these cues [8]. Zhang’s research group at Peking University six hospital was the first to report a positive association between altered polymorphisms in the OXTR gene and autism in the Chinese Han population in 2005 [9]. The research group of Han and Zhang has been engaged in OXT- and AVP-related studies since 2008, which have revealed that dysregulation of OXT and AVP occurs in children with ASD [10, 11] and that mothers’ neuropeptide dysregulation [12] can influence children’s susceptibility to ASD (Figure 2). In addition, plasma AVP levels were found to be negatively correlated with visual and listening response scores of ASD children and positively correlated with increased volume in the left amygdala and left hippocampus as well as significantly a significantly decreased volume in the bilateral hypothalamus [13]. In view of the above findings, exogenous

supplementation or endogenous activation of peptides is considered to be a potentially effective treatment for impaired social communication and interaction in autism. In the last decade, a number of studies have investigated the therapeutic efficacy of exogenously administered OXT [14–17] and AVP [18] for the treatment of ASD, although mixed conclusions may reflect the incomplete understanding of how the treatment should be administered and which types of individuals may be more responsive than others. Ongoing research is currently being conducted to systematically address these issues.

Acupuncture treatment for ASD

Acupuncture is a traditional medical technique that has been practiced since it was developed in ancient China, and research using modern neuroscience methods has generated an interesting dialogue between ancient and modern knowledge. Acupuncture has been used for treating pain and many functional disorders in more than 180 countries. Headed by Professor Jisheng Han (coauthor of this article), a research group at Beijing Medical School has been conducting basic and clinical research on the mechanisms underlying acupuncture therapy since 1965.

