Regaining control over opioid use? The potential application of auricular transcutaneous vagus nerve stimulation to improve opioid withdrawal treatment in China

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Abstract

Opioid use disorder (OUD) is a critical problem in China and is accompanied by depression and deficits in cognitive control. In China, the most successful intervention for OUD is the community drug rehabilitation where methadone maintenance treatment (MMT) plays a key role. Even though methadone for the treatment of OUD can be helpful, it can cause severe somatic side-effects, which limit its effectivity. Even worse, it can have detrimental effects on cognitive control, which is crucial to regain control over drug intake. Here, we consider the potential use of auricular transcutaneous vagus nerve stimulation (atVNS) as addition to MMT for opioid withdrawal treatment. Compared to other non-invasive brain stimulation methods, atVNS also targets the locus coeruleus (LC) important for noradrenaline (NA) synthesis. NA is an essential neurotransmitter impacted in opioid withdrawal and also critically involved in cognitive control processes. Its ADD-ON to MMT might be a useful mean to improve mood and to enhance cognitive control processes impacted in OUD. We discuss the translational advantages of atVNS in China such as the cultural acceptance of the modality of treatment similar to electroacupuncture. Additionally, the wearability of the ear electrode and at-home self-administration without intense medical supervision makes of atVNS a useful tool to enhance clinical and cognitive outcomes especially in everyday life situation. We discuss how atVNS can be integrated in tele-medical health approaches allowing that innovative treatments can widely be disseminated and continued even in situations of restricted medical access.

Keywords: atVNS, cognitive control, Locus Coeruleus, noradrenaline, opioid use disorder, withdrawal

1. Introduction

Opioid use disorder (OUD) is a condition characterized by continuing opioid use regardless of damaging consequences and which causes withdrawal syndrome when opioids are discontinued (1). In China the use of opioids started back three centuries ago when, in the 1760s, the introduction of widespread opioid use resulted from the import of illegal opium from British India (2). After losing the Second Opium War in 1860 to the United Kingdom and France, China was forced to import British Opium authorizing the opium trade with devastating outcomes for social and public health in China (Lu et al., 2008). In 1906 the 27% of the adult male population was addicted to opium and it is only after the foundation of the People's Republic of China, via very strict law regulations and punishment, that the Chinese government started a successful war eradicating the problem of opioid abuse in China (3). However, the problem resurfaced as main public health issue in the 1980s as a consequence of constitutional reform and open-door policies taking place in China at that time (3). Since then, the number of opioids users has enlarged steadily and reached 73% of drug abusers in 2010 (4) and, even though new synthetic drugs, such as 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine, are flooding the illegal market, by 2016 opioid users still accounted for 38.1% of all registered drug user in China (4). Yet, recent data on this issue, due to the pandemic, are not available.

Even though, there might be differences between provinces, in mainland China current interventions for OUD consist of compulsory isolation rehabilitation, voluntary detoxification and community drug rehabilitation where methadone maintenance treatment (MMT) plays a central and key role (4). Even though methadone seems quite effective during the detoxification and maintenance phases in the treatment of OUD (5–7), there are several limitations associated to this approach. First, methadone can cause severe cardiac and respiratory side-effects, such as respiratory depression and serious arrhythmia (8). Second, MMT in mainland China seems to be characterised by high drop-out rate and relapse (4). Third, at this point, there are not enough mobile clinics that offer MMT to reach the opioid users in situations of restricted medical access. However, due to the pandemic, precise data on this manner are not available. Last, methadone shows limited effectivity in restoring normal cognitive control functioning, which is crucial to regain control over opioid intake (9) and drug intake in general (10).

