Using lickometry to infer differential contributions of salience network regions during compulsion-like alcohol drinking

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Abstract

Alcohol use disorder extracts substantial personal, social and clinical costs, and continued intake despite negative consequences (compulsion-like consumption) can contribute strongly. Here we discuss lickometry, a simple method where lick times are determined across a session, while analysis across many aspects of licking can offer important insights into underlying psychological and action strategies, including their brain mechanisms. We first describe studies implicating anterior insula (AIC) and dorsal medial prefrontal cortex (dMPF) in compulsion-like responding for alcohol, then review work suggesting that AIC/ventral frontal cortex versus dMPF regulate different aspects of behavior (oral control and overall response strategy, versus moment-to-moment action organization). We then detail our lickometer work comparing alcohol-only drinking (AOD) and compulsion-like drinking under moderate- or higher-challenge (ModChD or HiChD, using quinine-alcohol). Many studies have suggested utilization of one of two main strategies, with higher motivation indicated by more bouts, and greater palatability suggested by longer, faster bouts. Instead, ModChD shows decreased variability in many lick measures, which is unexpected but consistent with the suggested importance of automaticity for addiction. Also surprising is that HiChD retains several behavior changes seen with ModChD, reduced tongue variability and earlier bout start, even though intake is otherwise disrupted. Since AIC-related measures are retained under both moderate- and higher-challenge, we propose a novel hypothesis that AIC sustains overall commitment regardless of challenge level, while disordered licking during HiChD mirrors the effects of dMPF inhibition. Thus, while AIC provides overall drive despite challenge, the ability to act is ultimately determined within the dMPF.

1. Alcohol drinking: scale of the problem

Alcohol Use Disorder (AUD) is a substantial contributor to human suffering and morbidity [1–10] . A 2014 study estimated that AUD extracts ~$250 billion/year and ~90,000 preventable deaths in the US [1] , and, more recently, problem drinking has become the leading cause of death of young to middle-aged US adults [11] . Further, these recent findings were before the Covid-19 pandemic, which led to a ~25–30% increase in alcohol

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intake [12–14] . In addition, problem drinking in women has significantly increased [15–17] , and women are more susceptible to having greater alcohol problems [18–21] . Thus, excessive alcohol drinking remains a considerable societal and health care challenge.

While several factors can contribute to AUD [22–28] , compulsion-like alcohol drinking (CLAD), where intake persists despite negative consequences, can be a strong driver of excessive intake and major obstacle to treatment [28–38] . Compulsion-like symptoms are prominent in the DSM-V diagnosis of AUD [10 , 39], and greater drinking is associated with more alcohol problems [9 , 10]. Importantly, willingness to respond despite adverse consequences during rodent CLAD has been considered to model some aspects of compulsive responding in humans [21 , 28 , 33 , 37], giving an avenue to better understand underlying psychological and brain circuit mechanisms [discussed further in [38]].

Despite the substantial harms of addiction, there continue to be few AUD pharmacological treatments [40 , 41], leaving a critical unmet need to develop better, personalized therapies [24 , 42]. Also, while pharmacological therapies have potential to reduce drinking, treatments such as cognitive-behavioral therapy are likely valuable and perhaps essential to help counteract psychological drives that underpin addiction. One inroad may come from deeply analyzing patterns of behavioral responding, which could provide novel insights into action and cognitive-emotional strategies that underlie and promote pathological behavior.

2. General introduction to lickometry

This commentary focuses on lickometry, a simple method to analyze licking patterns (Sects.5,6), with the goal of showing how a careful and broad assessment of different licking measures can provide novel insights into psychological state(s) utilized to act compulsively for alcohol, as well as critical brain mechanisms. For more than a half century, many rodent studies have attempted to infer relevant motivational states from changes in what is called the "behavioral microstructure " of licking patterns, e.g. in relation to conditions of higher or lower motivation (higher or lower sugar, lower or higher aversion, Sect.6.1). Consumption involves rhythmic patterns in both humans and rodents, providing many different aspects of responding to examine, such as the speed of licking or chewing, and whether a block of responding is longer or shorter. With other excellent reviews about lickometry [e.g. [43]], our goal here is to provide specific examples from our findings where lickometry has uncovered new and unexpected aspects of action strategies and brain circuits that promote CLAD. As we describe, unexpected changes in alcohol response patterns ultimately provided important new insights into possible internal cognitive-emotional states and related action strategies used to sustain aversion-resistant alcohol drinking, especially the use of attentional control on maintaining stereotyped, automatic action (which may also decrease the impact of negative consequences, Sect.7).

