REVIEW ARTICLE

EMERGING NON-INVASIVE NEUROPLASTIC-TARGETING THERAPIES FOR SUBSTANCE USE DISORDER TREATMENT

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Context: America is in the midst of a substance use disorder (SUD) epidemic, which has only worsened in the current COVID-19 pandemic. SUD is a public health crisis that affects an ever-increasing proportion of the population and is extraordinarily difficult to treat. Misused substances induce neuroplastic changes that not only predispose individuals to relapse but also persist after completing treatment recommendations.

Objective: To establish the phenomenon of neuroplasticity in relation to SUD and summarize non-invasive neuroplastic therapies designed to return the brain to its pre-dependency state.

Methods: On October 29, 2019, the search term "neuroplasticity addiction" was entered into PubMed. Articles were selected based on description of neuroplastic changes occurring in SUD and treatment modalities that foster neuroplastic improvements for SUD treatment.

Results: 1241 articles were excluded based on irrelevance to the specific topic, language or redundancy. 41 articles met inclusion criteria, with 18 illustrating neuroplastic effects induced by SUD and 23 describing therapeutic interventions.

Conclusions: SUD induces neuroplastic changes that predispose an individual to relapse and persist after completing SUD recommendations. Transcranial magnetic stimulation, environmental enrichment and exercise are shown to affect altered brain composition and reduce SUD-related negative behavior, while motor training appears to block neurophysiological changes normally caused by substance use. This illustrates that therapies targeting neuroplastic changes reduce adverse behaviors in those with SUD. The implementation of these modalities with current standard-of-care treatment may increase treatment success. Additional research into these modalities and their potential to enhance current treatments is warranted.

BACKGROUND

Substance use disorder (SUD) is a devastating disease that is both common and exceedingly difficult to treat. The American Psychiatric Association DSM-5 defines SUD as substance use in association with at least 2 of 11 criteria including impaired control, social impairment, risky use and pharmacologic indicators (withdrawal and tolerance).[1] In 2017, nearly 20 million Americans aged 12 or older (10% of the population) suffered from SUD, costing the United States $740 billion in health care, crime and decreased work productivity annually.[2]

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SUD treatment programs generally employ a combination of medication-assisted withdrawal management and detoxification, medication-assisted treatment, and psychotherapy.[3] Medication-assisted withdrawal management uses drugs, such as anxiolytics, antiepileptics, beta blockers,[4] antiemetics, antidiarrheals and anti-inflammatories, for withdrawal symptom relief. Medication-assisted treatment relies on prescription drugs that act on the same targets in the brain as the substance that was being abused to relieve cravings,[3] allowing the patient and their healthcare provider to manage dosing in a safer manner. Psychotherapy consists of regular visits with behavioral health counselors in individual or group settings with the goal of managing the exposure to environments, situations and emotional states that may contribute to SUD.[3] While the above modalities address different aspects of SUD, the return-to-use rate (even with treatment) remains 40%–60%,[5] illustrating the potential for improvement in the treatment of SUD.

In the field of SUD treatment, focus is increasing on the structural and functional changes that occur in the brain during substance use—termed neuroplasticity.[6] Neuroplastic changes influence an individual's drive for continued substance use and may increase their likelihood of return to use after years of abstinence.[6] Structural change that defines neuroplasticity occurs throughout the cortex,[7] with dopamine acting as a catalyst to increase the production of new synapses.[8] As certain substances can cause large increases in dopamine release,[9] it follows that substance use has the capacity to induce neuroplastic changes. This dopamine release occurs via the increase of dopaminergic transmission from ventral tegmental area neurons into the striatum, the location of the nucleus accumbens.[8] The nucleus accumbens is casually referred to as the "pleasure center" of the brain. The significance of dopamine in this context is its ability to prioritize memories. Dopamine levels increase and produce pleasure if an action yields a reward or decrease and produce less pleasure if no reward is perceived.[10] Thus, certain substances may cause SUD not only because they are pleasurable (note that nicotine is not euphorigenic), but also due to the coupling of the experience of taking the substance with a large dopamine release, which imprints the memory as highly salient.[4]

Mice that were administered a single dose of cocaine exhibited long-term potentiation, or synaptic strengthening, of the "AMPA-receptor-mediated currents at excitatory synapses onto dopamine cells in the ventral tegmental area" that lasted for 5 days.[11] Similar studies using amphetamine, morphine, nicotine, ethanol[12] and benzodiazepines[13] revealed nearly identical neural changes. Notably, these substances have differing mechanisms of action,[14] supporting the theory that neuroplastic changes induced by these substances are related to their addictive nature and not their mechanisms of action. Furthermore, non-addictive psychoactive drugs, such as fluoxetine and carbamazepine, do not appear to cause long-term potentiation in ventral tegmental area AMPA receptors.[12] It also appears that the extended amygdala, which influences the hypothalamic-pituitary-adrenal (HPA) axis, a key component in the stress response, is altered with chronic substance use.[15] Researchers believe elevated levels of a FKBP5 protein in the extended amygdala, as seen in rats following chronic cocaine use,[15] may lead to a loss of negative feedback yielding overactivity of the HPA axis,[16] resulting in more severe negative affective symptoms of cocaine withdrawal.[15] This may lead to an increased drive for relapse.[15]