Accordingly, considering all these facets, OUD might require and benefit from an approach encompassing multiple treatments which will be able to enhance both clinical and cognitive outcomes supported by strong translational elements. Specifically, in the last decade non-invasive brain stimulation techniques have been proposed as an alternative neuromodulatory, but yet non-pharmacological, treatment for patients suffering from substance use disorder who fail to adequately respond to other treatment options (11–14). At this point, repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been the target of previous investigations on brain stimulation intervention to treat OUD (15). Here, we consider the potential use of auricular transcutaneous vagus nerve stimulation (atVNS) as addition to MMT or stand-alone treatment for opioid withdrawal in China. Interestingly, atVNS has been recently approved by the Food and Drug administration (FDA) as adjuvant intervention of symptoms of acute opioid withdrawal (16). This method has four advantages compared to rTMS and tDCS: First, while rTMS and tDCS are employed to stimulate and activate specific cortical areas, they are not suited to specifically affect neurotransmitter systems that are involved in opioid withdrawal, such as the catecholamine noradrenaline (NA) (17,18). Second, rTMS and tDCS require to be administered under professional supervision in medical settings, whereas atVNS can be applied at-home via self-administration. Third, atVNS might be well received in China in the treatment of OUD because of the cultural acceptance of the modality of treatment (i.e., transcutaneous), similar to auricular acupuncture or electroacupuncture (EA). Fourth, atVNS is contactless and will assure accessibility and continuity of treatment also if medical access is limited (4).

In the forthcoming, we will outline the shared neurobiological and cognitive facets of OUD and atVNS. Second, we will propose atVNS as a valuable ADD-ON and/or stand-alone treatment for opioid withdrawal, with high translational advantages. We suggest that atVNS will decrease stress-related

symptoms during opioid withdrawal and to boost the affective and cognitive recovery in OUD and, in so doing, help the users to regain control over their addiction.

2. Shared neurobiological and cognitive facets of OUD and atVNS

Opioids affect many different brain areas and likewise also several neurotransmitter systems, such as catecholamines (17). Considering that the central point of this article relies on atVNS as a novel potential ADD-ON treatment for opioid withdrawal, in this section we opted to only examine shared facets modulated by both opioid withdrawal and atVNS. Cognitive control deficits and affective symptoms typical of OUD seem to underlie changes in levels of catecholamines (19–25). Crucially, these impairments in cognitive control are responsible for relapses and the failure to regain control over drug use (10). Hence, in view of the fact that atVNS targets catecholamines, this technique has the potential to accelerate the cognitive and affective recovery in OUD.

Neurobiology of OUD and connection to the LC, affective symptoms, chronic stress and vagus nerve

Heroin is the most used opioid drug in China (4). Heroin is a semisynthetic derivative of morphine that, because of its high level of hydrophobicity, easily passes the blood-brain barrier (26). After entering the brain, heroin is promptly converted into morphine and bind with high affinity to the mu-opioid receptors (17). The activation of these receptors generates the well-known euphoric effect of heroin which reinforces drug consumption and facilitates the onset of addiction (26). Mu opioid receptors are distributed all over the brain, but with highest concentrations in the midbrain known to be involved in coding pain and reward signals (17). The activation of mu-opioid receptors also triggers Gamma-aminobutyric acid (GABA) neurons to disinhibit dopaminergic neurons in the ventral tegmental area (VTA) (27). Specifically, morphine inhibits GABA inhibitory neurons, which cause an excitation of the dopamine (DA) neurons in the VTA (28). The excitation then propagates from the VTA to the nucleus accumbens and to the prefrontal cortex (PFC) (29) areas not only related to the reward system but also to cognitive control functioning, which is crucial to regain control over opioid intake (10).

Chronic opioid consumption causes not only tolerance but also a withdrawal syndrome when the drug is discontinued. Withdrawal triggers a cascade of adverse effects, and, in order to avoid them, opioid use is continued resulting in a process of negative reinforcement (i.e., consumption of the drug to prevent adverse side effects) (30). Notably, opioids use heavily impacts the stress pathway of which the LC-Noradrenaline (LC-NA) system is a key element (18). Indeed, the LC has been proposed as the core nucleus that plays a causal role in the expression of the opioid withdrawal syndrome (18). The LC has been demonstrated to be the area where stress and opioids overlap and interact to predict vulnerability to opiate abuse (18). Indeed, receptors in the LC not only bind to many opioidergic peptides but also to stress-related peptides, such as the corticotropin releasing factor (CRF) (18,31). It is not surprising then that the LC has been involved in both, the stress response and opiate actions (32) and that, both chronic stress and chronic exposure to opioids, produces changes in the plasticity of the LC (18). Crucially, it seems that CRF and endogenous opioids co-regulate the activity of the LC-NA system in a way that CRF released by stress activates the LC-NA system inducing increased arousal. However, when the stress is over, endogenous opioids inhibits the LC-NA system bringing it back to baseline activity (33). However, chronic opioids use causes the sensitization of the LC to CRF levels (34). In so doing, the repeated administration of this drug mimics the effects of chronic stress at the level of the LC (18). Such dysregulated functioning of the LC-NA system lasts long after a user has stopped consuming opioids suggesting that such alterations are a risk factor not only for the initiation and maintenance of opioid use but also for relapse (17,18). Further, the brainstem noradrenergic systems seem to be implicated in the development of anxiety and depression (35) which are also two of the most recurrent affective symptoms described in OUD (36) and in chronic stress (37). Withdrawal symptoms associated with OUD can increase anxiety and trigger the onset of panic attacks. To alleviate these unpleasant symptoms, individuals may turn to opioids again, resulting in a cycle of drug use that further worsens anxiety. Continued opioid use and the resulting dependence, along with increased anxiety levels, can

