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Review article

Habituation is altered in neuropsychiatric disorders—A comprehensive review with recommendations for experimental design and analysis

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ABSTRACT

Abnormalities in the simplest form of learning, habituation, have been reported in a variety of neuropsychiatric disorders as etiologically diverse as Autism Spectrum Disorder, Fragile X syndrome, Schizophrenia, Parkinson's Disease, Huntington's Disease, Attention Deficit Hyperactivity Disorder, Tourette's Syndrome, and Migraine. Here we provide the first comprehensive review of what is known about alterations in this form of non-associative learning in each disorder. Across several disorders, abnormal habituation is predictive of symptom severity, highlighting the clinical significance of habituation and its importance to normal cognitive function. Abnormal habituation is discussed within the greater framework of learning theory and how it may relate to disease phenotype either as a cause, symptom, or therapy. Important considerations for the design and interpretation of habituation experiments are outlined with the hope that these will aid both clinicians and basic researchers investigating how this simple form of learning is altered in disease.

"Together, nonassociative learning and nonassociative gating constitute an intelligent 'firewall' that constantly triages vast amounts of sensory information into actionable and non-actionable categories in order to prioritize. This firewall mechanism shields the mind from the vast amounts of inundating sensory information that constantly compete with one another for attention, and spares it the trouble of having to respond to every tingling except the most salient ones. The triage process not only helps to preserve mental sanity but also conserve physical energy, both of which are important for survival."

Poon and Young (2006)

1. Introduction

Although abnormal habituation has been observed in numerous neurological and neuropsychiatric disorders a comprehensive review of how this form of non-associative learning is altered in each disorder is lacking. Habituation is a non-associative form of learning, defined as a response decrement resulting from repeated stimulation that cannot be explained by sensory adaptation or motor fatigue, and has conserved behavioural characteristics present in all organisms studied (Table 1, adapted from Rankin et al., 2009). In lay terms, habituation may be described as the ability to "ignore the familiar, predictable, and inconsequential," a process almost ubiquitously presumed to be crucial for normal cognitive function. For this reason, habituation is conceptualized as a "building block of cognition," essential to attention, saliency mapping, and more complex forms of learning and memory. This is supported by the observation that there is a correlation between the rate of habituation in infancy and later IQ scores (Kavšek, 2004; McCall and Carriger, 1993).

Despite its ubiquity and importance to normal cognitive function, remarkably little is known about the cellular and molecular processes underlying habituation (Giles and Rankin, 2009; Glanzman, 2009; Ramaswami, 2014; Schmid et al., 2014; Wilson and Linster, 2008). Indeed, several lines of evidence suggest that this elementary form of plasticity is mediated by multiple mechanisms which are recruited by

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Table 1
The ten behavioural characteristics of habituation (Rankin et al., 2009).

The Behavioural Characteristics of Habituation
1. Repeated application of a stimulus results in a progressive decrease in some parameter of a response to an asymptotic level. This change may include decreases in frequency and/or magnitude of the response. In many cases, the decrement is exponential, but it may also be linear; in addition, a response may show facilitation prior to decrementing because of (or presumably derived from) a simultaneous process of sensitization.
2. If the stimulus is withheld after response decrement, the response recovers at least partially over the observation time ("spontaneous recovery").
3. After multiple series of stimulus repetitions and spontaneous recoveries, the response decrement becomes successively more rapid and/or more pronounced ("potentiation of habituation").
4. Other things being equal, more frequent stimulation results in more rapid and/or more pronounced response decrement, and more rapid spontaneous recovery (if the decrement has reached asymptotic levels).
5. Within a stimulus modality, the less intense the stimulus, the more rapid and/or more pronounced the behavioural response decrement. Very intense stimuli may yield no significant observable response decrement.
6. The effects of repeated stimulation may continue to accumulate even after the response has reached an asymptotic level (which may or may not be zero, or no response). This effect of stimulation beyond asymptotic levels can alter subsequent behaviour (e.g., by delaying the onset of spontaneous recovery).
7. Within the same stimulus modality, the response decrement shows some stimulus specificity. To test for stimulus specificity/stimulus generalization, a second, novel stimulus is presented and a comparison is made between the changes in the responses to the habituated stimulus and the novel stimulus. In many paradigms (e.g., developmental studies of language acquisition) this test has been improperly termed a dishabituation test rather than a stimulus generalization test, its proper name.
8. Presentation of a different stimulus results in an increase of the decremented response to the original stimulus. This phenomenon is termed "dishabituation." It is important to note that the proper test for dishabituation is an increase in response to the original stimulus and not an increase in response to the dishabituating stimulus (see point #7 above). Indeed, the dishabituating stimulus by itself need not even trigger the response on its own.
9. Upon repeated application of the dishabituating stimulus, the amount of dishabituation produced decreases ("habituation of dishabituation").
10. Some stimulus repetition protocols may result in properties of the response decrement (e.g., more rapid rehabituation than baseline, smaller initial responses than baseline, smaller mean responses than baseline, less frequent responses than baseline) that last hours, days or weeks. This persistence of aspects of habituation is termed long-term habituation.

