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Licking microstructure in response to novel rewards, reward devaluation and dopamine antagonists: Possible role of D1 and D2 medium spiny neurons in the nucleus accumbens

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ABSTRACT

Evidence on the effect of dopamine D1 and D2-like antagonists and of manipulations of reward value on licking microstructure is reanalysed considering recent findings on the role of nucleus accumbens (NAc) medium spiny neurons (MSNs) in the control of sugar intake. The results of this analysis suggest that D1 MSN activation, which is involved in the emission of licking bursts, might play a crucial role in response to novel rewards. D2 MSN activation, which results in reduction of burst size and suppression of licking, might mediate the response to reward devaluation. Elucidating the neural mechanisms underlying the licking response might lead to a better definition of its microstructural measures in behaviourally and psychologically meaningful functional terms. This could further support its use as a behavioural substrate in the study of the neural mechanisms of ingestive behaviour and motivation, as well as in animal models of pathological conditions such as eating disorders and obesity.

1. Introduction

Rats ingesting fluids emit discrete sequences of licks, referred to in this paper as licking ’bursts’ or ’bouts’, occurring at a rate of approximately 5–7 licks per second (Davis, 1989, 1996, 2004). The terms ’burst’ (e.g., D’Aquila and Galistu, 2017; Spector et al., 1998) and ’bout’ (e.g., D’Aquila, 2010; Higgs and Cooper, 1998), as employed here, are functionally equivalent to the term ’cluster’ (Davis and Smith, 1992; see D′Aquila, 2024 for a detailed discussion). Burst size, determined by the number of licks per burst, is mainly influenced by stimuli related to the orosensory contact with the reward, such as taste, with a direct correlation between this measure and the concentration of different sugars. In contrast, the number of bursts in an experimental session, indicating how many times the subjects initiate “bouts of ingestion”, is influenced also by stimuli unrelated to orosensory contact with the reward, such as post-ingestive cues (D′Aquila, 2024; D’Aquila and Galistu, 2017; Davis and Smith, 1992; Dwyer, 2012; Johnson, 2018; Naneix et al., 2020; Sclafani, 2001; Smith, 2001; Spector et al., 1998). Based on these observations, the number and size of licking bursts might be regarded, respectively, as indices of (i) the activation process of a reward-oriented response and (ii) an evaluation process occurring during the consummatory transaction with the reward, reflecting palatability and possibly related to the experience of pleasure (D’Aquila and Galistu, 2017; Davis, 1989; Davis and Smith, 1992; Dwyer, 2012; Schneider et al., 1990; Smith, 2001; Spector et al., 1998). Following a similar line of reasoning, within the framework of the incentive salience attribution hypothesis (Berridge, 2007), the number and size of licking bursts might represent, respectively, ’wanting’, i.e., the attribution of incentive salience to reward-related stimuli, and ’liking’, i.e., hedonic impact (Higgs and Cooper, 1998). Findings from studies on the effects on licking microstructure of systemic administration of dopamine D1 and D2-like receptor antagonists (Canu et al., 2010; D’Aquila, 2010; D’Aquila et al., 2012; Galistu and D’Aquila, 2012, 2013; Genn et al., 2003; Higgs and Cooper, 2000; Liao and Ko, 1995; Schneider et al., 1990) led us to suggest the hypothesis that (i) dopamine on D1-like receptors plays a role in the activation of ingestion and (ii) the level of response activation is updated – or reboosted – based on an evaluation process requiring dopamine on D2-like receptors (D’Aquila, 2010). This interpretation was further supported by the study of the licking response to changes in sucrose concentration either with or without reward devaluation, which paralleled the response to either D2 or D1-like receptor antagonism, respectively (D’Aquila and Galistu, 2017). (More details will be provided in the next sections.) The expression “reward devaluation” as used in this article indicates that subjects accustomed to a given reward value

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are presented with a lower reward value, such as a reduction in sucrose concentration, rather than being exposed to an aversive stimulus.

Numerous studies have provided an extremely detailed characterization of licking microstructure in relation to physiological states such as hunger and satiety, palatable and aversive tastes, manipulations of the reward value, taste novelty, and conditioned taste preference and aversion (reviewed in D'Aquila, 2024; Johnson, 2018; Naneix et al., 2020). However, the richness in behavioural detail is not matched by a detailed understanding of the underlying neurobiological substrates at the cellular level (see Section *3.1*). In view of a research programme aimed at filling this gap, the scope of this narrative review is to reanalyze the evidence regarding the effects on licking microstructure of (i) systemic administration of dopamine D1 and D2-like receptor antagonists and (ii) manipulations of reward value, in light of recent findings on the role of nucleus accumbens (NAc) medium spiny neurons (MSNs) subpopulations expressing either D1 or D2 receptors in the control of palatable solution ingestion.