cause the individual to experience depressive symptoms, such as feelings of sadness, hopelessness, and worthlessness, which can increase the likelihood of suicidal thoughts and behaviors.

One hypothesis put forward is that the vagus nerve, the 10th cranial nerve, has a crucial role in the parasympathetic nervous system and how mammals recover from stress (38). The failure to recover is indexed by a low vagal activity, also called vagal tone, which can be used as a biological marker of sensitivity to stress (38). Interestingly, afferent vagal signal spreads from peripheral nerves to nuclei in the brainstem, such as the nucleus of the solitary tract (NST) and the LC. These structures then propagate the activation to the hippocampus and cortical areas including the insula, the PFC, and the motor cortex (39–41). The LC synthesizes NA, a key neuromodulator known to be involved in many cognitive processes, including attention, memory and cognitive control, such as planning, decision making, and multitasking (19–25). Notably, as we will see in one of the following paragraphs, OUD impairs performance on precise those cognitive facets suggesting a disrupt NA signaling in this condition.

In sum, a dysregulated functioning of the LC-NA system which mimics the effects of chronic stress might be an important neurobiological factor contributing to the affective symptoms and cognitive deficits reported in OUD. That said, factors known to enhance stress resilience targeting the LC through boosting afferent vagal signaling to the brain, such atVNS does, might decrease stress-related symptoms and act as a protective factor to prevent relapse as we will propose in the next paragraph.

Neurobiological, affective and cognitive effects of atVNS

AtVNS stimulates the vagus nerve through a special earplug electrode developed to be exclusively mounted in the outer ear (i.e., pinna), where the auricular branch of the vagus nerve is located (39,42,43). The activation spreads in a bottom-up fashion from the afferent fibers of the auricular branch to the NST and LC, located in the brainstem, and from there to higher subcortical and cortical areas (e.g. the hippocampus, the insula, the motor cortex, and the PFC (39) (see Figure 1).

Insert Figure 1 about here

Several neuroimaging studies have demonstrated that atVNS activates, among other areas, the LC (40,41,44–47), which is considered to be the key structure involved in opioid withdrawal (17,18). Even though different neurotransmitter systems have been shown to be modulated by atVNS (12), the primary neuromodulator synthesized by the LC is the catecholamine NA (48). As suggested by Konjusha et al. (12), findings that atVNS modulates the LC present atVNS as an optimal method to modulate NA in contrast to unselective drug acting on the noradrenergic system (49). Given that a) NA drives many cognitive functions such as working memory, decision-making, planning and response inhibition (19–25,50) and that b) atVNS stimulates the LC which targets NA (39), it is not surprising that systemic reviews and meta-analysis reported atVNS as a reliable tool to enhance precise those cognitive processes (39,51), which are also impaired in OUD as a consequence of a dysfunctional LC-NA system, as we will see in the next section. Further, atVNS has been demonstrated to have a beneficial effect on markers of stress vulnerability (52–54). As pointed out in the previous paragraph, the failure to recover from stress is indexed by a low vagal tone, which can be used as a biological marker of sensitivity to stress (38). Vagal tone can be measured by heart rate variability (HRV): the variation in the time interval (i.e., inter beat interval (IBI)) between consecutive heartbeats in milliseconds (55,56). A low HRV is indicative of low vagal tone and less stress resistance, whereas a high HRV points to high vagal tone and optimal stress resistance (55,56). Interestingly, atVNS applied to the right ear has been found to be successful in enhancing vagal tone as measured by HRV (52–54). Further, greater responses to atVNS (i.e., improved vagally medicated HRV signals) have been demonstrated in those individuals with lower vagal tone, both acutely and with 2 weeks atVNS at home for 15 minutes daily (57), as indication that

