Astrocytes as a target of transcranial direct current stimulation (tDCS) to treat depression

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Highlights

- tDCS has been shown effective in treating depression, though its mechanisms remain elusive.
- Astrocytic Ca2+ elevation plays an essential role in tDCS-induced synaptic plasticity in mice.
- Astrocytic Ca2+ signaling mediates long-term mitigation of depression-like behavior in mice.
- The literature suggests that astrocytes are a potential therapeutic target for depression.

Abstract

Transcranial direct current stimulation (tDCS) has been reported to be effective in treating mood disorders such as major depressive disorder, however, its detailed mechanism of action is not fully understood. Human and animal experiments have demonstrated that tDCS promotes brain plasticity and have suggested that this consequence may underlie its therapeutic benefits. Nonetheless, the specific neurobiological underpinnings of tDCS-induced brain plasticity have only recently begun to be investigated. While brain plasticity occurs in synapses formed by neurons, astrocytes, a major glial cell type, have recently been shown to support synaptic plasticity via intracellular Ca^{2+} signaling. In this perspective article, we discuss our recent results demonstrating that tDCS induces the activation of astrocytic calcium signaling that constitutes a required component for treating chronic restraint stress-induced depressive mice. We put forward the notion that activation of astrocytic Ca^{2+} signaling could be used clinically as a potent remedy for depression.

1. Introduction

Major depressive disorder is a common mental illness affecting over 300 million people of all ages worldwide (WHO fact sheet on depression 2017). Depression of this type is long-lasting, over the course of months and years, and incapacitates one's physical and social abilities. Depression can also lead to suicide, which is the second highest cause of death in young adults (ibid.). Alleviation of depressive symptoms improves the quality of life of patients and increases the productivity of our society. While psychotherapy and drug treatment, such as by fluoxetine, have been shown effective for some patients with severe depression (Kirsch et al., 2008), statistics show that less than half of depressed people receive professional treatments (Pratt and Brody, 2014).

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation procedure whereby a direct current of 1-3 mA is applied for 10-30 min over the scalp of human subjects. An increasing number of human studies have reported that tDCS enhances brain functions including motor learning and memory (Marshall et al., 2004; Nitsche et al., 2003; Reis et al., 2009). Although tDCS has not yet been approved by the Food and Drug Administration (FDA), it has been gaining considerable social attention. This is in part because the circuit that generates tDCS is simple and stimulation devices are commercially available from on-line stores. In addition to memory and learning enhancements, tDCS has been probed for its therapeutic potential in various neuropsychiatric and neurological conditions. Of these, the most intensively examined use of tDCS in psychiatric conditions is major depressive disorder.

Despite several successful uses of tDCS in clinical trials neuropsychiatric and neurological conditions, its mechanism of action has not been completely understood. It has been theorized that the current from the anode increases the probability of action potential generation by elevating the resting membrane potential of neurons (for a review, Stagg and Nitsche, 2011). This enhanced excitability of neuronal network activity is hypothesized to lead to a state where long-term potentiation (LTP) of synapses is more prone to occur than the basal state (ibid.). As we will discuss later, more mechanistic explanations of circuit dynamics have begun to be addressed in the recent decade. Additionally, we propose that glial cells, in particular, astrocytes, also play an essential role in the expression of tDCS-induced plasticity via their intracellular Ca^{2+} signaling (Monai et al., 2016; Monai and Hirase, 2016). We will discuss how astrocytes

can be a major effector to mediate synaptic plasticity and how this mechanism extends our understanding of tDCS application in psychiatric conditions with a focus on clinical depression.