The results of this analysis suggest that (i) D1 receptors expressed in NAc D1 MSNs are involved in the activation of ingestion by inducing the initiation of licking bursts, playing a role in the response to novel rewards or to increase in the reward value, while (ii) D2 receptors expressed in NAc D2 MSNs are involved in "sensing" the devaluation of an expected reward, a process revealed by reduced burst size and resulting in the suppression of the licking response.

It is important to note that this interpretative framework relies on previous evidence on (i) the effect of dopamine antagonists and reward value manipulations on the within-session time course of burst number and (ii) the change across sessions in the ability of burst number and burst size to reflect the between-group difference in reward value. To the best of my knowledge, these aspects have only been investigated in my laboratory. In particular, two studies will be discussed in some detail (D'Aquila, 2010; D'Aquila and Galistu, 2017). (Apart from these unique aspects, these studies align with the literature in the field, see D'Aquila, 2024.)

The following sections will (i) recapitulate previous findings regarding the effect of dopamine antagonists and manipulations of reward value on licking microstructure and (ii) present a reanalysis that integrates these findings with the results of two recent studies, which provide a sufficiently detailed report on the effects of manipulations of D1 and D2 MSN function on licking microstructure (Guillaumin et al., 2023; Sandoval-Rodrìguez et al., 2023).

2. Effects of dopamine D1 and D2-like antagonists and of manipulations of sucrose concentration on licking microstructure

2.1. *Early evidence about the role of dopamine in sucrose ingestion*

Dopamine in the NAc plays a crucial role in licking for sucrose solutions (Hajnal and Norgren, 2005; Smith, 2004). Microdialysis studies have shown that licking for sucrose (Hajnal and Norgren, 2001), but also for fat (Liang et al., 2006), induces the release of dopamine in the NAc. Moreover, nomifensine-induced dopamine release in the NAc enhances licking for sucrose, an effect blocked by both D1 and D2-like dopamine antagonists (Hajnal and Norgren, 2001). Soon after the availability of dopamine receptor subtype selective antagonists, a study reported that the dopamine D2-like receptor antagonist raclopride reduced burst size in a dose-dependent fashion, mimicking the effect of sucrose dilution, which is an instance of reward devaluation (Schneider et al., 1990). This observation was considered as consistent with the "anhedonia hypothesis", which posits a role for dopamine in hedonic responses to rewards of different kinds (Fouriezos et al., 1978; Wise, 2008; Wise et al., 1978). The ability of D2 receptor blockade to reduce burst size was confirmed by successive studies (Canu et al., 2010; D'Aquila, 2010; D'Aquila et al., 2012; Galistu and D'Aquila, 2013; Genn et al., 2003; Higgs and Cooper, 2000; Liao and Ko, 1995). As for D1 receptor antagonism, Schneider et al. (1989) and Liao and Ko (1995) reported its lack of effect on burst size.

2.2. *D1 and D2-like receptor antagonists exert a different effect on the within-session time course of burst number*

In a study comparing the effect of the dopamine D1 and D2-like receptor antagonists SCH 23390 and raclopride on the microstructure of licking for a 10 % sucrose solution, we examined for the first time the effect of these drugs on the within-session time course of burst number (D'Aquila, 2010). A sharp distinction between the effects of dopamine D1 and D2-like receptor blockade was revealed by the analysis of this measure. Raclopride influence on burst number was manifest only after a few minutes from the beginning of the session and led either to an increase (at low doses) or to a decrease (at relatively high doses) of this measure. This response pattern was previously observed with reward devaluation – but also with neuroleptic administration – in instrumental responding for different rewards (Wise, 2008; Wise et al., 1978), and was interpreted as the consequence of a blunted hedonic response. A small reduction of the reward value would result in a compensatory increase in response rate, while a drastic reduction would lead to response extinction – indeed, the response pattern induced by neuroleptics as reported above was referred to as "extinction mimicry". Moreover, in keeping with previous evidence (Genn et al., 2003; Higgs and Cooper, 2000; Liao and Ko, 1995; Schneider et al., 1990), D2-like receptor antagonism resulted in a reduction of the size of licking bursts. No effects of raclopride were observed on the latency to the first lick, which can be considered as a measure of behavioural activation (Salamone et al., 1997, 2016). Therefore, these observations seem to exclude an involvement of D2-like receptors in the direct activation of the licking response, but might suggest a role in a process of reward evaluation/hedonic impact, consistently with the early interpretation of Schneider et al. (1990). In contrast, the D1-like receptor antagonist SCH 23390 reduced licking exclusively by reducing the number of bursts, while no effects were observed on burst size. As previously observed in operant responding for a food reward (Sanger, 1987), the reduction in burst number induced by SCH 23390 was present from the beginning of the session. In other words, the D1 antagonist failed to induce extinction mimicry. This suggests a role for D1 receptors in behavioural activation.

