Neuroscience and Biobehavioral Reviews 45 (2014) 350–368

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

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

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ARTICLE INFO

Article history:
Received 12 February 2014
Received in revised form 29 April 2014
Accepted 27 June 2014
Available online 7 July 2014

Keywords:
Neuroimaging
fMRI
Meta-analysis
Emotion
Reward
Motivation
Reinforcement
Valence
Electrophysiology
Human
Rat
Mouse
Monkey
Aversion
Affective neuroscience
Punishment

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.

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http://dx.doi.org/10.1016/j.neubiorev.2014.06.018
0149-7634/

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.

2. Methods and results

2.1. Meta-analysis of aversion- and reward-related brain activity in humans

2.1.1. Methods (humans)

The meta-analysis dataset in humans was made up of 34 aversion- and 38 appetitive-related functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies (including 44 and 52 contrasts, respectively). The aversion-related meta-analysis data were published previously (Hayes and Northoff, 2011) in which the inclusion/exclusion criteria are described in detail. Included articles were published from 2000 to August 2011, and the selection criteria were consistent for all studies. Studies were initially identified using PubMed (www.pubmed.gov) and Web of Science (http://apps.webofknowledge.com) using keywords such as "fMRI", "functional magnetic resonance", "PET", "positron emission tomography", "reinforcement", "aversion", "aversive", "avoidance", "punishment", "fear", "threat", "negative/positive emotion", "pleasant/unpleasant", "reward", "rewarding", "appetitive". We also searched the reference lists of identified papers, related reviews and looked for additional work by similar authors.

As our goal was to investigate brain activations corresponding to the most basic valuative processing, we included only those studies and contrasts which used the mere passive exposure to aversive/appetitive stimuli in healthy adults, and did not require any active responses (i.e. the contrasts focused on task-independent periods). Studies involving social aspects of valuative processing (e.g. social exclusion, empathy) were excluded to minimize potentially confounding issues. Similarly, those using higher-level conditioning designs (which include multiple learning periods) were also excluded, although we acknowledge that conditioning to the context also occurs during the passive presentation of stimuli and is an unavoidable potential confound. Studies involving painful stimuli were also excluded to avoid questions regarding the unique subjective experience associated with these stimuli (Hayes and Northoff, 2011), although painful and non-painful aversive stimuli are likely processed via similar networks (Hayes and Northoff, 2012). Studies involving subjects with a history of psychiatric illnesses, drug use, volumetric abnormalities or brain injuries, and subjects that would likely produce a sample bias (e.g. war veterans) were also excluded. Although we aimed to include all pertinent studies, it must be noted that because of the broad range of terms used throughout the affective neuroscience literature, some may have been missed.

Only studies reporting coordinates from whole-brain analysis were included; region-of-interest coordinates were not used. Talairach or Montreal Neurological Institute (MNI) coordinates were extracted and compiled from all of the selected articles. Many studies were excluded due to the absence of coordinates, identification of coordinate systems, and/or incomplete statistical information. The meta-analysis was performed in Matlab (Mathworks, Natick, MA, USA) using multilevel kernel density analysis (MKDA). Briefly, MKDA is a coordinate-based meta-analytic method which determines the activation probability of each voxel and contiguous voxel clusters across the brain. Each study is the unit of analysis (as opposed to individual coordinates) which prevents studies with lower statistical thresholds and more reported coordinates from biasing the results. Importantly, there is no clear way to weight studies by the strength or salience of stimuli. As such, some results may reflect a dysbalance between the processing of, for instance, highly salient aversive and moderately appetitive stimuli. Coordinate peaks are also convolved with a spherical kernel, 10 mm radius, to further ensure that a larger number of reported activations within a small region do not drive the final results. Significance thresholding was determined using a Monte Carlo simulation with 3000 iterations. Final results are reported in a binary map of activated or non-activated 8 mm^3 voxels within clusters greater than 10 voxels ($\geq$80 mm^3; contiguous voxels significant at $p \leq 0.001$, multiple-comparisons family-wise error rate whole-brain corrected at $p < 0.05$). Identified regions were labelled macroanatomically by the probabilistic Harvard-Oxford atlas using FSL (FMRIB's Software Library, http://www.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004). In-depth details of this technique are reported elsewhere (Wager et al., 2009).

2.1.2. Results (humans)

Findings related to value-selective processing across human neuroimaging studies are summarized in Fig. 1 and Table 1.

Aversion-selective regions (noted in blue) of functional significance include: Posterior midcingulate (pMCC), premotor, and posterior cingulate cortices (PCC), parahippocampal area (Parahipp), and inferior and middle temporal gyri (ITG, MTG).

Appetitive-selective regions (noted in red) include: Sensorimotor, ventrolateral and ventromedial prefrontal cortices (VLPFC, VMPFC), the left dorsolateral prefrontal cortex (L DLPFC), superior temporal gyrus (STG), and anterior cingulate and anterior midcingulate cortices (ACC, aMCC).

Regions of overlapping functional activity (noted in green) include: Thalamus (Thal), amygdala (Amyg) and hippocampal area (Hippo), anterior insula (AI), midcingulate cortex (MCC), left ventral striatum/nucleus accumbens (L VS/NAc), and subregions of the dorsomedial and ventromedial prefrontal cortex (DMPFC, VMPFC) and the orbitofrontal cortex (OFC).

Prominent asymmetrical activations (indicated by white-lettered labels) are noted for: VS/NAc (R reward; L overlap), caudate (R aversion; L reward), DMPFC (R aversion; L reward), inferior frontal gyrus (IFG: R overlap/aversion; L overlap/aversion/reward), lOFC (R overlap/aversion/reward; L overlap/reward), Middle insula (R aversion/reward; L reward), MCC (R aversion/overlap; L reward/overlap), DLPFC (L reward; R no activity).

In general, aversion-selective activations are more caudal and dorsomedial, whereas appetitive-selective activations are more rostral and ventromedial and have more lateral extensions. References for the meta-analysis can be found in Supplementary material.

2.2. Review of aversion- and appetitive-related mechanisms based on animal data

2.2.1. Methods (animals)

The selective review of animal data was guided by the human meta-analysis findings in the following way. Cortical and subcortical regions clearly reflecting aversion- or appetitive-selective activations, overlapping activity or asymmetrical activity in the meta-analysis were chosen for further investigation. A search was performed in PubMed and Web of Science for rodent and non-human primate animal literature for each region using phrases such as the following: ("medial prefrontal" or infralimbic or mPFC or VMPFC or "ventromedial prefrontal") (reward or rewarding or pleasant or appetitive) (aversion or aversive or unpleasant or fear or threat) (rat or mice or mouse or monkey) NOT human. Additional studies were identified similar to that in the human literature. As we aimed to understand the interplay between basic aversive and appetitive stimulus-related processing, studies directly comparing the underlying mechanisms associated with valuative brain function were considered first. If no, or too few, studies using both stimulus types were available, those investigating the processing of each stimulus type were included for further consideration.

We included only those studies which investigated changes in brain activity related to the passive presentation of stimuli (e.g.

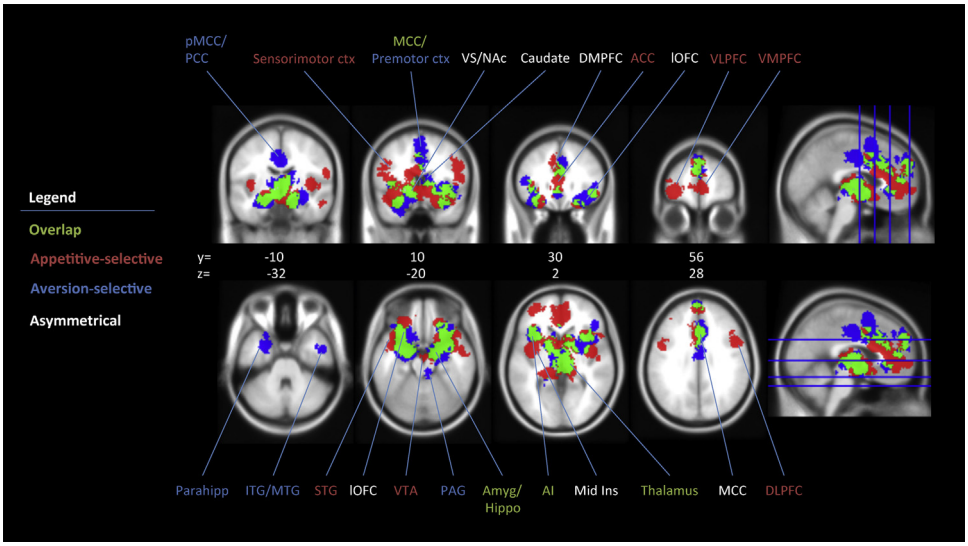

Fig. 1. Brain regions associated with aversion- (blue) and appetitive- (red) related activity, as well as common overlapping regions (green), from the human meta-analysis. White text labels indicate regions implicated in asymmetrical activity (i.e. the pattern of activity appears different for each side of the brain). Only clusters >10 voxels have been included here. See supplementary material for further description of appetitive-related clusters and Hayes and Northoff (2011) for aversion-related clusters alone; also for a complete list of studies used in the meta-analysis. *Abbreviations*: ACC, anterior cingulate cortex; AI, anterior insula; Amyg, amygdala; ctx, cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; Hippo, hippocampal area; ITG/MTG, inferior/middle temporal gyrus; lOFC, lateral orbitofrontal cortex; Mid Ins, middle insula; MCC, midcingulate cortex; NAc, nucleus accumbens septi; PAG, periaqueductal grey; Parahipp, parahippocampal area; PCC, posterior cingulate cortex; pMCC, posterior midcingulate cortex; STG, superior temporal gyrus; VLPFC, ventrolateral prefrontal cortex; VMPFC, ventromedial prefrontal cortex; VS, ventral striatum; VTA, ventral tegmental area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

sweet/bitter tasting liquids, predatory/appetitive odour), and not directly related to any behavioural task which might be involved. Studies involving adolescent animals, chronic exposure to stimuli, and exposure to drugs of abuse were largely excluded (although non-drug-exposed controls were considered where appropriate). This was done in order to avoid confounding issues related to neurodevelopment and drug interactions and/or drug-induced changes in brain structure or function unrelated to the acute treatment. Aside from identifying the unique value-related mechanisms for each selected region, we looked specifically for evidence of cells which responded selectively for appetitive or aversive stimuli, their distribution within the region, and the main neurotransmitters which might be involved.