We first address studies linking several brain regions, the anterior insula cortex (AIC) and medial prefrontal cortex (MPF), to compulsion-like responding in both rodents and humans (Sect.3). We then review findings indicating that AIC and dorsal MPF (dMPF) may regulate different aspects of licking and other behavior (Sect.4). With this background, Sect.6 details specific differences in lick patterns observed during CLAD versus alcohol-only drinking

(AOD, intake in the absence of overt negative consequences). Our long-term objective is to uncover cognitive-emotion states and action strategies utilized during CLAD versus AOD, especially the "mindset" that an individual adopts when drinking despite adverse consequences. We will argue here that a careful and broad assessment across lick measures has provided novel insights into CLAD-related action strategies. Also, we hope that gaining a more specific understanding of the circuit and psychological mechanisms of CLAD will aid in development of novel, directed therapeutic interventions.

3. Possible common brain circuits across species for compulsion-like alcohol drinking

As noted in Sect.1, excessive drinking presents substantial challenges, and thus there is considerable interest in understanding underlying brain mechanisms to help improve treatment. In particular, action that persists despite negative consequences can strongly contribute to the addiction (Sect.1), even with challenges in defining and assessing compulsion [see [22 , 38 , 44]]. Thus, we and others have tried to operationalize compulsion-like intake in terms of the willingness to continue drinking despite the presence of aversive/punishing consequences. In addition, the ability to maintain aversion-resistant responding likely requires the ability to minimize the impact of negative or aversive possibilities (which could be real or anticipated). This cost-ignoring is likely fundamental to emotional regulation more generally, and can be coopted during addiction (Sect.7).

Here, we focus on studies examining the Salience Network (SN), which, more generally, mediates rapid identification and responding to important situations, along with emotional regulation to limit arousal-related cognitive dysfunction. The SN is likely directed by the AIC and dorsal anterior cingulate cortex, a subregion of the MPF [45–49] [noting that these regional designations are oversimplified, since human MPF [50] and AIC [45 , 51] both have multiple subregions]. SN regions connect to broader circuits [45] , and while AIC and MPF are certainly not the only regions that regulate CLAD [e.g. [52 , 53]], AIC-MPF are central to at least some aspects of compulsion-like intake.

Interestingly, we find that particular AIC projections, AIC-ventral striatum and AIC-Locus Coeruleus area, and dMPFC projections to ventral striatum, all promote CLAD in male rats, while inhibiting these circuits does not alter AOD [54 , 55]. Similarly, AIC mediates CLAD but not AOD in male mice [56] , while dMPF has also been implicated in CLAD in mice [57] . Further, AIC cFos activation in male mice is greater under CLAD vs AOD conditions [56] , and greater punishment-resistance for alcohol in rats is associated with greater AIC cFos levels [58] . In concurrence with these preclinical studies, AIC-MPF-striatal circuit activity in heavy-drinking humans is correlated with both the level of punishment-resistant responding for alcohol and subjective compulsivity for alcohol (how compulsive the subject "feels") [59] . In addition, in a study of women with AUD, AIC-MPF display greater activity when imagining high-risk drinking relative to low-risk, and imagining higher risk is associated with behavioral shifts that indicate conflict processing [60] . This agrees with the proposition from several clinical groups, who conceptualize compulsion-like responding as overcoming conflict, and that it is the presence of conflict between competing drives

(desire for high reward versus desire to avoid adversity) that activates AIC-dMPF circuitry in order to manage challenge and allow sustained responding [32 , 61]. Thus, these cross-species findings support the importance of AIC-MPF during compulsion for alcohol, and also validate that rodent CLAD models have some relevance to humans [and see [21 , 36 , 38]].

Continued drinking despite adverse consequences likely requires the ability to ignore or mitigate the impact of negative possibilities, and Table 1 summarizes other findings suggesting that AIC-MPF are important for overcoming cost to allow action. CLAD might also involve internal attentional control (Sect.7), with the goal of minimizing attention to negative possibilities. Indeed, AIC-MPF are linked to many aspects of attention, including during distraction or emotion (Table 2). In addition, MPF activity that reflects directing attention away from pain is also related to decreased subjective intensity [62–64] . Thus, multiple lines of evidence support the possibility that AIC-MPF can play an important role in reducing the impact of negative information (perhaps by attentional regulation), which is critical for allowing action in the face of challenge.

We also note that human AIC activity occurs in relation to many aspects of alcohol drinking, and addiction and emotion regulation more generally [45] , along with dMPF [65 , 66]. For example, alcohol cue-[67 , 68] and negative affect-related [69] AIC activation predict real-world drinking [see also [70]], including transition to heavier drinking later in life [71] . Also, therapeutic treatments that decrease drinking are associated with reduced AIC activity and connectivity [e.g. [72 , 73]]. Thus, while some aspects of AIC function relate to problem drinking, some aspects of AIC signaling likely contribute to non-compulsive intake (Sect.8).

