Rats, and many other vertebrates, will work to deliver electrical pulse trains to certain brain loci via depth electrodes - a phenomenon known as intracranial self-stimulation (ICSS). The effect of the electrical stimulation that leads the animal to seek and reinitiate the stimulation is called brain stimulation reward (BSR) and is related to the effects of naturally rewarding stimuli. For example, BSR can compete with, summate with, and substitute for, the rewarding effects of natural goal objects such as food and water. However, unlike behavior maintained by natural rewards, the behavior controlled by BSR remains stable between and within sessions. This is due to the fact that the signal is injected directly into the brain, thus bypassing sensory adaptation and physiological feedback mechanisms that discount natural rewards. In addition, response-reinforcement delays that degrade natural rewards are minimized. Given that the electrically induced rewarding effect originates as a volley of observable action potentials in axons coursing past identifiable CNS sites, the phenomenon of BSR has long been regarded as a gateway to tracing the neural circuitry involved in the pursuit of natural rewards. It has also been proposed that dependence-inducing drugs gain their grip over behavior, at least in part, due to their ability to alter neurotransmission in the circuitry underlying BSR.

**Preliminaries: measuring pharmacological effects on BSR:** In early studies, the effects of drugs on BSR were inferred from changes in the rate of lever pressing. This practice was based on the intuitive assumption that the vigor of instrumental performance should reflect the strength of the rewarding effect. One problem with this assumption is that response tempo depends on multiple variables and can thus vary even when the intensity of the rewarding effect is constant. Another is that the magnitude of the change in response rate produced by a drug-induced change in reward intensity depends on the baseline rate and does so in a highly non-linear manner.

An initial challenge to the rate measure was posed by the finding that rats preferred higher-current to lower-current stimulation despite the fact that lower response rates were obtained when
higher currents were used. This finding illustrates how response rates can be altered by factors unrelated to reward, such as forced, stimulation-induced movements (which are more prevalent at higher than lower currents). The s-shaped form of the relationship between response rate and stimulation strength is particularly problematic for attempts to infer drug-induced changes in the rewarding effect from changes in rate. For example, if stimulation parameters that sustain a high baseline response rate are used, a reward-potentiating drug will have little or no ability to boost responding. In contrast, if parameters that sustain a low level of baseline responding are used, the same reward-potentiating effect of the drug will produce a large increase in response rate.

These limitations propelled the development of the “curve–shift” paradigm, which entails use of a range of stimulation strengths (pulse frequencies or currents) that drives response rate from minimal to maximal levels. The influence of drug treatments on intracranial self-stimulation is quantified by measuring lateral displacements (Figure 1) of the resulting psychometric functions, hence the name of the paradigm. These displacements are interpreted to reflect changes in reward potency, whereas vertical shifts of the upper asymptote and changes in slope are interpreted to reflect changes in performance capacity (Miliaressis et al. 1986).

| Figure filename: Psychopharmacology_fig1.tiff |
| Figure legend: The curve-shift paradigm. Drug-induced changes in the effectiveness of the rewarding stimulation are assessed by lateral displacement of curves relating the vigor of responding to the strength of the stimulation. The leftward shift of the dotted curve (1) with respect to the thick grey baseline curve is attributed to increased reward effectiveness, whereas the rightward shift of the dashed curve (2) is attributed to decreased reward effectiveness. The downward rescaling of the thin solid curve (3) is attributed to drug-induced attenuation of performance capacity. |
Although the curve-shift paradigm was a step forward in attempts to measure drug-induced changes in reward, it falls short of achieving a clean distinction between changes in reward intensity and performance capacity. For example, weighting the lever and thus increasing effort cost can shift rate-frequency curves laterally in a manner indistinguishable from the effects of variables, such as the current, that alter the strength of the rewarding effect. Moreover, indistinguishable shifts may result from changing either the intensity or the cost of reward. Video 1 shows that the two-dimensional perspective of the curve-shift paradigm can lead to erroneous inferences because of unseen changes along a third “hidden” dimension. In effect, the two-dimensional perspective fails to recognize the fact that when an organism pursues a goal object, it takes into account not only the strength of the reward, but also the effort entailed in procuring it and the cost of forgoing opportunities to pursue alternate goals.