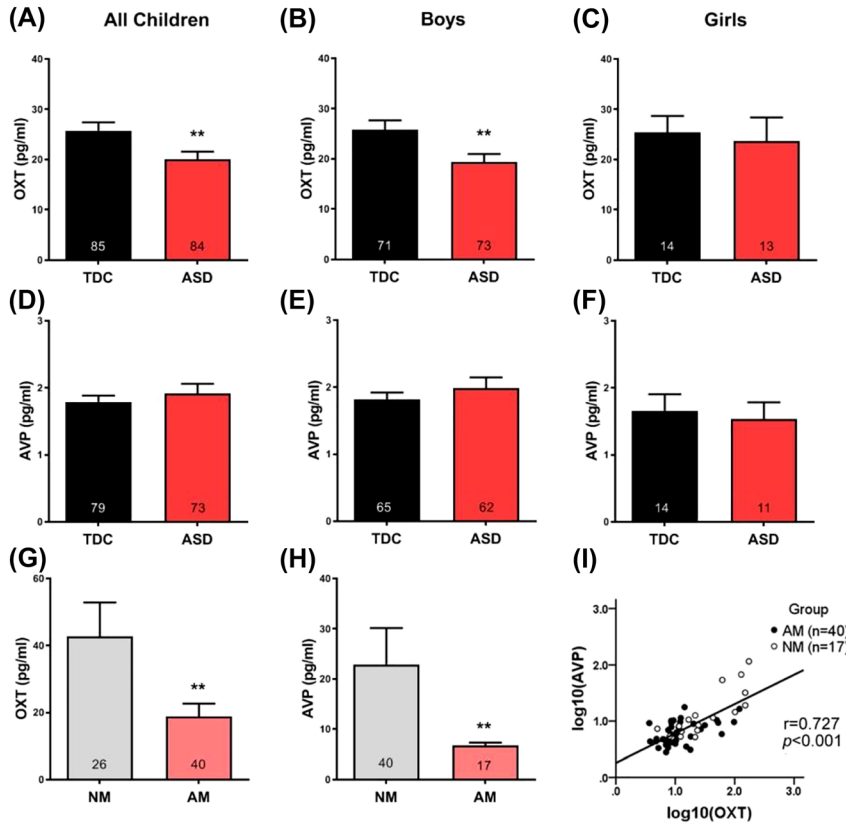


Figure 2: Plasma concentrations of oxytocin (OXT) and arginine vasopressin (AVP) in typically developing children (TDC) and autism spectrum disorder (ASD) children and their mothers. Children with ASD exhibited significantly lower plasma OXT levels than TDC ($P = 0.003$) after adjusting for covariates (A). Boys with ASD exhibited significantly decreased plasma OXT concentrations compared with TDC boys ($P = 0.0055$) (B). No significant difference in OXT levels was found between TDC and autistic girls (C). Regarding plasma AVP levels, no significant difference was found between ASD and TDC in the whole sample (D), boys (E) and girls (F). The mothers of ASD children showed significantly lower plasma OXT (G) and AVP (H) levels than those of TDC. A positive correlation was shown between log-transformed plasma OXT levels and log-transformed plasma AVP levels (I) ($r = 0.727$, $P < 0.001$). All values are expressed as mean \pm standard error of the mean (A–H). * $P < 0.05$. AM, mothers of autistic children; NM, mothers of normal children; SEM, standard error of the mean.

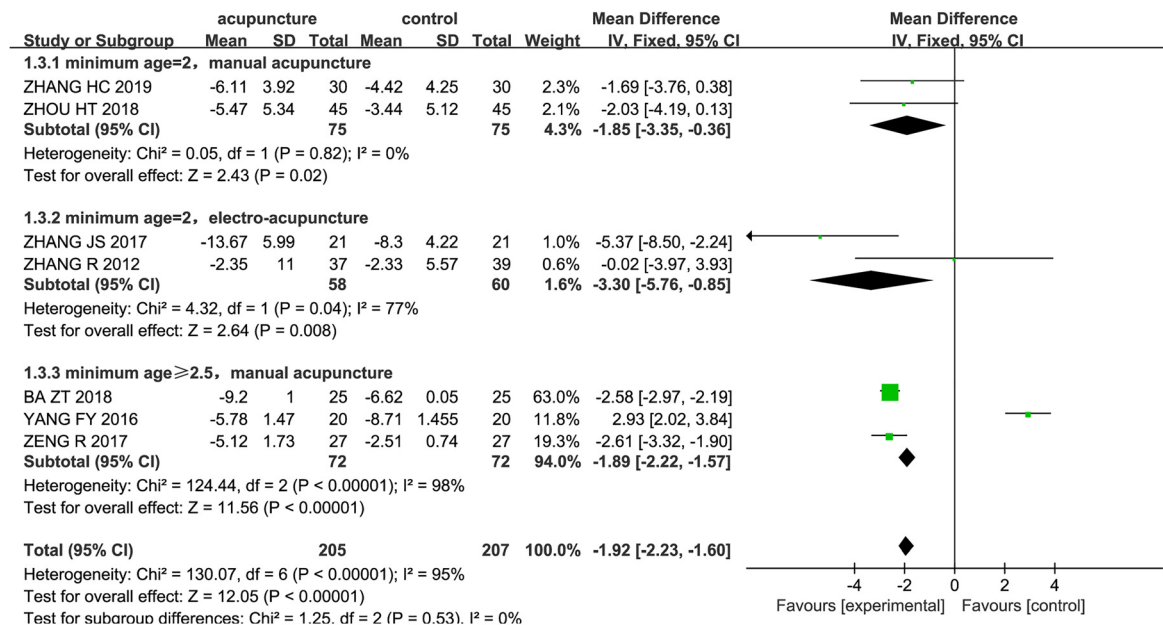


Figure 3: Meta-analysis results of effects of acupuncture on total Childhood Autism Rating Scale scores in autism spectrum disorder children.

Acupuncture has been recognized internationally for its role in pain control by stimulating the release of endogenous opioid peptides [9], raising the question of whether acupuncture can also alleviate symptoms of autistic children by increasing the endogenous production of “prosocial” neuropeptides.