4. Relating specific lick measures to AIC or MPF

We originally examined AIC-MPF importance for CLAD because of the likely central SN role in motivated behavior [45] , and the early seminal studies where insula lesions decrease drive for cigarettes in humans [74] . At the same time, we began to learn of a sizable literature suggesting that different aspects of responding might be differentially regulated by AIC/ventral-frontal cortex versus MPF. In particular, a number of studies converge on the possibility of a double dissociation, where AIC/ventral-frontal cortex regulates oral action, and dMPF is associated with moment-to-moment organization of action. Early work found that the ability to extend the tongue in rats was disrupted by lesion of ventral-frontal cortex [75–80] , but not dMPF[75 , 76 , 80–82]. In parallel, MPF disruption leads to more variable action timing and action fragmentation [77 , 78 , 81–87], while disordering of action is not seen with ventral frontal cortex disruption, including studies directly inhibiting AIC [86 , 88] or AIC/OFC [78] . Importantly, human studies corroborate these rodent findings, where damage to MPF but not ventral-frontal cortical areas leads to disorganized action [89 , 90]. Since then, localized, transient inhibitions have demonstrated a similar dissociation. For example, MPF inhibition leads to more variable lick timing, but does not alter tongue control (assessed through "lick volume, " Sect.6.4) [81 , 82]. Conversely, inhibiting AIC/OFC alters lick volume but not licking speed [78] . Together, these studies indicate that AIC/ventral frontal cortex and MPFC make differential contributions to licking

behaviors. As detailed below, we observe changes in tongue control measures when rats drink under CLAD vs AOD, and interpret these to reflect AIC-driven processes, while changes in moment-to-moment action timing would indicate MPF-directed processes. We also describe how AIC is implicated in maintaining overall action strategy (Sect.6.5), and discuss related behavioral and electrophysiological findings that eluci-date the putative action strategies and AIC contributions used to sustain CLAD.

5. Lickometry methods

Lickometry is technically simple to perform, and many systems detect small changes in electrical current to precisely determine the oc-currence of a lick. Here, we use examples from our published studies [91 , 92] where lickometry was performed in a standard Med-Associates operant box (normally used for lever-press studies). This system has a space about ~12 cm above the wire floor where one inserts a metal spout attached to an alcohol bottle. The rat has to rear up slightly in order to lick the spout and obtain alcohol. When the tongue contacts the metal alcohol spout, this completes an electrical circuit through the rat because its paw is in contact with metal floor. The computer then creates a time stamp every time a lick occurs.

More recently, we have utilized a simpler system to examine licking patterns in the rat's home cage. The typical home cage has a hole ~7 cm above the floor, into which one can insert a bottle containing alcohol. However, instead of electric current passing through the rat (which requires a metal floor), this system uses a capacitance-based lickometer which is programmed through an Arduino [see [93 , 94]]. In this method, a very small electric charge is applied to the metal licking spout, and when the rodent licks, the discharge of this capacitance is registered to detect that a lick has happened. This has several advantages over the method used in [91 , 92], including technical simplicity, low cost, and adaptability to any drinking environment; in particular, experiments in the home cage obviate the need for rodents to be adapted and trained in operant boxes. Another advantage is that the electrical change used by this capacitive system is small enough that it does not disrupt the ability to record single-unit (individual neuron) neuronal activity in vivo during licking. Indeed, several groups have recorded lick-related neuronal firing using very similar capacitive lickometers [95 , 96], including in the AIC [97 , 98], and we used this system to assess AIC firing patterns during CLAD versus AOD [(94), Sect.6.5]. A recent study also adapted this capacitive method for recording from multiple cages at once [99].

One challenge when comparing lickometry studies is that different physical geometry has the potential to alter how the animal responds. For example, licking from a slightly higher spout, where the rat has to rear up, might lead to more pauses in licking, compared to when the rat is standing comfortably on all four feet. For this reason, we have considered (but not carried out) more involved studies where spout height is systemically altered across different sessions, and each animal might have an ergonomically optimal height for "easiest" responding. For example, with the large difference in body size between long-term drinking females (~450 g average) and males (~750 g average), the basic geometry and execution of licking may differ, complicating the ability to relate lick patterns to underlying action strategies. However, we have found limited (although important) differences in licking

measures between females and males [93] (Sect.6.6). In addition, our recent home-cage studies [93 , 94] observed some several patterns consistent with earlier work [91 , 92], including where higher-challenge CLAD shows reduced intake, slower licking, and shorter bouts.

Finally, lickometry methods can have more extensive use beyond free intake. The Davis box is a sophisticated system with 8–12 lick spouts that contain different substances and can be quickly moved. By giving rats brief access at different spouts across a session, one can dissociate different contributors of taste processing. For example, this system was used to show that cocaine-related aversion does not change the ability to discriminate the sensory properties of different tastes, but does slow the latency to respond for sugar (suggesting anhedonia, a decrease in motivation) [100] . Other variants of lickometry can measure the force of licking, the duration of tongue contact, and other more sophisticated measures [43] , when appropriate.