The ambiguity inherent in the curve-shift method can be reduced by measuring operant performance as a function of both the strength and the cost of reward. The resulting three-dimensional (3D) structure has been dubbed the “reward-mountain” (Breton et al. 2013). Shizgal modeled this structure (Figure 2a) by combining the generalized matching law with an account of how the neural firing induced by the electrode is translated into a stored record of reward intensity (Gallistel et al. 1981). The electrically induced reward signal is encoded in the aggregate firing rate of the directly stimulated neurons within a time window defined by the duration of the stimulation train. The resulting spike count is then transformed non-linearly into a single time-varying quantity representing the intensity of the reward; growth of the reward signal decelerates over time and eventually levels off (darker curve in the graph on the left of Figure 2a). With train duration fixed, the reward signal grows as a function of the stimulation-induced spike count and eventually saturates (lighter curve in the graph on the left of Figure 2a). The peak reward intensity achieved during a stimulation train is recorded in
memory (not shown). A vertical grey line in Figure 2a demarcates the boundary between the BSR-specific and the more general processes involved in the control of the reward-seeking behavior. The elements to the left of the grey line include the directly stimulated neurons and the circuitry that integrates their output over time and space, compressing the effects of the electrically triggered volley into a single quantity recorded in memory. To the right of the grey line, this stored reward-intensity signal is combined with information about the probability that a reward will be delivered once the response requirement (e.g., pressing the lever a given number of times) has been satisfied, the physical effort (“effort cost”) and time (“opportunity cost”) required to do this, and the delay (not shown) between meeting the response requirement and delivery of the reward. In keeping with the generalized form of the matching law and with behavioral-decision theories in general, the subjective values of all of these variables are combined in scalar fashion to yield an estimate of the payoff the subject can expect in return for satisfying the response requirement. Finally, in the spirit of the generalized single-operant matching law, the payoff from BSR (UB, suitably transformed) is compared to the sum of all of the (suitably transformed) payoffs available in the test environment, which include the payoffs (UE, suitably transformed) from behaviors such as grooming, exploring, resting, etc. The result determines the proportion of time (“time allocation” or TA) devoted to pursuit of the electrically induced reward; consequently, TA is shown to grow as the payoff from BSR increases (darker curve in the graph on the right of Figure 2a) and as the payoff from competing activities falls (lighter curve in the graph on the right of Figure 2a). With the use of the reward-mountain paradigm, and by varying both the strength and cost of reward, the influence of drugs on components of the reward circuitry prior to the output of the spatiotemporal integrator in Figure 2a can be distinguished unambiguously from influences brought to bear on downstream components.
The curve-shift method provided a clear methodological advance by eliminating the dependence of drug-induced changes on arbitrarily selected stimulation parameters. The 3D method (Breton et al. 2013) promises to better distinguish the influence of drugs on different components of the circuitry underlying pursuit of the rewarding stimulation, and to better distinguish the effects of drugs on performance capacity from effects on reward integration. However, Figure 2 points to a limitation of this new method: numerous interacting variables (depicted to the right of the vertical grey line in Figure 2a) influence performance in ways that will be indistinguishable unless the mapping of the objective to the subjective values of these variables is non-linear and these non-linearities can be exploited experimentally. Thus, there will be a need for continued methodological advances in order to fully account for the effects of drugs on BSR and to maximize the contribution of such experiments in determining the neurochemical basis of reward.

The neurochemical basis of BSR. The curve-shift method is currently the most common means of assessing the influence of drugs on BSR, and it was employed in most of the work summarized in this
essay. In the recent cases in which the improved 3D method has been used, the results are contrasted with those obtained with the curve-shift method. We summarize the contributions of the most extensively studied neurotransmitter systems to intracranial self-stimulation.