2. Application of tDCS to treat depression

Early attempts to use tDCS for the treatment of mood disorders were motivated by a study by Lippold and Redfearn (1964), in which they reported an elevation of mood by the application of a 0.5 mA current from an anode placed above the eye brows to a cathode on the right leg. This effect was polarity dependent and a reverse current resulted in a suppression of mood. Due to the association of mood and subcortical neuromodulators, the effect was speculated to be in part due to possible brainstem stimulation (ibid., Nitsche et al., 2009a). In retrospect, the effect could as well be exerted via vagus nerve stimulation, which has been reported to improve mood (Elger et al., 2000; Harden et al., 2000) and could be more electrically accessible at the stimulation points. Following this study, Redfearn and colleagues tested tDCS on treatment-resistant depression patients and reported positive effects in about half of the twenty-nine patients (Redfearn et al., 1964). In another double-blind clinical trial with twenty-four patients, statistically significant effects of tDCS were reported (Costain et al., 1964). As reviewed in Nitsche et al. (2009a), subsequent studies in the late 1960s and 1970s have reported beneficial effects on depression, although stimulation parameters varied from study to study. In contrast, a study Arfai et al. failed to see effects (Arfai et al., 1970). Moreover, the initial Lippold and Refearn study could not be replicated (Sheffield and Mowbray, 1968), although only six subjects were examined in this study. As such, the significance of tDCS treatment was considered inconclusive.

Electrode placement and stimulus parameters were empirically determined in these early studies. In the 1990s, human functional imaging studies identified that hypofunction of the left prefrontal cortex is a commonly observed feature among patients with depression (George et al., 1994), thereby suggesting a target area for non-invasive brain stimulation. Indeed, transcranial magnetic stimulation (TMS) of the left dorsolateral prefrontal cortex (DLPFC) has been reported to improve standardized diagnostic scores in about half of the treated patients (George et al., 1995; Pascual-Leone et al., 1996). Meanwhile, the stimulation parameters for tDCS have become less arbitrary in the 2000s, owing to the work by Nitsche and Paulus that reported a

reliable protocol to enhance motor evoked potential by motor cortex-targeted tDCS, allowing an objective assessment of tDCS effects (Nitsche and Paulus, 2001, 2000).

These developments encouraged scientists and clinicians to apply tDCS to the left DLPFC for the treatment of depression. Accordingly, application of tDCS to the F3 position of the 10-20 system, which corresponds to the left DLPFC, has been shown to be effective for depressed patients by Fregni and colleagues about a decade ago, by using stimulation parameters commonly used today (1 mA over 35 cm^2 interfacing area, 20 min/day, anodal, applied daily for five days) (Fregni et al., 2006). Subsequent studies from the same group have demonstrated the target specificity (Boggio et al., 2007) and longer effect duration by dosage increase (2 mA, 20 min/day, anodal, for 10 days) (Boggio et al., 2008). Similar outcomes were reported in other independent studies as well (Segrave et al., 2014; Wolkenstein and Plewnia, 2013). Notably, Segrave et al. (2014) reported that combined treatment of tDCS and cognitive control training is more effective than tDCS alone.

It appears that tDCS offers a nonpharmacologic therapeutic approach to patients where drug treatment is non-trivial. For example, tDCS was applied to HIV-infected depressed patients, who often show relatively small improvements after treatment by medications or psychotherapy. As a result, the subjects displayed a decrease of depressive symptoms (Knotkova et al., 2012). This effect lasted for at least two weeks after the completion of tDCS treatment. To give another example, amelioration of depressive symptoms has been reported in well-controlled temporal epilepsy patients after tDCS treatment (Liu et al., 2016).

Studies that reported a lack of effect of tDCS have also been published. For example, Palm and colleagues reported that similar tDCS dosage and target area to Boggio & Fregni groups' studies (1 or 2 mA, 20 min/day, anodal, for 10 days, left DLPFC) did not show a significant effect on clinical depression ratings in treatment-resistant patients, although increases of positive emotion were observable (Palm et al., 2012). Ineffectiveness of tDCS in treatment-resistant depression was also reported for patients who had been treated with escitalopram, a selective serotonin reuptake inhibitor (SSRI) (Bennabi et al., 2015). The variable nature of tDCS outcomes has also been documented for motor evoked potential experiments (Wiethoff et al., 2014)—the very paradigm that revived tDCS in the 2000s from

being unreliable. According to this study, half of the subjects showed significant enhancements of motor evoked potential, whereas the remaining half were inert to tDCS.