6. Lickometry analyses

6.1. Two classic licking strategies, related to bout number versus bout length

While lickometry is technically simple to perform, the central strength of lickometry comes in the analysis and interpretation. Thus, the following sections are designed to help better understand how particular licking patterns might suggest the utilization of different action strategies.

There are several more basic lick-related measures that are often assessed. One could determine the average licking speed, as well as changes in speed across time, which will be limited by the biomechanics of licking [101] . One could also examine variability in the licking speed, e.g. having faster or slower periods of licking within a particular lick train (Sect.6.3). In addition, one could examine whether responding is sustained for longer or shorter times. A train of licks is termed a bout, here called Bout Length; different criterion have been used to define when two licks far enough apart are considered to be in different bouts, and we use 1 s between licks as a threshold [discussed in [91]]. In addition to licking speed and duration, there are two other important basic measures. One is Bout Number, the number of licking bouts a rodent achieves in a session. The other is total intake, which is typically the most important measure for non-lickometry studies; for alcohol, this is measured as g/kg intake, which is ~0.8–1.2 g/kg/5 min in our hands [54 , 55 , 94 , 102 , 103], and greater in females [21 , 93].

Classic studies led to the possibility that licking patterns often reflect one of two general strategies [1] : where changes in bout number, without shifts in bout length, may reflect differences in motivation more generally, while [2] changes in motivation driven by palatability involve longer bouts and faster licking [104–108] . For example, in a 2000 review [109] , alcohol intake in rats was altered by varying response cost, or across some genetically preferring lines, and nearly all such manipulations led to changes in bout number but not bout length. Instead, bout length was only changed by adding sugar to alcohol, sometimes resulting in 2–3-fold longer bouts. Another study [105] found that rats have different alcohol behaviors, with some rats showing high pressing for and drinking of

alcohol (called Drinkers), while other rats had high pressing but low drinking (Responders). Interestingly, Responders had fewer bouts than Drinkers, but, importantly, bout length was similar. In addition, different patterns resembling the two classic models have been seen across genetically-selected alcohol-preferring mouse lines, where HDID1 mice have longer bouts and HDID2 mice have more bouts without changes in bout length [110] .

However, while many studies support this contrast, sometimes other lickometry patterns are observed which fall outside this dichotomy. For example, we found that females had significantly longer alcohol bouts than males, but with no differences in licking speed, which are unlikely to represent palatability shifts [93] (other caveats detailed in Sect.6.6). Thus, one purpose of this commentary is to reinforce the importance of assessing across many behavioral microstructure measures, and the critical importance of comparing such measures across a systematic set of drinking conditions, in order to have the greatest confidence that shifts in responding occur in robust and interpretable patterns.

6.2. Alcohol-only and compulsion-like conditions

Since compulsion-like drives can promote pathological drinking (Sect.1), we utilized lick microstructure analyses to help uncover important shifts in action strategy across different types of alcohol consumption. For this, we have compared licking microstructure during AOD with several forms of CLAD, including moderate challenge (ModChD, containing 10 mg/L quinine in alcohol, where intake level is not reduced) and higher challenge (HiChD, containing 100 or 60 mg/L quinine in alcohol, where intake is reduced ~30–40%) [38 , 91 , 92 , 94]. Below, we detail how lickometry helped uncover surprising, and likely translationally relevant, understandings of possible action strategies and related psychological states that rats utilize to maintain CLAD. In particular, ModChD licking is significantly less variable than AOD across a number of licking measures, perhaps suggesting adoption of more stereotyped action patterns to help overcome aversive challenge [91 , 92] (Sect.7).

6.3. Licking speed

Classic studies relate faster responding, along with longer bouts, to indicate higher motivation driven by greater palatability [91 , 92 , 104 , 106 , 107 , 111]. Thus, we reasoned that, if ModChD reflected higher motivation for alcohol (especially being willing to expend effort to overcome negative consequences), we might see longer bouts and faster licking when compared to AOD; alternately, we might observe changes in bout number without changes in licking speed. Thus, to determined lick speed, we measured the Inter-Lick Interval (ILI), the duration of time between two successive licks, across licking bouts. However, contrary to our hypothesis, we found no differences in bout length or bout number between ModChD and AOD. Instead, we strik-ingly found that ModChD licking speed was significantly less variable than AOD, and also slightly but significantly faster [91 , 92]. Reductions in lick variability have not, to our knowledge, been observed before, and are addressed in detail below (Sect.7).

In contrast to less variable lick speed with ModChD, HiChD intake is significantly slower and more variable [part of the evidence that response organization and timing is disrupted

under higher challenge [91 , 92]]. Other challenge conditions also showed increased variability in licking speed, including during sugar or water intake when paired with quinine [107 , 112] or LiCl sickness [113] . Interestingly, a recent study [114] gave mice repeated exposure to alcohol vapor (which results in high alcohol exposure), and observed higher intake and longer bouts, but also more variable licking speed. As noted in Sect.4, disrupted timing of licking might reflect disordered dMPF activity. Thus, these lickometer analyses of lick variability might suggest that vapor-exposed mice have alcohol-related dMPF disruption (perhaps akin to hypofrontality that has been associated with addiction), which could allow bottom-up urges (e.g. from amygdala) to promote excessive alcohol-only drinking.