**Dopamine**

Dopamine is the neurotransmitter most closely associated with BSR and reward-seeking (Wise and Rompré 1989). ICSS is accompanied by a prolonged increase in the extracellular concentration of dopamine, as observed by means of in-vivo microdialysis probes in dopamine terminal fields. Dopamine transients associated with phasic release, as measured by means of fast-scan cyclic voltammetry, are also observed repeatedly in response to BSR trains provided that their delivery is spaced in time by post-reinforcement time-outs. In early accounts it was argued that direct stimulation of dopamine neurons is responsible for the rewarding effect of the stimulation. However, the properties of dopaminergic fibers are largely incompatible with the inferred characteristics of the directly stimulated neurons subserving ICSS. The axons of dopamine neurons are unmyelinated and of fine caliber; their thresholds for activation by extracellular currents are high. Thus, relatively few such fibers should be excited directly under the typical conditions of BSR experiments, which entail the use of stimulation electrodes with large exposed tips and currents that are low with respect to the thresholds of dopaminergic fibers at the short pulse durations commonly employed. The refractory periods of dopaminergic fibers are long and their conduction velocities low in comparison to the estimated values for the directly stimulated axons mediating self-stimulation of the medial forebrain bundle. Given the limited overlap between the excitability properties of dopaminergic fibers and those of the directly stimulated fibers mediating BSR, it would appear that activation of midbrain dopaminergic neurons during ICSS is achieved largely via a trans-synaptic route (Shizgal 1997). As predicted by this proposal, blockade of glutamate receptors in the ventral tegmental area (VTA) decreases the magnitude of
ventral striatal dopamine transients elicited by rewarding MFB stimulation, and optical activation or disinhibition of VTA dopamine neurons via descending afferents serves as an effective reward for operant responses.

Although it is unlikely that dopaminergic neurons are activated directly by rewarding MFB stimulation, it was shown recently that rats and mice will perform operant responses to trigger direct optical activation of VTA dopaminergic neurons. These statements can be reconciled if VTA dopamine neurons are positioned at or beyond the ∑ symbol in Figure 2a. This possibility was envisioned by Moisan and Rompré (Moisan and Rompré 1998). They varied the current and pulse frequency of rewarding brainstem stimulation so as to determine two sets of stimulation parameters that produced the same level of behavioral responding: one that activated many directly stimulated neurons at low frequency, and a second that activated fewer directly stimulation neurons at higher frequency. They then demonstrated that putative midbrain dopamine neurons trans-synaptically activated by the rewarding stimulation fired at similar rates in response to the two different sets of stimulation parameters. On this basis, Moisan and Rompré proposed that midbrain dopamine neurons may compose an integral part of the spatiotemporal integrator or relay its output to efferent stages of the circuit.

Pharmacological manipulations of dopamine neurotransmission have profound impact on ICSS. Reductions lower the effectiveness of the electrical stimulation in supporting self-stimulation, leading to rightward displacements of psychometric functions as measured by the curve-shift method; higher stimulation strength is required to produce a given rate of lever pressing following administration of a dopamine receptor blocker. Conversely, drugs that enhance dopaminergic neurotransmission increase the effectiveness of the electrical stimulation in supporting self-stimulation and thus, produce leftward shifts; such drugs reduce the simulation strength required to produce a given level of behavioral
output. When two drugs that exert opposing influences on dopaminergic neurotransmission were co-administered, their effects on performance for BSR cancelled. Drugs that block D-2 receptors have also been shown to produce rightward curve shifts, and there is evidence that D-1 and D-2 receptors exert synergistic influences in this regard, as well. These, among many other observations, led to the hypothesis that dopamine alters the sensitivity of brain reward circuitry, an action tied to the early stages of the circuit (to the left of the gray line in Figure 2a. However, this long-standing hypothesis was challenged by the application of the reward-mountain paradigm. The indirect dopamine agonist, GBR-12909 (Hernandez et al. 2012), or the antagonist, pimozide (Trujillo-Pisanty et al. 2013), produce complementary, reliable displacements along the axis of the 3D space representing reward cost in the absence of reliable changes along the axis representing reward strength (Figure 3). These results suggest that changes in dopaminergic neurotransmission alter factors to the right of the grey line in Figure 2a, downstream from the directly stimulated neurons. These factors could include scalar