It is always important to consider the question of homology/similarity when comparing results from humans, non-human primates and rodents. While comparisons of subcortical structures typically raise less concern (Panksepp, 1998), cortical areas usually show many region- and species-specific differences. As such, the generalizability of the animal findings to humans should be considered with caution. Nonetheless, there are many strong structural and functional similarities across primates and rodents and in this work we relied mainly on criteria established by many authors (Dalley et al., 2004; Kobayashi, 2011; Ongur and Price, 2000; Sul et al., 2011; Uylings et al., 2003; Vogt and Paxinos, 2012). Moreover, key studies in monkeys further support the main findings in rodents and humans. Further discussion of homology for each respective cortical structure is included in Section 2.2.2.

Taken together, the final selected regions were based on the clarity of results from the meta-analysis, on the quality of studies (e.g. those using well-defined procedures for directly comparing aversion- and appetitive-related circuit function), and on the abundance of animal studies available. As the spatial limitations of human PET/fMRI studies and the typical 'smoothing' of activation maps can result in apparent, but perhaps not actual, overlaps in activity, we chose comparative regions which showed clear and substantive overlap and which were also strongly implicated in the animal literature. One cortical and subcortical region for each condition (aversion- and appetitive-selective, overlapping,

Table 1
Results of multilevel kernel density analysis (MKDA).

	Cluster	MNI			Voxels	Volume (mm^3)
		X	*Y*	*Z*		
Overlap	1	2	3	−8	8370	66,960
	2	1	20	30	636	5088
	3	−3	32	−5	83	664
	4	47	18	8	15	120
Aversion-selective	1	3	7	4	13,021	104,168
	2	−22	−49	−5	155	1240
	3	−16	−40	−6	13	104
Appetitive-selective	1	1	12	1	16,078	128,624
	2	−3	3	41	128	1024

See Fig. 1 for associated activations. Only clusters >10 voxels have been included here. Coordinates are in Montreal Neurological Institute (MNI) space. See supplementary material for further description of appetitive-related clusters and Hayes and Northoff (2011) for aversion-related clusters alone; also for a complete list of studies used in the meta-analysis. Note that given the methodological and conceptual issues discussed here, the number of activated voxels for each condition is approximate and should be considered with caution.

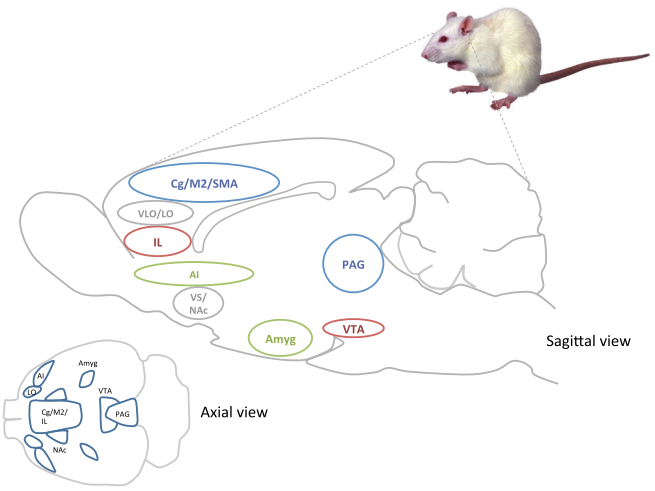

Fig. 2. Illustrated regions in animals selected for reviewed further. Homologous cortical and subcortical regions (human–animal) corresponding to human neuroimaging meta-analysis results from Fig. 1 include: aversion- (Cg/SMA/M2-pMCC/PCC/premotor/SMA; PAG-PAG), appetitive- (VMPFC-IL; VTA-VTA), overlapping- (AI-AI/gustatory cortex; Amyg-Amyg), and asymmetrical- (lOFC-VLO/LO; NAc/VS-NAc/VS) related. *Abbreviations*: AI, anterior insula; Amyg, amygdala; Cg, rodent cingulate cortex; ctx, cortex; IL, infralimbic cortex; lOFC, lateral orbitofrontal cortex; NAc, nucleus accumbens septi; PAG, periaqueductal grey; PCC, posterior cingulate cortex; pMCC, posterior midcingulate cortex; SMA/M2, secondary motor area; VS, ventral striatum; VMPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area; VLO/LO, ventrolateral/lateral orbital cortex.

asymmetrical) was selected for a total of eight reviewed brain regions.

2.2.2. Results (animals)

All selected animal regions are illustrated in the context of a rodent brain in Fig. 2. The results outlining the putative mechanisms associated with value-selective processing within these regions are summarized in Table 2 and discussed below.

Aversion-selective activity: From the aversion-selective regions noted in the human meta-analysis, the periaqueductal grey (PAG) and a large cluster including the human posterior cingulate (PCC), a posterior portion of the midcingulate and premotor/supplementary motor area (SMA) cortex were chosen for further investigation in animals. The larger area was considered because of the contiguous activitation noted in the meta-analysis, the fact no clear value-related processing studies were available in animals, and because they share overlapping and highly connected motor functions (Wu et al., 2000). As such, studies investigating either aversive or appetitive stimulus processing independently were considered. Clear homologies to non-human primate and rodent cortical regions are less well known and terminology is not consistent across or within species. Nonetheless, there is structural and functional evidence for similarities to the rat anterior cingulate (Cg) and secondary/supplementary motor cortex (SMA/M2) as well as within monkey PCC, premotor, SMA and frontal eye field regions (Sul et al., 2011; Uylings et al., 2003; Vertes, 2006).

In general, these studies indicate more cellular activity in response to aversion-related stimuli in both the cortical regions and PAG, though there is some evidence for appetitive-related activity (see Table 2). However, as no studies used aversive and appetitive stimuli together, the relative proportion or exact nature of activity is currently unclear. While limited evidence suggests that both GABA and glutamate within the Cg/M2 regions are involved in mediating aversion-related processing, particularly related to pain and fear (Albrechet-Souza et al., 2009, 2012; Wang et al., 2005, 2008), non-GABAergic cells within these regions also respond during reward anticipation linked to action selection and effort (Berdyyeva and Olson, 2011; Hillman and Bilkey, 2012; Sul et al., 2011).

Although the PAG is a collection of many inter-related subnuclei, most studies so far have underscored its overarching role in mediating defensive behaviour and its descending modulation of spinal pain pathways (Reichling et al., 1988; Vianna and Brandao, 2003). Nonetheless, a couple of studies have implicated the PAG in appetitive-related motivation, as dorsal PAG inactivation reduces defensive, and increases maternal, behaviours (Sukikara et al., 2010) while ventrolateral PAG inactivation reduces hunting motivation (Mota-Ortiz et al., 2012). Nonetheless, the increase in such behaviours could be interpreted as decreases in aversive behaviours; this is supported by the fact that large PAG lesions do not affect electrical brain self-stimulation in rats (Waraczynski et al., 1998).

When considered together, studies have suggested that the valuative processing in these motor-related cortical regions may reflect value-action integration as opposed to basic valuative processing alone (Hillman and Bilkey, 2012; Walton et al., 2007). The evidence for the PAG suggests that it is a region that mainly regulates aversion-related autonomic-motor integrative information. Nonetheless, it is presently unclear whether cells in any of these regions respond selectively for aversive or appetitive stimuli.

Appetitive-selective activity: From the regions noted in the human meta-analysis, the ventromedial prefrontal cortex (VMPFC) and ventral tegmental area (VTA) were chosen for further investigation in animals. In rodents, the infralimbic (IL) cortex is similar in structure and function to the primate VMPFC, even though it is less complex and has lower inter- and intra-connectivity (Uylings et al., 2003; Vertes, 2006). While the VTA is highly homologous across mammals, its small volume makes it challenging to accurately localize in neuroimaging data and so our use of the term VTA should be considered with caution (as it likely also covers additional regions such as the substantia nigra). Nonetheless, our anatomical identification of so-called VTA activity in the meta-analysis is consistent with other human fMRI studies (D'Ardenne et al., 2008; Klein-Flugge et al., 2011) and with its highly validated role in appetitive processing.

In general, electrophysiological studies in monkeys show that few VMPFC cells respond to affective stimuli (~15–20%), while those that do typically respond to aversion- or appetitive-related stimuli somewhat selectively. There are at least three equally represented types of cell (appetitive-, aversion-, or non-value-selective – by which we mean they respond similarly to appetitive and aversive stimuli) and they appear to be evenly distributed throughout the region (Amemori and Graybiel, 2012; Monosov and Hikosaka, 2012). These results are consistent with early rodent studies showing that electrical stimulation of the rat IL resulted in both appetitive and escape behaviours (Miserendino and Coons, 1989). While studies looking at neurotransmitter involvement for both appetitive and aversive processing are limited, rodent psychopharmacological studies have demonstrated that aversion-related activity may involve GABAergic inhibition of the IL which may depend on the stimulation of both glutamatergic (mGluR1/5) and GABAergic ($GABA_A$) receptors (Ji and Neugebauer, 2011). In addition, norepinephrine release in the IL may also be necessary for the processing and learning of salient stimuli (Mueller et al., 2008; Reyes-Lopez et al., 2010; Ventura et al., 2008).