As mentioned above, the statistical significance of tDCS effectiveness on depressed patients is confounding, even after the DLPFC has been set as the target. Several attempts to perform meta-analysis of the published studies again led to mixed conclusions (Kalu et al., 2012; Shiozawa et al., 2014). This could be due to small sample sizes in individual studies, heterogeneous experimental conditions, and/or the choice of aggregate data approach for meta-analysis. To overcome these points, an individual patient data meta-analysis has been conducted over six randomized sham-controlled clinical trials including a total of 289 subjects (Brunoni et al., 2016). This study concluded that tDCS is effective in treating depression in a dose-dependent manner and less effective in treatment-resistant depression. However, it should be noted with a caveat that a majority of data points (ca. 75%) came from datasets that have been published for having significant effects of tDCS.

In summary, the efficacy of tDCS for the treatment of depression remains controversial. However, the latest meta-analysis with stronger statistical assessments favors the significance of tDCS in treating relatively mild depression. Skepticism toward tDCS could arise also due to the lack of clear understanding of tDCS mechanism, which we discuss in next sections.

3. tDCS and subcortical neuromodulators

One of the prevailing views of clinical depression mechanism is based on the monoamine hypothesis. In the monoamine hypothesis, depression is explained as the condition in which monoaminergic transmission (i.e., dopamine, noradrenaline/norepinephrine, and serotonin) is compromised in the brain. The monoamine hypothesis is indeed supported by the current therapeutic approach that aims to elevate extracellular monoamine levels by, for instance, SSRIs or selective noradrenaline reuptake inhibitors. Since tDCS has been reported effective to treat depressed patients, the influence of tDCS on monoaminergic system has been hypothesized.

In humans, lines of indirect support for the involvement of (chemical) neuromodulators in tDCS-induced plasticity have been reported in a series of studies by Kuo, Nitsche, and colleagues. They administered enhancers of neuromodulators (e.g. precursors and inhibitors of reuptake or breakdown) in conjunction with tDCS-induced plasticity in healthy human subjects.

As a result, they observed differential motor evoked potentials by enhancing acetylcholine (Kuo et al., 2007), dopamine (Kuo et al., 2008), serotonin (Batsikadze et al., 2013; Nitsche et al., 2009b), or noradrenaline (Kuo et al., 2017). In these experiments, baseline motor evoked potentials with or without drug intake did not differ significantly. Taken together, these results could be interpreted as possible releases of several neuromodulators by tDCS, although the drug specificity and effects in the peripheral nervous system must be carefully taken into account.

In experimental animals, direct evidence for dopamine increase by tDCS has been presented in the rat striatum (Tanaka et al., 2013). The microdialysis data showed that striatal dopamine level is gradually elevated over the time course of 400 minutes after 10 minutes of anodal (but not cathodal) tDCS. By contrast, serotonin levels did not change. A recent study reported an elevation of c-fos activity in the ventral tegmental area (Peanlikhit et al., 2017), which is the major source of dopaminergic projection to the prefrontal cortex. In the mouse sensory cortex, tDCS has been implied to elevate noradrenaline level, because tDCS effects were diminished by blocking alpha-1 adrenergic receptors or ablating noradrenergic neurons (Monai et al., 2016). In mammals, subcortical neuromoduratory neurons are located subcortical areas (e.g., the ventral tegmental area and substantia nigra for dopamine; locus coeruleus for noradrenaline), which might be electrotonically distant from the transcranial stimulation site (but see Huang et al. (2017)). Whether the tDCS-induced elevation of neuromodulators is due to somatic firing, axonal activation, or terminal leak without action potential generation has not been resolved (Monai and Hirase, 2016).

In addition to synaptic transmission, neuromodulators are known to influence the brain through volume transmission, by which neuromodulators are released from presynaptic boutons and diffuse to the extracellular space to influence a wider area than synaptic transmission. Recent *in vivo* studies indicate that glial cells receive volume-transmitted neuromodulator signaling via respective receptors (mostly, G protein-coupled receptors) and in turn, modulate local neuronal circuits (for a review, Hirase et al., 2014), which will be discussed in later sections.