These results – and in particular the different response patterns of the within-session time course of burst number – were confirmed in a study examining the effect of SCH 23390 and raclopride on the microstructure of licking for a NaCl solution (Galistu and D'Aquila, 2013). Moreover, an independent replication of these results was provided by a study showing the ability of the D2 antagonist eticlopride – administered to mice *via* lateral ventricle infusion – to induce a within-session decrement of lick number in absence of effects on burst size, which, therefore, could be accounted for only by a parallel reduction of burst number (Robles and Johnson, 2017). It might be worth noting that such replication was obtained with a different drug, a different route of administration, and in a different species.

These data support the involvement of dopamine D2-like receptors in reward evaluation/hedonic impact, and of dopamine D1-like receptors in the activation of the ingestive response. In the framework of the incentive salience attribution hypothesis (Berridge, 2007), these data might suggest that D1 receptors are involved in 'wanting' – the transformation of reward-associated stimuli into potent motivational incentives, i.e., triggers for the activation of the reward-oriented behaviour – and D2 receptors in 'liking' – hedonic impact of the reward – and/or in 'reboosting', a process by which the contact with the reward reboosts the attribution of incentive salience to the reward-associated stimuli.

2.3. Effect of manipulations of sucrose concentration on the within-session and across-session time courses of licking microstructural measures

In a subsequent study (D'Aquila and Galistu, 2017), we observed that reducing the reward value by exposing rats accustomed to a high sucrose concentration (10 %) to a lower sucrose concentration (2 %) not only led to a decrease in burst size, confirming previous findings (e.g., Schneider et al., 1990), but also caused a similar change in the within-session time course of burst number as seen with dopamine D2-like receptor blockade, specifically a decline following contact with the reward. This lends support to the suggested interpretation of raclopride's effect in terms of extinction mimicry (D'Aquila, 2010). (A critical discussion of the evidence against the interpretation of the effect of dopamine antagonists as extinction mimicry, which is beyond the scope of this article, is provided in D'Aquila, 2024.)

In a parallel experiment reported in the same paper, the response to daily exposure to a high (10 %) *versus* a low (2 %) sucrose concentration solution was compared between two groups of rats. This condition involves a difference in the reward value between the two groups, in *absence* of reward devaluation. A difference in whole-session lick number in favour of the 'high concentration' group was observed in all experimental sessions. Such difference was accounted for by a difference in whole session burst number in the first four sessions. Importantly, in these sessions (with the notable exception of the first session, see Section *3.4*), the difference in the within-session time course of burst number was present from the beginning of the session, with a lower level in the 'low concentration' group, thus reproducing the response pattern previously observed with dopamine D1-like receptor blockade in licking (D'Aquila, 2010; D'Aquila et al., 2019; Galistu and D'Aquila, 2013) and in instrumental responding for a food reward (Sanger, 1987). In the successive sessions, the different sucrose intake between the two groups was accounted for by a difference in burst size. To the best of my knowledge, this is the only study reporting changes across sessions in the ability of burst number and burst size to reflect between-group differences in reward value. Finally, exposure to an upshift in sucrose concentration of the subjects accustomed to the low concentration solution resulted in an increased burst number from the beginning of the session, without affecting burst size.

Thus, these results show that burst number reflects the reinforcing effect of novel rewards or increases in reward value, while burst size reflects the reinforcing effect of expected rewards or reward devaluation. This might question the commonly held notion that burst number and burst size are indices of 'wanting' and 'liking', respectively. Moreover, these observations, taken together with previous findings on the effect of dopamine antagonists on the within-session time course of burst number, show that dopamine D2-like receptor blockade mimics the effects of reward devaluation, while dopamine D1-like receptor blockade mimics the response to a smaller novel reward, which consists in a lower level of activation of the licking response (with respect to the response of a different group of subjects exposed to a larger reward). Finally, the resemblance between the effects of dopamine antagonists and manipulations of reward value on both the emission of licking bursts and operant behaviour suggests that these responses may be governed by similar neural mechanisms.

