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Exploring Reinforcement Processes using Intra-Cranial Self-Stimulation

Intra-cranial self-stimulation, ICSS

In 1953 the two Canadian scientists, James Olds and Peter Milner, discovered that rats would willingly expose themselves to electric stimulation of the brain (Olds & Milner, 1954). In further studies, Olds and Milner placed a lever in the cage and connected the lever to a stimulator so that each press would result in the delivery of a pulse (Figure 1). They found that rats with the electrode implanted in the lateral hypothalamus rapidly learned to press the lever and would press it up to 7000 times per hour repeating the behavior for hours if allowed, ignoring thirst and hunger. Later research has shown that intra-cranial self-stimulation is general; ICSS has been shown in a variety of species ranging from goldfish to humans (including guinea pig, bottlenose dolphin, cat, dog, goat, and monkey) and several brain areas support responding for ICSS.

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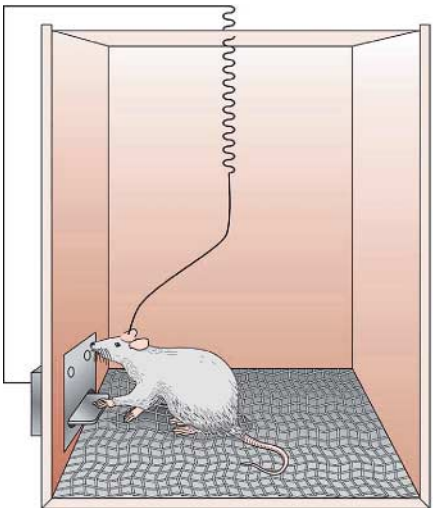
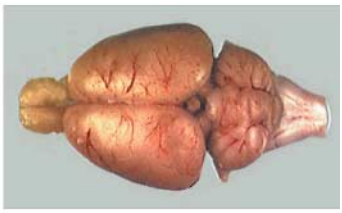
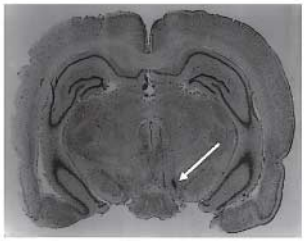
Figure 1. Rat in self-stimulation chamber (left, from Bear, 2001). Rat brain (upper right, from Synapse Web, Medical College of Georgia, http://synapses.mcg.edu/) and section of rat brain from present study showing that the bipolar electrode was positioned in the ventral tegmental area (lower right, from Johansen et al., 2005).







Working mechanism of ICSS

An early interpretation of the mechanisms behind ICSS was that pleasure and displeasure centres were stimulated by the electrical pulses. Early reports from self-stimulation in humans supported the suggestion that responding for electrical brain stimulation produced a feeling of pleasure:

> *"During these sessions B-19 stimulated himself to a point that he was experiencing an almost overwhelming euphoria and elation, and had to be disconnected despite his vigorous protests"*
>
> (Moan, C.E., & Heath, 1972)

However, other studies showed that in some people the site most frequently chosen to stimulate induced an irritable feeling or a feeling of being about to remember something. These and other findings lead to the conclusion that self-stimulation in humans is not synonymous with a feeling of pleasure. Thus, the working mechanisms behind ICSS probably depend upon stimulation site and which brain structures are activated by the stimulation. The rewarding effects of ICSS may work through inducing positive affective experiences, but can also be produced through activation of other brain systems without generating a positive effect.

The mesolimbic dopamine system and ICSS

The mesolimbic dopamine system originates in the ventral tegmental area (VTA) in the brain stem and projects to a collection of neurons in the basal forebrain called nucleus accumbens, NAc. There is overwhelming evidence that the mesolimbic dopamine system is involved in reward and reinforcement processes. Primary reinforcers such as food, sex, and also drugs of abuse are associated with dopamine release in NAc.

In a simplified form, function of the mesolimbic dopamine system may be summarized as follows:

- Respond to novelty in the environment
- Focus behaviour into approach, seeking, and investigation of these novel stimuli, especially if they are related to reinforcers
- Strengthen adaptive behaviour and connections between environmental stimuli and responses that may help sustain survival (Figure 2)
    - however, this system does not mediate affective experiences (pleasure, satisfaction, or hedonic aspect)

Studies have shown that positioning the electrode in VTA or its dopamine projection to NAc produces the highest and most reliable ICSS response rate (Wise, 1996). The reinforcing effects of ICSS in VTA and NAc are mediated by dopamine neuron activity, but the effects appear not to be mediated by a feeling of pleasure. ICSS in VTA might be described as a short-circuiting of the brain's reinforcement system by stimulating the neurons directly, thereby bypassing the sensory systems and other systems normally important for initiating behaviour (Figure 2).

