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Targeting the Salience Network: A Mini-Review on a Novel Neuromodulation Approach for Treating Alcohol Use Disorder

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Alcohol use disorder (AUD) continues to be challenging to treat despite the best available interventions, with two-thirds of individuals going on to relapse by 1 year after treatment. Recent advances in the brain-based conceptual framework of addiction have allowed the field to pivot into a neuromodulation approach to intervention for these devastative disorders. Small trials of repetitive transcranial magnetic stimulation (rTMS) have used protocols developed for other psychiatric conditions and applied them to those with addiction with modest efficacy. Recent evidence suggests that a TMS approach focused on modulating the salience network (SN), a circuit at the crossroads of large-scale networks associated with AUD, may be a fruitful therapeutic strategy. The anterior insula or dorsal anterior cingulate cortex may be particularly effective stimulation sites given emerging evidence of their roles in processes associated with relapse.

Keywords: alcohol use disorder, neuromodulation, transcranial magnetic stimulation, treatment, salience network, neurocircuitry

INTRODUCTION

Alcohol use disorder (AUD) is the most prevalent substance use disorder (1), imposes the greatest burden of illness (2), and alcohol-induced deaths in the United States are currently on the rise (3). AUD is associated with poor medical, psychological, and social outcomes, such as adverse overall physical health, neuropsychological deficits, psychiatric comorbidities, homelessness, unemployment, and relationship dysfunction (4–6), which contribute to a subsequent poor quality of life for individuals suffering from this devastative disorder. The estimated costs to the American economy were $223.5 billion in 2006 for excessive alcohol drinking (7). Current evidence-based interventions, be it psychotherapy or pharmacological, still result in approximately two-thirds of individuals relapsing by 6-months post-treatment (8). Emerging research into the key brain-based factors that contribute to relapse may reveal novel targets for prediction, intervention, and relapse prevention. To this end, we aim to briefly review the neurocircuitry of addiction, the role of the salience network (SN) in treatment outcomes, the latest trends in neuromodulation for psychiatric disorders, and conclude with a potential avenue for advancing brain-based interventions for AUD.

FUNDAMENTAL CONCEPTUALIZATION OF ADDICTION: A BRAIN-BASED CONDITION

Neurocircuitry of Addiction

Converging lines of evidence from preclinical and human research have resulted in the empirically driven, brain-based conceptual framework of addiction. Animal and human models of addiction have allowed for a sophisticated interrogation of the neurocircuitry that underlies addictive behaviors. Koob and colleagues describe the dynamic allostatic process of the addiction cycle in three stages: (1) binge and intoxication, (2) withdrawal and negative affect, and (3) preoccupation and anticipation stage (9, 10). During the binge and intoxication stages, the reward system is initially hyperactive, specifically the ventral tegmentum and the nucleus accumbens, and following chronic alcohol use, a homeostatic shift to hypoactivation occurs. During withdrawal and negative affect, there is a focus on reduced experiences of reward for conventional stimuli and increases in negative affect. These psychological experiences are coupled with changes in the striatum, extended amygdala, and insula functioning. Finally, the third stage is influenced by stress, increased disinhibition, and leads to preoccupation and anticipation of reward, including craving, which increases relapse risk (11, 12). A core part of this model is the shift from impulsivity fueling early stages of addiction to compulsivity fueling later stages of addiction (including relapse). This co-occurs with a shift from positive reinforcement mechanisms to negative reinforcement mechanisms, which can drive motivated behaviors. At the crossroads of this transition is the SN (13).

The Salience Network

The SN is a multifunctional, intrinsically connected, large-scale neural circuit implicated in several psychiatric conditions, such as addiction. Specifically, the SN is associated with the detection of salient changes in the environment, both interoceptive and external, and signals the need for cognitive control (14). Critical cortical nodes of the SN include the anterior insula (AIns) and the dorsal anterior cingulate cortex (dACC) (14–16). Additionally, these core nodes functionally connect with subregions of the prefrontal cortex (PFC) inferior parietal lobule (IPL) (14, 16–18) and downstream, subcortical regions of the extended amygdala, ventral striatum, and substantia nigra/ventral tegmental area (19, 20). Although intrinsic connectivity of the SN is most often reported during states of rest in humans, SN function is also interrogated during active tasks involving cognition, action, and emotion (19).