3. Licking microstructure, D1 and D2-like antagonists and manipulations of sucrose concentration: A reanalysis in light of evidence on the role of NAc MSNs in the control of hedonic eating

3.1. Studies on D1 and D2 MSN function, hedonic eating and lick pattern

To the best of my knowledge, among the studies reporting the effect of manipulations of NAc D1 and D2 MSN function on licking for sugars or other highly palatable solutions (Bakhurin et al., 2020; Chen et al., 2021; Coss et al., 2022; Guillaumin et al., 2023; O'Connor et al., 2015; Sandoval-Rodríguez et al., 2023; Tellez et al., 2016; Vachez et al., 2021; Villavicencio et al., 2018; Walle et al., 2024; Yang et al., 2020), only two provided the necessary information for a meaningful combined analysis with the evidence, described in the previous sections, on the effects of D1 and D2-like antagonists and manipulations of reward value. Indeed, only these papers (Guillaumin et al., 2023; Sandoval-Rodríguez et al., 2023) reported results from experiments that, within the same study, (i) examined the effects on ingestion of both gain and loss of function of D1 and D2 MSNs in the NAc, (ii) detected the activity of these neurons during ongoing ingestive behaviour, and, crucially, (iii) provided a detailed analysis of licking microstructural measures – such as the size and number of licking bursts, along with changes in inter-lick intervals – which might be interpreted in terms of palatability/'liking' or behavioural activation/'wanting'. Consequently, the comparative analysis that constitutes the subject of this paper will focus on these two studies.

Other studies might provide support to, or highlight possible discrepancies with, the results of the two selected studies. Indeed, these studies show that D1 MSN activation is positively correlated with (Guillaumin et al., 2023), or even causally responsible for (Sandoval-Rodríguez et al., 2023), the activation of licking. In keeping with these results, Chen et al. (2021) reported that inactivation of D1 and D2 MSNs in the ventrolateral striatum results in suppression and activation of licking, respectively, aligning with the results of a previous study investigating the effects of activation of the direct and indirect pathways – originating in D1 and D2 MSNs, respectively – in the same area (Bakhurin et al., 2020). However, O'Connor et al. (2015) – in line with previous findings (Baldo et al., 2002, 2005) – showed that optical activation of D1 MSNs in the NAc shell inhibited licking for a palatable solution. Consistent with these results, a subsequent study (Vachez et al., 2021) reported that a subpopulation of ventral pallidal neurons projects back to the NAc shell (the ventromedial region) where they exert an inhibitory effect, resulting in increased reward consumption due to increased bout duration (with no effect on bout number). Although they demonstrated that most of the cells targeted by this inhibition were MSNs, no distinction was made between D1 and D2 MSNs. Adding to the complexity, other studies have shown that some NAc shell neurons are activated, and others inactivated, when animals engage in licking (Krause et al., 2010; Tellez et al., 2012; Villavicencio et al., 2018). Moreover, D1 and D2 MSNs in the lateral NAc shell were shown to form ensembles whose activity predicts licking behaviour and categorizes sucrose concentration (Coss et al., 2022). A number of factors might contribute to explaining the apparent discrepancies between studies, such as frequency and pattern of delivery of light pulses for the optogenetic studies, difference in the methods employed to pursue gain and loss of function of MSNs, molecular identification of MSNs and method of detection of neuronal activity, to name a few. However, the limited data on lick pattern provided by these studies, when present, do not allow for comparison with the data that are the object of our analysis. Therefore, a detailed and exhaustive report about the studies investigating the role of D1 and D2 MSNs in hedonic eating is beyond the scope of this article. Finally, it should be noted that the study by Guillaumin et al. (2023) investigated the role of MSNs located in the NAc medial shell, while Sandoval-Rodríguez et al. (2023) have "preferentially targeted the […] shell sector" of NAc. As for the NAc core, a recent study reported that chemogenetic inhibition or activation of either D1 or D2 MSNs in this region had no effects on licking patterns during consumption of a palatable sweetened milk solution (Walle et al., 2024).