individuals more vulnerable to stress, such as opioid users (58,59), might be the ones who profit the most from atVNS intervention during opioid withdrawal.

The selection of different stimulation parameters for atVNS is critical in achieving the best outcomes for the treatment of affective symptoms and cognitive function enhancement (39,42). These parameters include the stimulation frequency, pulse width, on-off cycle, current intensity, location of the stimulation, side of stimulation, position of the sham stimulation, and time of stimulation. Presently, most of the studies on the effects of atVNS on humans utilize commercial equipment like NEMOS® with predetermined parameters such as a maximum current intensity of 5 mA, 25 Hz frequency, 200 μs pulse width, and continuous stimulation or a 30s on / 30s off-cycle (39). Although studies have shown that administering right atVNS doesn't induce cardiac side effects (52–54), left atVNS is generally preferred as the left vagus has no connection to the heart, thus avoiding and limiting the possibility of cardiac adverse reactions (39). An imaging study investigated different areas of the ear that are innervated by the vagus nerve to find the optimal stimulation location (40). The study discovered that the cymba conchae region is the most effective at activating the NST and the LC (40). Moreover, for sham stimulation, the earlobe is the preferred location due to the absence of vagal innervation (60). In both animal and recent human studies, higher frequencies of stimulation (120 Hz) resulted in the maximal firing rates of the LC, as confirmed by the pupil dilation response to atVNS (61). Additionally, the study noted that adjusting stimulation parameters can also modulate the intensity of LC activity, leading to enhanced pupil dilation and an increase in noradrenergic activity (62). Although stimulation intensity and the activation of LC showed a positive correlation, this relationship didn't translate to the best cognitive performance for human patients with epilepsy (63). According to the study by Clark et al., only intermediate levels of stimulation were associated with optimal recognition memory performance, suggesting an inverted U-shaped function between stimulation intensity and cognitive performance (63). That is, moderate levels of stimulation, rather than high or low levels, seem to be ideal for inducing the release of NA to support the best cognitive performance (48). Concerning the duration of the stimulation period, a recent study focusing on depressive patients indicated that a four-week intervention involving four hours of daily stimulation led to a significant reduction in depression severity and an increase in cognitive speed (64).

In the USA, atVNS has recently been approved by the FDA as adjuvant intervention for symptoms of acute opioid withdrawal (16) and in the treatment of pharmacoresistant depression (43). Regarding addiction and vagus nerve stimulation (VNS), several animal studies on rats have examined the effects of this stimulation on drug-seeking behavior. First, a study demonstrated that VNS was effective in reducing heroin- or heroin cue-induced relapse, possibly through a NA-induced activation from the LC to the nucleus accumbens via the hippocampus (65). Consistent with this evidence, VNS was successful also in reducing the drug seeking behavior of cocaine-addicted lab rats (66,67). Hence, these findings indicate that VNS might accelerate the extinction of strong drug cue/reward associations in a wide spectrum of drugs, such as heroin (65) and cocaine (66,67). One study in human opioid users showed that atVNS effectively reduced opioid withdrawal symptoms as measured by the opioid withdrawal scale (68) supporting the idea that atVNS might be a valid tool in ameliorating this condition (16). Concerning depression, quantitative evidence has pointed out that via enhancing vagal signaling to the brain, atVNS is a valid tool to optimize the cortical frontal-vagal network and to reduce depressive symptoms (69). Hence, atVNS delivers a non-pharmacological option to treat depression, especially in patients non-responders to pharmacotherapy (69).