In 1997, Dr. Zhang first reported that acupuncture was effective for treating children with autism [19]. To collect information regarding the effects of acupuncture on ASD in the literature, we conducted a meta-analysis (unpublished data). We searched 10 databases (English databases: Cochrane Library, Pubmed, Embase, Medline and Web of Science; Chinese databases: China National Knowledge Infrastructure, Wanfang Database, Weipu Database, SinoMed and Chinese Clinical Trial Registry) for randomized controlled trials on acupuncture for ASD. The MeSH terms were (“acupuncture” OR “electro acupuncture” OR “acupuncture point”) AND (“autism” OR “autism spectrum disorders”). Studies were included if they met the following criteria: (1) participants had a confirmed diagnosis of ASD; (2) the study was a randomized controlled trial and included a clear description of the randomization method; (3) acupuncture was conducted alone or in combination with behavior correction training in the acupuncture group, and the control group underwent behavior training if the treatment group underwent behavior training. Studies were excluded for the following reasons: (1) the article was a review or meta-analysis and did not involve original research; (2) the article reported an animal study; (3) participants also had other neurodevelopmental disorders; or (4) the article did not report a randomized controlled trial. After screening, seven articles were included in our meta-analysis. The Childhood Autism Rating Scale total score was chosen as the primary outcome. The results of our meta-analysis of randomized controlled trials revealed that, according to an efficacy evaluation led by child psychiatrists, the beneficial effects of acupuncture or acupuncture-related techniques combined with behavior training were greater than those of behavior training alone [20–26] (Figure 3). The subgroup analysis revealed that the source of heterogeneity was the lower limit of the age of the beginning, the treatment, and beginning the treatment earlier had better effects. However, regardless of the age group, both manual and electro-acupuncture were effective.

In the current study, an acupuncture-derived technique called transcutaneous electrical acupoint stimulation (TEAS) was used to treat children with ASD. The acupuncture points used were LI 4 (Hegu) and PC 6 (Neiguan) on one side, and ST 36 (Zusanli) and SP 6 (Sanyinjiao) on the other side, with 30 min per session and five sessions per week for 3 months. Trained investigators

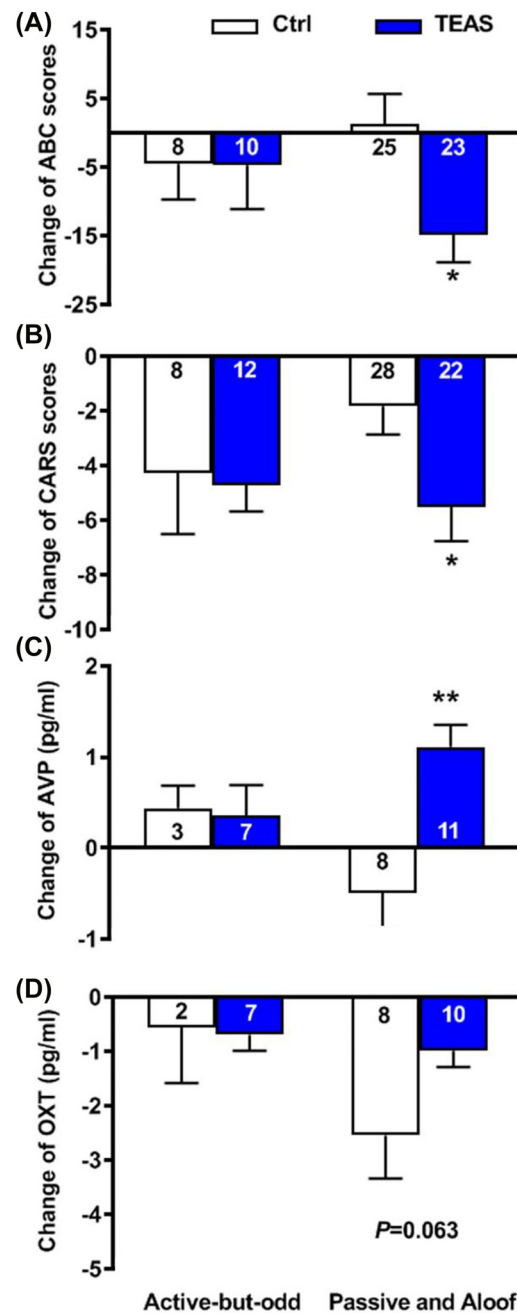


Figure 4: Social interaction style and behavioral and neurochemical responses to transcutaneous electrical acupoint stimulation (TEAS). The Autism Behavior Checklist (A) and Childhood Autism Rating Scale (B) total scores decreased significantly in autistic children with passive and aloof, but not active-but-odd, social interaction styles after TEAS treatment. The plasma AVP level increased in children with passive and aloof, but not active-but-odd, social interaction styles after TEAS (C). No significant changes were observed in OXT level after TEAS treatment (D). Columns and bars represent the mean \pm SE. The Mann–Whitney U test was used to compare changes in the scores in A and B; an unpaired *t* test was used to compare changes in the plasma AVP and OXT levels in C and D; *: $P < 0.05$, **: $P < 0.01$. Ctrl, control; TEAS, transcutaneous electrical acupoint stimulation; ABC, Autism Behavior Checklist; CARS, Childhood Autism Rating Scale; AVP, arginine-vasopressin; OXT, oxytocin.

carried out efficacy evaluation without knowledge of the treatment of the individual. The results revealed that TEAS in addition to rehabilitation was associated with a significant improvement in social communication and interaction, sensation, intelligence, food aversion, and anxiety, compared with the rehabilitation alone group. It has been reported that TEAS is not equally effective in all children with ASD.