Recent landmark studies in monkeys and rodents have contributed greatly to characterizing value-related processing in the VTA. Of particular note, Cohen et al. (2012) used electrophysiological and optogenetic techniques to demonstrate that most VTA cells respond to value. They identified at least three cell types. Type I dopaminergic cells increase activity to appetitive stimuli (reward-predicting odours), while type II GABAergic and unidentified type III cells increase activity to aversive stimuli (air puff) and

Table 2
Summary of major regional mechanisms identified for aversion- and appetitive-related processing in animals.

	Human/primate regions	Rodent regions	Main cell types involved	Aversion-, appetitive-, non-value-(salience) selective			Cell distribution	Notable mechanisms	Selected references
Aversion-selective	Posterior MCC/PCC/premotor/SMA	Cg/SMA/M2[a]	Glu/GABA	?	?	?	There are currently no studies investigating basic responding to valuative stimuli – observations are based on studies looking at either appetitive or aversive stimuli. Many cells respond to aversive (~50–90%) stimuli across these regions. Less information is available for appetitive stimuli, but it appears that far fewer cells respond to such stimuli.	Aversion – Cg activity appears required for context-related aversive responding. Cg GABAergic inhibition appears involved in reducing the affective dimension of pain, which is blocked by NMDA/AMPA receptor antagonism. Corticosterone-reduced fear is associated with increased $GABA_A$ receptors in Cg and M2.	Albrechet-Souza et al. (2012) and Wang et al. (2005)
								Appetitive – Cg/SMA/M2 cells (presumably Glu) respond to the anticipation of appetitive stimuli and seem linked to valuation-action selection and effort prediction involved in goal-directed activity.	Berdyyeva and Olson (2011), Hillman and Bilkey (2012) and Sul et al. (2011)
	PAG	PAG	GABA/opioids/Glu/DA/NE	?	?	?	There are currently no studies investigating basic responding to valuative stimuli – observations are based on studies looking at complex motivated behaviours (e.g. defense/foraging) or appetitive or aversive processing alone.	Most studies focus on the role of the PAG in aversive (particularly defensive and pain-related) processing; there is limited evidence for its role in appetitive-related behaviour.	Reichling et al. (1988) and Vianna and Brandao (2003)
								Two examples of how the PAG may be involved in both appetitive and aversive processing include: (1) The dorsal PAG may help mediate defensive behaviours, as lactating rats continued maternal behaviours in the presence of a threat when this region was lesioned. (2) The ventrolateral PAG may be important in regulating both anti-nociceptive and hunting/foraging-related motivation responses.	Mota-Ortiz et al. (2012) and Sukikara et al. (2010)
								However, large PAG lesions did not affect brain self-stimulation reward.	Waraczynski et al. (1998)
Appetitive-selective	VMPFC	IL	Glu/GABA	Yes	Yes	Yes	Few cells respond to valuative stimuli (~15–20%); those that do are evenly distributed throughout the vmPFC with perhaps one area of slightly higher concentration of aversion-selective cells noted in monkey cingulate ventral bank (similar to human BA25/subgenual ACC)	Aversion-related activity may involve GABAergic inhibition of mPFC cells, which appears to depend on the stimulation of both glutamatergic (mGluR1/5) and GABAergic ($GABA_A$) receptors.	Amemori and Graybiel (2012), Hayes et al. (2013), Ji and Neugebauer (2011) and Monosov and Hikosaka (2012)
								Aversive stimuli alter dopaminergic synapses and increase AMPA/NMDA receptor ratios in VTA projecting to mPFC. Norepinephrine release in IL cortex may signal general salience, and may help strengthen highly emotional memories.	Lammel et al. (2011) Mueller et al. (2008) and Ventura et al. (2008)

Table 2 (*Continued*)

	Human/primate regions	Rodent regions	Main cell types involved	Aversion-, appetitive-, non-value-(salience) selective			Cell distribution	Notable mechanisms	Selected references
	VTA	VTA	DA/GABA	Yes	Yes	Yes	Most cells respond to valuative stimuli. According to Cohen et al. (2012) there are at least 3 cell types: Type I (~50%; dopaminergic) respond to reward cues and reception, Type II (~31%; GABAergic) and Type III (~18%) were mostly excited by aversive stimuli but showed positive and negative modulation, respectively, of continuous firing following reward cues; without responding to reward receipt.	Aversive stimuli alter dopaminergic synapses and increase AMPA/NMDA receptor ratios in VTA projecting to mPFC; appetitive stimuli similarly alter synapses in VTA projecting to NAc medial shell; both stimulus types similarly alter synapses in VTA projecting to NAc lateral shell (perhaps involved in salience processing).	Cohen et al. (2012) and Lammel et al. (2011)
								VTA inputs from laterodorsal tegmentum synapse preferentially on appetitive-related dopamine cells projecting to the NAc lateral shell; VTA inputs from lateral habenula synapse on aversion-related GABAergic cells and dopamine projections to the mPFC.	Lammel et al. (2012)
								Most VTA dopamine cells respond excitedly to appetitive-related cues. Most also respond to aversion-related cues in some way, either by decreasing or increasing their firing rates (though see Section 3.1 for additional discussion).	Brischoux et al. (2009), Matsumoto and Hikosaka (2009), Mileykovskiy and Morales (2011) and Wang and Tsien (2011)
								Intra-VTA neuronal networks (thought to be GABAergic) show correlational appetitive-related activity to theta band power, while aversive stimuli show decreased correlation. Network activity is flexibly related to value information (i.e. if appetitive cue is re-conditioned to become aversive, it will then trigger aversion-related functional activity).	Kim et al. (2010, 2012)
								Also, VTA GABAergic projections inhibit NAc cholinergic interneurons which might be important in salience processing.	Brown et al. (2012)
Overlap	AI	AI[c]	Glu/GABA	Yes/?	Yes/?	Yes/?	Few studies have investigated basic responding to valuative stimuli; they have focused on processing in the gustatory cortex (which includes portions of the anterior as well as the middle insula). As such, little is known about basic valuative processing in this region.	The rodent AI is known to be broadly involved in appetitive- and aversion-related gustatory and pain-related processing.	Carleton et al. (2010) and Wang et al. (2011)
								There appears to be a rostral (appetitive-related)/caudal (aversion-related) organization in the rat gustatory cortex, although much overlap is also noted. Most cells (type I; $n = 29$) were either excited or inhibited by palatable or unpalatable tastants, while a smaller fraction of cells (type II; $n = 6$) showed bidirectional responding (i.e. those that were excited by appetitive, were inhibited by aversive, tastants; type II cells).	Accolla et al. (2007) and Yamamoto et al. (1989)

	Amyg	Amyg	Glu/GABA	Yes	Yes	Yes	About ~50% of cells encode value. No clear distribution for roughly equal proportions of appetitive-, aversion-, and non-selective cells throughout lateral and central amygdala. Their activity appears to be highly flexible (i.e. is tied to the value of the stimulus and not other characteristics of the stimulus).	Along with preferential aversion/appetitive cell-selectivity, tonic changes in general cell firing rates may help to encode appetitive (decreased firing) and aversive (increased firing) stimuli. Moreover, the context-dependent nature of some cells is better revealed when a 'safety' signal is included in the design.	Belova et al. (2008), Parsana et al. (2012), Paton et al. (2006), Sangha et al. (2013) and Shabel and Janak (2009)
								Few studies have investigated amygdala neurochemistry in studies combining appetitive and aversive stimuli. Current data suggest that intra-central, but not basolateral, amygdala AMPA receptor stimulation may be involved in arousal and affective cue learning.	Haney et al. (2010) and Stalnaker and Berridge (2003)
								Some studies have found regionally-selective activations within the amygdala. For instance, c-Fos labelling suggested that medial CeA may be more involved in appetitive processing (for food-deprived rats in response to a cue signalling food, or water-deprived mice in a place preference task) while the BLA and lateral CeA may reflect salience processing. However, another group suggested that BLA activity is higher during aversive conditioning in mice.	Cybulska-Klosowicz et al. (2009) and Knapska et al. (2006)
								Few studies have focused on the role of amygdalar neurotransmitters in designs combining aversion- and appetitive-related stimuli. There is evidence that AMPA receptor activation in the CeA, but perhaps not the BLA, is important for salience learning and arousal. Opioid receptors in this region may also be important for creating differential responses, as intra-CeA opioid receptor stimulation is known to affect aversion- and appetitive-related behaviours and separate cell populations were found to be regulated by mu- and kappa-opioid receptors. While BLA opioid and cannabinoid receptors also appear involved in mediating value-related signalling, they may both work by affecting GABAergic transmission to alter conditioned reinforcement and motivation.	Haney et al. (2010), Holahan (2005), Knoll et al. (2011), Mahler and Berridge (2009), Ramot and Akirav (2012), Simmons et al. (2007), Stalnaker and Berridge (2003), Zarrindast et al. (2004) and Zhu and Pan (2004)
Asymmetrical	Lateral orbitofrontal cortex (lOFC)	Ventrolateral orbital (VLO)/lateral orbital (LO)[b]	Glu/GABA	Yes	Yes	Yes	~50% of cells reflect value-based activity (unconditioned and conditioned). Cells respond preferentially to appetitive or aversive stimuli (though all appear to respond to both value types) and are equally represented and distributed.	Appetitive-selective OFC cells respond more quickly to cues with new values (i.e. during reversal training), while aversion-selective cells in the Amyg respond more quickly to new cue values. Once values are well-established, however, the OFC cells respond faster.	Morrison et al. (2011) and Morrison and Salzman (2009)
								Interestingly, lesion studies suggest that while the gustatory cortex appears important for learning gustatory cue-drug reward associations, it may not be necessary for cue-aversion associations, again suggesting some separation of roles for these networks.	Geddes et al. (2008)
								While about 6% (of 12, 659 cells across 11 monkeys) of cells are taste-responsive, they do not show a clear topographical organization in monkey insula. Although overlapping responsivity was common, taste-responsive cells preferred glucose (38%), NaCl (34%), quinine (22%), or HCl (5%). Multimodal activation was also noted.	Scott and Plata-Salaman (1999)