Investigating reinforcement mechanisms in an animal model of ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is a disorder affecting 3–5 % of children, and is characterized by a persistent pattern of inattention, impulsivity, and hyperactivity. Findings from several research areas

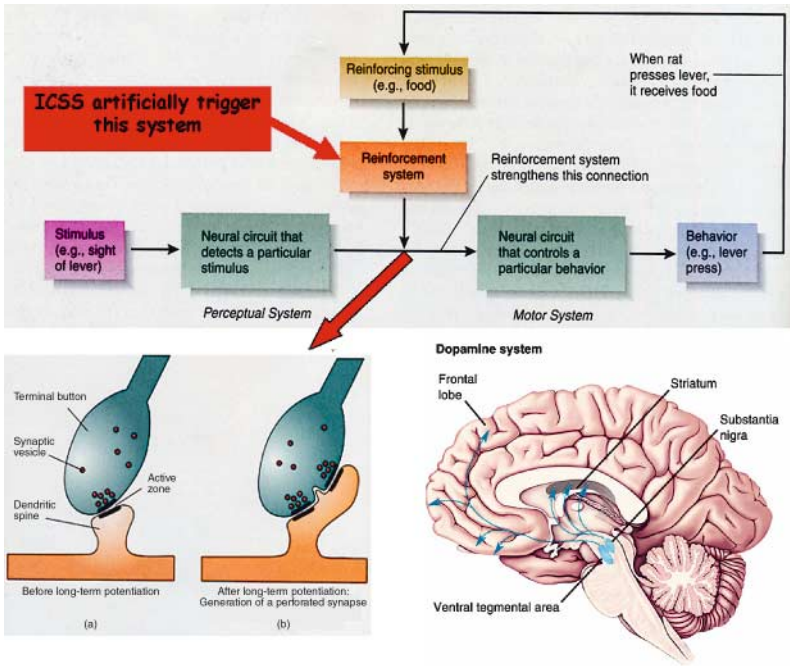


Figure 2. External stimuli are detected by neural circuits acting on motor circuits and may lead to initiation of behaviour (upper, from Carlson, 2004). Behaviour that has a favourable outcome (food) produces dopamine release in nucleus accumbens (lower right, from Bear, 2001). ICSS reinforcement can lead to synaptic long-term potentiation (LTP) (Reynolds, Hyland, & Wickens, 2001), the neuronal correlate to learning(lower left, from Carlson, 2004). The reinforcing effects of ICSS in the ventral tegmental area (lower right, from Bear, 2001) may be an artificial triggering of the reinforcement system and the strengthening of behaviour that produces electrical stimulation.

strongly suggest that dopamine dysfunction is at the core of ADHD etiology. Further, children with ADHD react abnormally to reinforcers and reinforcement contingencies. The known association between reinforcement and dopamine neuron activity further points to a dopamine dysfunction in ADHD.

Based on behavioural studies of children with ADHD and spontaneously hypertensive rats (SHR) which is possibly the best-validated animal model of ADHD (Sagvolden, 2000; Sagvolden, Russell, Aase, Johansen, & Farshbaf, 2005), we have presented a behavioural theory of ADHD suggesting that symptoms are produced by dopamine dysfunction leading to altered effects of reinforcers (Sagvolden, Johansen, Aase, & Russell, 2005).

Using ICSS reinforcement in VTA, we have investigated how reinforcement processes may be different in SHR compared to normal controls by varying important reinforcement parameters: Current intensity, reinforcer frequency, and reinforcer delay (Johansen & Sagvolden, 2005). The method of ICSS was chosen due to its many advantages: Reinforcers can be delivered with millisecond accuracy, consummation of every reinforcer produced is ensured and no or little time is spent on consummation (e.g. drinking), reinforcer value can be studied by varying ICSS current, and satiation effects are to a large extent avoided.

Varying current intensity (reinforcer value)

The most commonly used ICSS paradigm is the curve shift paradigm (Miliaressis, Rompre, Laviolette, Philippe, & Coulombe, 1986). By varying ICSS current, the resulting current-response rate curves resemble the traditional logarithmic dose-response curves commonly obtained in pharmacology (Figure 3). The drug's effects on reinforcement can be estimated by comparing curves from saline and drug sessions. Dopamine agonists will increase the effects of the ICSS reinforcers and produce the same response rate with lower ICSS current values (left-shift) while dopamine antagonists will have the opposite effect (Miliaressis et al., 1986).

The results from varying current during frequent and infrequent reinforcement show that the current-response curve-shift in SHR compared to controls is two-dimensional (Johansen et al., 2005). During frequent reinforcement (fixed interval 0.5 s), maximal response rate in SHR was found at a lower current than in the controls (Figure 3, right, A, Johansen et al., 2005), while infrequent reinforcement (variable interval 60 s) caused a shift towards higher response rates in SHR (Figure 3, right, B, Johansen et al., 2005). These findings support the suggestion that reinforcers act differently on responding in SHR compared to controls and indicate that strain differences may be linked to frequency of dopamine release (Johansen et al., 2005).