Recent work confirms these SN nodes are paralleled in preclinical models (21). In humans, the AIns, dACC, and dorsolateral PFC (dlPFC) co-activate in response to tasks of cognitive demand, cognitive control, decision-making, and environmental uncertainty. This co-activation has previously been implicated in negative mood states (17, 22–24), and synchronous activation has been shown to increase with task difficulty and stimulus ambiguity. This finding, of task difficulty-dependent, increased activation, suggests that the dACC and AIns both play an integral role in cognition by filtering and integrating internal and external stimuli during a variety of cognitive tasks (25).

The insular cortex is involved in various cognitive and affective processes, such as responding to internal and external emotionally salient stimuli, decision-making, threat recognition, and conscious urges (26). The insula is also heavily implicated in interoception, which involves integrating a wide array of somatic physiological conditions to maintain homeostasis (27, 28). The role of the AIns in the SN includes bottom-up detection of salient stimuli *via* integration across perceptual modalities (29–33). Specifically, the AIns plays a key role in externally orienting attention and internally orienting self-related cognitions through engagement with default mode and executive networks (14, 34–37).

Conversely, the dACC plays a crucial role in initiation, motivation, and goal-directed behaviors (38–41), with key projections that influence motor responses (42–44) and interactions with other large-scale networks that have a major role in motor/behavioral selection (25). In addition to co-activation with separate functional networks, the dACC also possesses extensive cortico-cortical connections within the PFC, including the dorsolateral prefrontal cortex (dlPFC) and premotor regions, making it critical for learning and behavior (45). Taken together, the fundamental nodes of the SN—the AIns and dACC—are implicated in the processing and synthesis of several complex human experiences, such as cognition, action, and emotion (19). These critical functions are central to the development and maintenance of addiction (10).

SN in AUD: Intersection With Neurocircuitry of Addiction

Regardless of clinical phenotype, the AIns and dACC are consistently implicated in the development and persistence of multiple psychiatric disorders, such as addictive disorders, suggesting they are critical for psychological well-being and adaptive functioning (46–48). For addiction specifically, the SN may interact and influence incentive salience (49, 50), negative affect (51–55), and executive function (56–60) networks, which are core neurocircuitry underlying AUD (61, 62). The Competing Neurobehavioral Decision System theory, alongside the Impaired Response Inhibition and Salience Attribution models, among others, are established conceptual frameworks of addiction that unite both behavioral and neurobiological systems involved in AUD (63). These models specify that the cortico-striatal circuits involved in processing salient internal or external stimuli, as well as cognitive decision-making, are compromised in AUD. Preclinical literature has identified regions, such as the dACC, insula, and striatum, as targets that are causally linked to alcohol-seeking behaviors (64). In humans, SN abnormalities contribute to difficulties with impulsivity, compulsivity, and executive dysfunction (65, 66), and an increased relapse risk in AUD (4).

The first study to suggest the AIns may have a critical role in the addiction cycle was by Naqvi et al. (67), showing that structural damage to the insula disrupted cigarette consumption. Following a right or left insula lesion, individuals demonstrated

rapid and extended smoking cessation, had fewer conscious smoking urges during abstinence (67), and were five times more likely to quit smoking compared with people with no insula lesion (68). Structural damage to the insula has also been shown to decrease the occurrence and severity of nicotine withdrawal symptoms (69), and smoking cessation difficulty (68). Taken together, these fundamental lesion studies highlight the role of the insula in withdrawal and relapse.