![Figure filename: Psychopharmacology_fig3.tif](Psychopharmacology_fig3.tif)

**Figure legend:** Displacement of the reward mountain along the axes representing stimulation strength (pulse frequency) and opportunity cost. Location-parameter estimates for each rat are represented by diamonds. The top and bottom of each box define the inter-quartile range of the estimates, and the middle line represents the median; the mean is designated by a square. The effects of both pimozide and GBR-12909 are confined to the opportunity-cost axis and produce shifts in opposite directions. These results challenge the long-standing view that dopaminergic manipulations alter reward sensitivity. Instead, they argue that the effects of such manipulations on BSR arise at or beyond the output of the integrator (Figure 2a) and may thus entail changes in reward scaling, subjective costs or the value of alternate activities. The ratio values on the right show the proportional drug-induced change in the values of the location parameters that determine the position of the 3D structure.
changes in reward intensity (i.e., changes in the gain of the BSR substrate), changes in subjective effort costs, and changes in the value of alternate activities.

**Noradrenaline**

Noradrenalin figured heavily in early psychopharmacological research on BSR. The early interest waned after the reductions in response rate produced by agents that decrease noradrenergic neurotransmission were attributed to sedation, and early claims that self-stimulation of sites in the vicinity of the locus coeruleus were due to activation of noradrenergic neurons were disputed. Nonetheless, neurons in the locus coeruleus and lateral tegmental A7 cluster do show increased double labeling for the rate-limiting enzyme in noradrenalin synthesis, tyrosine hydroxylase, and the immediate early-gene product, Fos, following self-stimulation of the medial forebrain bundle. Injection of the α1 receptor antagonist, terazosin, into the locus coeruleus has been shown recently to produce rightward shifts in rate-frequency curves obtained from rats working for electrical stimulation of the MFB. Given evidence that activation of α1 receptors excites noradrenergic neurons in the locus coeruleus, this finding suggests that the firing of these neurons contributes in some way to the pursuit of rewarding MFB stimulation.

**Acetylcholine**

Acetylcholine has been implicated in self-stimulation by experiments entailing manipulation of projections to midbrain dopamine neurons from cholinergic cell bodies in the pedunculopontine and lateral dorsal tegmental nuclei (Yeomans 2011). Activation of these excitatory projections potentiates MFB self-stimulation and drives dopamine release in the nucleus accumbens. Neurotransmission in the cholinergic projections to the VTA is suppressed by the action of cholinergic agonists at autoreceptors on or near the cholinergic somata or by the action of cholinergic antagonists in the VTA terminal field. These manipulations reduce reduce the effectiveness of rewarding MFB stimulation (i.e., they cause
rightward curve shifts). Disinhibition of the cholinergic projections by administration of cholinergic antagonists in the vicinity of the cholinergic cell bodies potentiates MFB self-stimulation, as evinced by leftward curve shifts. Enhanced release of acetylcholine is observed during self-stimulation of the MFB, both in the vicinity of the cholinergic cell bodies and in the VTA terminal field. Although modest effects on MFB self-stimulation have been reported following nicotinic manipulations of the cholinergic projections to the VTA, muscarinic receptors, the M5 sub-type in particular, appear to mediate most of the effect of the cholinergic drive on MFB self-stimulation and on dopamine release in the nucleus accumbens. Administration into the VTA of antisense oligonucleotides for the M5 receptor suppresses MFB self-stimulation. The potent modulation of MFB self-stimulation by cholinergic agents suggests that the effects of activating MFB fibers are relayed to VTA dopamine neurons, at least in part, by constitutively active cholinergic afferents.