Table 2 (*Continued*)

	Human/primate regions	Rodent regions	Main cell types involved	Aversion-, appetitive-, non-value-(salience) selective			Cell distribution	Notable mechanisms	Selected references
								Many OFC cells are timed to gamma or theta oscillations during valued-cue presentations; a subset of cells show phase-locked behaviour which is linked to action-value selection. Learning a cue-response association is correlated to phase encoding in the theta band of a subpopulation of cells.	Gutierrez et al. (2010) and van Wingerden et al. (2010)
	NAc/VS	NAc/VS	GABA	Yes	Yes	Yes	Many cells appear to selectively encode appetitive- or aversion-related information during both presentation and in response to cues (though ~50% do not, and may be more involved in value-motor and/or effort-related processing). These responses appear, at least partly, related to value and not to characteristics of the stimulus itself. Animal neuropharmacology studies and human imaging studies support an asymmetry in NAc processing of affective stimuli.	Appetitive-selective cells (putatively GABAergic) generally decrease their firing rates, whereas aversion-selective cells increase their firing. However, how dopaminergic release into this region relates to responses to appetitive or aversive stimuli is an active area of investigation (see Section 3.1 for further discussion). Nonetheless, these results are in line with those noted above indicating separate mesocorticolimbic circuits for appetitive and aversive processing.	Day et al. (2011), Roitman et al. (2010) and Setlow et al. (2003)
								Glutamatergic signals in the NAc shell appear involved in the differential processing of appetitive/aversive stimuli. mGlu2/3 receptor antagonism decreases appetitive and increases aversive behaviours. AMPA receptor blockade in rostral NAc shell increases appetitive behaviour (D1 receptor-dependent), blockade in caudal shell increases aversive behaviour (D1/2 receptor-dependent).	Richard and Berridge (2011a, b)
								$GABA_A$ receptors also appear involved, as stimulation increases appetitive responding in the rostral shell and increases aversive responding in the middle and caudal shell. Blockade in the middle shell also increases appetitive-related behaviours.	Hayes et al. (2011) and Reynolds and Berridge (2001, 2002)
								Evidence of asymmetrical function: Right NAc has a higher concentration of resting state DA levels, shows a preference for appetitive-related DA release and D2R levels are higher (~10%). Dopaminergic agonists injected into the right, over left, NAc results in more locomotor activity.	Belcheva et al. (1990), Budilin et al. (2008) and Schneider et al. (1982)
								Novel aversive and appetitive stimuli result in similar NAc DA release. Familiar appetitive and aversive stimuli increase DA release more in right and left NAc shell, respectively.	Besson and Louilot (1995)
								A human PET study showed that D2/3 receptor antagonism decreases activity for appetitive stimuli in right ventral striatum.	McCabe et al. (2009)

Anatomical abbreviations are the same as noted in Fig. 2. Additional abbreviations include: BLA, basolateral amygdala; CeA, central nucleus of the amygdala; DA, dopamine; GABA, gamma-aminobutyric acid; Glu, glutamate; NE, norepinephrine; OFC, orbitofrontal cortex.

[a] No similar PCC region.

[b] Some similarities to IL cortex as well.

[c] Unclear to what degree the rodent insula is similar.

are modulated by reward cues (Cohen et al., 2012). Lammel and colleagues used retrograde labelling techniques in mice to identify at least three circuits associated with value-related processing. They showed that a rewarding stimulus (cocaine) selectively modified synapses on dopaminergic projections to the NAc shell, an aversive stimulus (formalin hindpaw injection) modified dopaminergic synapses projecting to the mPFC/IL, and both stimuli modified dopaminergic synapses projecting to the NAc lateral shell (Lammel et al., 2011). Moreover, VTA inputs from laterodorsal tegmentum synapse preferentially on appetitive dopaminergic projections to the NAc lateral shell, supported by the finding that conditioned place preference following laterodorsal tegmentum activation could be blocked by intra-NAc lateral shell D1 and D2 receptor antagonism. Alternately, inhibitory lateral habenula inputs to VTA synapse primarily on dopaminergic projections to mPFC/IL and GABAergic cells in rostromedial tegmental nucleus and are associated with aversive processing, noted by conditioned place aversion following lateral habenula stimulation which could be blocked by intra-mPFC D1 receptor antagonism (Lammel et al., 2012).

As the majority of VTA cells are dopaminergic and GABAergic, it is unsurprising that they play important roles in valuative processing. While it is beyond the scope of this review to outline the precise putative role of VTA dopamine cells (but see below for further comments), the work by Lammel and others have suggested that dopaminergic projections are differentially involved in appetitive-, aversion- and 'salience'-related processing (Lammel et al., 2011, 2012; Stamatakis et al., 2013). Moreover, although the precise localization within the VTA/substantia nigra complex is still debatable it is clear from some studies that perhaps at least 25% of dopaminergic cells are excited by aversive stimuli (Wang and Tsien, 2011), while others show inhibitory responses or more complex phasic/tonic excitatory/inhibitory activity (Brischoux et al., 2009; Frank and Surmeier, 2009; Matsumoto and Hikosaka, 2009; Mileykovskiy and Morales, 2011). Despite these findings, there is still considerable uncertainty about the precise function and localization of dopaminergic cells in this context (e.g. Anstrom et al., 2009; Anstrom and Woodward, 2005; Brischoux et al., 2009; Guarraci and Kapp, 1999; see below for additional discussion). Although the role of VTA GABAergic cells is less studied, many appear flexibly responsive to appetitive (increased activity) and aversive (brief excitation followed by longer inhibition) cues (Kim et al., 2010), suggesting that they respond to the learned value of the stimulus and not its static properties. Along similar lines, networks of intra-VTA GABAergic cells show increased correlations to theta band power in response to appetitive, but not aversive, cues (Kim et al., 2012).

Taken together, these results demonstrate that a significant population of VMPFC/IL cells are involved in value-related processing. Most of these value-responsive cells change their firing rates to both aversive and appetitive stimuli, while also demonstrating a preference for one valence. Although the precise role of VTA cells is still somewhat unclear, the valuative circuits are separable and involve at least three cell populations. Although many cells show selectivity for appetitive stimuli, some clearly show selectivity for aversive stimuli. Moreover, the activity of this latter cell group appears highly contingent on the valence of future cues (see Table 2).

Overlapping activity: Two regions showing aversion- and appetitive-related overlapping activity, the anterior insula (AI) and amygdala (Amyg), were chosen for further investigation in animals. As is the case with other cortical regions, it is unclear to what extent the rodent anterior insula is homologous with that of the primate. For instance, the rat insula is much thinner, the cortical layers are less defined compared to humans and the rest of the rat cortex, and it is less densely and intricately interconnected compared to primates (Aleksandrov and Fedorova, 2003; Augustine, 1996). Nonetheless, many of the functions associated with AI such as gustatory/visceral/sensory/emotion-related processing are present in both primates and rodents (Kobayashi, 2011), and neuroimaging meta-analyses in humans support this broad functional categorization (Kelly et al., 2012; Kurth et al., 2010). Nonetheless, recent animal studies may help shed light on why the AI appears involved in both aversion- and appetitive-related processing in humans. In comparison, less controversy exists for the homology of the amygdala across mammals (Phelps and LeDoux, 2005; Price, 2003).

The few studies on value-related processing in the animal insula focus on the gustatory cortex. While it is unclear if this region in rodents is analogous to that identified in our human meta-analysis, the location of human gustatory processing within insular cortex is consistent with our findings (Veldhuizen et al., 2011) – suggesting at least that there may be functional similarities. In general, this portion of the anterior/mid-insula is known to be involved in value-related gustation (Accolla et al., 2007; Carleton et al., 2010) and pain-related processing (Wang et al., 2011).

In vivo optical imaging and electrophysiological data in rats showed that appetitive and aversive tastants were represented by more rostral and caudal activations, respectively, although considerable overlap was noted (Accolla et al., 2007; Yamamoto et al., 1989). Moreover, further work showed that the aversive conditioning of appetitive tastants (e.g. conditioned taste aversion to saccharin) resulted in aversion-related cortical responses following future access to saccharin (Accolla and Carleton, 2008), suggesting flexible value-related representations. It is likely that these responses are not restricted to taste stimuli, as multimodal connectivity and reactivity to thermal and olfactory stimuli have also been found. Although studies in monkeys similarly identified a small proportion of cells that were taste-responsive and showed a taste preference (see Table 2), unlike in rodents the cells showed no clear topographical organization. However, some type of organization was evident as, for instance, cells with a sucrose preference were likely to be closer to other similar cells (Scott and Plata-Salaman, 1999).