From this brief overview, one can conclude that the striatal subregion involved in the control of licking microstructure is the NAc shell (Bakhurin et al., 2020; Chen et al., 2021; Coss et al., 2022; Guillaumin et al., 2023; O'Connor et al., 2015; Sandoval-Rodríguez et al., 2023; Tellez et al., 2016; Vachez et al., 2021; Villavicencio et al., 2018; Yang et al., 2020), since manipulations of MSNs of the NAc core failed to show any effect (Walle et al., 2024). This might have important implications for the use of the analysis of licking microstructure as a tool for investigating the neural substrates of hedonic eating. Indeed, the NAc shell is situated within a neural circuit that plays a central role in the control of consumption of palatable foods (Kelley et al., 2005; Roitman et al., 2005; Villavicencio et al., 2018) and in related hedonic reactions (Smith and Berridge, 2005), while dopamine in the NAc core plays an important role in tracking the need-based motivational value of the food (Aitken et al., 2016). However, further topographical subdivisions within the NAc shell might have a decisive relevance. For example, *in vivo* fiber photometry measurements of calcium activity during aversive and reward conditioning tasks showed that ventral NAc medial shell dopamine terminals are activated by salient motivational stimuli, both appetitive and aversive. However, excitation to reward-predictive cues is detected in the NAc lateral shell, but is almost absent in the ventral NAc medial shell (de Jong et al., 2019). A review of the cited literature reveals that studies investigating the role of medium spiny neurons (MSNs) in the NAc shell in hedonic eating do not target perfectly superimposable anatomical regions, e.g., medial NAc shell (Guillaumin et al., 2023), NAc shell (O'Connor et al., 2016), and lateral NAc shell (Coss et al., 2022). This lack of consistent targeting may account for discrepancies between studies and constitutes a limitation of the analysis presented in this paper.

3.2. Ablation of D1 MSNs and activation of D2 MSNs in the NAc mimic the effect of D1 and D2 receptor antagonists on licking microstructure

A recent study aimed at clarifying the role of NAc MSNs expressing either D1 or D2 dopamine receptors in the control of sugar intake, combining cell-specific manipulations with single cell electrophysiological recording, optogenetics, and behavioural tests (Sandoval-Rodrìguez et al., 2023), provided evidence which might possibly account for the effects of systemic administration of dopamine antagonists, and of manipulations of the reward value, on licking microstructure.

Firstly, the results of this study – using cell-specific retrograde polysynaptic mapping tools – showed that NAc D1 and D2 MSNs receive segregated sensory inputs from the periphery. D1 MSNs receive inputs from both central and peripheral gustatory relays, such as rostral nucleus tractus solitarius, medial parabrachial nucleus, geniculate ganglion and neuroepitelial cells within taste buds. A high proportion of these neurons responded to gustatory stimuli, being excited by sweet and inhibited by bitter tastants. Moreover, the results showed that NAc D1 MSNs send projections to craniofacial motor neurons, thus being in an ideal position to activate ingestive motor acts in response to gustatory signals. More relevant to the scope of this article, CRE-dependent caspase-induced ablation of NAc D1 MSNs – but not ablation of D1 MSNs in the dorsomedial striatum – resulted in reduced licking for sucralose (0.2 mM) due to a reduced burst number, with no effects on burst size, yielding the same response observed with systemic administration of D1 receptor antagonists (D'Aquila, 2010; D'Aquila et al., 2012, 2019; Galistu and D'Aquila, 2012, 2013; Liao and Ko, 1995; Schneider et al., 1989). Conversely, optical activation of NAc D1 MSNs, contingent to the contact of the tongue with the bottle spout while licking for water, significantly increased lick number due to an increase in burst number.

In contrast, NAc D2 MSNs were shown to receive input from the area postrema – an area involved in appetite suppression (Zhang et al., 2021) – and were excited in response to intraperitoneal administration of liraglutide, an analogue of the satiety gut hormon glucagon-like peptide 1 (GLP-1). A small proportion of NAc D2 MSNs also responded to gustatory stimuli. Ablation of NAc D2 MSNs had no effects on licking for water and for different sugars. However, optical activation of NAc D2 MSNs reduced lick number, due to a reduction of both the size and the number of licking bursts, yielding the same effects observed with D2 antagonists at relatively high doses (Canu et al., 2010; D'Aquila, 2010; D'Aquila et al., 2012, 2019; Galistu and D'Aquila, 2013; Genn et al., 2003; Higgs and Cooper, 2000; Liao and Ko, 1995; Schneider et al., 1990). It is important to note that D2 receptor activation, in contrast to D1 activation, exerts an inhibitory effect on MSN excitability (McCutcheon et al., 2019).

Thus, these results, taken together with previous evidence on the effects of dopamine antagonists, suggest that dopamine D1 receptor antagonists decrease the number of licking bursts by counteracting the effects of dopamine acting on excitatory D1 receptors expressed by D1 MSNs. Conversely, D2 receptor antagonists diminish burst size by counteracting the effects of dopamine acting on inhibitory D2 receptors on D2 MSNs. Moreover, these findings support the notion that dopamine acting on D1 receptors activate the emission of licking bursts (D'Aquila, 2010, 2024).