In sum, atVNS has been demonstrated, on the one hand, to reduce depressive symptoms (69) and to enhance stress resilience (52–54). On the other hand, it is assumed to boost the same cognitive control functions impacted in OUD, as we will see in the next paragraph (39,51). Hence, by ameliorating the functioning of the LC-NA system, the same system heavily impacted by opioid withdrawal (17,18), atVNS has the potential to decrease stress-related symptoms during opioid withdrawal and to boost the affective and cognitive recovery in OUD and, in so doing, help the users to regain control over their addiction.

Cognitive control deficits in OUD

Similar to other drugs, systemic reviews suggest that opioid use is associated with deficits in cognitive control, defined as top-down processes essential for goal-directed thought and action, such as working memory, decision-making, planning and response inhibition (70–73). First, concerning working memory, opioid users seem to be particularly impaired in the maintenance of contents in memory (74–76), but also when information needs to be quickly updated, monitored and manipulated (77,78). Interestingly, years of heroin consumption were negatively correlated with working memory performance (i.e. deficits in working memory were greater the longer opioid use lasted) (75). Second, regarding decision-making, opioid users show impairments in gambling tasks with explicit rules for gains and losses pointing to the fact that users tend to select the riskiest alternatives (79,80) and that these deficits persist also after short- to long-term abstinence (81). These results suggest that users opt for incentives with large short-term gains disregarding potential risks. Interestingly, using computational modeling, Ahn and colleagues (82) indicated that decision-making impairments in opioid users are likely to be enduring (or pre-existing) and resulting from reduced sensitivity to loss. Third, opioid users reported impairments in planning tasks, such as the Tower of London and the Porteus Maze, measuring the ability to plan and to adapt to new situations (74,83–85). Notably, these detrimental effects on planning seem to persist also after long period of abstinence (86). Last, a crucial cognitive control function which seems to be impaired in OUD is response inhibition, the ability to suppress actions that are no longer requested or considered to be inappropriate (73,87–89). Not surprisingly, drug-related cues seem to exacerbate these deficits suggesting that exposure to opioid-related cues increase the risk of relapse (90,91). In contrast to working memory, decision-making, planning and response inhibition, cognitive flexibility, as measured by the Wisconsin Card Sorting Test, does not seem to be impaired in OUD (83,92,93) suggesting that not all facets of cognitive controls are impaired as a consequence of opioid use. In this regard, Verdejo-García and Pérez-García (77) suggested that chronic use of different drugs (e.g., heroin and cocaine) reveal common but also differential effects on different and separate executive components which results in unique profiles of cognitive control deficits. Further, it is important to note that baseline levels of cognitive control predict the likelihood of, not only entering treatment (94), but also can predict treatment response in OUD (95) as an indication of how crucial is regaining cognitive control for the recovery of OUD.

The findings described in this section should not be surprising given that cognitive control functions have been demonstrated to be modulated by catecholamines (20–22,25,48,96) which are synthesized, among others, by the LC, the same nucleus severely affected by opioid withdrawal (17,18).

In sum, OUD seems to impair working memory, decision-making, planning and response inhibition but not cognitive flexibility, suggesting a unique profile of cognitive control deficits. These impairments are in the same cognitive functions driven by NA, the neurotransmitter originating from the LC, which is severely impacted by opioid withdrawal. Hence, modulating NA through atVNS may be a useful tool to regain cognitive control in OUD considering that, as we have seen in the previous paragraph, atVNS has been proved to quantitatively enhance cognitive control (51).

3. AtVNS as adjuvant treatment to MMT?

In mainland China, treatments for OUD entail compulsory isolation rehabilitation, voluntary detoxification and community drug rehabilitation where MMT plays a crucial role (Chen & Zhao, 2019). Methadone is a synthetic agonist drug which targets mu opioid receptor (17). It is typically dispensed orally in liquid or tablet form. After oral consumption, peak plasma levels are roughly achieved in 2-4 hours and methadone elimination in the body happens within 28 hours making feasible for one single dose a day (17). The majority of opioid users respond positively to doses between 60mg–120mg daily (17). Even though methadone seems quite effective during the detoxification and maintenance phases in the treatment of OUD (5–7), there are several shortcomings linked to this pharmacotherapy. First, methadone can cause severe cardiac and respiratory side-effects, such as respiratory depression and serious arrhythmia (8). Second, MMT in mainland China seems to be characterized by high drop-out

rates and relapses likely due to daily lower dosages (< 60mg) of methadone administered (4), or due to the fact that many users don't come to the clinic with the motivation of abstain from drugs but use methadone as an alternative to relieving the onset of a temporary absence of opioids. Third, at this point, there are not enough mobile clinics that offer MMT to reach opioid users in cases where there are limitations to obtaining medical care .