Although sometimes considered a structure mainly involved in aversion- or fear-related processing, many studies have identified the amygdala's role in appetitive processing. Recent studies have used both stimulus types in order to detail its role in valuation at a cellular level. While human imaging studies often refer to the amygdala as a singular structure due to resolution limitations, it is actually a collection of interrelated nuclei, in which sensory information enters largely through the lateral nucleus, and then flows through the basal, accessory basal, central and medial nuclei. In general, subcortical projections originate from the central nucleus, whereas projections to cortex and striatum are from basal, accessory basal or lateral nuclei (Salzman et al., 2007). Most studies which look at valuative processing have focused on the central (CeA), basolateral (BLA), and/or lateral (LA) amygdalar nuclei.

Using trace-conditioning and single cell recordings in primates, one group showed that among the 51% of value-responsive cells tested (100/196), separable populations responded preferentially to appetitive ($n = 61$) or aversive ($n = 39$) cues. These cells would also rapidly change their response to a new conditioned stimulus, implying that they encode value and not stimulus characteristics per se. The recording sites across regions of the BLA and CeA showed no clear anatomical distribution for cue or direct value-preferring cells (Paton et al., 2006). Follow-up studies by Salzman's group supported these findings, showing that ~50% of evenly distributed BLA and CeA cells are value-responsive, of which most are general responders followed by appetitive- and then those that are aversion-preferring. Also, cells responding to one cue type may still respond strongly during the presentation of a stimulus of

the opposite valence, and these effects appear to be independent of modality (Belova et al., 2007, 2008).

In general, the findings in primates have been well-supported by those in rodents. For instance, Shabel and Janak (2009) used conditioned stimuli from different modalities (i.e. sound/sucrose; light/shock) to test whether rat amygdalar cells respond differentially (i.e. different circuit hypothesis) or similarly (i.e. similar circuits hypothesis) to appetitive and aversive stimuli. Of the 518 cells monitored, 68% responded to the conditioned stimuli where 42% were selective for either the appetitive (23%) or aversive cue (19%) and 26% responded similarly to either. Recording electrodes were located throughout the BLA and CeA and no clear anatomical organization was noted across the regions (Shabel and Janak, 2009). Another study looking at LA cell responses to 22 kHz (aversive) or 50 kHz (generally appetitive) ultrasonic vocalizations in rats showed that 82% (104/127) of cells responded to stimuli, while most of these (62%) responded to either call type (with 50% showing a preference for aversion- and 50% for appetitive-related calls). Interestingly, while both stimulus types increased phasic firing, aversive calls tonically increased firing rates whereas appetitive calls decreased them (Parsana et al., 2012).

Importantly, a recent study differentiated responding in the basal amygdala to appetitive, aversive and safety cues (Sangha et al., 2013). Of all neurons recorded from ($n = 112$), ~18% responded to aversive and aversive + safety cues, ~44% showed no change, and ~38% responded selectively to the aversive + safety/appetitive cues (of which ~26% were aversion-selective, ~23% were safety-selective, ~37% fired similarly for aversive + safety and safety and appetitive, and ~14% fired similarly for aversion and appetitive cues). The authors suggested that these data identified basal amygdala cells that are safety-signal-selective and that safety and appetitive learning may involve similar mechanisms.

Taken together, though the work in insular gustatory cortex reveals many similarities in primates and rodents, such as the presence of aversive and appetitive stimulus-preferring cells, it should be noted that there are some potential differences. For instance, there is a rostrocaudal appetitive-aversive gradient in rats compared to the lack of clear organization in a large sample of monkey taste-selective neurons. While it appears as though there are value-selective cells in the anterior insula, and that many of the cells in this region are multimodal, it must nonetheless be emphasized that there is little data outside of gustatory processing and so the results should not be generalized beyond taste. Regarding the amygdala 50–60% of all cells are value-responsive and show a preference for appetitive or aversive stimuli. Interestingly, cells that show a preference for one type of conditioned stimulus (e.g. a light previously paired with shock) can still respond strongly during the reception of stimuli of the opposite valence (e.g. while consuming sucrose).

Asymmetrical activity: Two regions from the meta-analysis which showed aversion- and appetitive-related asymmetrical activity, the lateral orbitofrontal cortex (lOFC: showing appetitive- and aversion-preferences on left and right hemispheres, respectively) and nucleus accumbens/ventral striatum (NAc/VS: showing an appetitive-preference on right side and overlap on left), were chosen for further investigation in animals. As is the case with other cortical regions, it is unclear to what extent the primate lOFC is homologous with that of the rodent. Nonetheless, the ventrolateral orbital (VLO) and lateral orbital (LO) regions in the rat show anatomical and functional similarities to the primate orbitofrontal cortex (Price, 2007). For instance, primate OFC and rodent VLO/LO appear to be similarly important in higher cognitive processing such as in reversal learning (Dalley et al., 2004). However, primates have extensive granular and dysgranular cortex whereas rodent OFC is entirely agranular, and some aspects of primate OFC may also be reflected in the functioning of rodent IL cortex (Ongur and Price, 2000). As the most consistent evidence suggests that IL cortex is most like primate VMPFC (outlined above), we have not included studies of the IL cortex here.

Few studies have used both aversive and appetitive stimuli while investigating the role of the orbitofrontal cortex in animals. Single cell recordings in monkeys have indicated that the orbitofrontal cortex plays a broad role in valuative and motivational processing (Hikosaka and Watanabe, 2000; Thorpe et al., 1983). Recent evidence from Morrison and colleagues refine these findings showing that half of OFC cells reflect value-based activity, for both conditioned and unconditioned stimuli, irrespective of sensory modality (Morrison and Salzman, 2009). Cells showed a convergence of aversion- and appetitive-related information while maintaining a preference for one valence. Simultaneous recordings in OFC and amygdala showed that neurons which respond preferentially to aversive stimuli (airpuff) in the amygdala respond more quickly to new values (during reversal learning) than those in the OFC, while the opposite relationship was found with appetitive (juice) stimuli for the OFC (Morrison et al., 2011). Interestingly, once the new value relationship was coded, OFC cells consistently responded faster than those in the amygdala for either valence. These results suggest that a large proportion of OFC cells encode the valuative association between cues and their predictive outcomes. These authors looked mainly at the right OFC, but found no clear anatomical distinction between appetitive- and aversion-related cells, as they appeared to be interspersed evenly.

Studies in rats generally support these findings and have added to the specificity of action. For instance single cell recordings in rat OFC and BLA during an odour-liquid go/no-go task show that while cells in the BLA fired preferentially to the anticipation of aversive signals, cells in the OFC responded equally to cues signalling appetitive or aversive stimuli (Schoenbaum et al., 1998). Another go/no-go experiment in rats trained to discriminate between five odours for appetitive stimuli (or to avoid drinking aversive quinine) showed that of the OFC cells which responded to various components of the task (~16%), most showed differential responding for the magnitude of the appetitive stimulus, before and after delivery. However, the aversive stimulus (quinine) was not considered independently, making direct comparisons difficult (van Duuren et al., 2007).

In another vein, multi-unit and local field potential recordings have identified a relationship between gamma oscillations (~60–70 Hz) and action-outcome value-related signals in rat OFC (van Wingerden et al., 2010). They found that a subgroup of OFC cells were phase-locked to gamma rhythms during odour sampling during a go/no-go odour conditioned task (e.g. cinnamon scent = sucrose; jasmine = quinine). The authors suggested that OFC gamma-band synchronization may reflect inhibitory control required to withhold unfavourable or non-chosen behavioural responses. Moreover, theta oscillations (~6–10 Hz) were also noted during odour sampling, and individual neurons locked to gamma or theta rhythms but not to both – suggesting the presence of at least two separate OFC networks. In line with work above, Gutierrez and colleagues used simultaneous single-unit recordings in rats across four regions of the so-called 'taste-reward network' (OFC, NAc, insula, amygdala) to show that a large proportion of cells are value-selective and that learning results in increased phase encoding (within the theta band, ~4–12 Hz in this case) between licking for fluid and cue-induced firing in a subpopulation of cells. The authors suggest that this improvement in spike-timing precision may be related to affective learning (Gutierrez et al., 2010).

In the human meta-analysis, while there is some bilateral overlap, the left OFC appears to be involved more in appetitive, whereas the right appears more involved in aversive, processing. However, no studies have looked at the possible asymmetrical or lateralized function of the OFC during appetitive or aversive processing in animals. Interestingly, at least one study has shown that the left OFC

in rats has much higher concentrations of dopamine than the right, which is broadly consistent with the meta-analytic findings and dopamine's role in appetitive processing (Slopsema et al., 1982).

Most data for the NAc/VS region in animals come from studies investigating neurotransmitter function, particularly dopamine. Electrophysiological studies indicate that around 50% of NAc cells respond to conditioned and unconditioned appetitive stimuli, although others may be involved in valuative processing related to value-motor and effort-based integration, consistent with early suggestions of this region as a motivation–action integrator (Mogenson et al., 1980). Single unit recordings in rats show that NAc cells fired selectively to cues predicting appetitive (sucrose) or aversive (quinine) stimuli (Setlow et al., 2003). Although slightly more neurons appeared selective for aversive cues following conditioning in this study, it is unclear how many of their recordings were from the left vs. right NAc (as all coordinates were indicated on the left). NAc cells appear to mostly encode the cue-related value of stimuli with appetitive and aversive stimuli generally resulting in decreased and increased firing, respectively – although it is currently unclear how this cell activity relates to the widely-studied phenomenon of NAc dopamine release (see further discussion below). In line with the results noted above indicating separate mesocorticolimbic circuits for valuative processing, separate subpopulations of NAc cells may also encode cost-value, current-value, and effort- and anticipation-based information (Day et al., 2011).