While these studies illustrate the nature of the brain's response to substances of abuse, others demonstrate how long these effects last. Rats exposed to a single dose of nicotine displayed upregulation of AMPA receptors 72 hours after administration.[17] In a different study, rats that self-administered cocaine for 14 days displayed neuroplastic changes after 3 months of abstinence.[18] Similar results were seen in humans, where chronic cocaine use sustained substance-induced neuroplastic changes after 4 months of abstinence[19] and chronic alcohol use showed persistent neuroplastic changes at 11 weeks post-detoxification.[20] These structural changes are significant, as they may predispose an individual to relapse.[21] These studies establish that substances of abuse lead to increased dopamine release onto the nucleus accumbens and increase the production of synapses. These dopamine-catalyzed[8] changes alter the wiring of the brain and may last for an extended period.[20] Moreover, they prime an individual to be more likely to use these substances[21] even after prolonged abstinence.[20] Thus, to achieve the highest success in the treatment of SUD, patients must not only detoxify and have their withdrawal symptoms managed, but also receive treatment to restore their brain to a pre-substance use state. The motivation for this paper is to explore non-invasive, nonpharmacological treatments that may reset the brain's composition to the pre-substance use state with a goal of improving treatment success.

METHODS

In this narrative review, we aim to establish the phenomenon of neuroplasticity in relation to SUD and summarize emerging non-invasive therapies that may alter SUD-induced neuroplastic changes with the goal of returning the brain to its pre-addicted state. On October 29, 2019, the search term "neuroplasticity addiction" was entered into PubMed. Inclusion criteria consisted of articles that illustrated neuroplastic changes occurring in SUD and studies that explored potential therapeutic interventions yielding neuroplastic improvements in the context of SUD. Exclusion criteria included articles not written in English, irrelevance to the topics of neuroplastic changes induced by SUD and therapies to address these neuroplastic changes, and redundancy to selected studies. Furthermore, studies evaluating therapeutic interventions that were not directly transferable to human application were excluded.

RESULTS

The results of this database search yielded 1282 articles. After applying the aforementioned exclusion criteria, 41 articles were selected. Of that total, 18 articles illustrated neuroplastic effects induced by SUD, and 23 of the articles evaluated various therapeutic interventions.

DISCUSSION

Promising non-invasive neuroplastic treatment modalities

TRANSCRANIAL MAGNETIC STIMULATION

Transcranial magnetic stimulation (TMS) is a therapy in which a coil placed on the scalp generates a magnetic field directed at specific locations of brain tissue to induce intracranial currents.[22] The induction of energy both excites and inhibits neurons and axons, with repetitive TMS (rTMS) producing a neuroplastic effect that persists following stimulation.[23] These neuroplastic changes may modulate behaviors that incite drug cravings and relapse.[22]

In a trial studying rTMS and cocaine use disorder, rTMS was targeted to the dorsolateral prefrontal cortex to attempt to reduce addiction and craving behavior.[24] Individuals received 8 rTMS sessions over 29 days, resulting in a significant decrease in cocaine use and craving scores.[24] To assess rTMS in the context of alcohol use disorder, individuals who fit the DSM-5 criteria for alcohol use disorder received 10 sessions of rTMS targeted

to the medial prefrontal cortex.[25] It was observed that rTMS yielded a decrease in the mean number of alcoholic drinks per day. Decreased craving levels persisted for one month following treatment.[25] The most compelling evidence for rTMS regarding SUD is seen in its treatment of nicotine use disorder. Smokers who consumed 20 cigarettes per day and were previously unsuccessful in treatment received rTMS directed to the lateral prefrontal cortex and insula for 13 sessions.[26] This treatment design resulted in significant decreases in nicotine dependence and cigarette use, with an abstinence rate of 44% following treatment and 33% at 6 months post-treatment.[26]

While the specific mechanism of TMS varies with the substance of abuse it is treating (as different areas of the brain are targeted for different substances of abuse treated), it is theorized that rTMS modulates SUD-altered dopamine release and homeostasis.[24–27] rTMS has been shown to increase dopamine levels in the mesolimbic and mesostriatal pathways[26] and in the caudate nucleus,[27] mimicking the dopamine release induced by substances of abuse.[28] This may prompt the uncoupling of the conditioned response of drug cue and drug use as summarized above. However, despite the successes observed, it must be noted that there are concerns about potential complications from microstructural changes in ferrous-containing structures[29] and that more research is needed.