different stimuli and training paradigms (Giles and Rankin, 2009; Rankin and Broster, 1992). Although studies using animal models have revealed that both short- and long-term forms of habituation can be observed (Castellucci et al., 1978), this review will focus on short-term habituation reflecting the focus of the clinical literature to date. While short-term habituation develops within a single training session, long-term habituation persists across training sessions and requires spaced training and protein synthesis for its production and maintenance (Ramaswami, 2014; Rankin et al., 2009). Despite being the simplest form of learning there is very little known about the cellular mechanisms of underlying habituation. Studies using *Aplysia* and rats show that short-term habituation can result from homosynaptic depression of excitatory neurotransmission (Armitage and Siegelbaum, 1998; Castellucci et al., 1970; Castellucci and Kandel, 1974; Farel and Thompson, 1976; Kupfermann et al., 1970; Weber et al., 2002) and studies using *Drosophila* have shown that habituation can also manifest at the network-level by potentiation of inhibitory synapses (Das et al., 2011; Glanzman, 2011).

Consistent with the ubiquity, adaptive importance, and diversity of underlying mechanisms of habituation, habituation abnormalities have been implicated in numerous etiologically diverse neuropsychiatric disorders. The purpose of this review is to bring together accounts of habituation and neurological/neuropsychiatric disorders with the hope that this will lead to insights about both habituation, and the neuropsychiatric disorders in which habituation is altered. It is our hope that this review will serve as a resource for both clinicians and basic researchers investigating habituation and disease. Understanding the habituation deficits in one disorder may serve as a catalyst for studies of another disorder. An additional goal of this review is to provide experimental design and interpretation guidelines that will allow for more consistent observations across studies. An accurate understanding of how habituation is altered in a disorder will facilitate the use of habituation as a tool for differential diagnosis and will allow for more accurate animal models to investigate the cellular and molecular mechanisms underlying these learning impairments.

2. Neuropsychiatric disorder inclusion criteria

Not all neuropsychiatric disorders show abnormal habituation, however a surprising number do. To generate a list of the most prevalent neuropsychiatric conditions for which there is also a substantive literature investigating habituation we queried PubMed for each of the disorder categories listed in DSM-V (American Psychiatric Association, 2013) and the 12 disorders listed as the most common neurological disorders according to Hirtz et al. (2007). Only disorders with more than five empirical research articles comparing habituation in a clinical population to habituation in one or more control groups were included in this review. The disorders that met this criterion were: Autism Spectrum disorder, Fragile X syndrome, Schizophrenia, Parkinson's disease, Huntington's disease, Attention Deficit Hyperactivity Disorder, Tourette's syndrome, and Migraine. Despite the diverse etiology of these disorders the degree of habituation alteration correlates with symptom severity in most of the disorders suggesting that understanding the alterations in habituation might lead to new approaches to understanding, diagnosing, and treating these disorders. To our knowledge, the neuropsychiatric disorders reviewed here represent all disorders for which there are five or more studies examining habituation in human patient populations.

3. Study selection criteria

This work heavily focuses on studies investigating non-associative learning alterations by comparing differences in response plasticity to repeated stimulation in two or more groups. To delimit the scope this review and provide a cohesive narrative, we excluded studies of habituation to drugs in addiction research. For disorders with pre-existing reviews examining habituation alterations (e.g., ASD, Schizophrenia, Migraine), the reviews are briefly summarized and work published since the most recent review are covered in detail. For disorders without a pre-existing review focused on alterations in habituation all studies are reviewed.

We have included only articles whose authors explicitly stated they were investigating altered habituation in a neuropsychiatric disorder group compared to one or more control groups. However, it is important to note that any response change due to repeated non-associative stimulation is the sum of putatively independent underlying sensitization (incremental) and habituation (decremental) processes which are integrated to produce the final behavioural response (Groves and Thompson, 1970). Therefore, the observed changes in habituation discussed here could in principle reflect changes in sensitization.

4. Methods for studying habituation in humans

The training paradigms and methods used to study habituation in humans are as diverse as the diseases and disorders they have been used to study. In order to facilitate accessibility to a broader scientific audience we have provided a description of the common methods used to study habituation in adult humans: acoustic startle, event-related potentials, electrodermal activity, and functional magnetic resonance imaging (Table 2). The methods described in Table 2 are not exhaustive, but rather represent the most common methods that researchers build upon when designing more complex habituation