It is very important to point out that many of the advancements in the field of appetitive or 'reward' processing have been made with a focus on dopamine at the cellular/biochemical level. Our focus on animal studies which use the passive presentation of both aversive *and* appetitive stimuli has precluded many of the seminal studies in this area, but it is important to acknowledge the work of some of the main contributors not otherwise noted here. For instance, Fibiger and Phillips sketched an early brain map of dopamine's impact on positive reinforcement (Phillips et al., 1992; Phillips and Fibiger, 1973), Shultz and colleagues were instrumental in uncovering the role of dopaminergic responses in prediction errors (Lak et al., 2014; Mirenowicz and Schultz, 1996), Carelli, Deadwyler and colleagues were integral in separating dopaminergic responses to drug vs. 'natural' rewards (Carelli et al., 2000; Deadwyler, 2010), and the work of both Wise and Salamone continue to greatly influence our conceptual understanding of this neurotransmitter in response to both appetitive and aversive stimuli (for interesting recent reviews see Salamone and Correa, 2013; Wise, 2013).

Moreover, although a review of the extensive literature related to NAc value-related neurochemistry is beyond the present scope, it should be briefly noted that dopamine, glutamate, and GABA appear to play particularly important roles. Briefly, while the role of dopamine in processing is increasingly well understood to be tied to motivational aspects of appetitive processing, as opposed to hedonia (Salamone and Correa, 2012), a clearer understanding of the mechanisms involved in aversive processing is also emerging (McCutcheon et al., 2012). In general, although aversive cues typically increase cell firing in the NAc shell, phasic dopamine release may still be contextually, or cell-specifically decreased or increased (see below for further discussion). Moreover, this behaviour appears tied mainly to the motivational value and not the static characteristics of stimuli. Similarly, there is growing evidence for the role of glutamatergic and GABAergic systems in value-related processing, with a particular emphasis on subregional differences related to the stimulation of mGlu2/3 (Richard and Berridge, 2011a), AMPA (Faure et al., 2008; Richard and Berridge, 2011b), and $GABA_A$ receptors (Hayes et al., 2011; Reynolds and Berridge, 2001, 2002). There is also evidence that some VTA GABAergic projections to the NAc synapse onto cholinergic interneurons that may be involved in responding to the salience of stimuli (Brown et al., 2012).

Regarding the asymmetrical function noted in the human meta-analysis, the left NAc/VS shows an overlap for appetitive and aversive processing whereas the right appears more involved in appetitive processing. Curiously, no studies in animals have looked explicitly at the possible asymmetrical or lateralized function of the NAc/VS. However, a human imaging study showed that the dopamine $D_{2/3}$ receptor antagonist sulpiride decreases activity for appetitive stimuli in the right VS (without changes in mood) and for aversive stimuli in the right lateral OFC (McCabe et al., 2011), which is consistent with the present findings of asymmetrical activity. Rat studies looking at dopaminergic release and turnover (Besson and Louilot, 1995; Fride and Weinstock, 1988) and receptor levels and function (Belcheva et al., 1990; Budilin et al., 2008; Rosen et al., 1984; Schneider et al., 1982) all support the notion of asymmetrical function, generally showing increased resting state, release, and D_2 receptor concentrations on the right side tied to appetitive processing, with similar or increased function on the left related to aversive processing. The purpose of this asymmetry is not understood, but recent studies support the idea that this asymmetry may reflect individual differences in motivational effort and learning related to appetitive and aversive decision-making (Maril et al., 2013; Porat et al., 2014).

Taken together, both the OFC and the NAc appear to mediate appetitive and aversive processing, with both areas displaying a large proportion of value-responsive cells (~50% in each case). The OFC appears to be involved in both the acquisition of value-related information, showing a particular preference for reward-related learning, but is equally important in processing well-established appetitive- and aversion-related information. There is little animal evidence for asymmetrical OFC function, so more evidence should be gathered before determining the potential significance of this relationship. Alternately, there is neurochemical support particularly regarding dopamine for asymmetrical functioning in the NAC/VS with a right side preference for appetitive processing. Moreover, signals in the NAc/VS appear more closely tied to motivational, as opposed to strictly value-perception-based, processing.

3. Discussion

The meta-analysis of human neuroimaging studies on the passive perception of appetitive and aversive stimuli revealed a number of functionally shared brain regions (i.e. overlapping regions noted in green in Fig. 1) as well as regions which appeared to be selective for appetitive (red) or aversive (blue) processing. Selected cortical and subcortical regions from each category were selected based on criteria described above. Regions of overlapping activity included the anterior insula (AI) and amygdala. Aversion processing regions included a broader cortical cluster encompassing the supplementary motor/premotor, midcingulate, and posterior cingulate cortices as well as the subcortical periaqueductal grey (PAG) while appetitive processing regions included the ventromedial prefrontal cortex (VMPFC) and ventral tegmental area (VTA). In addition, the lateral orbitofrontal cortex (lOFC) and subcortical nucleus accumbens septi/ventral striatum (NAc/VS) were identified as showing asymmetrical activity, with the lOFC showing appetitive- and aversion-preferences for left and right hemispheres, respectively, and the NAc/VS showing an appetitive preference on the right side and overlapping activity on left.

Consideration of rodent and monkey studies using combined aversive and appetitive stimuli, and those looking at only one stimulus type when such studies were not available, revealed two main findings. First, every area described above showed some degree of both aversive and appetitive (i.e. value-related) processing. Second,

each area appears to contain dissociable mechanisms for separate processing although integrative mechanisms are also typically present. While the mechanisms are specific to each region, there appears to be many spatial and temporal commonalities across how value is encoded. As a whole, animal and human data support the functional sharing of many cortical and subcortical brain regions across aversion- and appetitive-related networks and may have larger implications for cognitive-emotional brain function.

3.1. Value-related processing is dissociable but interconnected

Emerging findings related to valuative processing are beginning to raise questions about previous assumptions. For instance, studies investigating the underlying mechanisms of valuation in the classical mesocorticolimbic 'reward' circuit (i.e. VTA, NAc/VS, VMPFC), using mainly electrophysiological and optogenetic techniques, have shown that each region contains dissociable, but interconnected, circuits for appetitive- and aversion-related function.

Specifically, most cells in the VTA respond to valuative stimuli although subsets of dopaminergic and GABAergic neurons appear to respond differently to appetitive or aversive cues: dopamine cells are involved in processing motivational-salience signals and prediction errors related to the prediction of appetitive and aversive outcomes and GABA cells appear more involved in aversive processing and the anticipation of appetitive stimuli (Cohen et al., 2012). Moreover, both appetitive and aversive stimuli produce alterations in VTA synapses through changes in glutamatergic AMPA/NMDA receptor ratios, but may do so on selective circuits–i.e. aversive stimuli alter lateral habenula-VTA synapses on cells projecting to mPFC, appetitive stimuli alter synapses projecting to the medial shell of the NAc/VS, and both stimuli appear to alter laterodorsal tegmentum-VTA synapses projecting to the lateral shell of the NAc/VS, perhaps reflecting an appetitive and/or salience signal (Lammel et al., 2011, 2012).

Most areas investigated here contain a roughly equal number of cells which fire preferably, but rarely exclusively for, appetitive or aversive stimuli. The percentage of cells electrically responding to value varies across regions, from relatively low in the VMPFC/IL (~15–20%), and about half of all cells monitored in the amygdala, OFC, and NAc/VS, to a majority in the VTA (see Table 2). In the amygdala, for instance, similar numbers of cells responding preferentially for appetitive or aversive stimuli or equally to each stimulus type (i.e. non-selective responders which may be involved in signalling salience) appear to be equally distributed throughout the lateral and central nuclei of the amygdala (Shabel and Janak, 2009). Some exceptions to equal cell distribution include an apparent medial–lateral differentiation in the NAc/VS (noted above) as well as the existence of a small cluster of aversion-dominant cells in the ventral bank of the monkey VMPFC, similar to the subgenual anterior cingulate in humans (Amemori and Graybiel, 2012). It should be noted that the latter were identified using a highly cognitive approach-avoidance decision making task, but are nonetheless consistent with aversion-related activations in human fMRI studies (Grupe et al., 2012).

Firing patterns within each region, and between intra-regional circuits, likely contribute to the differential encoding of valuation, and appear largely independent of sensory modality and stimulus properties. For instance, a single-unit electrophysiological study looking at lateral amygdalar responses to appetitive and aversive vocalizations in rats showed that while both stimulus types resulted in increased phasic firing (in their preferred cell types), there were notable differences in the longer tonic activity of such cells (Parsana et al., 2012). Aversive and appetitive calls corresponded to increased and decreased tonic firing, respectively, which the authors suggest reflect stimulus valence while phasic signals may reflect stimulus detection. Another study on amygdala function revealed that safety-signal-responsive cells are also involved in valuative processing, along with appetitive- and aversion-preferring cells (Sangha et al., 2013), raising the issue of whether such a mechanism is more wide-spread as has been debated for other regions such as the NAc/VS (Josselyn et al., 2005; Oleson et al., 2012). Intra-regional cell dynamics also appear key in at least the VTA and NAc where local GABAergic dynamics are likely involved in valuative processing and may involve the inhibitory gating of signal throughput (Hayes et al., 2011; Kim et al., 2012; Shi and Rayport, 1994; Steffensen et al., 2001).