**Serotonin**

An important role in emotional and behavioral control has been attributed to serotonergic neurons. However, the multiplicity of serotonergic receptors, the widespread distribution of the serotonergic projections, and the action of serotonin both at the cell bodies and in the terminal fields of dopamine neurons make it challenging to build a comprehensive account of the action of serotonin on brain reward circuitry. Nonetheless, there is good agreement on the overall pattern to the results obtained to date in studies of the role of serotonin in ICSS: Release of this neurotransmitter generally exerts a suppressive influence on ICSS and opposes the influence of dopamine release. For example, stimulation of inhibitory cell-body autoreceptors decreases the activity of serotonergic neurons in the rostral raphé nuclei and potentiates self-stimulation of sites along the LH-VTA segment of the MFB. The effects of systemically administered agonists vary as a function of dose, stimulation site, and affinity for different subtypes of serotonin receptors. That said, rightward curve shifts or related increases in ICSS
thresholds have been observed following administration of agonists for the 5-HT1A, 5-HT1B, and 5-HT2C receptors. Intracerebral administration of 5-HTC2 agonists into the medial prefrontal cortex (mPFC) or nucleus accumbens attenuates the facilitating effect of cocaine on performance for BSR. Systemic administration of antagonists for the 5-HT1A, 5-HT1B, and 5-HT2C and 5-HT3 receptors usually leaves ICSS unaltered but can reverse changes produced by concurrent administration of serotonergic or dopaminergic agonists.

**Glutamate and GABA**

Given the ubiquity of these amino-acid neurotransmitters in the brain, it would be surprising indeed if they did not play important roles in the rewarding effects of electrical brain stimulation.

Glutamate is released in the VTA during MFB self-stimulation. Numerous nuclei provide glutamatergic input to the VTA, and it is not yet known which subset of glutamatergic neurons are responsible for the release of this neurotransmitter during ICSS. Identifying these neurons is of substantial potential interest because they may well contribute to the directly activated stage of the circuit responsible for BSR. The notion that directly activated MFB fibers provide excitatory input to dopamine cells is compatible with the abovementioned hypothesis of Moisan and Rompré.

Experience with ICSS of the MFB has been shown to down-regulate the expression of the GluR1 subunit of AMPA receptors, a phenomenon that has been proposed as an explanation of the lack of sensitization observed over the course of long periods of ICSS testing. Viral-induced increases in the expression of GluR1 in the shell region of the nucleus accumbens produce rightward curve shifts whereas increased expression of the GluR2 subunit in these region shifts the psychometric curves leftward.
Alteration in the signaling of NMDA receptors in the VTA also alters ICSS of the dorsal raphe.

Intracerebral injections of antagonists for the NR2A subunits; but not for the NR2B receptors produce a dose-dependent leftward shift in rate-frequency curves for ICSS. The effect is consistent with the idea that the decreased glutamate signaling altered the inhibitory drive on DA neurons.

Microinjection of GABAergic agonists or antagonists into the VTA or into basal forebrain regions such as the sub-lenticular extended amygdala can produce systematic shifts in rate-frequency curves obtained from rats working for MFB stimulation (Waraczynski 2006). In the case of VTA injections, the level of activity of the local dopaminergic cell bodies appears to determine the sign of the effect. For example, the GABAA agonist, muscimol, produces rightward curve shifts when injected alone, but can reinstate self-stimulation after it has been abolished by intra-VTA injection of a large dose of morphine in rats pre-treated with the dopaminergic receptor blocker, pimozide. This effect has been interpreted to reflect the restoration of firing in dopamine cell bodies that had been driven into depolarization block by the combination of autoreceptor blockade and strong opioidergic excitatory drive; the GABAA stimulation is posited to have hyperpolarized the dopamine cells sufficiently to restore their ability to generate action potentials (Wise and Rompré 1989)).

Positive allosteric modulation of GABAA receptors via benzodiazepines dose-dependently shifts rate-frequency curves for ICSS leftward. This reduction was not observed after systemic injections of diazepam on animals in which the α2 or α3 subunit of the GABAA receptor was modified to make the receptor insensitive to benzodiazepines without altering its sensitivity to GABA. This result suggests that the potentiating effect of benzodiazepines on ICSS is mediated by α2, or α3 receptor subtypes.
**Endorphins**

The role of endogenous opioids in reward has been investigated extensively, and studies of ICSS have played an important role in this endeavor. Peripherally administered opiates and opioids to drug-naïve rats exert a biphasic influence on performance for BSR: an initial decrease in the vigor of responding is followed by an increase above baseline levels. The initial depression tolerates with repeated administration of the drug whereas the enhancement of performance does not, and thus the potentiation of ICSS by systemically administered opiates and opioids emerges as the principal effect of these drugs as a regimen of repeated administration proceeds.