Dysfunction of the dACC has also been intensively described as having a role in psychiatric conditions, such as the development and maintenance of AUD. For example, prior studies have demonstrated that reduced dACC activation and compromised connectivity of the SN nodes are associated with greater decision-making latency in AUD (70, 71). Similarly, in individuals who reported binge drinking, acute alcohol consumption caused blunted functional connectivity between the bilateral AIns and the ACC (72). Several groups have demonstrated that such neurobiological abnormalities of the SN are related to the inability to restrain subjective urges (71) and evaluate emotionally salient stimuli (72) in AUD, further supporting that dysregulation of the SN in AUD (63), across resting state, social and emotional processing, and inhibitory control tasks, such as specific reductions in blood flow (73). Acute alcohol consumption significantly attenuates bilateral anterior insula activation to emotional face cues relative to neutral faces and is exacerbated by the level of response to alcohol, which increases the risk for AUD development (74, 75). SN dysfunction, such as structural and metabolic abnormalities (4, 5, 76) and reduced functional connectivity among nodes of the SN, is also predictive of future relapse in AUD (77, 78).

Similar evidence also points to the insula and the dACC playing major roles in reactivity to alcohol cues. A systematic review of over 100 task-related imaging studies by Zilverstand et al. revealed hyper-activation and hyper-connectivity during substance cue exposure, but blunted activation and reduced connectivity during all other tasks, such as cognitive control, non-substance reward, and social/emotional tasks (63). Other cue reactivity studies have found that neural activation in the insular cortex and the ventral striatum can be used to differentiate between heavy and light alcohol drinkers, with heavy drinkers having a higher activation in those regions in response to alcohol cues (79). This differentiation of neural activation between levels of alcohol use may also provide insights into who is at the highest risk of relapse (26). For example, Kohno and colleagues reported that individuals who did not complete AUD treatment showed increased resting-state connectivity between the striatum and the insula, demonstrating that SN dysfunction could be predictive of future drinking (77).

In summary, evidence suggests that insula and dACC activation and connectivity to other key nodes of the SN and how they relate to the neurocircuitry of addiction are highly relevant to the development and maintenance of AUD. One approach to improving treatment outcomes for these individuals may be to directly target SN function through novel therapeutic techniques that have demonstrated efficacy in other psychiatric conditions.

RESEARCH GAPS: ADVANCING TREATMENT FOR AUD

Among the different treatment options available for AUD, inpatient detoxification for alcohol appears to be the most frequently utilized (80). Residential treatment programs typically apply pharmacotherapies and/or behavioral interventions, such as cognitive-behavioral therapy, group-based peer support, and relapse prevention strategies. However, even with extensive, residential treatment, relapse rates remain high. One potential limitation of existing interventions is that they modify behaviors globally with indirect effects on the brain. Non-invasive neuromodulation techniques demonstrate promise by modifying specific and selective neural targets shown to be associated with symptoms. The current modest efficacy of evidence-based interventions, combined with increasing rates of alcohol-related deaths, makes the development of new brain-based therapeutics a high priority.

Transcranial magnetic stimulation (TMS) is a brain modulation technique that involves the use of different frequencies and patterns of stimulation to generate an electromagnetic field to depolarize neurons and influence cortical excitability. Apart from having FDA clearance for treatment, several resources describe guidelines for treatment and safety protocols (81–86). Extensive research supports the clinical efficacy of TMS for psychiatric disorders, most commonly for major depressive disorder (MDD), after FDA approval in 2008 (81). Since 2008, TMS has received FDA clearance for the obsessive-compulsive disorder (OCD) and smoking cessation (87, 88). Researchers have aimed to expand TMS indications for comorbidities associated with MDD, such as OCD, bipolar disorder, PTSD, and substance use disorder (83, 84). Additionally, researchers have tested altering the standard treatment protocol (89) or using high-efficiency forms of TMS, such as intermittent Theta Burst Stimulation (iTBS) (90) in hopes of increasing efficacy and/or decreasing overall treatment time.