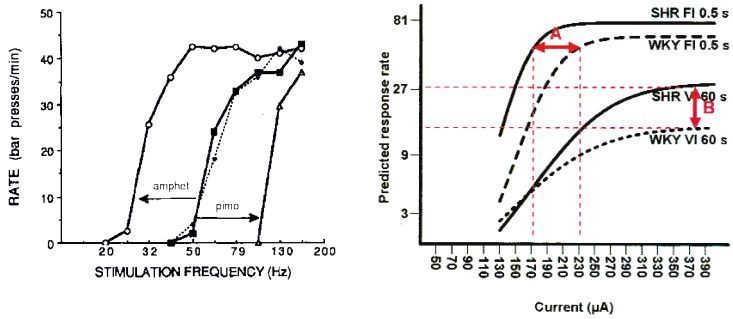


Figure 3. Shifts in relation between response rate and ICSS current frequency produced by dopamine agonists and antagonists (left, from Wise, 1996). Current-response curves in SHR and controls (right, adapted from Johansen et al., 2005) as functions of reinforcement frequency: a significant shift towards lower currents (A) was found in SHR during frequent reinforcement (fixed interval 0.5 s), while a significant shift towards higher response rates (B) was found in SHR during infrequent reinforcement (variable interval 60 s).

Varying reinforcement frequency and reinforcer delay

Our study (Johansen et al., 2005) included testing effects of varying reinforcement frequency on response rates in SHR and controls using variable interval schedules with different lengths (Figure 4). The relation between response rate and reinforcement frequency is described by the VI input-output relation, also referred to as the Matching law: $B = k * r / (r+c)$, where B represents response rate; k is a constant representing the asymptotic response rate during high reinforcer frequency; r represents the reinforcer frequency ($r = 1/t$, t = time); and c is a constant describing the rate of reinforcement maintaining half of the asymptotic k (Catania, 1973; Herrnstein, 1970).

Included was also a condition imposing a specified delay interval between the response and reinforcer delivery (Johansen et al., 2005). Theoretically, the relation between response rate and reinforcement delay is described by the hyperbolic decay function

V = A / (1 + k*delay), where V is the reinforcer value when the reinforcer is delivered after a delay, D; A is the reinforcer value when there is no delay; and k describes the rate of decay of the reinforcing effect (Mazur, 1995).

Our results show that the ICSS reinforcement contingencies rapidly change the behaviour and produce systematic responding even after only a few sessions on each condition. ICSS produced response rates that were highly consistent with the equations. Fitting the equations to response rates, explained variance in individual response rates were in excess of 90% showing high correspondence between theoretical models and behavioural observations during ICSS reinforcement (Figure 4).

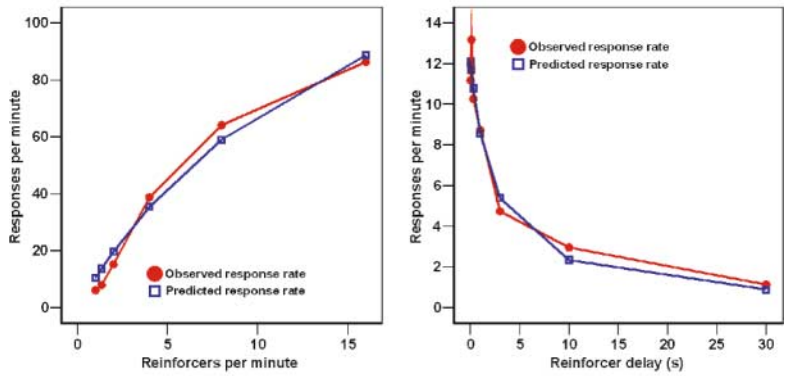


Figure 4. The figure illustrates the correspondence between theoretical models and behavioural observations during ICSS reinforcement in one individual rat. The VI input-output equation was fitted to the observed response rates across six rates of reinforcement and parameter estimates were used to plot predicted response rates (left). The hyperbolic decay function was fitted to observed response rates during reinforcement delay and predicted response rates are plotted based on parameter estimates (right).

In general, the findings from investigating reinforcement processes in SHR are consistent with results from previous studies using water reinforcers and support the suggestion that reinforcers work differently on responding in SHR compared to controls (Johansen, Sagvolden, & Kvande, 2005; Johansen et al., 2005). Further, due to the excellent experimental control and the possibility of experimental manipulations not easily performed with water or food reinforcers, the results suggest that ICSS reinforcement may be a valuable method for further investigating reinforcement processes in SHR. Future studies should investigate effects of dopamine agonists and antagonists on current-response rate curves, thereby examining the association between the suggested altered reinforcement processes in SHR and a possible dopamine dysfunction.

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