ENVIRONMENTAL ENRICHMENT

Environmental enrichment (EE) consists of exposing subjects to stimulating environments[30] and has been shown to produce favorable changes in the brain in the setting of compulsive substance use.[31,32] Regarding EE and primates, a study utilized environments containing large, complex cages with straw nests, vegetation, branches and many unique objects that allowed for foraging, including "branches with holes filled with dried fruit and live worms," in contrast to a control environment of plain cages with no enriching stimuli.[33]

In a study examining cocaine use disorder and EE, mice were exposed to cocaine, then housed in either an enriched environment or a standard environment without access to cocaine.[31] After 30 days in the enriched environment, dependency-related behaviors were eliminated (ie, cues and environments that previously induced cocaine use no longer compelled the mice to self-administer).[31] A similar study investigated EE's effects on methamphetamine, heroin and nicotine use disorder.[32] Across all 3 substances, drug-seeking behavior was decreased following EE, with no change in drug-seeking behavior in the control environment.[32]

The mechanisms for EE's effects on SUD and neuroplasticity remain up for debate.[32] Multiple studies have reported that EE may increase dendritic size, number of dendritic spines[33,34] and dendritic complexity in the hippocampus and prefrontal cortex of subjects, as well as increase the levels of proteins such as GluR2, a subunit of the AMPA receptor.[33] As dendritic spines are the location of excitatory synapses,[35] the combination of an increase in dendritic spines and synaptic receptor subunits has led researchers to conclude that EE induces the formation of new excitatory synapses.[31] Additionally, research has shown that EE increases the rate of destruction of dendritic spines.[34] As the receptors modulated by EE are the same receptors altered by dependency (AMPA receptors), it is possible that through the effects of EE building up new dendritic trees while pruning others, the synapses previously altered by dependency are replaced with new, "nondependent" synapses. In other words, individuals in EE-related situations may make new memories quicker while leaving behind their dependency-associated memories. One could argue that much of standard behavioral therapy, including vocational training and 12-step programs that expand social networks, is a form of EE and works in part because of its neuroplastic changes. More research is needed to understand what an expanded emphasis on human EE would include and accomplish; some considerations may include utilizing meditation, art and music therapy and improving general life conditions.[32]

MOTOR-SKILL LEARNING

Motor-skill learning is the increased accuracy of specific movements with repetition.[36] It has been explored in the context of SUD treatment because motor-skill learning rewires the brain in the same manner as nicotine use.[37] Smoking tobacco induces neuroplastic changes in the dorsomedial striatum and nucleus accumbens core in the acute smoking phase.[37] During withdrawal the dorsolateral striatum, nucleus accumbens shell and central nucleus of the amygdala are affected.[37] The potential utility of motor-skill learning in the treatment of nicotine use disorder is the prevention of rewiring in the acute smoking phase and, most importantly for nicotine use disorder treatment, during the withdrawal phase.

To test the effect of motor-skill learning on neuroplastic changes induced by nicotine, researchers administered nicotine to rats over 15 sessions in a three-week period, followed by 5 days of rotarod training.[37] A rotarod is a device that contains a horizontal, rotating rod that may be accelerated.[38] The mouse must learn to walk on the moving rod to remain upright.[38] To determine neuroplastic changes and functionality, researchers performed post-mortem electrophysiological field potential recordings.[37] It was found that training on the rotarod extinguished neurophysiological changes induced by nicotine use in the acute phase, and blocked neurophysiological rewiring that occurs during the withdrawal phase.[37] Intriguingly, rotarod training restored plasticity to the endocannabinoid system,[37] a lipid signaling system[39] that has been theorized to contribute to SUD in general.[40] This finding is significant as it broadens the potential utility of motor-skill learning from the treatment of nicotine use disorder to the treatment of other SUDs.

EXERCISE

With the knowledge that individuals may become addicted to exercise itself,[41] it is not surprising that both exercise and substances of abuse fire the same reward pathways and alter the same neural substrates in the brain.[42] These findings led to the exploration of exercise as a treatment for SUD, with encouraging results.

In a study evaluating exercise's effect on cocaine-seeking behavior, rats were trained to self-administer cocaine, exposed to 10 days of free access to the substance, then restricted from cocaine for 14 days.[43] During the abstinent period, rats were given access to a running wheel for 2 hours daily.[43] Researchers discovered that prefrontal cortex levels of phosphorylated extracellular signal-regulated kinase (pERK), a biomarker positively correlated with the development of cocaine cravings,[44] significantly decreased in the exercise group and concluded that exercise may halt prefrontal cortex neuroadaptations that develop in the cocaine abstinence period.[43] Conflicting results were found in a trial that evaluated ethanol use and running.[45] Rats maintained high ethanol intake for 5 weeks, then made abstinent.[45] Rats with access to a running wheel after 1 or 2 weeks of ethanol withdrawal had an increased craving and consumption of ethanol following exercise, while rats that had access to the running wheel only after week 4 of ethanol withdrawal did not show increased craving and consumption.[45] This study brought to light the potentially complex nature of exercise and SUD treatment and possible timing sensitivities.