Licking speed has also been utilized to study what is termed front-loading, where animals and humans drink quickly and heavily at the beginning of alcohol access, ostensibly to rapidly reach intoxication [115] . Greater front-loading predicts higher alcohol intake in non-human primates [116] and more drinking problems in humans [117] . However, since licking is typically rapid during the front-loading period, front-loading can be studied without lickometry. In a recent study, rats drink almost half their intake in the first 5 min of a 30 min access period [118] , similar to rat drinking in our [91–93] and other [118 , 119] work. This study also found significantly greater front-loading in females during 30 min sessions, but that shortening the session to 15 min increased male front-loading to female levels (perhaps reflecting differences in urgency in males depending on the amount of time available for licking). Thus, lickometry is not always necessary to see interesting and important shifts in responding, although measures such as lick speed variability would not be detectable.

6.4. Lick volume

Lick volume, which can be assessed by the total volume of intake divided by total licks, has been of great value for our work. Lick volume is likely a measure of tongue control, and may reflect the ability to control tongue shape. As noted in Sect.4, several studies have converged upon the possibility that AIC/ventral frontal cortex but not MPF is critical for such tongue control. Thus, it is particularly interesting to us that lick volume is one of the measures that was less variable under ModChD relative to AOD [91] .

For findings described here, we examined 3 AOD, 3 ModChD, and 2 HiChD sessions per rat in 14 rats, which resulted in 56 AOD sessions, 56 ModChD sessions, and 42 HiChD total sessions [91 , 92]. We then determined the lick volume for each session, and compared lick volume values across the three drinking conditions, separate from rat identity [as detailed in [92]]. Interestingly, the average lick volume is not different across AOD, ModChD, and HiChD, but the standard deviation of lick volume is significantly lower in ModChD and HiChD when compared to AOD. Further, and even more interesting, is the observation that lick volume is less variable under HiChD versus AOD [92] (which is also observed in our newer studies during home-cage drinking [94] ,). This contrasts with changes in licking speed, which are faster and less variable for ModChD versus AOD, and slower and more variable for HiChD vs ModChD [91 , 92]. In particular, since HiChD has disrupted lick timing and overall less intake, it is striking that lick volume shifts seen with ModChD are also retained under HiChD.

6.5. Shifts in bout initiation and sustained measures under CLAD

Similar to less variable lick volume under both CLAD conditions versus AOD [91 , 92] (Sect.6.4), we observe other measures that show similar changes in the two challenged conditions, relative to AOD. For example, there are no differences across drinking conditions in the timing of the first lick of a session. However, after this first lick, HiChD and ModChD both have significantly earlier initiation of bouts, with both starting ~100 s earlier than AOD [91 , 92]. This is particularly interesting, since the drinking session is only 20 min and with most intake in the first ~5 min (front-loading), suggesting a substantial change in initiation of responding under challenged drinking. To explain these findings, we propose that animals rapidly assess whether they are drinking under CLAD or AOD, which could happen within one lick [120] . If an animal determines it is licking under CLAD conditions, it quickly adjusts response strategy to start licking sooner so that it can finish more quickly, which we call the Head Down and Push model of challenge-resistant action (Sect.7). One interesting implication is that rats quickly switch response strategy, but then maintain that new strategy across the rest of the drinking session (Sect.6.5), and we propose that adopting a session-long action plan minimizes the need to attend to moment-to-moment responding, reducing the potential to notice and be impacted by adverse consequence.

Together, these findings show that ModChD and HiChD have similar shifts in lick volume variability and earlier bout start, when compared with AOD. Sect.4 described studies associating AIC with tongue control, and with similar shifts in lick volume in ModChD and HiChD, one possibility is that AIC contributes to some aspects of CLAD behavior which are maintained even under higher challenge. In this light, it is also interesting that AIC has been associated with encoding a session-long action plan, the kind that would result in session-long earlier bout initiation [and other session-long changes detailed in [92]]. Persistent AIC signals reflect the main goals of a task [121 , 122] and persisting emotion [123] in humans, and encode the long-term reward value of a context in non-human primates [124] . Behaviorally, AIC maintains cue responding across longer delays in rats [125] . Although there are quite limited in vivo activity studies in rodents, Guillem and colleagues [126] show hours-long plateau firing changes across a 3hr cocaine intake session in half of AIC cells. This can be interpreted as AIC persistently encoding the main goal of the session (to get cocaine), which is separate from moment-to-moment actions (acting to get cocaine, experiencing the cocaine, exploring, grooming, etc.). Further, AIC was the predom-inant region that exhibited sustained, long-term value signals in [124] , while Pribut and colleagues [127] note that AIC shows longer-term firing changes related to cocaine behavior, different from the other regions (including dMPF) that they have examined.