Even though medications are widely used to treat OUD in China, drug therapy undergoes the issue of non-responders which is worrying given that a weak or no response to pharmacological agents might preclude an exacerbation or continuation of the withdrawal symptoms causing longer absence from social and working life (97). Accordingly, it is crucial to consider potential non-pharmacological intervention to treat the withdrawal symptoms caused by discontinuation of opioid use. Non-pharmacological agents will be particularly useful in preventing toxic drug–drug interactions (98). Indeed, mixing benzodiazepine, a drug prescribed to treat opiate withdrawal symptoms, with MMT can be lethal because of respiratory depression (98). Further, given that atVNS has been approved for the treatment of pharmacoresistant depression (43), it might be better suited for OUD than standard pharmacotherapy such as antidepressants, which are often accompanied by side-effects or withdrawal and rebound phenomena when discontinued (99). More importantly, a systemic review revealed that MMT does not only show a very limited effectivity, but even detrimental effects in restoring normal cognitive control functioning, which is crucial to regain control over opioid intake (9). Indeed MMT patients, compared to abstinent heroin users or non-user healthy controls, displayed reduced psychomotor speed and impairments in working memory, planning and response inhibition (9,100–105). To address this issue, new ADD-ON interventions that can be combined with standard pharmacological agents are needed to achieve effective therapies to enhance mood and cognitive control functions impacted by OUD. In contrast to other types of non-invasive brain stimulation methods, like rTMS and tDCS, which have been demonstrated to augment cognitive processes (106), atVNS is a feasible tool because it exclusively targets the LC (40,41,44–47), which has been demonstrated to be dysfunctional during opioid withdrawal (17,18). It is expected that combining atVNS and MMT could have a beneficial additive effect because MMT targets mu opioid receptors (17) and atVNS targets LC synthesizing NA (40,41,44–47). Studies have shown that the noradrenergic system can modulate the activity of mu opioid receptors (33), so the activation of noradrenergic neurons by atVNS might enhance the analgesic effects of methadone. This additive effect could potentially support users in overcoming withdrawal symptoms more comfortably. A randomized controlled trial should be conducted in the near future to test this hypothesis.

In the next section, we will outline how atVNS may work as auxiliary tool for MMT and/or as stand-alone opioid withdrawal treatment , describing the safety and practicality of atVNS in regard to OUD.

4. AtVNS's safety and feasibility in real-world setting for OUD and compatibility with MMT and CBT

As discussed in the section "Neurobiological, affective and cognitive effects of atVNS", atVNS can be regarded as an useful mean to improve mood and enhance cognitive control processes in opioid withdrawal (51,69,107,108). These aspects are very important given that these factors are crucial to regain control over drug intake (10). Further, atVNS is a safe and a well-tolerated electroceutical that does not require any surgical intervention and which elicits only minor adverse effects (i.e., tingling, warming, or prickly skin under the electrodes) (109). AtVNS can be safely administered across the life-span and, to date, there seems no indication of any gender differences in terms of its efficacy (42). Nonetheless, it's crucial to note that atVNS should not be administered to pregnant women, individuals with head injuries, or those who have metal objects implanted in their bodies such as pacemakers or other active medical devices. Additionally, it's important to avoid atVNS on wounded skin as it could lead to potentially more cutaneous irritation. The atVNS device does not necessitate any particular positioning or evaluation as the ear electrode can be worn only on one location within the auricular concha (see Figure 2) where the strongest activation of vagal afferents linked to the auricular branch of the vagus nerve has been observed (40). Individuals are free to move around and carry out their daily

