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Review

A comparison of neural responses to appetitive and aversive stimuli in humans and other mammals

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ABSTRACT

Distinguishing potentially harmful or beneficial stimuli is necessary for the self-preservation and well-being of all organisms. This assessment requires the ongoing valuation of environmental stimuli. Despite much work on the processing of aversive- and appetitive-related brain signals, it is not clear to what degree these two processes interact across the brain. To help clarify this issue, this report used a cross-species comparative approach in humans (i.e. meta-analysis of imaging data) and other mammals (i.e. targeted review of functional neuroanatomy in rodents and non-human primates). Human meta-analysis results suggest network components that appear selective for appetitive (e.g. ventromedial prefrontal cortex, ventral tegmental area) or aversive (e.g. cingulate/supplementary motor cortex, periaqueductal grey) processing, or that reflect overlapping (e.g. anterior insula, amygdala) or asymmetrical, i.e. apparently lateralized, activity (e.g. orbitofrontal cortex, ventral striatum). However, a closer look at the known value-related mechanisms from the animal literature suggests that all of these macroanatomical regions are involved in the processing of both appetitive and aversive stimuli. Differential spatiotemporal network dynamics may help explain similarities and differences in appetitive- and aversion-related activity.

Contents

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1. Introduction

The ongoing ability of an organism to appropriately evaluate its environment is essential to both its well-being and continued survival. The evaluation process requires the dynamic assessment of many positive and negative stimuli within the organism's external and internal environments. Appetitive and aversive stimuli are salient, valenced (i.e. positive and negative), stimuli which typically lead to the opposing behaviours of approach and avoidance, respectively. This type of value-related processing in humans and other mammals reflects the activity of aversion- and appetitive-related brain networks (Hayes and Northoff, 2011; McBride et al., 1999; O'Doherty, 2004). As both potentially rewarding and punishing stimuli are often present simultaneously, appetitive- and aversion-related circuits must interact in some way in order to share and compare information about the combined value of such stimuli which ultimately contribute to a behavioural outcome. Despite much work on each circuit separately, it is not clear to what degree they function independently and/or whether they share the bulk of their circuitry.

While 'rewards' are often used synonymously with 'appetitive stimuli', we have chosen to use the terms appetitive and aversive here as constructs reflecting the value of stimuli which lead to approach and avoidance (Madan, 2013). These constructs are therefore independent of reinforcement per se which reflect changes in the rate of responding to stimuli, although it is acknowledged that in practice these concepts are difficult to disentangle. As such, we have focused on studies which aim to investigate the brain's responses to appetitive and aversive stimuli, independent of hedonia, reinforcement or motivated learning per se. Although this valuative processing may be analogously tied to subjective hedonic states, this issue is not the focus of the current work and it is not assumed that these stimuli are necessarily considered either pleasant or unpleasant (Berridge and Robinson, 1998, 2003). Our focus here is on studies which use appetitive or aversive stimuli which are known to produce positive or negative psychological and physical states in the organism. These states map roughly to what has been previously termed as 'primal' or 'core' affect in both humans and animals (Barrett et al., 2007; Panksepp, 2011).

Although there are classical neuropsychological accounts of these processes interacting (Cabanac, 1971; Solomon and Corbit, 1974), most studies to date have focused on appetitive- or aversion-related processing in isolation. For instance, appetitive research has largely focused on the function of the mesocorticolimbic dopamine system. Dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens/ventral striatum (NAc/VS) and prefrontal cortex have been implicated in many processes such as in the learning, anticipation, and reception of rewards in both animals and, more recently, in humans (O'Doherty, 2004; Pappata et al., 2002; Wise, 2004). Alternately, aversion-related studies have focused largely on the brain circuitry associated with the processing of fearful conditioned and unconditioned stimuli. In particular, amygdalar circuitry is well understood from this perspective (LeDoux, 1998). However, continually-mounting evidence has shown that many of these classical aversion- or appetitive-related brain regions also process information related to the opposite valence. For instance, an increasing number of studies are revealing the precise mechanisms by which the mesocorticolimbic circuit and amygdala play fundamental roles in processing both aversion- and appetitive-related information (Baxter and Murray, 2002; McCutcheon et al., 2012). However, the idea that components of the mesocorticolimbic system are involved in processing aversive information has been greatly overshadowed by those focused on reward- or appetitive-related processes, as first noted by studies conducted over twenty years ago (e.g. Salamone, 1994). Nonetheless, the question of whether these processes use many similar brain circuits, and what kinds of mechanisms might be involved, is still under intense investigation.

The aim of this paper is to summarize and compare the available data characterizing the brain networks of aversion- and appetitive-related processing across humans and other mammals. We investigate the available human neuroimaging data as well as the primate and rodent data to help sketch the relationship between these two brain networks at the macroscopic and mesoscopic levels. We address the question of how selected components of these networks might allow for the interaction of aversion- and appetitive-related processing and whether these relationships appear consistent across species.

We began by performing a meta-analysis of human neuroimaging studies to identify regions which appear independent or shared in aversion- and appetitive-related processing in humans. We used the results from this analysis to guide a targeted review of animal data. Beyond a primary interest in human brain function, starting with the human data allowed for a focus on *passively* activated neural responses to valuative stimuli – as most animal studies involve active responses to such stimuli. Measures in animals typically lack subjective assessments of value and almost always involve behaviours which can complicate the interpretation of findings (e.g. which neural responses are related to value processing alone, and which to motor-related activity). Subcortical and cortical regions in humans were subsequently identified and selected for further exploration in animals: appetitive-selective (ventral tegmental area, VTA; medial prefrontal cortex, mPFC), aversion-selective (periaqueductal grey, PAG; motor-related cluster containing the posterior midcingulate, pMCC; premotor, and posterior cingulate cortices, PCC), overlapping regions (amygdala; anterior insula, AI), and regions showing asymmetrical (i.e. apparently lateralized) activity (nucleus accumbens/ventral striatum, NAc/VS; lateral orbitofrontal cortex, lOFC). We then looked at animal studies which included both appetitive and aversive stimuli to investigate the mechanisms of valuative processing within the selected regions. When considered together, we believe these findings help better contextualize results in these fields.