As a note of caution, it should be borne in mind that the effect of the D2-like receptor antagonist raclopride in the nucleus accumbens might depend not only on the blockade of dopamine D2 receptors expressed by D2 MSNs but also on the blockade of D2 presynaptic receptors on dopaminergic (Ford, 2014) and glutamatergic terminals (Goto and Grace, 2008), as well as D3 receptors expressed by a limited proportion of D1 MSNs (Farré et al., 2015; Ridray et al., 1998). Thus, one might speculate that the effect of blocking presynaptic receptors on dopaminergic terminals, resulting in increased dopamine release, should be null on D2 and D3 postsynaptic receptors – also blocked by the antagonist – while it might result in increased D1 receptor stimulation. However, in the absence of experimental data, it is impossible to evaluate the weight of such contributions on the net effect.

3.3. Further evidence on the role of NAc shell D1 and D2 cells in the control of licking microstructural measures

Another study investigating the role of D1 and D2 cells in the medial NAc shell in hedonic eating (Guillaumin et al., 2023) – combining optogenetic stimulation/inhibition with photometric detection of cell activity – reported results which show apparent discrepancies with the observations of Sandoval-Rodrìguez et al. (2023), although important differences in methodology should be taken into account: (i) Optogenetic stimulation and inhibition of D1 and D2 cells were performed during licking for a palatable milkshake solution, with the optic stimulus switched on for the whole duration of the licking bout, while, in the Sandoval-Rodríguez study, light pulses were contingent upon the contact of the tongue with the bottle spout while licking for water; (ii) MSN function was inhibited with optogenetics in the Guillaumin study and with CRE-dependent caspase-induced ablation in the Sandoval-Rodríguez study; (iii) Different methods of detection of neuronal activity were employed in the two studies.

Briefly, photometric measurements demonstrated transient increases of both D1 and D2 cell activity beginning immediately before the initiation of a licking bout and peaking just after licking onset, which were followed by a return to baseline of D1 cell activity and a suppression of D2 cell activity during the licking bout. Activation of D1 cells and suppression of D2 cell activity were correlated to bout duration, which was interpreted as an index of 'liking', while no correlation was found for burst number increments and for decrements of the intervals between licking bouts, which were considered as indices of 'wanting'. To some extent, these observations align with the findings of Sandoval-Rodríguez et al. (2023), as they demonstrate a positive correlation with licking for D1 MSN activation and D2 MSN activity suppression.

At variance with the results of Sandoval-Rodríguez et al. (2023), optical activation of D1 cells during the licking bout was devoid of effects. This discrepancy might be due both to the pattern of delivery of optical stimulation (see above) and to the use of the palatable solution instead of water, possibly yielding a ceiling effect.

Optical activation of D2 cells led to an increase in bout number, interpreted as heightened 'wanting', and inter-lick intervals, suggesting a decrease in 'liking' (see Baird et al., 2005). This effect is reminiscent of the effect of a *low* dose of D2 antagonists on licking, which results in reduced 'liking', as revealed by decreased bout size, along with an increase in bout number. In apparent contradiction, the effect of D2 MSN optical stimulation in the study conducted by Sandoval-Rodríguez et al. (2023) resulted in the reduction of both the size and number of licking bursts. However, this is the same effect observed with a *high* dose of D2 antagonists on licking (Canu et al., 2010; D'Aquila, 2010; Galistu and D'Aquila, 2013; Genn et al., 2003).

Optical inhibition of D1 cells resulted in reduced inter-lick intervals, interpreted as an increase in 'liking' (see Baird et al., 2005). Such proposed prohedonic effect is paralleled by the increased burst size, another measure which might represent 'liking', occasionally observed with D1 antagonists (D'Aquila et al., 2019; Liao and Ko, 1995) or after D1 cell ablation (Sandoval-Rodrìguez et al., 2023).

Thus, the analysis of these results in combination with the analysis of the effects of dopamine antagonists provides an interpretative framework which might reconcile the discrepancies between the two studies (i.e., Guillaumin et al., 2023 *versus* Sandoval-Rodríguez et., 2023).