Injection of opioid receptor agonists into either the VTA or the nucleus accumbens terminal field of VTA dopamine neurons can produce leftward shifts in psychometric curves obtained from rats working for rewarding MFB stimulation. In the case of the nucleus accumbens injections, such effects are observed following administration of agonists for either μ or δ-opioid receptors. In contrast, systemic administration of the κ agonist, U-69,593 produced rightward curve shifts and counteracted the left-shifting influence of cocaine.

The modulation of ICSS by opiates and opioids is linked strongly, but not exclusively, to the effects of these drugs on dopaminergic signaling. For example, GABAergic interneurons in the VTA are hyperpolarized by μ-opioid agonists, thus disinhibiting dopaminergic cell bodies. Opioid agonists have also been shown to increase release of dopamine in the nucleus accumbens. That said, opposite effects on dopamine tone in the core and shell subregions of the nucleus accumbens were observed following local administration of μ- and δ agonists. Given that opioid receptors are found both pre- and post-synaptically in the nucleus accumbens and have been identified on dopaminergic, cholinergic,
glutamatergic, and GABAergic neurons, there are multiple ways that opiates and opioids could influence the processing of reward-related signals in the ventral striatum.

**Cannabinoids**

An abundant literature links the endogenous cannabinoid system to the pursuit and evaluation of rewards, and there is evidence that cannabinoid agonists activate both dopaminergic and opioidergic neurons. Within this literature, the data on ICSS are anomalous: in the hands of different investigators, drugs that alter cannabinoid signaling have been observed to enhance, suppress or fail to alter pursuit of BSR. Methodological issues could be at the root of these conflicting reports, and application of the reward-mountain model may help shed light on these issues. Indeed, blockade of CB1 receptors produces a reliable displacement along the axis of the 3D space representing reward cost (as in Figure 2c) without reliably shifting the 3D structure along the pulse-frequency axis (Trujillo-Pisanty et al. 2011). Thus, the conflicting evidence regarding the contribution of endocannabinoids to ICSS could reflect limitations of the curve-shift paradigm. Rate-frequency curves are 2D projections of the reward-mountain, a 3D structure with a diagonally oriented face (Figures 2b,c). Displacement of the mountain along the price axis will produce an orthogonal shift of the 2D projection (Video 1) and could lead to the erroneous inference that the observed displacement on the 2D rate-frequency curve was product of a change in the reward intensity. Given that steep slope of the “intensity-growth function” (lighter curve in the left-hand graph in Figure 2a), substantial changes in the values of variables on the right-hand side of Figure 2a can produce only modest shifts in 2D projections of the 3D surface, such as rate-frequency curves, which can prove hard to discern through the measurement noise and individual differences in drug sensitivity.
Concluding remarks.

Together with the conditioned place-preference paradigm, ICSS has been, and continues to be, a mainstay of research on the psychopharmacology of reward. As this essay suggests, rather a lot has been learned from ICSS experiments about the roles of different neurotransmitter systems in brain reward circuitry. Nonetheless, much additional work will be required to fully account for the powerful influence of drugs on ICSS. Advances in behavioral measurement methods promise to tie the effects of pharmacological manipulations to specific psychological processes that contribute to the pursuit of BSR. New methods, such as techniques for optical stimulation or silencing of specific neuronal populations or for altering neural signaling with designer receptors and ligands, promise to refine our understanding of reward processing at the cellular and circuit levels.

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Stages prior to memory encoding

directly stimulated neurons → aggregate spike rate → intensity-growth function → intensity scaling → peak detector → memory → computation of payoff → behavioral allocation function

- Reward intensity
- Probability
- Effort cost
- Opportunity cost

payoff from BSR ($U_B$) / payoff from everything else ($U_E$) → reward-seeking behavior

- Mountain shifted along pulse-frequency axis
- Mountain shifted along price axis

Time allocation

Opportunity cost (price)

Spike rate (pulse frequency)