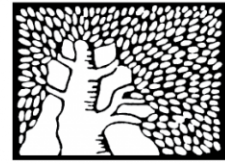


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Physiological needs: Sensations and predictions in the insular cortex

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Abstract:

Physiological needs create powerful motivations (e.g., thirst and hunger). Studies in humans and animal models have implicated the insular cortex in the neural regulation of physiological needs and need-driven behavior. We review prominent mechanistic models of how the insular cortex might achieve this regulation, and present a conceptual and analytical framework for testing these models in healthy and pathological conditions.

Keywords:

Insular cortex; insula; interoception; mouse; rat; human; homeostasis; prediction; predictive coding; physiological needs; hunger; thirst; motivation

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Physiological needs

Life requires continuous regulation of obligatory conditions. Maintaining the appropriate intracellular environment, often termed homeostasis, is a task that all cellular organisms face (1; e.g., maintaining osmolarity, acidity, specific chemical building blocks, etc.). As multicellular organisms have become more complex, the mechanisms that maintain homeostasis have become more and more elaborate, such that in animals (as opposed to single cell organisms) they involve the concerted actions of different tissues and organs (e.g., utilizing fat or muscle tissue to fulfill energetic demands, or kidney retention of salt vs. water). When necessary conditions are not supplied by the immediate environment, and organisms cannot regulate them internally, they must take actions to return to the desired state. These requirements can be conceptualized as ‘needs’, and the actions taken are meant to fulfill them. For example, the needs for energy or fluids, produce powerful motivations – hunger or thirst – to obtain specific goals, such as food or water.

As the environment becomes more and more complex, obtaining these goals has come to require more and more elaborate behaviors (2). Among these behaviors are so-called ‘cognitive functions’ such as learning, decision-making, navigation, and many others. Much of modern neuroscience is dedicated to understanding the neural underpinnings of these cognitive functions. Yet a fundamental understanding of the neural basis of the motivations that drive these behaviors in the first place is lacking. Furthermore, we still do not understand how the specificity of need-driven goal-seeking is achieved. That is, how does the nervous system drive water-seeking, but not food-seeking, when thirsty but not hungry. Moreover, we join others in arguing that understanding the neural basis of basic need-based motivations can serve as a powerful model to understand other motivations, such as those that drive us to choose one profession over another, to excel in our studies, or to plan a vacation (3, 4).

Specific motivationally relevant predictions arise from needs

To fulfill the current need using goal-directed behavior, an animal’s nervous system must combine two types of information. First, it must have knowledge of the specific need – what is the current deficiency, and what can alleviate it? (Fluids? Energy? Heat?) Second, it must be able to survey the external environment and predict what could supply what is necessary to satisfy the need (a food source, a water source, shelter). Based on the integration of internal and external information, and the formation of specific predictions, behavior is directed toward potential resolutions.

Another important layer in this goal-directed behavior is arbitration between multiple needs (5, 6). Indeed, because animals need to maintain multiple physiological parameters at certain levels (e.g., fluids, energy, temperature, salt, amino acids, etc.), more than one need might require addressing at any given moment in time (3, 7). For example, if you are hiking in the desert for a few hours, you will likely have to actively maintain temperature, fluids, salt, and energy. Thus, the nervous system must identify each deficiency, prioritize the arising needs identified based on their severity, survey

the environment to predict what could be used to resolve the deficiencies, and choose a course of action based on this information. Importantly, despite the fact that prioritization of one need over another can be conscious (stay in a shelter or go seek water), most deficiency-driven decisions are resolved without our awareness (should we sweat to cool the body or avoid it to reduce water loss?).