tasks without any hindrances while using the atVNS device. Concerning feasibility, atVNS is a non-invasive electroceutical that can be useful as an ecological momentary intervention (EMI): it is a pocket-sized, light, and handy device that can be easily operated by the users without any medical supervision, as long as they have undergone thorough training under a physician's supervision (12,110). It should be noted that the NEMOS® at-VNS device has predetermined parameters, such as stimulation frequency, pulse width, on-off cycle, which users cannot adjust. Additionally, current intensity cannot be set higher than 5 mA and the device has a built-in safety feature that automatically stops functioning once the maximum daily stimulation time of 4 hours has been reached, preventing overstimulation or misuse. Against this background, atVNS may be a feasible method to treat OUD, compared to other non-invasive brain stimulation techniques, such as TMS and, to a smaller degree, tDCS, which are confined to medical settings. Crucially for our purpose, newly developed atVNS devices, such as tVNS® L, come with APPs which are intuitive and easy to use. Further, earphone-like electrodes are comfortable to be worn in day-to-day life and can be disguised as regular in-ear headphones and, in so doing, protecting opioid users from social stigmatization, which is still very high in China in the context of drug detoxification (111). Hence, within the context of Chinese society, atVNS is not only a useful EMI but can at the same time also be regarded as a means to reduce stigmatization in this society given that treatment-seeking opioid users in contemporary China seem to be extremely hesitant to be admitted in a government-sponsored treatment facility for worry of a stigmatized identity (111). Indeed, Chinese citizens disclosed as opioid users, are enlisted lifelong in an official register disregarding confirmed successful rehabilitation and/or recovery (111). The option of self-administering atVNS at home is particularly attractive for OUD for three reasons. First, when medical services are not easily accessible or available due to certain circumstances, atVNS will provide them accessibility and continuity of treatment to overcome withdrawal symptoms. Second, atVNS might be well accepted in China in the treatment of OUD because of the cultural resemble of the modality of treatment (i.e., transcutaneous), similar to auricular acupuncture or EA. Even though, acupuncture has been demonstrated to have beneficial effects in the treatment of opioid withdrawal in combination with opioid agonists (112), within the context of afferent vagal stimulation, its mechanisms of actions are still under debate and imaging or other neurobiological evidence regarding whether auricular acupuncture really activates vagal afferents in the brain, such as the LC and NST, is still missing. Further, traditional acupuncture, EA or even acupuncture patch therapy require the needles and/or patches to be put by practitioners whereas atVNS is contactless (i.e., it can be applied by the patients themselves without the professional help of third). Even though full-time staff of a regular MMT clinic usually includes at least two doctors (4), given that in China practitioners need to follow a specific training and obtain a special medical license in acupuncture, such specialized practitioners might be often missing in MMT clinics where the patients undergo treatment for acute opioid withdrawal. Further, in line with official treatment guidelines, MMT clinics are only supposed to provide methadone and psychological rehabilitation and/or social skills training (4). As in 2016, a total of 773 MMT clinics, most of them located in big cities, had opened in 29 of 34 provinces and about 160.000 opioid users have been treated there in the same year (4). However, only 24 of 773 MMT are mobile clinics with the specific goal to address who has limited access to the facilities (4). Hence, atVNS might be particularly useful to provide accessibility and continuity of treatment to users during lockdowns and/or living in those provinces where no MMT clinic has been opened yet. Third, MMT in mainland China seems to be characterized by high drop-out rates and relapses (4), likely due to the low dosages of methadone administered and negative attitudes of medical staff towards opioid users (4). Adherence to treatment with atVNS might be increased using digital technologies (113) given that in China the level digitalization in daily life is very high. Indeed, everyone possess a smart phone in view of the fact that since the start of Covid-19 pandemic it was necessary to present the digital health code for work-related or daily activities. For example, a mini-APP module could be developed in “WeChat”, a free messaging and calling app extremely popular in China, in order to collect data of opioid users and to detect patterns to enhance adherence to the atVNS treatment. Within the framework of an individualized approach, in accordance with the opioid users about a time of the day, the digital assistant of the mini-APP could send daily direct reminder to them when to self-administer atVNS and when to stop the stimulation. After the completion of the atVNS