3.4. Effect of manipulations of sucrose concentration on the within-session and across-session time courses of licking microstructural measures: A reanalysis in light of the evidence on NAc D1 and D2 MSNs' role in the control of sugar intake

3.4.1. A brief overview on the role of dopamine in the mesolimbic system in the response to reward

Before sketching a possible account of the licking response to different sucrose concentrations, either with or without reward devaluation (D'Aquila and Galistu, 2017), in terms of NAc D1 and D2 MSN function, it is important to recall several basic notions about dopaminergic responses to reward in the mesolimbic system and dopaminergic neurotransmission at the receptor level.

Firstly, microdialysis studies have shown that palatable rewards evoke an increased dopamine release in the NAc shell, a response that undergoes habituation after repeated presentations of the same reward. Aversive tastes might induce a reduction of dopamine levels in the same area. By contrast, dopamine release in the NAc core in response to taste stimuli occurs independently of their hedonic valence (Di Chiara and Bassareo, 2007). Moreover, single-cell recordings of dopamine neurons in the ventral tegmental area (VTA), which project to the NAc among other targets, exhibit a transient increase in firing rate in response to a novel reward and a transient decrease when an expected reward is omitted. This provides the basis for the computation of reward prediction error, i.e., the mismatch between the expected reward and the reward obtained (Schultz et al., 2017). These essential notions provide an important premise for analysing the evidence on the possible role of NAc D1 and D2 MSNs in the effect of manipulations of sucrose concentration on licking microstructural measures (addressed in the next subsection). However, it should be noted that more recent findings, facilitated by the advent of new technological tools, have revealed a far more complex picture. Dopamine neurons in the VTA and dopamine terminals in the NAc, far from behaving homogeneously in response to rewards and reward-related stimuli, also respond to aversive stimuli and their predictive cues, showing diverse responses depending on cell type and anatomical location (de Jong et al., 2022). Indeed, medial and lateral VTA dopamine neurons project, without overlap, to different regions of the NAc (Beier et al., 2015; Lammel et al., 2008). Dopaminergic projections from the VTA to the lateral NAc shell are involved in reward-related behaviours, while medial VTA dopamine neurons project to the ventral NAc medial shell and encode aversive stimuli (de Jong et al., 2019; Nieh et al., 2016). While a detailed account of these findings is beyond the scope of this article, they further highlight that the lack of sub-regional specificity within the NAc in the experimental measurements and manipulations underlying the analysis presented here constitutes a significant limitation in data interpretability, and may be a key source of inconsistency between studies.

Finally, D2-like receptors exhibit a significantly higher affinity for dopamine, ranging from 10 to 100 times greater than that of the D1-like receptor family (Martel and Gatti McArthur, 2020). Thus, low affinity D1 receptors are stimulated by increases in dopamine concentration in response to novel rewards (Bech et al., 2023; Di Chiara and Bassareo, 2007; Koob and Volkow, 2016), while high affinity D2 receptors might "sense" the decreased dopamine levels in response either to aversive stimuli or to omission of an expected reward (Bech et al., 2023; Chang et al., 2016; Danjo et al., 2014; Ino et al., 2020; Tan et al., 2012).

3.4.2. Possible role of NAc D1 and D2 MSNs on the effect of manipulations of sucrose concentration on the within-session and across-session time courses of licking microstructural measures

This section will deal with a detailed reanalysis of the experiment, described in Section *2.3* (D'Aquila and Galistu, 2017), comparing the effect of daily exposure to two different sucrose concentrations (high, 10 % *versus* low, 2 %) between two groups of rats. The first time that the animals are exposed to the sucrose solutions, the emission of licking bursts progressively increases within the session in proportion to the concentration of sucrose, leading to a higher level of burst number in the group exposed to the high concentration solution. In the first four daily tests the difference in ingestion levels between the two groups – indicated by the difference in lick number – is exclusively due to a difference in whole-session burst number. This observation might be accounted for by an increase in dopamine levels, occurring in presence of a novel reward, which, *via* low affinity D1 receptors, activate D1 MSNs. Indeed, optogenetic activation of D1 MSNs while licking for water was shown to yield an increase in burst number, producing "sweet-like licking responses" (Sandoval-Rodrìguez et al., 2023). Interestingly, when a stable difference between the two groups in terms of whole-session lick number is established (from the 5th up to the last daily session), such difference is supported only by a difference in burst size, i.e., the measure which is sensitive to D2 MSN activation (Sandoval-Rodrìguez et al., 2023), as well as to D2 receptor antagonism (Canu et al., 2010; D'Aquila, 2010; D'Aquila et al., 2012; Galistu and D'Aquila, 2013; Genn et al., 2003; Higgs and Cooper, 2000; Liao and Ko, 1995; Schneider et al., 1990). At this stage, when the reward is no longer novel, dopamine levels are presumably relatively low, so that the role of the high affinity D2 receptors becomes critical. Then, possible further reductions of dopamine levels, due to reward devaluation, can be "sensed" by the D2 receptors expressed in D2 MSNs, resulting in the activation of these neurons (as a consequence of reduced D2 receptor stimulation). Consistently with this account, reward devaluation results in reduced burst size along with a reduced burst number, i.e., the same response observed after activation of D2 MSNs by Sandoval-Rodrìguez et al. (2023), and in earlier studies with D2 antagonists (see above). Interestingly, Guillaumin et al. (2023) have shown that NAc shell D1 cell activation associated to licking for a milkshake solution decreases, while D2 cell activity suppression increases, across sessions.