At the inter-regional level, studies using recordings simultaneously in different regions may help reveal unique dynamics at play. For example, simultaneous single-cell recordings in OFC and amygdala showed that neurons which respond preferentially to aversive stimuli (airpuff) in the amygdala respond more quickly to new values, using reversal learning, compared to those in the OFC (Morrison et al., 2011). However, the opposite relationship was found for appetitive stimuli (juice), suggesting that the OFC activity is initially appetitive-preferring. Interestingly, once the new value relationship is well-established OFC cells consistently respond faster than those in the amygdala. These results suggest that a large proportion of OFC cells encode the valuative association between cues and their predictive outcomes, and may best reflect the state value of previously learned associations. Moreover, the amygdala may be functionally selective for the processing of new aversion-related associations, although, as noted above, there are roughly an equal number of appetitive- and aversion-responsive cells.

Valuative processing in some regions, such as the AI, PAG, and the motor-related cluster noted here, is more difficult to determine given the absence of studies using passive appetitive and aversive stimuli together. Nonetheless, although PAG activity, for instance, is associated mainly with pain-related and defensive behaviours, its activity also appears to be involved in socially motivated actions such as maternal behaviour in the presence of threat and hunting and foraging (Mota-Ortiz et al., 2012; Sukikara et al., 2010), as well as in the appetitive effects of heroin (Flores et al., 2006). Moreover, PAG activity may be context-dependent as a recent human fMRI study showed that comparatively low levels of pain (the 'relief' condition) are perceived as pleasant and correspond to increased connectivity between the PAG and classical reward-related circuitry (Leknes et al., 2013). It is curious that large PAG lesions do not appear to affect brain self-stimulation reward in rats (Waraczynski et al., 1998). However, this may be because its activity is related specifically to the modulation of pain circuits and/or is related to the contextual, over primary, processing of value.

Neurochemical factors, such as localized concentrations of neurotransmitters and specific receptor subtypes, are also important in the control of value-related circuits. Although few studies have investigated the role of selective neurochemicals during the presentation of both appetitive and aversive stimuli, there are two main points to be gleaned from the available data. First, neurochemical and/or receptor density gradients within a region can allow for the spatial differentiation of these circuits. For instance, the work by Lammel and colleagues elegantly demonstrates that VTA synapses on dopaminergic projections to the NAc/VS can be selectively modified (reflected by changes in glutamatergic AMPA/NMDA receptor ratios) depending on the valence of the stimulus (Lammel et al., 2011, 2012). Second, neurotransmitter type, release timing, and precise intra-regional connections can allow for a temporal differentiation. In this way, the difference between appetitive- or aversion-related signals might be the way in which a neurotransmitter is released.

The precise mechanisms behind such control are unclear and as such, although a detailed account is beyond the scope of the present

review, a brief discussion of the highly studied roles of the VTA and NAc/VS is warranted. For instance, although one group has suggested that VTA GABAergic cells generally show increased phasic activity to appetitive stimuli and fast phasic increases to aversive stimuli followed by longer inhibitions – with presumably similar release dynamics (Kim et al., 2010, 2012) – it is important to note that methodological limitations prevented a clear identification of these cells. Nonetheless, optogenetic techniques have been used to identify important micro-circuits in this regard. One study identified a select population of putative VTA dopaminergic-GABAergic 'hybrid' cells which send GABA-mediated inhibitory projections to the lateral habenula, which in turn corresponded to an increase in VTA dopaminergic cell firing and appetitive behaviour (Stamatakis et al., 2013). A separate study found evidence of dissociable glutamatergic and GABAergic circuits from the bed nucleus of the stria terminalis which project to GABAergic VTA cells and appear to respond primarily to aversive and appetitive stimuli, respectively (Jennings et al., 2013).

Regarding the spatiotemporal dynamics of VTA dopaminergic cells, it is important to note that there exist some inconsistencies which remain unanswered. For instance, while Lammel and colleagues suggest the existence of medial/lateral anatomical gradients, others have reported a dorsal/ventral (Brischoux et al., 2009) or absent (Anstrom et al., 2009) gradient, although the relatively low number of recorded cells in the latter studies could prevent the identification of an existing pattern. Moreover, the intensity/salience and the type of aversive stimulus could also impact the responsivity of dopaminergic cells, as studies using restraint or social stressors or conditioned aversive stimuli have all demonstrated robust increases in cell firing (Anstrom et al., 2009; Anstrom and Woodward, 2005; Guarraci and Kapp, 1999) in contrast to some studies noted above.

Similar to the VTA, most of the work on the NAc/VS region has focused on understanding the complicated role of dopaminergic neurotransmission. Strangely, although the NAc is composed mainly of GABAergic cells, this area has been far less explored (Carlezon and Thomas, 2009). More recent work, noted above, has uncovered a complex role of NAc GABA in valuative behaviours. For example, our own work has shown that NAc $GABA_A$ receptor activation and blockade decreases and increases electrical brain stimulation behaviour, respectively, while having little effect on appetitive feeding (Hayes et al., 2011). Although there are many factors to consider (e.g. timing of drug activity, parameters of the behavioural paradigms), these results along with others point to a nuanced control at the single-receptor, single-region, level which should be further explored.

Studies on NAc dopamine transmission have also revealed a complex, context-dependent, role in valuative processing. Some studies have shown that appetitive and aversive stimuli can lead respectively to increased and decreased dopamine release in the NAc/VS (Roitman et al., 2005, 2008, 2010). However, many other studies have shown robust increases in dopamine release in response to aversive stimuli alone (McCullough and Salamone, 1992; Young, 2004) or in combination with typically appetitive stimuli (Sorg and Kalivas, 1991). The differential dynamics of this release across repeated exposures to valuative stimuli further supports the notion of independence between appetitive and aversive NAc dopaminergic circuits (Imperato et al., 1992). Importantly, dopamine release dynamics may also depend on the type of aversive stimulus and the context in which it is presented, as has been demonstrated in studies using social defeat and exposure to subchronic doses of methamphetamine (Broom and Yamamoto, 2005; Tidey and Miczek, 1996). Other studies have emphasized that dopamine cells are not a homogeneous population, and that while some are involved in processing both aversive and appetitive prediction errors (Oleson et al., 2012), others seem more responsive to the motivational aspects of stimuli (Bromberg-Martin et al., 2010; Matsumoto and Hikosaka, 2009).

Importantly, although necessary to include here, these sections identifying a handful of key papers on the VTA and NAc neurochemistry underlying valuative behaviour are by no means exhaustive. Although most of the work in this area has focused on the mesocorticolimbic circuitry, the reader should note that this is still an intensely studied area which contains apparently conflicting data and opposing views.

Taken together, various electrochemical mechanisms may help to encode different aspects of the valuation signal throughout a similar network of brain regions. Cellular distribution, firing patterns, neurochemical gradients, and inter- and intra-regional dynamics all appear to contribute to the differential encoding of appetitive and aversive stimulus processing (Table 2). There is little current understanding of how these electrochemical factors work together. For instance, it is not understood why there is a general lack of topographical organization in some regions (amygdalar nuclei, most of VMPFC/IL), and organization in others (NAc/VS), while these same regions may show differential neurochemical/receptor gradients. Also, while the role of dopamine has been relatively well studied, though still controversial, the role of other key neurotransmitters, such as GABA and glutamate, need greater study. Interestingly, the differential spatiotemporal dynamics involved across regions may help explain why the human and animal data appear inconsistent at first glance.

3.2. Considering the human imaging and animal studies together

An important question raised by these data is why neuroimaging studies frequently report some regions as being specific for the processing of one valence. For instance, the NAc/VS is considered primarily in appetitive processes (Costa et al., 2010; Hamann and Mao, 2002). This interpretation may result in part from an attempt to view one's appetitive-positive/aversion-negative findings in light of the classically considered mesocorticolimbic 'reward' circuit. However, these differences may also be related to spatiotemporal dynamics and a consideration of the different resolutions inherent in each technique. Animal studies employ techniques with resolutions at the second or sub-second level, whereas typical fMRI studies use sampling intervals over several seconds. Indeed, some human studies have shown that repeated exposure to aversive but not appetitive stimuli can result in an apparent habituation of NAc/VS responses (Gottfried et al., 2002). However, this may only be the case for conditioned stimuli as, for instance, one study showed increased activity in bilateral NAc/VS to the passive listening of both appetitive and aversive sounds (Levita et al., 2009). In a separate study, Levita et al. (2012) showed that active avoidance of aversive stimuli tended to result in increased fMRI BOLD signals, while passive avoidance resulted in greater deactivations (see Hayes and Huxtable, 2012, for a discussion on interpreting BOLD deactivations). Although many fMRI studies do report NAc/VS activity in response to aversive stimuli (Delgado et al., 2011; Hayes and Northoff, 2011), the apparently opposing actions seen by Levita and colleagues might be partly why many fMRI studies using aversive stimuli fail to see significant NAc activations.

Interestingly, in the former study by Levita et al. (2009), only the right NAc/VS showed a valence x stimulus onset interaction which revealed greater activity in response to aversive stimuli. In other words, while the bilateral NAc/VS responds to stimulus valence independently of other characteristics, the right side displays an aversion preference. This is in line with the meta-analysis results showing that the NAc/VS has an asymmetric value-related function, but is curiously in the opposite direction (the meta-analysis shows that the right side prefers appetitive, not aversive, stimuli).

This discrepancy might be because the meta-analysis looked at these groups separately and then compared the resulting maps, whereas Levita and colleagues included both valences in their design. Additionally, their findings might reflect that aversive auditory stimuli are more salient than appetitive stimuli (considered 'neutral' sounds by some) (Kumar et al., 2008). Regardless, many animal studies have consistently suggested increased appetitive-related function in the right NAc/VS, and potentially increased aversive processing on the left side, though this work relies almost entirely on dopaminergic markers making their interpretation more difficult (Belcheva et al., 1990; Besson and Louilot, 1995; Budilin et al., 2008; Fride and Weinstock, 1988; Rosen et al., 1984; Schneider et al., 1982).