Thus, we have worked to identify AIC in vivo firing patterns during CLAD and AOD in male Wistar rats [94] . The majority of AIC neurons showed sustained, session-long changes in firing, whether increased or decreased. Importantly, only cells with strong firing elevations at the onset of consumption had higher plateau activity for CLAD vs AOD, and this greater sustained increase was similar for ModChD or HiChD. The importance of initial firing, then sustained responding, comports well with the behavioral findings that rats quickly evaluate the licking condition (AOD or CLAD) and adjust their action strategy under CLAD conditions (to start bouts significantly earlier). Together, these findings indicate

greater firing levels in these AIC initial response cells, and earlier bout initiation, in both ModChD and HiChD (compared with AOD). Along with lick volume, another AIC-linked behavior that shows similar changes in the two challenged conditions, these findings have led us to propose a novel hypothesis that one primary role of the AIC is to provide sustained commitment to respond for a high-valued reward despite the challenge level (Sect.7).

6.6. Other exceptions to classic lickometry models

Different licking patterns can give important clues to action strategies and psychological states that underlie CLAD (Sect.7), even though such changes are different from predictions based on classic lickometry studies (Sect.6.1). Before considering the implications of our alcohol findings, we want to address some other exceptions to such classic models. In one example, alcohol-dependent mice have increased intake, more bouts, and longer and faster bouts, although no change in lick volume [128] . Simultaneous increases in bout number and bout length might suggest a combination of the two classic licking mechanisms (Sect.6.1), and is also seen with higher sugar [112] . Further, even though many studies find longer, faster bouts with higher sugar, bout length and licking speed can be unlinked [82 , 107]. In particular, we found that female alcohol-drinking rats have significantly longer bouts than males, without sex differences in average lick speed [93] . However, faster licking was associated with greater intake in males (concurring with the many classic studies), while drinking level was not related to licking speed in females; thus, lickometry has provided important information suggesting that the action strategies used in females and males may have some fundamental differences [93] . Further, destruction of parvalbumin-positive GABA neurons in the dorsolateral striatum of mice decreases alcohol drinking (by ~35%), but drinking becomes faster, with fewer but longer bouts, and greater variability in bout length; these changes are specific to alcohol, since GABA cell lesion does not alter water or sugar intake [53] . Across the studies examined here, those utilizing mice tend to have more divergence from classic models. Thus, additional more basic studies may be required to understand whether mice have favored licking strategies that differ from rat. Finally, even lick volume studies can show mixed results, e.g. where lick volume can decrease when drinking either aversive [107 , 112 , 113] or sweetened [106 , 129] fluid. For the latter, fast licking associated with palatability may impede tongue control, although the much longer bouts would assure that a high quantity is consumed. These alternative findings under-score the importance of measuring multiple lick-related measures, and also the value of testing across a series of different response conditions (parametrically balanced as much as possible), in order to generate the most comprehensive understanding of any lickometry changes.

7. Lickometry can uncover novel information about action strategies, including the role of particular brain regions

We have used lickometry to try to identify whether pathological behaviors, especially CLAD, utilize specific action strategies and related internal psychological mechanisms. In particular, by comparing CLAD under different levels of aversive challenge [91 , 92], we try to uncover action strategies utilized under moderate challenge (where adversity does not reduce drinking level) and higher challenge (where consumption is disrupted), and attempt

to interpret our microstructural analyses in light of existing interpretive models. However, while we had predicted faster responding and longer bouts with ModCHD (indicating greater motivation and drive), we surprisingly found that ModChD is significantly less variable than AOD across many different lick measures. Further, while HiChD shows greater variability than ModChD in some measures (lick speed, bout length), HiChD also exhibits the same reduced variability in lick volume and earlier bout initiation seen with ModChD (relative to AOD.) As described below, we have built upon these and other findings to develop novel models about cognitive-emotional states and action strategies that promote CLAD. By understanding such internal mechanisms, we hope that novel therapeutic avenues can be implemented to better counteract compulsive drives.

Reduced variability across licking measures during ModChD [91] is particularly interesting, since such findings are unexpected and un-precedented in existing lickometry literature, but do comport with the suggested importance of automaticity for habit and compulsion [37 , 130 , 131]. Indeed, while ModChD intake levels are not reduced relative to AOD, rats greatly avoid the same quinine level when in water, suggesting that responding for alcohol is indeed aversion-resistant [21 , 93 , 132]. Thus, we have proposed the Head Down and Push model of challenge-resistant responding [91] . In particular, we hypothesize that decreased response variability reflects a psychological strategy where "internal " attention is focused on acting in a stereotyped, automatic manner. One benefit of this strategy may be to minimize the need to attend to (and be impacted by) adverse consequences that are present during the action. This may also relate to "intake defense, " e.g. having to eat rotted food when starving (see [133]), where the goal is to consume a "sufficient " amount (in our case, alcohol), not to more finely titrate the amount of intake [91 , 92 , 133].