The insular cortex – where internal meets external

The insular cortex (InsCtx, also referred to as ‘insula’) encompasses within it the first cortical site to receive peripheral internal sensory information via spinal and vagal pathways, and is thus considered to be the primary interoceptive cortex (7-9; Fig. 1A). Dominant models suggest that InsCtx receives *internal* sensory information about changes in bodily physiology and integrates this with *external* sensory information, as well as associated actions and expected outcomes. According to these models, InsCtx uses these different streams of information to compute “interoceptive predictions”, which can then be compared to the actual outcomes to also compute “interoceptive prediction error signals” (10-13). If necessary, these can then regulate bodily physiology accordingly (Fig. 1B).

Several lines of experimental evidence lend some initial support to these models. InsCtx in humans and animal models has been shown to represent internal physiological states, such as hunger, thirst, visceral malaise, and elevated heart rate (14-20). Additionally, InsCtx in humans and animal models has been demonstrated to respond to salient predictive cues across different sensory modalities (17, 21-25). Accordingly, the InsCtx is considered an important part of the salience network (26). In line with these observations, we have previously suggested that fast changes in InsCtx activity (e.g., in response to a salient external cue) may represent a prediction of future outcomes, while slow changes in the InsCtx, represent current internal physiological states (7, 18).

More specifically, in the context of ingestive behavior, we suggest that InsCtx activity represents the current physiological state, which reflects an integration of multiple inputs, e.g. regarding blood sugar levels, heart rate, gastric stretch, etc. Responses to predictive cues drive a brief change in the pattern of activity, which reflects the future predicted outcome. Thus, in a state of hunger, prediction of upcoming food will result in a change from activity that reflects the current calorie-deficient state to transient activity patterns that reflect future predicted satiation. Importantly, InsCtx activity is necessary for cue and context induced food seeking (22-24, 27), as such it remains to be clarified how both slow and rapid changes in InsCtx activity (reflecting current and future physiological states, respectively) contribute to food seeking.

What is the role of the insular cortex?

Numerous studies have investigated the InsCtx and its involvement in diverse behaviors, yet its precise function has remained elusive. It has been known for decades that internal and external

sensory information converge in the InsCtx. Indeed, as described above, previous work has postulated that the InsCtx computes interoceptive predictions that can be used to regulate bodily physiology in anticipation of upcoming changes (10-13). Nevertheless the InsCtx has been suggested to play an important role in many diverse and seemingly unrelated processes, including decision making, risk assessment, social interactions, emotional regulation, and more (reviewed, e.g., in refs. 10, 28-33). Accordingly, the InsCtx has also been implicated in various pathologies, including autism spectrum disorder, schizophrenia, drug addiction, anxiety, depression, anorexia nervosa, and more (31, 34-36). Indeed, based on these observations and the aforementioned models, the InsCtx has been suggested to contribute to many cognitive and emotional processes by representing the interoceptive aspects of these processes. While cognitive and emotional processes are likely expressed in the InsCtx due to their interoceptive properties and the deviation from homeostasis that accompany them, some of the pathologies that involve the InsCtx are thought to result from its abnormal activity. It is particularly likely that the InsCtx plays a role in pathologies associated with abnormal reactions to upcoming physiological changes, such as obesity and drug addiction (31, 35).

While the above conceptual framework is compelling, we argue that many important mechanistic aspects are still missing. Thus, our understanding of the InsCtx and its role in healthy and pathological conditions would be advanced by further investigations focused on elucidating these aspects. Moreover, the fact that the InsCtx is involved in so many diverse functions suggests that manipulating its activity in many different behavioral contexts would have an observable effect, as has been reported by many groups. However, we suggest that the field would greatly benefit from animal model studies that use an explicit focused conceptual framework aimed at revealing a fundamental logic of the mechanism. This would help the whole field test explicit mechanistic hypotheses and then either validate or invalidate them.

What are we missing?

We describe below three outstanding questions. We propose that the answers to these questions will advance our understanding of the InsCtx in healthy and pathological conditions.

Question 1: Does the InsCtx perform the same computation but for different sensory inputs?

