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Human brain responses to gastrointestinal nutrients and gut hormones

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Functional mapping of human brain activation has made it possible to understand how different nutrients in the gut impact on homeostatic and appetitive brain responses. Current data are limited, but nutrient-specific effects are observed, with differential responses to lipid and sugars. Responses are not a simple function of calorie intake. Gut hormones such as CCK, PYY, GLP-1 and ghrelin are implicated in these responses, but may not exert effects directly on the brain. Research is now addressing how these homeostatic signalling states (fasting/fed) interact with hedonic responses, such as those evoked by images of appealing food. Differences are also beginning to emerge in obese versus lean subjects. These platforms will enable a new understanding of normal and disordered eating behaviours in humans.

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The presence of nutrients in the gut inhibits appetite and reduces food intake. The secretion of gut hormones in response to luminal nutrients is pivotal to these responses by signalling to the brain to influence both homeostatic functions and appetitive behaviours. There are also hedonic and emotional drives to eat, opposing homeostatic physiological pathways: how these interact is a focus of current attention [1].

Most experimental data on brain responses to nutrients and hormones necessarily come from animal models that have employed a variety of techniques for example immunohistochemistry and electrophysiological recordings, often in response to direct application of nutrients or gut hormones. Selective afferent vagotomy studies in rodents demonstrated that signals neurally transduced from the gut are essential for nutrient-induced responses in the brainstem and hypothalamus [2]. Crucially then, homeostatic responses to feeding are not solely metabolic post-absorptive responses to circulating nutrients, which access the cerebrospinal fluid and brain without hindrance [3]. Rather, the CNS responds directly to luminal gut content, prior to absorption. This has major implications for understanding feeding behaviour, and how to approach consequences such as obesity.

This review will initially focus on recent advances in imaging technologies, review the limited literature on gut hormones and nutrients effects on the human brain, and explore some of the potential interactions between homeostatic signals and higher domains being uncovered in functional experiments.

Studies in humans: limitations and opportunities

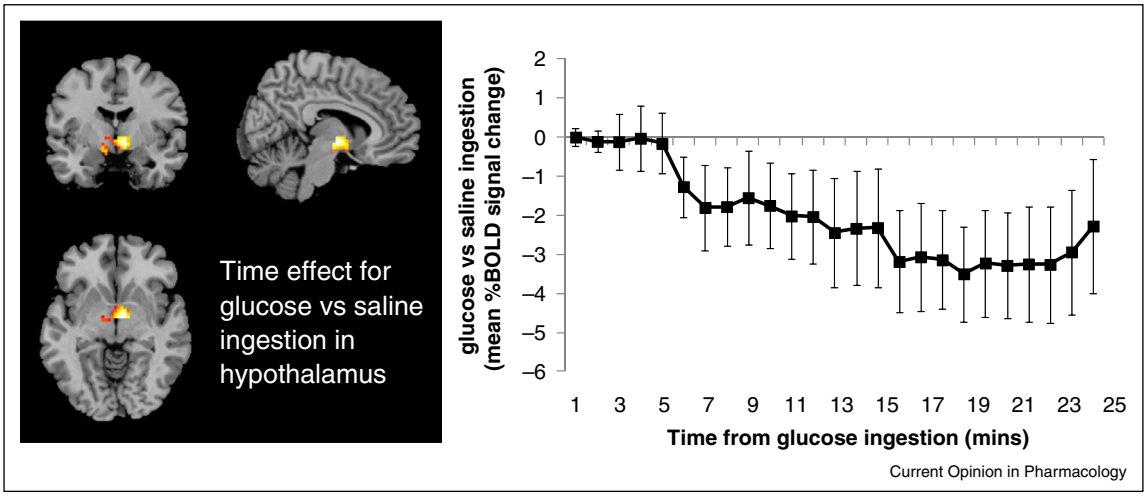
There are clearly major experimental limitations, yet only human studies can answer fundamental questions about the complex mechanisms leading to over-consumption or under-consumption of food. Recently, the use of functional MRI scanning has begun to map out human brain responses and interactions.