4. tDCS mechanism: neuronal view

Since the observation that an anodal direct current applied on the pial surface of the rat brain increases cortical neuronal discharge (Bindman et al., 1964; Creutzfeldt et al., 1962), tDCS has

been recognized to elevate the excitability of neurons in the anodal area. A great amount of literature seems to support the notion that anodal tDCS causes a subthreshold depolarization of neuronal membrane potential, resulting in an increased probability of neuronal discharge and/or synaptic transmission. However, slice experiments show that such the effect depends cellular compartment—compartments proximal to the anode (e.g. apical dendrites in case of cortical circuit) are hyperpolarized whereas compartments proximal to the cathode (including the soma) are depolarized (Akiyama et al., 2011; Bikson et al., 2004). The degree and direction of membrane potential polarization most likely depend on how close the respective compartment is to the direct current stimulation (DCS) electrodes. Further, evoked synaptic inputs are also affected by the electric field (Bikson et al., 2004).

The slice experiment results are partially consistent with an earlier *in vivo* observation that pyramidal tract cells (presumably, the cell body is in layer 5) did not have a profound membrane potential change by a weak anodal current (< 80 $\mu A/mm^2$) applied on the cat brain surface, whereas superficially located cells were hyperpolarized (Purpura and McMurtry, 1965). Computer simulation of electric field and membrane potentials by compartmental modeling also supports this observation (Rahman et al., 2013). Together, these studies indicate that the impact of DC electric field on membrane potential is heterogeneous and depends on the location and geometry of the cell.

Of note, Gardner-Medwin has described that potassium ion (K^+) redistribution occurs by DCS. The data suggested that a cathodal current results in accumulation of K^+ towards the brain surface. Moreover, the K^+ flow is independent of neuronal activity and predominantly through glial cells (presumably through astrocytes, since they have a large K^+ conductance at rest) (Gardner-Medwin, 1983a, 1983b; Gardner-Medwin and Nicholson, 1983). Considering that the resting membrane potential of a neuron is largely determined by K^+, such a mechanism may influence the excitability of neurons and their axon terminals and dendrites.

Somatic depolarization by a weak electric field is sub-threshold. For example, Fröhlich and McCormick reported that a 2 mV/mm field strength results in 0.5 mV depolarization. Interestingly, such a small field strength was found to be sufficient to modulate the network activity of neurons in ferret cortical slices (Fröhlich and McCormick, 2010) and in rat hippocampal slices (Reato et al., 2010). We should, however, note that recent studies have

described that the field strength within the human cerebral cortex during tDCS is one to two orders of magnitude lower (Huang et al., 2017; Opitz et al., 2016). Intriguingly, Huang et al. (2017) also predicted a significantly higher field strength in the brain stem area where there subcortical neuromodulatory neurons are located (N.B. the cathode is at the occiput).

Following the enhancement of motor evoked potentials by tDCS in human subjects (Nitsche and Paulus, 2001), rodent slice physiology studies have shown that LTP is enhanced by DCS (Fritsch et al., 2010; Ranieri et al., 2012). Importantly, enhanced synaptic plasticity is observed in slices that were prepared from animals that received tDCS (Rohan et al., 2015). This metaplastic effect occurs even 24 hours after tDCS, suggesting the involvement of long-lasting factors. For instance, Fritsch et al. (2010) found that brain-derived neurotrophic factor (BDNF) is involved and Podda et al. (2016) found epigenetic regulation of the BDNF gene. It is tempting to speculate that tDCS elevates neuromodulator levels and BDNF expression is consequently induced which results in metaplasticity. For instance, noradrenaline is known to induce BDNF (Chen et al., 2007) and a similar scheme appears to hold in a rat vagus nerve stimulation model (Follesa et al., 2007).