It is also interesting that HiChD retains several behavioral measures that are observed with ModChD, despite reduced intake. As described in Sect.6.4, HiChD and ModChD both have less variable lick volume, as well as significantly earlier initiation of bouts (relative to AOD) [91 , 92]. In addition, AIC plateau firing is significantly greater during both challenge conditions, relative to AOD, in neurons that have strong increases in firing. Thus, we propose that animals rapidly assess whether drinking under CLAD or AOD conditions right at the onset of licking. If drinking under challenged conditions, they quickly adjust response strategy, adopting a new, session-long strategy that involves maintaining internal attention on stereotyped responding (the Head Down and Push strategy). Of particular interest is that several aspects of this putative attentional control are seen under both moderate- and higher-challenge. With AIC implicated in both oral control (expressed as lick volume) and maintaining a session-long representation of the main task plan (Sect.6.5), we integrate these findings to suggest that one central role of AIC is sustained commitment to respond, regardless of challenge level. This is fully effective under ModChD, where AIC controls some aspects of responding (tongue shape, overall commitment to act) and also helps shape dMPF activity (less variable lick timing). However, under HiChD, AIC retains commitment to act, but we propose that the battle to act or not is ultimately won or lost in the dMPF. Indeed, we build upon the observation that disrupted action organization under HiChD is similar to what is observed when dMPF is inhibited, including more variable lick speed [e.g. [81 , 82].] and disrupted action organization (Sect.4). Firing is dMPF is known to be disrupted by stress [134 , 135], and we propose that dis-coherence in dMPF activity and/or

changes in dMPF-AIC functional connectivity under higher challenge disrupts the ability to maintain orderly action, regardless of AIC commitment to act.

Thus, AIC and dMPF likely work together under a number of conditions [45 , 49 , 91 , 92 , 123 , 136] (Table 2), including to promote alcohol drinking [54 , 55 , 137–139]. Indeed, nearly all AIC-related behaviors are likely dependent on dMPF to carry out action, with the few exceptions we are aware of being related to taste- or odor-guided actions [140 , 141]. However, our lickometry and firing studies (Sect.6) also provide valuable insights and novel hypotheses about the potential differing roles of AIC and MPF during alcohol intake, especially when taken together with other literature on lick-related circuitry (Sect.4). This AIC-dMPF model is also likely related to the often-discussed possibility that AIC is more the input and integration portion of the SN, with dMPF more the motor output [45 , 47 , 49 , 136]. More colloquially, we consider AIC and MPF for more "overall " versus "proximal and/or nuts and bolts " aspects of behavior (Table 3), especially when evaluating and then deciding to approach or avoid a high-importance situation [see also [51]]. AIC-dMPF contributions also likely depend on context, e.g. where AIC/SN are engaged under uncertainty or elevated affect, but are much less important during simple, routine, more certain actions [45 , 51 , 142 , 143]. Indeed, inhibiting AIC or its projections in rats does not impact sweet fluid [54 , 55 , 137 , 144] or water [145 , 146] intake, simpler operant responding [147–149] , or locomotion [55 , 137 , 145 , 146 , 150 , 151], suggesting important selectivity in the behaviors AIC contributes to.

8. Potential for different roles for particular AIC and/or MPF outputs

One important caveat to the AIC-dMPF model presented above, with AIC for sustained commitment and dMPF for organizing moment-to-moment action, is that both regions have different cell populations that project to different target regions, and are likely to serve varied roles [e.g., AIC [152–154] :; dMPF [155 , 156]:]. In particular, our AIC studies suggest that there are at least two AIC pathways with different impact on alcohol drinking. As noted in Sect.3, AIC projections to subcortical areas (ventral striatum, Locus Coeruleus Area) strongly regulate CLAD, as do dMPF-ventral striatal projections. In strong contrast, inhibiting any of these projections has no impact on AOD [54 , 55], but global inhibition of AIC using GABA receptor agonists greatly depresses AOD [55 , 157] as well as CLAD [55] . Similarly, AIC inhibition reduces intake of palatable food [145] and other intoxicants [149 , 158 , 159]. Alcohol intake more generally is also linked to dMPF [57 , 138 , 160–163].

Thus, both AIC and MPF regulate alcohol-only drinking, in addition to contributions to CLAD, and one possibility is that different projections mediate these different alcohol behaviors. Indeed, behavioral evidence suggests that punishment-resistance for alcohol does not correlate with AOD consumption levels [33 , 55 , 58], suggesting separable underlying mechanisms. In an interesting convergence, a recent human study [164] used intravenous self-administration in heavy human drinkers to compare low and high response requirements to get alcohol. Not only was there no relationship between responding under low and high response requirements across individuals, high work for alcohol was associated with craving but not enjoying alcohol, while low work was associated with enjoying and not

craving (even though total intake was comparable). Together, these support the possibility that different mechanisms regulate CLAD versus AOD.