Asymmetric functioning of the lOFC, noted in the human meta-analysis, is supported by few animal studies, for instance one showing higher baseline levels of dopamine (Slopsema et al., 1982). However, a study in healthy humans showed that asymmetric dopaminergic functioning in the right NAc/VS and right OFC is tied to appetitive and aversive processing, respectively, which might reflect the apparent left lOFC preference for appetitive stimulus responding (McCabe et al., 2011). However, as Morrison and colleagues found no clear anatomical distinction between appetitive- and aversion-preferring cells in the right OFC (Morrison et al., 2011; Morrison and Salzman, 2011), this asymmetrical function may rely on neurochemical over electrical mechanisms.

Few studies in either humans or animals investigate asymmetrical activity in this context suggesting that this phenomenon may be largely under-reported. Moreover, the utility of such function is not well understood, though it may not be uncommon (Concha et al., 2012). Positive results in this vein may help explain the asymmetrical findings noted in some clinical studies. For instance, an investigation in an at-risk psychiatric population suggested that lower left lOFC volume was related to more aggression and impulsivity (Gansler et al., 2009) – it is speculatively possible that decreased left lOFC volume (the appetitive-selective side noted in the present analysis) may reflect a dysbalance of underlying aversion-appetitive processing in which the right aversion-selective OFC becomes dominant.

3.3. Limitations

It is important to make a few notes on the methodological and conceptual limitations inherent in this kind of investigation. Although we aimed to select a representative sample of cortical and subcortical regions within each category from the meta-analysis, we recognize that any conclusions made about each region are not readily generalizable to others. As these conclusions are based on animal data, we must be cautious when interpreting these results in light of the human data and in assuming similar mechanisms and anatomical homology (as discussed above). Moreover, as our focus was on studies which included *both* appetitive and aversive stimuli, many informative studies using one stimulus type have not been included here. For a similar discussion which includes primarily studies on aversive and appetitive stimuli in isolation, see Bissonette et al. (2014). Nonetheless, we have aimed to provide a balanced discussion by considering studies employing *only* appetitive or aversive stimuli where appropriate – for instance, when fewer studies were available (e.g. for the PAG and motor-related regions) or when excluding these studies might present an unintentionally biased story (e.g. when considering the vast and complex data on the mesolimbic circuit).

By starting with the human neuroimaging data, we only investigated regions which show consistent peak activations across many studies. However, we are aware that other mechanisms may be revealed in areas which show relatively lower activity, and thus do not exceed the conservative thresholds for identifying peak activity in most studies. While many of these areas are likely to be subcortical (e.g. habenula, bed nucleus of the stria terminalis), due to limitations in resolution and signal-to-noise ratios in these smaller, deeper, regions, there is nonetheless evidence in both humans and animals that even some cortical regions, such as primary visual cortex, are involved in appetitive (Shuler and Bear, 2006; Weil et al., 2010) and aversive (Amir and Stewart, 1999; Vuilleumier and Pourtois, 2007) processing. Thus, while we have provided comparative evidence for valuative processing in select regions, it may well be that it occurs throughout many, perhaps all, regions of the brain to some degree. Similarly, the spatial limitations of neuroimaging techniques mean that interpretations of activations within regions composed of many subregions (e.g. thalamus, amygdala, PAG) should be considered with additional caution. Another example worth noting is the ventral pallidum, rarely identified in neuroimaging work, given its proximity to the NAc, and its demonstrated role in both appetitive and aversive processing in animal studies (Johnson et al., 1993; Tindell et al., 2006).

The apparent selectivity of the large motor-related cluster across fMRI studies (see Fig. 1) may be explained by a dominance of aversion-responsive cells within these regions. However, this conclusion must be interpreted with caution as there is little alternative evidence available in animals for many of these cortical regions. As such, it is often unclear whether mechanisms noted in other regions (e.g. intra-regional NAc/VS or VTA network activity) might also be of relevance in these less-studied regions, and whether the lack of evidence is related to a publication bias for positive findings or a true difference in regional mechanisms. It may turn out that putative aversion-selective regions are similarly involved in processing positive stimuli, just as more evidence emerges for a role in processing aversive stimuli in the so-called mesocorticolimbic dopaminergic 'reward' system. Interestingly, some studies are providing tentative links to appetitive processing in motor regions, e.g. enhanced cell firing and synchrony following operant learning, which are initially independent of behavioural activity (Sakurai and Takahashi, 2013). These kinds of studies might speculatively be providing additional mechanistic evidence for why, for instance, music therapy appears effective for those with motor impairments (Sarkamo and Soto, 2012).

Conceptually, it is important to note that, due to the challenging nature of studying hedonic states, behavioural and motivational activities are often substituted – though we aimed to include studies which focused on the neural processing of passively perceived stimuli in order to reduce confounds from highly cognitive or behaviourally-intensive processing. It is also worth noting that distinct psychological constructs (e.g. aversion, fear, and punishment) will likely involve differences in processing, though we are focused here largely on regions which respond to all or most types of aversive or appetitive stimuli regardless of the conceptual approach of each study. Lastly, we did not explicitly consider potential differences between the many putative subcomponents of valuative processing (e.g. 'wanting' and 'liking' of rewards, anticipation, prediction errors) which may be of interest.

3.4. Open questions and future directions

There are currently many open questions regarding the processing of value. Traditionally, research on appetitive processes has focused on the mesocorticolimbic system, while aversion-related investigations have been largely limited to the functioning of the amygdala, periaqueductal grey and hypothalamus. However, recent findings have implicated these same structures in the processing of the opposite valence, and have underscored their role within wider brain networks. Moreover, few studies have used both aversive and appetitive stimuli, often leading to conclusions limited to one valence.

Appetitive and aversive stimuli need not activate 'opposing' systems, but can also equally initiate enhancements of arousal or attention (Barberini et al., 2012). This is in line with our subjective sense that pleasure and displeasure can be experienced simultaneously (Larsen and McGraw, 2011). The simultaneous processing of appetitive and aversive cues from the external and internal environment suggests a complex interaction of processes for determining affective states. Future research should continue to explore the impact of external stimuli on valuative processing, but should also increasingly consider the role of interoceptive stimuli, the impact of mixed aversive-appetitive signals, and possible interactions between other brain networks (e.g. primary sensory networks). This last point is especially interesting, as emerging findings suggest that the disentanglement of sensorimotor and value-related processing in sensory and motor cortices is not straightforward (e.g. Apitz and Bunzeck, 2012; Borgomaneri et al., 2013; Weis et al., 2013).

Context is also an important component of valuative processing, as some animal studies discussed here show that many neurons flexibly encode affective stimulus associations, and not the physical characteristics of the objects themselves. Human neuroscience studies are also beginning to explore the role of affective context. For instance, recent studies have implicated classic 'reward' regions such as the ventromedial prefrontal cortex in context-dependent aversive processing (Hayes et al., 2013), pain-pleasure 'flipping' (Leknes et al., 2013), and within a neuroeconomics perspective (Mullett and Tunney, 2013). Taken together, these results support the notion that the emotional brain is intrinsically organized into domain-general, distributed functional networks – the so-called constructionist approach (Barrett and Satpute, 2013; Lindquist and Barrett, 2012). This approach is being further supported by neuroimaging research in humans showing that complex emotional expression (e.g. sadness, happiness) cannot be mapped one-to-one onto brain function and instead appears guided by more basic core affective-valuative processes (Wilson-Mendenhall et al., 2013).

Perhaps the most important questions which remain centre around how we can best translate the human and animal findings – from each other as well as into clinically-relevant approaches. Human studies will undoubtedly help focus on the function and interactions of whole-brain networks while animal studies can help explore the potential importance of precise mechanisms such as the role of intra-regional network activity noted in the VTA and NAc/VS (Kim et al., 2012; Shi and Rayport, 1994; Steffensen et al., 2001). The synthesis of both literatures is surely the only way forward, and the best approach to understanding emerging findings on value-related network dysbalances in neuropsychiatric disorders as varied as addiction, depression, anxiety, borderline personality disorder and chronic pain (Blood et al., 2010; Borsook et al., 2007; Lammel et al., 2014; Ludascher et al., 2007).

4. Conclusion

Taken together, these results help to integrate a broad range of findings and support the notion that differential spatiotemporal network dynamics may, in part, help explain similarities and differences in valuative activity – at least when considering the eight regions included here (i.e. AI, amygdala, motor-related cortex, PAG, VMPFC, VTA, lOFC, NAc/VS). They also underscore the need to consider non-human animal studies for a clearer interpretation of human data, and vice versa. These results also emphasize the many gaps left to bridge. More studies should employ both aversive and appetitive stimuli to address whether their findings are valence-specific or more broadly reflect the principles of valuative processing. Moreover, authors should be cautious about ascribing psychological events to brain function at a one-to-one level, as this approach has likely impeded progress on understanding the link between dysfunctions of affect and many neuropsychiatric disorders. Finally, additional work is needed to support or refute the notion that core affective/valuative circuit function reflects a basic underlying principle of broader emotional brain function.

Acknowledgements

We would like to thank Christina Zhang for her assistance in gathering some of the articles used here. The work was supported by grants to GN from the Canadian Institutes of Health Research (CIHR), the Michael Smith Foundation for Health Research (EJL-94190), and Hope for Depression Research Foundation (HDRF/ISAN). DJH was funded through a CIHR Postdoctoral Fellowship.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2014.06.018.

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