To date, treatment approaches for TMS in AUD have predominantly targeted two brain regions: the dlPFC, and the medial prefrontal cortex (mPFC). While meta-analytic studies are difficult to utilize given the inconsistency in the treatment parameters used (e.g., as shown in Ref. (91)), a few brief trends have emerged: (1) 10 Hz left or right-sided, dlPFC protocol for the treatment of AUDs is generally helpful in reducing craving (92, 93); (2) the right-sided dlPFC has variable results which may or may not be related to the frequency at which treatment is delivered (92, 94); (3) mPFC stimulation consistently reduce brain reactivity to alcohol cues (95–97), and may reduce alcohol use post-treatment (98, 99); and (4) regardless of stimulation site and chosen TMS parameters, applying 10+ sessions of TMS appears to consistently decrease alcohol craving (94, 98, 100, 101). While results are promising, it is notable that many of these studies focus on craving and have not directly reduced alcohol consumption or relapse risk (92, 94–97, 100–106). While the mixed results within the field may be due to differences in parameter application (frequency, strength of stimulation, and

TABLE 1 | Summary of all transcranial magnetic stimulation (TMS) studies in alcohol use disorder (AUD) to date.

Ref	N (Active, Sham)	rTMS parameters					Outcome measure				Findings	Blind	Active sham control
		Site	Hz	%MT	Sessions; Duration	Pulses/ Session	Drinking Behavior	Craving	Brain/ Biology	Other Bx			
Mishra et al. (93)	45 (30,15)	R.dlPFC	10	110	10 1 month	1,000	1-mo relapse	ACQ-NOW	N/A	N/A	↓ in craving; relapse 14% active, 33% sham	S	Y
De Ridder et al. (115)	1	dACC	1	50	1 1 day	600	N/A	VAS	BOLD	N/A	↓ in craving ↓ BOLD in dACC and PCC	N/A	N/A
Höppner et al. (102)	19 (10,9)	L.dlPFC	20	90	10 10 days	10,000	N/A	OCDS	N/A	AB	No diff in craving/dep sx ↑ in AB effect to alc-stim	S	N
Herremans et al. (103)	31 (15,16)	R.dlPFC	20	110	1 1 day	1,560	N/A	OCDS	N/A	N/A	No diff in craving	S	N
Herremans et al. (104)	29 (29,29)	R.dlPFC	20	110	1 2 days	1,560	N/A	OCDS	N/A	Go-NoGo	No difference in craving ↓ IIRTV of Go-NoGo	S	N
Ceccanti et al. (99)	18 (9,9)	dmPFC	20	120	10 10 days	1,000	TLFB	VAS	cortisolemia, prolactinemia	N/A	↓ craving ↓ # drinks per day/max ↓ cortisol and prolactin	D	Y
Girardi et al. (100)	10	L.dlPFC	20	120	20 1 month	2,200	N/A	OCDS	N/A	N/A	↓ craving/depressive sx	N/A	N/A
Herremans et al. (94)	26 (13,13)	R.dlPFC	20	110	15 4 days	1,560	N/A	AUQ, OCDS	BOLD	N/A	↓ craving, not cue-induced ↑ reward ↓ DMN BOLD	N/A	N/A
Jansen et al. (105)	38 (20,18)	R.dlPFC	10	110	1 1 day	3,000	N/A	VAS	FC	N/A	↑ fcMRI of frontal pole	S	N
Mishra et al. (92)	20 (10 L, 10 R)	L.dlPFC R.dlPFC	10	110	10 10 days	1,000	N/A	ACQ	N/A	N/A	↓ in craving both left and right stimulation	D	N/A
Rapinesi et al. (101)	11	L.dlPFC	18	120	20 4 weeks	1,980	N/A	OCDS	N/A	N/A	↓ in craving/dep sx sustained at 6-months	N/A	N/A
Herremans et al. (116)	19	R.dlPFC	20	110	14 3 days	1,560	1-mo relapse	N/A	BOLD	N/A	68% relapse at 1mo ↓ dACC BOLD abstainers ↑ dACC BOLD relapsers	S	N
Qiao et al. (106)	38 (18,20)	R.dlPFC	10	80	4 5 days	800	N/A	N/A	MRS	HVLT, BVMT	↑ memory ↑ NAA/Cr and Cho/Cr	D	N
Del Felice et al. (117)	17 (8,9)	L.dlPFC	10	100	4 2 weeks	1,000	N/A	VAS	EEG	Stroop, Go-NoGo	No change in craving ↑ Stroop/Go-NoGo ↓ EEG/dep sx	S	N
Addolorato et al. (118)	11 (5,6)	L.dlPFC R.dlPFC	10	100	12 4 weeks	1,000	TLFB	OCDS	SPECTDAT	N/A	No diff in craving/dep sx ↓ in STAI-Y, DAT ↑ # of abstinent days,	D	Y
Hanlon et al. (95)	50 (25 coc, 25 alc)	vmPFC	5	110	6 1 day	3,600	N/A	N/A	BOLD	N/A	Alcohol: ↓ BOLD mPFC, AIns, MTG, and parahippocampal gyrus	S	Y
Hanlon et al. (96)	49 (25 coc, 24 alc)	vmPFC	5	110	6 1 day	3,600	N/A	VAS	BOLD	N/A	Alcohol: ↓ BOLD OFC, insula, and lateral sensorimotor cortex	S	Y
Kearney-Ramos et al. (97)	49 (25 coc, 24 alc)	vmPFC	5	110	6 1 day	3,600	N/A	VAS	FC	N/A	Alcohol: No diff in craving ↓ cue-related fcMRI of reward regions	S	Y
McNeill et al. (119)	20 (w/in-design)	R.dlPFC	50	80	1 1 day	600	drinking	N/A	N/A	Stop-signal	↓ inhibitory control ↑ alcohol consumption	N/A	N
Wu et al. (120)	51 (22, 29)	R.dlPFC	20	110	153 days	1,560	1-mo relapse	N/A	GMV	N/A	↓ GMV in relapsers, No change in TMS GMV but baseline predicted relapse	N/A	N/A
Perini et al. (121)	56 (29,27)	Bi-Insula	10	120	15 3 weeks	1,500	No TLFB	AUQ, PACS	BOLD	N/A	No diff in craving, drinking measures, fMRI	D	Y
Harel et al. (98)	51	mPFC ACC	10	100	15 3 weeks 5: 3mo fu	3,000	TLFB	PACS	FC	AUDIT ADS	↓ craving, ↓ % heavy drinking ↓rsFC dACC to caudate nucleus ↓FC mPFC to subgenual ACC.	D	Y