5. Astrocytes as a target of tDCS and implication in depressive disorder

Astrocytes are glial cells that interface synapses and blood vessels, making them an attractive target of therapeutic interventions by systemic drugs. Astrocytes maintain the extracellular environment by removing neurotransmitters and absorbing excess K^+ (Verkhratsky and Butt, 2013). Astrocytes are also implied in mediating energy substrate transfer from the blood stream to neurons. In addition to these so-called classical functions of astrocytes, gliotransmission—secretion of bioactive molecules from astrocytes, has been proposed to be a key mechanism to modulate synaptic transmission and/or plasticity. For example, astrocytic activation has been demonstrated to promote LTP-like synaptic plasticity by elevation of extracellular D-serine in in vitro (Henneberger et al., 2010; Yang et al., 2003) and in vivo (Takata et al., 2011) in rodents.

While the membrane potential of astrocytes fluctuates only within a few millivolts *in vivo* (Amzica and Steriade, 2000; Kuffler et al., 1966; Mishima and Hirase, 2010), astrocytes display large-amplitude cytosolic calcium ion (Ca^{2+}) elevations (Hirase et al., 2004). Large-amplitude

astrocytic Ca^{2+} elevations are predominantly caused by internal release of Ca^{2+} via the type 2 IP_3 receptor (IP_3R2, which is also a Ca^{2+} channel) (Petravicz et al., 2008). In awake mice, large-amplitude astrocytic Ca^{2+} elevations are mostly triggered by noradrenergic activity via alpha-1 adrenergic receptor activation (Ding et al., 2013; Paukert et al., 2014).

We have recently found that an anodal current of 0.1 mA (over a circular area ~2 mm in diameter) for 10 minutes passed through the skull results in cortex-wide Ca^{2+} elevations in mice (Monai et al., 2016). In this work, we reported that tDCS-induced Ca^{2+} elevations have been identified to be of astrocytic origin, while cortical neuronal activities appear unchanged. Moreover, tDCS-induced Ca^{2+} elevations depended on the alpha-1 adrenergic receptor and were diminished by the ablation of noradrenergic neurons. Additionally, consistent with the hypothesis of astrocyte-promoted synaptic plasticity, sensory evoked potentials were potentiated after tDCS (Fig. 1).

Importantly, our study demonstrated that a single dose of tDCS improved the depression-like behavior induced by chronic restrained stress in mice. In this experiment, immobility time during a tail suspension test was measured following 5 consecutive days of daily restraint stress in a small plastic cylinder (Fig. 2A, 8–9 hours/day). As a result, the sham control group showed a monotonic increase of immobility time for the following 7 days, indicating progression of depression. By contrast, immobility time did not increase in the group which received a single dose of anodal tDCS after 5 days of restrained stress, suggesting an anti-depressant effect of tDCS (Fig. 2B). Remarkably, the anti-depressant effect was not observed in mice that had alpha-1 adrenaline receptor blockade, ablation of noradrenergic neurons, or IP_3R2 deficiency, which all diminish astrocytic Ca^{2+} elevations (Fig. 2C). Noticeably, IP_3R2 KO mice seem to show a susceptibility to chronic restraint stress ($p = 0.0003$ at Day 0; -10 min, data have been published in Monai et al. (2016) and were further analyzed in the current review). Collectively, these results suggest that tDCS-induced astrocytic Ca^{2+} signaling stimulates the recovery from depression-like behavior/states.

In support of the notion that astrocyte targeting is effective in depression, Cao et al. (2013) reported a decrement of extracellular adenosine triphosphate (ATP) in a social defeat model of depression in mice. Accordingly, administration of ATP to the prefrontal cortex reversed the depression phenotype. They also reported that IP_3R2 knockout mice have low extracellular ATP

levels and exhibit depressive phenotype without stress. The study proposes that Ca^{2+} dependent regulation of extracellular ATP levels by astrocytes is a key target of mood restoration. Intriguingly, another recent study (Tanaka et al., 2017) reported that social isolation in IP_3R2 KO mice negatively impacts the amplitude and occurrence of sharp wave-associated ripples, the hippocampal neural activity pattern known to take part in memory consolidation (Ego-Stengel and Wilson, 2010; Girardeau et al., 2009). Given the reliable astrocytic Ca^{2+} elevations by tDCS, it is of high interest to measure extracellular ATP level and how it may impact neuronal network activity after tDCS.