Consistently with this interpretation, the presentation of an increased reward value to the subjects exposed to the low concentration solution (D'Aquila and Galistu, 2017) yielded an increased burst number from the beginning of the session, with no effect on burst size, i.e., the same effect that was observed following optogenetic activation of D1 MSNs (Sandoval-Rodrìguez et al., 2023).

The anatomical connection of D2 MSNs with area postrema – which is involved in appetite suppression and is sensitive to satiety gut hormones (Zhang et al., 2021) – and the behavioural effects of the optogenetic stimulation of these neurons (Sandoval-Rodrìguez et al., 2023) might suggest that their activation is involved in the decline of the emission of licking bursts within a sucrose drinking session as a consequence of satiety signals building up as ingestion proceeds, possibly *via* dopamine independent mechanisms. In contrast, the characteristic anticipated within-session decline of licking bursts – i.e., the extinction-(like) curve – (D'Aquila, 2010, 2024) might be accounted for by D2 MSN activation *via* reduced stimulation of D2 receptors due to (i) reduced dopamine levels in response to reward devaluation or (ii) D2 receptor antagonist administration. Consistently with this interpretation, a recent study reported evidence showing that D2 MSNs play a prominent role (compared to D1 MSNs) in the response to reward omission and in extinction learning (Domingues et al., 2024).

The study of the within-session time course of burst number, along with the comparison of burst size and burst number across sessions between groups exposed to different sucrose concentrations (i.e., different reward values), was crucial in the reanalysis of the reviewed studies and is decisive in the experimental testing of the proposed interpretation.

4. Conclusions

In summary, the evidence about the effects of systemic administration of dopamine antagonists and of manipulations of the reward value on licking microstructure, reinterpreted in light of recent data about the role of NAc MSNs in palatable solution intake (Guillaumin et al., 2023; Sandoval-Rodrìguez et al., 2023), suggests that dopamine D1 receptors, stimulated by increases in dopamine concentrations in response to novel rewards or to increased reward value, activate NAc D1 MSNs, leading to an increase in the number of licking bursts. D2 receptors might be involved in "sensing" reward devaluation, signalled by decreased dopamine levels, thus resulting in NAc D2 MSN activation. This process yields a reduced burst size and might underlie the extinction-(like) pattern of the within-session time course of burst number, but also of operant responding, observed both with reward devaluation and with D2 antagonists.

This hypothesis relies on (i) the results of two selected studies on the manipulations of D1 and D2 MSNs, (ii) previous evidence on the effect of dopamine antagonist and manipulations of reward value and (iii) several established notions about dopaminergic neurotransmission in response to reward. Importantly, apparent discrepancies between the results of the two selected studies might be resolved within the proposed interpretative framework. Experiments that combine the manipulation of MSN function with dopamine level detection, along with a detailed analysis of both the within-session and the across-session time courses of licking microstructural measures, can be designed to test the proposed hypothesis.

Elucidating the neural mechanisms underlying the licking response might lead to a better definition of its microstructural measures in behaviourally and psychologically meaningful functional terms. This could further support its use as a behavioural substrate in the study of the neural mechanisms of ingestive behaviour and motivation, as well as in animal models of pathological conditions such as eating disorders and obesity. However, a coherent understanding of the role of NAc MSNs in hedonic eating is still lacking. Thus, further studies are necessary to integrate the proposed hypothesis, the results of the two selected studies, and the current evidence on the role of NAc MSNs in hedonic eating into a common interpretative framework. Importantly, these studies should take into account the growing evidence on the precise topographical organization of the NAc shell subregions. Finally, the analysis presented here highlights the importance of the within-session time course of burst number in the analysis of licking microstructure.

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Declaration of Competing Interest

None to declare.

Data availability

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

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