Search terms included: alcohol use disorder and transcranial magnetic stimulation between 2010 and 2021. A review of the resulting articles was conducted by CBP and excluded position papers and reviews.

number of sessions), another limitation may be that protocols were only able to stimulate the outermost cortex, rather than deeper nodes within the SN.

Recent technological advances in TMS coil design have made it possible for TMS-induced electric fields to penetrate deeper into the brain, modulating areas, such as the dACC and AIns in addition to superficial cortical areas (107). Recent studies indicate that these newly developed H-coils tend to provide both a broader area of stimulation and increased depth as compared with the Figure-of-8 coil [see Tendler et al. (107) for a review of the various H-coil designs and exact cortical targets]. Furthermore, the design of the H-coils can provide simultaneous activation of both the left and right lateral and medial prefrontal cortices depending on the specific coil and the treatment parameters used (107). Although this design stimulates both hemispheres, there is evidence to suggest that it stimulates the left hemisphere more than the right (108, 109). Given that the electromagnetic fields delivered by TMS decay exponentially with distance (110, 111), specific confirmation is needed to determine if these deep TMS devices can stimulate subcortical regions, such as the AIns and the dACC. This is of particular relevance in AUD, wherein alcohol is known to induce widespread cortical atrophy (112). That said, a recent study investigating the distance from the scalp to the cortex at the dlPFC and mPFC among a sample of individuals with AUD and healthy controls did not find a significant difference between the groups (113).