session at home, the screenshot of the atVNS operating-APP could be sent to the digital assistant, where time of the day, date, length and stimulation intensities are reported. Last, in WeChat weekly video calls with social workers could be easily implemented to monitor the ongoing treatment and to assure optimal adherence. Fourth, atVNS can be combined with herbal traditional medicines which includes natural products such as plants, animals, and minerals. Indeed, several Chinese herbal medicines, such as Banxia-Houpu decoction (114,115), Fu-Yuan pellet (116), Jinniu capsules (117), Qingjunyin (118) and Tai-Kang-Ning capsule (119), have been tested in clinical trials for the treatment of OUD in virtue of their sedative, pain relief and anti-convulsion properties (2). Even though, Chinese herbal medicines have been reported to be less efficient than methadone, they have been proved to be more valuable than non-narcotic detoxification agents (e.g., clonidine or lofexidine) in controlling opiate withdrawal symptoms (2,3). Chinese herbal medicines could be easily combined with atVNS with the goal to reduce relapses because they target different aspects of OUD, while the former helps to deal with neurological symptoms, the latter addresses affective and cognitive outcomes. However, given that these Chinese herbal medicines are not covered by health insurance, recovering opioid users in financial distress don't use them. Fifth, atVNS could also be jointly administered with cognitive behavioral therapy (CBT) given that a) the stimulation of the vagus nerve has been proposed to augment the efficacy of psychotherapy (120) and b) a meta-analysis proved CBT to be effective for Chinese people, especially when CBT was adapted to Chinese culture (121). Within the context of OUD, CBT can help the users to recognize the most compelling cues for opioid use and atVNS can have a role in supporting such cognitive strategies to limit the negative influence of these cues. For example, OUD users could turn on the atVNS device whenever they are confronted with any triggers related to opioid use (e.g., a disposable syringe with needle or a tourniquet). Hence, combining CBT with atVNS could be useful in preventing relapses and the efficacy of such combination could be directly measured by the newly validate Chinese version of obsessive compulsive drug use scale (122).

In sum, atVNS is a safe, feasible and compatible tool, which can be regarded as a an optimal non-invasive electroceutical to boost affective and cognitive outcomes to overcome the effects of opioid withdrawal. Further, newly developed atVNS devices come with user-friendly APPs by means of which duration, current intensity and stimulation frequency can be customized in order to tailor treatments for individual opioid users within the framework of precision medicine.

5. Conclusion

OUD is associated with depression and deficits in the domain of cognitive control. MMT, the most used pharmaceutical agent to treat OUD in China, is helpful in managing acute symptoms during withdrawal, but shows detrimental effects on cognitive control, which is crucial to regain control over opioid intake. We propose the potential application of atVNS as an ADD-ON tool to boost cognitive control and mood in opioid withdrawal treatment . In contrast to other non-invasive brain stimulation methods, such as TMS and tDCS, this method a) exclusively targets the LC, which has been demonstrated to be dysfunctional in opioid withdrawal, b) decreases depressive symptoms, and c) boosts working memory, decision-making, planning and response inhibition, the same cognitive control facets affected in OUD. Considering that atVNS is a non-pharmacological tool, its ADD-ON to MMT will be especially valuable for non-responders by preventing toxic drug–drug interactions, making of this electroceutical a feasible mean to help users to regain control over opioid intake. Furthermore, in China, atVNS has great potential because of the cultural acceptance of the modality of treatment (i.e., transcutaneous), similar to EA. Moreover, within the context of opioid withdrawal, atVNS is an EMI characterized by unique translational advantages such as the earphone-like electrodes that can be worn in everyday life. Finally, considering that atVNS can be self-administered at home without the help of third, it can guarantee accessibility and continuity of treatment in situations where there are constraints or obstacles in accessing medical treatment..

Authors contribution

LSC drafted the manuscript. JE designed the graphical abstract and Figure 1. CB, JE, XX, QZ and BH provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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Figure legends

Figure 1:
Panel A: graphic representation of the main subcortical and cortical regions modulated by atVNS: the NST and, crucially for our purpose, the LC which synthetizes NA. Following a bottom-up fashion, once the stimulation has started, from the auricular branch of the vagus nerve the activation propagates to the nuclei located in the brainstem and from there to the the hippocampus, the insula, the PFC and the motor cortex. Panel B: the correct placement of atVNS is depicted illustrating the active (through the cymba conchae) and sham stimulation (through the earlobe which is free from vagal fibres), as it is usually used in experimental settings.