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This Week's Citation Classic

Crow T J. Catecholamine-containing neurones and electrical self-stimulation: 1. A review of some data. *Psychol. Med.* **2:**414-21, 1972. [Dept. Mental Health, Univ. Aberdeen, Aberdeen, Scotland]

Intracranial self-stimulation was obtained with electrodes located close to dopamine-containing cell bodies in the ventral midbrain and to the noradrenaline-containing cells of the locus coeruleus; earlier findings could be explained as activation of one or the other of these two systems. [The *Science Citation Index* (SCI®)* **and the** *Social Sciences Citation Index®* (SSCI®) **indicate that this paper has been cited over 115 times since 1972.]**

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"Intracranial self-stimulation described in 1954 by James Olds and P.M. Milner[1] with electrodes in septal and lateral hypothalamic regions demonstrated the existence of powerful central reward mechanisms but the neural identity of these was obscure. In 1962, Larry Stein suggested a noradrenergic system was involved.[2] I thought this was an exciting theory and in 1969 I visited the Karolinska Institute where K. Fuxe, U. Ungerstedt, and colleagues had recently completed the first comprehensive maps of central catecholamine neurones. Fibres of these systems in the medial forebrain bundle might well have been activated in previous self-stimulation experiments.

"I embarked on a study of self-stimulation sites in relation to cell body groups in the brainstem. In the midbrain such sites were close to dopamine cell bodies, a quite unexpected finding.[3] Systematic mapping revealed a second group of dorsally located sites just lateral to the central grey substance. This suggested two systems were involved: the second system might be the noradrenergic fibres ascending from the locus coeruleus in the mid-pons. With Cordon Arbuthnott and Jane Spear, I devised a technique for implanting electrodes in this region; with difficulty and after a number of attempts we were able to obtain the behaviour here also.[4]

"The *Psychological Medicine* paper reviewed these findings and argued that much of the previous literature (including the studies of Olds) could be explained by the two catecholamine system hypothesis. Curiously, subsequent studies have strongly supported what at the time seemed most controversial —that activation of dopamine neurones has rewarding effects. The involvement of the locus coeruleus system remains disputed although I think this is rather strongly suggested by evidence that with such electrodes the behaviour is associated with increased turnover of noradrenaline in the ipsilateral cerebral cortex.

"The paper may have been well cited because it put anatomical flesh on Stein's humoural hypothesis, though with a dopamine twist that he took time to assimilate. Also the theory has remained controversial, particularly with respect to the view that the functions of the two pathways can be related to the learning theory concepts of 'incentive' or 'drive induction' (the dopamine system) and 'reinforcement' or the 'results of action' signal (the locus coeruleus noradrenaline system), and may be phylogenetic derivatives of olfactory and gustatory pathways, respectively.[5,6] Most gratifying was the interest which Olds later took in this theory.[7] His tragic death in 1976 prevented him from pursuing it with the electrophysiological techniques of which he was master.

"I nearly forgot Olds's role in the original papers.[3,4] When I first met him three years after their publication he told me he had refereed them and recommended rejection; then he wrote to the editor to say he thought he had made a mistake. Catecholamine neurones might indeed play a critical role. The editor replied he had already decided to publish."

1. **Olds J & Milner P M.** Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Physiol. Psychol.* **47**:419-27, 1954.
2. **Stain L.** Effects and interactions of imipramine, chlorpromazinc, reserpine and amphetamine on self-stimulation: possible neurophysiological basis of depression. (Wortis J, ed.) *Recent advances in biological psychiatry.* New York: Plenum. 1962. p. 288-308.
3. **Crow T J, Spur P J & Arbuthnott G W.** Intracranial self-stimulation with electrodes in the region of the locus coeruleus. *Brain Res.* **36:**275-87, 1972.
4. **Crow T J**. A map of the rat mesencephalon for electrical self-stimulation. *Brain Res.* **36**:265-73, 1972.
5. ..... Catecholamine-containing neurones and electrical self-stimulation: 2. A theoretical interpretation and **some psychiatric implications.** *Psychol. Med.* **3**:66-73, 1973.
6. ..... A general catecholamine hypothesis. *Neurosci. Res. Program Bull.* **15:**195-205, 1977.
7. **Olds J.** Reward and drive neurones: 1975. (Wauquier A & Rolls E T, eds.) *Brain stimulation reward.* New York: Elsevier-North Holland, 1976. p. 1-27.