Similar to the mood disorders literature, targeting may be critical in addition to overall dosage (i.e., the total number of pulses administered during a treatment course) when considering how best to achieve downstream network effects (114). **Table 1** summarizes all TMS studies to date in AUD, which clearly emphasizes that the field of targeting subcortical nodes within the SN is in its infancy. Among the sparse,

existing literature, evidence suggests that cue-induced craving may be better modulated by targeting inferior structures, such as the ACC, the insula, or the mPFC (99, 122). However, the literature on how to best modulate insular and cingulate activity also provides disparate information. Results from Perini et al. suggest that insular stimulation made no difference in resting-state connectivity or craving in treatment vs. sham groups (121) for AUD. These results are particularly important to consider given the involvement of the insula in AUD circuitry (26). Harel and colleagues recently reported that an H7 stimulation protocol targeting the dACC resulted in changes in functional connectivity *and* fewer heavy drinking days in the active condition compared with the sham condition (98). While these early works have produced mixed results, the converging preclinical and clinical evidence regarding the centrality of SN nodes in the development and maintenance of AUD warrants further investigation.

Other Considerations Moving Forward

As described above, the SN nodes are likely promising brain-based targets for therapeutic intervention, particularly by utilizing unique forms of TMS as tools to modulate deeper brain structures. However, one of the constraints of TMS is that current technology cannot reach the insula or dACC without also delivering a strong electric field to the superficial cortical areas between the TMS coil and the deeper brain target (as shown in **Figure 1**). To move the field forward, it is important to think creatively about non-invasive brain stimulation options that may allow us to selectively activate core SN nodes without simultaneously activating off-target cortical regions.

There are several complementary non-invasive approaches that may be useful for the field to consider as it evaluates the SN as a fruitful target for AUD treatment. One possibility

FIGURE 1 | Proposed theoretical electrical field models (113). **(A)** Targeting dACC stimulation and **(B)** targeting AIns stimulation. Both models demonstrate additional delivery of a strong electrical field to the superficial cortical areas between the TMS coil and the deeper brain target.
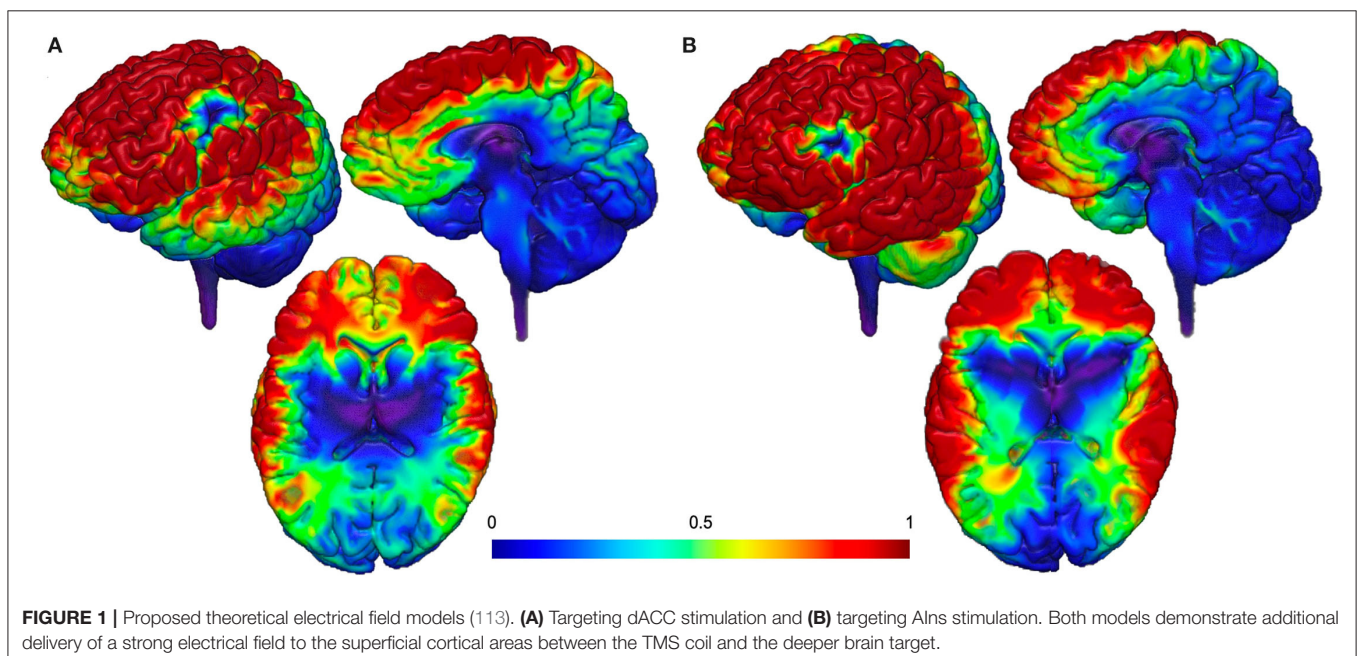
is to use temporally interfering electric fields non-invasively applied at multiple cortical locations simultaneously. Grossman and colleagues recently demonstrated that by exploiting the inherent sensitivity of neural populations to varying frequencies, it is possible to selectively stimulate the mouse hippocampus. It remains unclear if this would yield similar results in humans.

