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Inhibition and impulsivity
Q1 Behavioral and neural basis of response control

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ABSTRACT

In many circumstances alternative courses of action and thoughts have to be inhibited to allow the emergence of goal-directed behavior. However, this has not been the accepted view in the past and only recently has inhibition earned its own place in the neurosciences as a fundamental cognitive function. In this review we first introduce the concept of inhibition from early psychological speculations based on philosophical theories of the human mind. The broad construct of inhibition is then reduced to its most readily observable component which necessarily is its behavioral manifestation. The study of 'response inhibition' has the advantage of dealing with a relatively simple and straightforward process, the overriding of a planned or already initiated action. Deficient inhibitory processes profoundly affect everyday life, causing impulsive conduct which is generally detrimental for the individual. Impulsivity has been consistently linked to several types of addiction, attention deficit/hyperactivity disorder, mania and other psychiatric conditions. Our discussion of the behavioral assessment of impulsivity will focus on objective laboratory tasks of response inhibition that have been implemented in parallel for humans and other species with relatively few qualitative differences. The translational potential of these measures has greatly improved our knowledge of the neurobiological basis of behavioral inhibition and impulsivity. We will then review the current models of behavioral inhibition along with their expression via underlying brain regions, including those involved in the activation of the brain's emergency 'brake' operation, those engaged in more controlled and sustained inhibitory processes and other ancillary executive functions.

Contents

Abbreviations: 5-CSRTT, 5-choice serial reaction time task; 5-HT, serotonin; ACC, anterior cingulate cortex; ADHD, attention deficit/hyperactivity disorder; BA, Brodmann area; DA, dopamine; DNAB, dorsal noradrenergic bundle; DRD2, dopamine receptor 2 gene; ERP, event-related potentials; FEF, frontal eye field; IFC, inferior frontal cortex; IFG, inferior frontal gyrus; IFJ, inferior frontal junction; LC, locus coeruleus; M1, motor area 1; MDMA, 3,4-methylenedioxy-N-methylamphetamine; MRI, magnetic resonance imaging; NE, norepinephrine; OCD, obsessive-compulsive disorder; OFC, orbitofrontal cortex; Pre-SMA, pre-supplementary motor area; PFC, prefrontal cortex; RT, reaction time; SMA, supplementary motor area; SSD, stop-signal delay; SSRI, selective serotonin reuptake inhibitor; SSRT, stop-signal reaction time; SST, stop-signal task; STN, subthalamic nucleus.

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1. Historical introduction

In the words of the father of American psychology William James (1842–1910) inhibition [Lat. *inhibere*, to restrain] is *"... not an occasional accident; it is an essential and unremitting element of our cerebral life"* (James, 1890; p. 583). Scientists and philosophers have long been interested in the nature of inhibitory processes at the psychological, neurophysiological and cognitive level. Plato's allegory of the human soul viewed as a charioteer driving a chariot pulled by two horses having opposite characters, well represents the inhibitory function of will. In order of being able to drive the chariot in the intended direction, the inclination of the two horses has to be tightly controlled. Similarly, in 1650 Descartes wrote that: *"if anger makes us rise our hand to strike, our will can usually hold it back; if fear incites us to run away, our will can stop us, and so on with the other passions"* (as cited in Diamond et al., 1963; p. 15). Inherent to this philosophical view of inhibition is the existence of a choice between conflicting courses of action, which has been extensively discussed in their influential book 'Inhibition and choice' by Diamond et al. (1963). The concept of inhibition was introduced in the scientific literature at the beginning of the 19th century to explain a large number of phenomena, from simple spinal reflexes to more abstract psychological processes, although it became commonly used in neuroscience only in the second half of the century (Smith, 1992). Before then inhibition was thought to derive from some form of excitation or by its cessation (Macmillan, 1992), and even when directly observed during controlled experiments, it was ignored, rejected as an error in the experimental procedure or as deriving from fatigue ('exhaustion') of the nerves (Meltzer, 1899).