Even though the identity of AOD-regulating AIC pathways remains unknown, other human studies suggest the presence of AIC pathways with separate functions, including one that is more basic, and another more involved in emotional regulation. For example, a recent study found that AIC activity more generally was related to interoception (sensing the body, a fundamental function of AIC), while emotional regulation involves AIC connectivity with striatum [165] . AIC connectivity with ventral striatum has been linked to compulsion for alcohol [54 , 59], and also finding pleasure in violence or some criminal acts [166 , 167]. As noted above, many studies implicate AIC in discounting, ignoring, and a variety of other "emotional regulation " activities in humans [45] , and it is likely that this emotional regulation (dampening of arousal) can be essential for maintaining adaptive responding under challenge, but also coopted to powerfully anchor pathological urges. We propose that emotion regulation (whether adaptive or maladaptive) is mediated through AIC's subcortical projections, while alternate AIC pathways mediate more fundamental emotion/arousal regulation. This more primary pathway would be of value for motivated responding (e.g. for alcohol without overt challenge), but also might be valuable for more basic avoidance, e.g. to quickly evaluate tastes and spit out if deemed dan-gerous [97 , 98 , 168], which this more primary AIC projection might sub-serve. Thus, AIC-subcortical outputs may be critical when there are two (or more) competing drives, e.g. between desire for a high-value reward (alcohol) and desire to avoid negative consequences. The field is very early in understanding of the functional importance of different AIC or dMPF projections, but greater, more specific insights have the potential to provide novel behavioral and other treatment inroads to reduce the harm of addictions.

9.   Conclusion

Lickometry is technically simple to perform, but, with careful assessment across a number of lick measures, can provide valuable and novel insights into motivational drives and action strategies used in a particular drinking situation. The technique is strongest when comparing across a series of different response conditions (such as the AOD, ModChD, and HiChD here), and when response patterns are carefully evaluated in relation to the existing knowledge base. In our case, changes in variability and lick timing, when taken together with the larger literature, have led to the possibility that AIC provides sustained commitment regardless of challenge level which persists during HiChD (even though overall drinking is disrupted, which we blame on the MPF). Thus, lickometry has potential to expand the ability to understand the mechanisms that drive pathological alcohol drinking, and other intake behaviors.

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Data availability

No data was used for the research described in the article.

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Table 1

Studies relating AIC–MPF to discounting and/or overcoming costs.

AIC-MPF: Discounting of risk, task difficulty, and other costs	[143,169–173]
dMPF-ventral striatum: decreased sensitivity to loss, which promotes risk taking	[148,173–175]
AIC-MPF: action that occurs despite effort, delay, risk of loss	[169–171]
AIC-MPF: action that occurs despite urge to stop	[176]
Less AIC-MPF when dieters are able to resist temptation	[177]
AIC-dMPF: resisting a belief change	[178]
AIC-dMPF: trusting even when betrayal is possible	[179]
AIC-dMPF: imagining higher reward, which decreases the impact of delay	[180]
AIC-dMPF: overcoming automatic attentional drives	[181]

Table 2

Potential AIC–MPF similarities, and MPF for sustained responding (like AIC, Sect.6.5).

AIC-MPF: task set maintenance (to facilitate consistent, sustained reward-directed action)	[121,143]
dMPF initiates extended, sustained action in rat	[182,183]
Stronger MPF activity: persisting, challenge-resistant reward approach	[172]
AIC-MPF: continued attention to reward under distraction	[184]
AIC-MPF: sustained attention	[122,185]
AIC-MPF: tonic alertness under uncertainty	[186]
Both AIC/OFC and dMPF cells fire for licking in rat	[78,88,187,188]
dMPF firing continues during rat licking when reward delivery stops briefly	[189]
AIC activity for food continues even when sated	[190]

Table 3

Potential differences in AIC versus MPF for input/integration versus motor output for SN. More colloquially, AIC vs MPF may reflect more overall versus more proximal and/or "nuts and bolts," especially to evaluate and act under higher-salience conditions.

AIC as input and integration, more overall	MPF as motor output more proximal "nuts and bolts"	
Action- and cognition-related behavioral control	Action-related behavioral control	[191]
	MPF better predicts action choice and reaction time	[183]
Salience for effort and reward	Cost avoidance, effort prediction errors	[192]
Sustained salience of unexpected emotional events	Attentional switching related to unexpected emotional events	[123]
Aversion and reward	Aversion	[193]
Negative affect during regret	Negative affect, desire to change choice during regret	[194]
Outliers	Variability	[195]
Most important events	All features within an environment	[50,196]
AIC: sustained, long-term global value signals		[124,127]
AIC/OFC: time delays, reward-action value	Physical effort	[125,197–201]