Finally, while our focus has been on deep TMS (dTMS) potential, it is also possible to modulate these brain regions through a targeted cortical area with strong afferent projections to the cingulate or insula. This "cortical window" approach relies on the known ability of TMS to modulate areas monosynaptically connected to the area targeted by the electric field. This simple principle is evident by the basic generation of a motor evoked potential in the hand following stimulation of the primary motor cortex (a 2-synapse network). For example, active TMS applied to the frontal pole can change functional connectivity with the insula and cingulate cortex, when compared with sham TMS (96, 97). These are just a few considerations that the field may find fruitful when searching for a strategy to non-invasively modulate the SN nodes.

CONCLUSION/DISCUSSION: POTENTIAL DEVELOPMENTS FOR THE FIELD

Alcohol use disorder is highly prevalent, devastating, and notoriously difficult to effectively treat, as evidenced by the nearly two-thirds relapse rate within 6 months of treatment (123–125). One potential limitation of existing psychosocial and pharmaceutical interventions is that they modify behaviors more globally with indirect effects on the brain. Non-invasive neuromodulation techniques are showing promise toward the aim of modifying specific and selective neural targets related to AUD. However, device-based interventions to date for AUD have focused on superficial cortical stimulation, with most outcomes being related to craving. In contrast, preclinical and

clinical studies suggest that deeper nodes within the SN could be promising targets, particularly the AIns and the dACC. Deep rTMS (dTMS) is one type of neuromodulation technique, utilizing an H-coil design (currently FDA-cleared for OCD and smoking cessation) that can potentially reach the AIns and dACC (126). However, it remains unclear if these targets are modifiable in AUD and which SN node (AIns or dACC or both) would have a greater impact on SN function, and importantly on reducing relapse risk post-treatment. Several lines of evidence support the SN as a promising future target for neuromodulation to impact treatment outcomes for AUD, and this warrants further investigation.

AUTHOR CONTRIBUTIONS

CP: conceptualization, resources, writing—original draft, supervision, and funding acquisition. L-TT: writing—original draft and writing—review and editing. DM: writing—review and editing and visualization. HA-D: literature review and writing—review and editing. CH, LW, FK, BK, TD, and JY: writing—review and editing. MM: conceptualization, resources, writing—original draft, and supervision. All authors contributed to the article and approved the submitted version.

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