1.1. Development of the concept of inhibition

> "When physiologists have solved the problem of inhibition, they will be in a position to consider that of volition". (Morgan, 1891; p. 461)

According to Smith (1992) the word 'inhibition' initially made its appearance in the scientific literature as the mechanism by which intellect controls passions and the will wins over impulses, in an intellectual context influenced by Plato and Aristotle's moral psychology. In the first half of the 19th century, making the first steps towards an empirical psychology with his controversial work, Franz Joseph Gall thought that *"The laws of nature, for instance, ordain that the faculties of an inferior order should obey those of a superior order..."* (Gall, 1835; Vol. I, pp. 230–231). Although Gall did not explicitly consider inhibitory interactions between the different 'faculties', his hierarchical view of mental processes resembles most modern conceptualization of inhibitory control. On the contrary, the German philosopher-psychologist Herbart (1776–1841) extensively used the term inhibition ('hemmung') in a non-hierarchical fashion to describe the force that prevents cognitive contents to aggregate indiscriminately by keeping dissimilar ideas momentarily out of consciousness (Dunkel, 1970; Macmillan, 1996). However, while he used the concept of 'associative inhibition' as an umbrella term for what we now call proactive and retroactive inhibition in the context of learning and memory, various theorists after him tried to explain the loss of consciousness during hypnosis as some sort of cerebral inhibition (Bramwell, 1903). In psychiatry, the concept of inhibition was soon adopted to describe the behavior that characterizes certain mental disorders. As reported by Macmillan, in 1843 the German psychiatrist Griesinger *"adopted a straightforward physiological explanation"* suggesting that "*Ideas passed into normal action whenever they were not hindered by this* [volitional] *control but in the two main classes of insanity – the depressive and the excited – there was either too much or not enough inhibition, respectively. In this conception, will and inhibition were virtually equated and symptoms were interpreted physiologically*" (Macmillan, 1996; p. 9). The common idea in the early theorizing about inhibition seems very much linked to the concepts of will and consciousness, such that only with high levels of self-awareness is possible to exert (or contrast) inhibitory control over one's behavior. Things were different in neurophysiological theories.

One of the first observations of the inhibitory action of nerve impulses was made by John and Charles Bell in the muscles of the eye. They did not use the term inhibition and wrote as a footnote: "*The nerves have been considered so generally as instruments for stimulating the muscles, without thought of their acting in the opposite capacity...*" (Bell and Bell, 1827; Vol. 2, p. 223). Similarly, drawing from his experiments on the frog's sciatic nerve stimulation, in 1838 Volkmann wrote: *"It becomes clear* [...] *that the brain contains the cause for the hindrance in the activation of the nervous principle...*" (as in Smith, 1992; p. 77). However, it is generally acknowledged that it was the early observations on the effects of vagal nerve stimulation on heart rate that posed the foundations for the first theories on the inhibitory action of nerve impulses (Gaskell, 1886; Weber and Weber, 1966). This phenomenon was first observed by Volkmann, who subsequently dismissed it as resulting from an invalid procedure (Volkmann, 1838a,b, 1842). Weber and Weber (1845) made the same observation, but were the first to define it 'inhibition', whereas the concept of 'inhibitory system' in physiology was first discussed by Lister in a communication to the Royal Society of London (Lister, 1858). Thus, while Smith (1992) emphasizes the description of peripheral inhibition by the Weber brothers in 1845, according to MacLeod et al. (2003), the observation made by Sechenov (1863) that stimulation of certain areas of the frog's brain inhibits spinal reflexes can be considered the point of origin of the concept of (central) inhibition in physiology. Finally, in 1874, the concept of inhibition was included by the father of experimental psychology Wilhelm Wundt (1904) in his seminal textbook: *"The two mutually supplementary forms of energy that we designated, from their mechanical effects, excitation and inhibition* [...] *appear throughout as the simple substrate of nervous function."* (Vol. 1, p. 324); *"The whole course of the* [nerve] *stimulation is then dependent upon the constantly varying play of excitation and inhibition."* (Vol. 1, p. 70).

Still widely cited, the classical definition of inhibition formulated by Brunton in 1883 is reported in the Oxford English

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