A study evaluating the effects of exercise on methamphetamine-related cravings in humans subjected methamphetamine users undergoing detoxification to three 30-minute sessions of exercise for 12 weeks. Craving levels were evaluated every 3 weeks. The exercise group began to experience reduced craving levels after 6 weeks of exercise, which persisted to the end of the study.[46] Nicotine use disorder and exercise have also been evaluated with similar success. Smokers assigned to a smoking cessation program were fitted with a pedometer. These individuals were recommended to increase their steps by 10% biweekly, with a goal of reaching 10,000 steps per day. After 24 weeks it was found that increases in physical activity were an accurate predictor of abstinence, while smoking relapse was associated with a decrease in exercise.[47]

The mechanism for exercise improving SUD treatment outcomes is a subject of debate. Knowledge that both exercise and substances of abuse activate the same reward pathways[42] may provide an answer. Prolonged substance use results in increased

TABLE 1:

Comparison of neuroplastic therapies used in the treatment of various substance use disorders

NEUROPLASTIC THERAPIES	SUBSTANCES	OUTCOMES	STATISTICAL SIGNIFICANCE (P VALUE AND N)
Transcranial Magnetic Stimulation	Cocaine[24]	Humans. Significantly decreased levels of craving.	*P*=.038 n=16
	Alcohol[25]	Humans. Significantly decreased levels of craving and mean number of drinks per day.	*P*=.0315, *P*=.021 n=9
	Tobacco[26]	Humans. Achieved an abstinence rate of 44% at end of treatment and 33% 6 months post-treatment.	*P*=.039, *P*=.0026 n=32
Environmental Enrichment	Cocaine[31]	Mice. Substance use disorder–related behaviors eliminated after 30 days of environmental enrichment.	*P* <.0001 n=64
	Methamphetamine, heroin, nicotine[32]	Rats. In contrast to standard environments, exposure to enriched environments reduced drug-seeking behavior.	*P*=.0062 n=unavailable
Motor Training	Nicotine[37]	Mice. Training of mice on a rotarod following the establishment of nicotine dependence extinguished nicotine-induced striatal neuroadaptations and restored synaptic plasticity.	*P*=.03, *P*<.01 n=16
Exercise	Cocaine[43]	Rats. Wheel-running reduced cocaine-seeking in rats who were previously exposed to cocaine.	*P*=.015 N=21
	Ethanol[45]	Rats. Wheel-running during 1 or 2 but not 4 weeks of ethanol withdrawal increased ethanol intake and preference.	*P*<.01, *P*<.01 Wk1: n=8 Wk2: n=6 Wk3: n=8
	Methamphetamine[46]	Humans. Reduced methamphetamine craving levels and increased behavioral inhibitory control after 6 weeks of the exercise program.	*P*<.01 n=25
	Tobacco[47]	Humans. Increased moderate-to-vigorous physical activity predicted sustained smoking abstinence at 24 weeks and decreased perceived difficulty staying smoke-free.	*P*=.028 (sustained smoking abstinence) and *P*=.038 (decreased perceived difficulty remaining smoke-free) n=163

dopamine signaling,[48] a component of the reward pathway.[49] As dopamine signaling results in increased levels of glutamate[50] (produced from glutamine[51]), the finding that striatal glutamine levels are decreased after running[52] suggests exercise as offsetting the increased sensitivity of dopamine signaling. This is in addition to exercise's effect on the extracellular signal-regulated kinase system.[43] Exercise also promotes increased executive control.[53] This may point toward exercise as reversing the damaging effects of substances of abuse.

CONCLUSION

While many advancements have been made in the field of addiction medicine, the substance use epidemic is far from over, and there is a continued call for the exploration of additional therapeutic modalities. To ensure greater success, further research needs to be done on the neuroplastic changes that occur with substance misuse as well as changes that occur during the recovery state. SUD treatment should include therapies that are targeted at returning the brain to its pre-dependent state. While the non-invasive neuroplastic-directed therapies summarized above are in the infancy of their exploration, they hold promise. In the subjects studied in each of the studies reviewed, many of the nontraditional therapeutic approaches resulted in not just observable changes in behavior, but also measurable, objective changes in brain signaling. Interventions like enriching a patient's environment, exercise and mindfulness training are all consistent with the holistic approach of osteopathic medicine. These interventions deserve to be studied further, with the goal of complementing current SUD treatment practices.

AUTHOR DISCLOSURE(S)

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