6. Concluding remarks

Although the effectiveness of tDCS as a treatment for depressive disorder is still controversial, meta-analyses of published papers seem to indicate that tDCS is effective in at least milder stages of depression. Our recent mouse study indicates that tDCS activates cortical astrocytes via noradrenergic receptors in the sensory cortex. Moreover, the activation of astrocytes, observed by Ca^{2+} elevations, is highly influential to the expression of LTP-like synaptic plasticity and amelioration of depression-like behavior. tDCS targeted to the prefrontal cortex, a common experimental procedure for treating depression in patients, might also activate astrocytes by dopamine, since the prefrontal cortex is preferentially innervated by dopaminergic fibers, in addition to other subcortical neuromodulator projections. We speculate that patients with drug-resistant depression may exhibit compromised Ca^{2+} elevations in cortical astrocytes in response to (chemical) neuromodulators and tDCS. It is certainly a challenge to demonstrate this in humans, however, development of animal models of drug-resistant depression will help to validate this hypothesis. tDCS has additionally been tested for other neuropsychiatric and neurological conditions such as schizophrenia, addiction, chronic pain, and Alzheimer's disease, to name a few (Kuo et al., 2014; Utz et al., 2010). If the beneficial effects occur with similar mechanisms, astrocytes are certainly a prime target for therapeutic intervention for a wide range of brain diseases.

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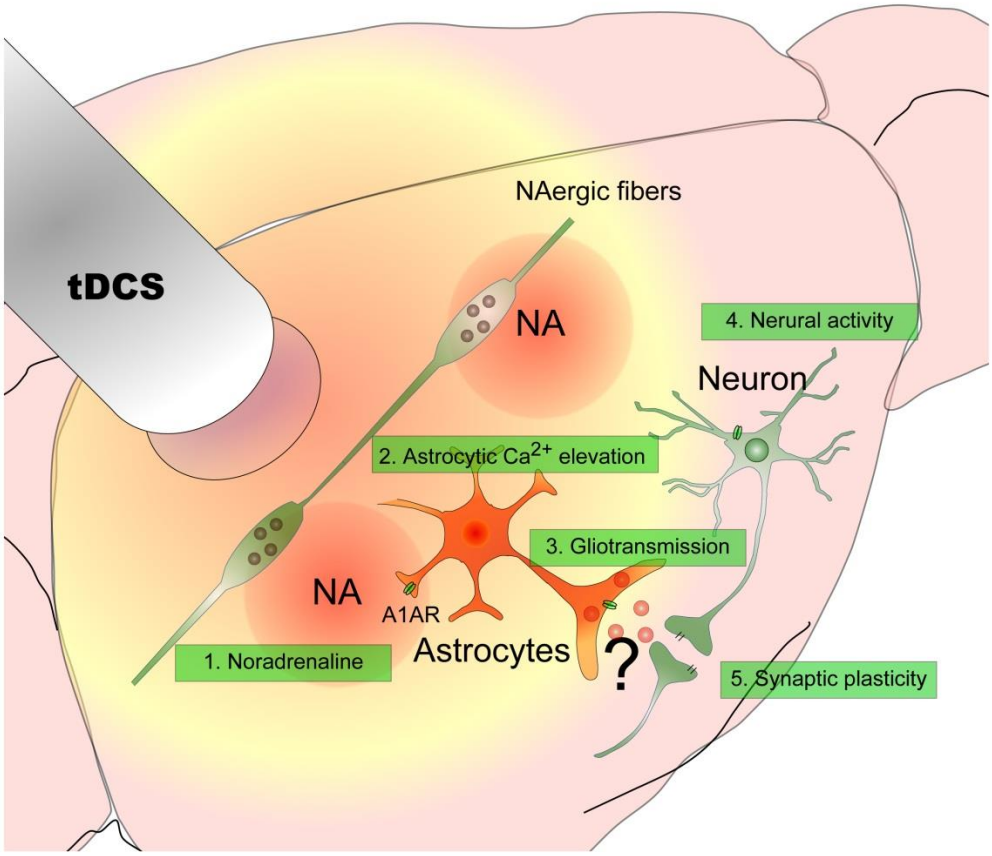
Figure 1



Schematic diagram for tDCS-induced Ca^{2+} elevation in the mouse cortex (modified from Monai and Hirase, 2016).