The InsCtx receives multiple types of internal and external sensory information – inputs pertaining to cardiovascular function (e.g., heart rate and blood pressure), gastrointestinal function (e.g., gastric stretch, motility, and nutrient sensing), gustatory function (e.g., taste, texture, and temperature), auditory inputs, tactile inputs, and more (reviewed e.g., in ref. 7). This raises the possibility that the InsCtx performs one canonical computation (e.g., predictions and prediction errors) on each input category. One extreme option is that it would do so for each input modality separately. The opposite extreme option is that it would integrate all inputs to form one general prediction. And of course the answer could be on a spectrum between these two extremes. More specifically, we speculate that there could be local computations for each group of sensory inputs, and then an integration of

multiple groups occurring simultaneously in a hierarchical manner (37). These distinct computations could occur in different cortical layers and/or in different InsCtx subregions (anterior/posterior, granular/agranular (7, 10, 38)). Importantly, seeing as the InsCtx is highly connected to multiple brain regions (38-41), these general functions and computations likely also involve interactions with other brain regions. For example, internal and external multi-sensory integration could already occur upstream of the InsCtx at the brainstem and thalamus. Additionally, hypothalamic pathways also process internal sensory information (42), at least partially in parallel to the InsCtx (7, 18). Furthermore, different types of sensory inputs may be processed separately in the InsCtx and then integrated only downstream, for example in the orbitofrontal and/or prefrontal cortex (43, 44) (see also Question 3 below). The integration in downstream cortical regions could then be used to guide many different behaviors, not only those related to consumption and physiological homeostasis.

Question 2: Is InsCtx function modular? Do different InsCtx subregions serve different functions?

A large corpus of previous work has focused on the InsCtx's gustatory function, both for processing incoming sensory information, as well as on storing it in short- and long-term memory for future use (45-50). Indeed, the InsCtx is likely a central site in which flavor sensations are associated with their subsequent post-ingestive outcomes (51, 52). Interestingly, the gustatory memory of an association with malaise appears to be relatively localized to a specific subregion of the InsCtx in rodents (53). Other work has suggested a broader topographic organization of gustatory function in the InsCtx (54, 55). However, topographic segregation of gustatory function in the InsCtx remains somewhat controversial as some groups have failed to observe it in animal models and in humans (56-62). A possible explanation for these discrepancies could be that, beyond initial taste representations, the InsCtx represents the physiological outcomes predicted by different tastes (7). For example, sweet taste could represent a prediction of caloric intake, whereas an extreme salty taste may represent a change in blood osmolarity or blood pressure, and a bitter taste may represent a prediction of visceral malaise and ensuing sickness (due to poisoning). Therefore, the topographic layout of tastes in InsCtx, which is observed in some circumstances, could reflect gastrointestinal predictions in the mid-anterior part, and cardiovascular and immune predictions in the more posterior part (63). Indeed, some studies have found that when a sweet taste is associated with visceral malaise, InsCtx representation of this tastant is shifted more posteriorly and becomes more similar to a bitter tastant (61, 64). To further test this potential explanation, future studies could experimentally manipulate the association between tastes and the physiological changes that accompany them.

Beyond gustatory function, there have been reports of a posterior-to-anterior topographic organization of cardiovascular, gastrointestinal, and gustatory inputs in the InsCtx (65-68). However, neuroimaging in humans has shown substantial overlap in gustatory and visceral function in the InsCtx (69).

Beyond sensory processing, other work has suggested that general emotional valence and motivation are topographically organized in the InsCtx in a multi-sensory manner (16, 70-73). In summary, it

still remains unclear to what extent sensory information in the InsCtx is segregated and/or integrated (e.g., across cardiovascular, gastrointestinal, and gustatory sensory systems). As a result, it is still unclear if and to what extent InsCtx function is localized to specific subregions or distributed throughout.

Question 3: Does the InsCtx compute interoceptive predictions that then inform decisions, or does it compute predictions of the already decided action? (Or both?)