According to their daily social interaction styles, ASD children were classified to the following three groups based on Wing and Gould's description: (1) "active-but-odd individuals", who displayed and pursued inappropriate or peculiar approach behaviors; (2) "passive individuals", who accepted social approaches but would not make contact spontaneously; and (3) "aloof individuals", who had no interest in social contact. The therapeutic results of TEAS was found to be most significant in "aloof" and "passive" types of children, who account for 72.4% of autistic children; no effect were found for "active but odd" children [25] (Figure 4). To further improve the method of subtyping, we revised the Wing Subgroups Questionnaire published by Dr. Geraldine Dawson [27] and developed the "Beijing Autism Subtyping Questionnaire" for Chinese children [28] (Chinese copyright, 2016-1-00275072). Furthermore, the identified ASD subtypes varied in terms of the level of symptoms especially for impairments of language skills (aloof>passive>active but odd). Results of a newly randomized placebo controlled double-blind trial indicated that ASD children with more severe symptoms and lower oxytocin level had better effects but not the mock TEAS group (unpublished data). This finding suggests that ASD subtypes (aloof and passive) with lower oxytocin (biomarker) may able to better predict the clinical efficacy of TEAS in the treatment of ASD. These preliminary data are promising.

The mechanisms of acupuncture therapy – involvement of OXT and AVP

OXT and AVP release within the hypothalamus and in other limbic brain regions in response to physiological stimuli (e.g., suckling, parturition, touching and hyperosmotic challenge), social or emotional experiences (e.g., maternal defense and social defeat), and physical stimuli (such as chronic homotypic stress and forced swimming) [29, 30]. For the first time, the research group of Han and Zhang incorporated acupuncture, OXT and AVP into the treatment of autism [25].

In a previous clinical study, the effects of TEAS treatment are correlated with the degree of increased plasma OXT and AVP levels [25]. In addition, the change in the plasma AVP level paralleled the improvement of some of the behavioral factors in the Childhood Autism Rating Scale, including adaptation to environmental change, listening response, perceptual response and fear or anxiety [25].

In normal SD adult rats, single sessions of electro-acupuncture have been reported to lead to region-specific upregulation of OXT and AVP mRNA levels in SON, and repeated sessions of electro-acupuncture led to significant improvement of social behavior of low socially interacting rats accompanied by upregulation of mRNA and peptide levels of OXT or AVP in SON [31]. In the valproic acid-induced Wistar rat model of autism, OXT and AVP are expressed at low levels, and both exogenous OXT [32] and AVP [30] (postnatal day 0–6) administration has been reported to have positive effects on social interaction. TEAS treatment in the early life stage (postnatal day 7–13) can improve social and cognitive abilities and rescue the impairment of pain sensation in adolescence among VPA offspring [33] along with the recovery of OXT in the cerebrospinal fluid and paraventricular nucleus. In addition, TEAS has been reported to stimulate the expression of neurotrophic factors (nerve growth factor, insulin-like growth factors) in the primary sensory cortex (unpublished data) along with an improvement of dendritic spine pruning [33]. These effects might also contribute to the therapeutic effects of acupuncture on ASD in addition to activating OXT or AVP systems.

Follow-up plan

Acupuncture, as a safe, inexpensive and effective means of treating functional diseases, is widely applied in clinical practice, and is covered by health insurance in many countries. However, current understanding of the underlying mechanisms of acupuncture and how to maximize its therapeutic efficacy is limited. Several important questions remain unanswered: What are the optimal stimulus parameters and the optimal intervention time? What are the long-term effects? What are the characteristics of the neurochemical spectrum and brain networks of children with ASD who are suitable for acupuncture treatment? How do acupuncture signals affect the brain's social interaction control center? These questions may be answered by examining the circuits and mechanisms underlying social behavior.

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