Conventional fMRI study models used in other areas of neuroscience are task based, so in early studies this involved simple consumption of a test meal. The technique is based on the change in blood oxygenation level dependent (BOLD) signal, a marker of regional activity since blood flow is altered in active brain regions allowing mapping of activity in regions of interest.

A further development is physiological (phys)MRI in which a nutrient is infused into the gut after a short baseline period and the change in BOLD signal over time compared to the baseline period. This is analogous to pharmacological challenge MRI (phMRI) which uses psychoactive drug infusions instead of nutrient ingestions therefore physMRI has the same advantages and disadvantages as phMRI [4].

There are advantages of physMRI over conventional food based fMRI tasks [5]. physMRI has the ability to map the direct effect on the BOLD signal of the nutrients being

Figure 1



A representative image of the selected human brain region (hypothalamus, left panel) and time course of the BOLD-signal response to glucose directly infused into the stomach. The response is always subtracted from a control condition in the same subjects, in this case saline.

ingested. As the nutrient-induced BOLD signal change is slow in comparison to the 30 second blocks used in conventional fMRI paradigms, nutrient-induced changes will not be detected using fMRI tasks. Also, the fMRI tasks are designed to target the hedonic regions of the brain, such as the ventral striatum and basal ganglia, rather than the more physiological brain regions such as the brainstem and hypothalamus. With physMRI both the reward and deep brain regions can be probed [6]. A representative image of the effect of glucose is shown in Figure 1.

For all fMRI, there is a low frequency signal drift due to mechanical vibrations causing increases in temperature in the gradient coil system [7]. For conventional task-based fMRI, the drift can be filtered out of the time series however as the nutrient-induced BOLD signal change is slow, and in the same frequency space of the drift, then no filtering can be applied to physMRI data. In order to eradicate signal drift, a saline control scan is needed per person, so that any drift can be modelled and subtracted with respect to time per voxel. This leads to multiple scans per person and therefore increases costs and time. Another disadvantage is that physMRI, like fMRI, is a non-quantitative measure (BOLD signal change is compared to a pre-ingestion baseline) so there is no direct comparison with circulating nutrient or hormone concentrations and only temporal correlations are possible [8•].

Though not yet applied to this field, MR acquisition techniques such as multi-echo EPI [9] or arterial spin labelling (ASL) [10] can be used to separate slow changing BOLD effects from drifts. ASL can also provide quantitative information on cerebral blood flow and in some instances arterial arrival time which can be used to provide a direct comparison with nutrient and hormone levels.

Imaging brain responses to nutrients present in the gut

The literature is currently small, mostly addressing glucose. Studies focussed on oral taste are not reviewed here.

Carbohydrate

A study by Liu *et al.* was one of the first to use fMRI following 'eating', that is the ingestion of glucose solution. Decreased hypothalamic BOLD signals occurred from around 7 minutes [11]. Subsequent studies have reinforced these findings showing a dose-dependent and prolonged decrease in BOLD signal in the hypothalamus following glucose [12]. A larger response was seen following oral than intravenous glucose [13]. In addition no hypothalamic BOLD decrease occurred following artificial sweetener (aspartame) or non-sweet maltodextrin. This suggests activity is not due to sweetness [14]. It may depend on the ability to release gut hormones or affect gut function, which may not occur in response to sweetness *per se* in humans [15,16].

These studies are potentially confounded by sensory responses via oral tasting. Movement of the head and neck during swallowing results in imaging artefacts, preventing analysis of key early time points.

More recently, detailed imaging of brain responses to glucose have been investigated by physMRI [8•]. In particular, detailed imaging of the brainstem and hypothalamus and other regions of interest was investigated immediately following intragastrically administered glucose. In line with previous observations BOLD signal