1. Direct current activates noradrenergic fibers or boutons to release noradrenaline (NA).

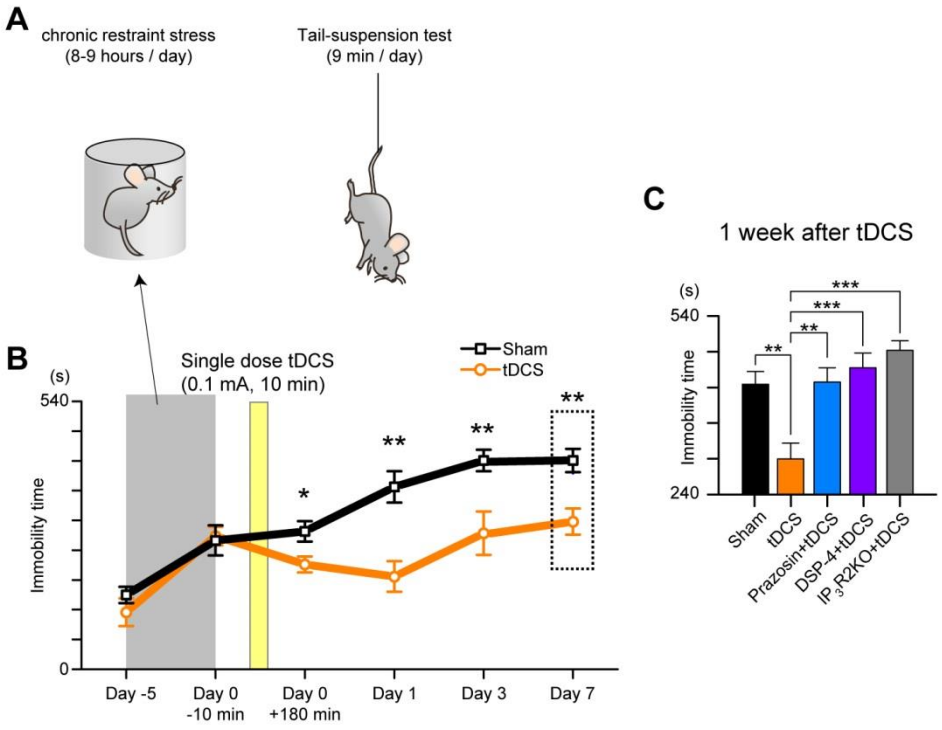
2. Volume-transmitted NA induces astrocytic Ca^{2+}elevation thorough the α-1 adrenergic receptor (A1AR).

3. Gliotransmitters (glutamate, ATP, D-serine, etc.) are possibly released from astrocytes.

4. Direct current also induces subthreshold depolarization of neuronal processes at the peri-anodal side.

5. NMDAR-dependent long-term synaptic plasticity is promoted for the active synapses.

Figure 2



tDCS alleviates a mouse model of depression by chronic restraint stress (modified from Monai et al., 2016, Supplementary Fig. 8). A. Schematic diagram the behavioral test. B. tDCS reduces depression-like behavior over 1 week. Tail suspension tests performed 1 week after tDCS show that tDCS group (N = 10) are more active than the group without tDCS treatment (sham; N = 10, Day -5: $p = 0.45$, Day 0 (-10 min): $p = 0.83$, Day 0 (+180 min): $p = 0.029$, day 1: $p = 0.001$, day 3: $p = 0.004$, day 7: $p = 0.003$, repeated measures two-way ANOVA). C. This effect is blocked by acute prazosin administration 30 min before tDCS (N = 10) and DSP-4 (toxin for NAergic neurons) treatment (N = 9), as well as in IP_3R2 KO mice (N = 9). Data are shown as mean ± SEM. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.