While there is some evidence that the InsCtx represents ongoing internal sensory information (14-20), and computes predictions and prediction error signals (18, 74, 75), the functional significance of this remains unclear. It stands to reason that the InsCtx's representation of current physiological state would be an important consideration for ongoing decision-making. Similarly, the InsCtx's predictions about how certain actions could affect bodily physiology should also inform the decision-making process. However, we and others have previously shown that ongoing activity in the InsCtx reflects changes in physiological state independently of behavior or subjective experience (18, 19). In contrast, the predictions of future physiological states in the InsCtx were dependent on current behavior (18). This distinction raises the possibility that InsCtx's computation of interoceptive predictions is actually downstream of behavioral choice. Thus, after a choice is made the InsCtx may represent the anticipated interoceptive outcomes of the chosen action so that appropriate anticipatory physiological responses can be initiated. Importantly, anticipation of the interoceptive outcomes of actions is a central aspect of physiological regulation (42, 76-81). We speculate that both options are likely true. This example should emphasize that new experiments should be designed to explicitly test how specific computations in the InsCtx are involved in different phases of behavioral choice.

How can we fill the gaps?

From the experimental perspective, we propose that a basis for understanding the function(s) of the InsCtx will be to perform experiments in which one records and manipulates multiple physiological signals simultaneously. This should be done even in experiments that seemingly do not involve physiological changes, such as assays for anxiety and depressive-like behavior (17, 82). Doing so will enable one to measure the bidirectional relationship between changes in InsCtx activity, changes in bodily physiology, and changes in behavior. Furthermore, selectively perturbing each aspect separately and assessing the effects on the other will reveal the potential causal relationships between them.

We also stress the importance of cellular-resolution recordings of InsCtx activity (e.g., electrophysiology or cellular imaging), since the InsCtx is a heterogeneous structure, composed of different functionally distinct populations (7, 8, 38, 48). Moreover, just like other cortical regions, InsCtx *activity patterns*, rather than *global activity levels* convey information about bodily

physiology. As such, the combination of cellular-resolution recordings of InsCtx activity together with recordings/manipulations of multiple physiological parameters, will allow researchers to decipher InsCtx activity patterns with an unprecedented level of detail (Fig. 2A).

From the analytical perspective, we propose that detailed analyses of InsCtx population activity patterns should be both data driven, as well as hypothesis driven. Data driven analyses will reveal the low dimensional internal structure of population activity (83-86). Moreover, relating the low dimensional internal structure of InsCtx population activity with multiple physiological and behavioral parameters will reveal how it potentially relates to ongoing behavior and bodily physiology. Hypothesis driven analyses will explicitly test specific hypotheses, helping us answer the aforementioned questions, and also allowing further synthesis with work in humans. For example, we and others have recently used empirically defined axes in population activity space, which relate to physiological needs (7, 18, 87). These axes could be defined based on empirical estimation of hydration deficiency, caloric deficiency, and arousal. Using this approach we found that InsCtx population activity slowly progresses along these axes from deficiency to repletion (Fig. 2B *left*). Cues that predict availability of water/food drove transient movement along these axes to repletion-like patterns (18; i.e., satiety; Fig. 2B *right, C*). Moreover, the axes of water deficit and arousal were orthogonal and therefore the representation of these two is potentially independent in InsCtx (but probably not in other brain regions, where activity related concomitantly to arousal and action is prevalent (87-91)). Further analyses using similar approaches could reveal the potential “components” of InsCtx representations of bodily physiology. For example, does InsCtx activity represent osmotic thirst, volaemic thirst, or both (92, 93)? Does in InsCtx representation of food satiety represent gastric stretch, intestinal nutrient sensing, circulating satiety hormones, or all of them together (7, 42)? Moreover, data-driven analyses could reveal to what extent these empirically defined axes represent the internal structure of InsCtx activity, and how its intrinsic activity may be related to them.

Importantly, based on the knowledge gained from the proposed experimental and analytical approach, careful manipulations of InsCtx activity should be designed and executed. For example, optogenetic manipulations of specific InsCtx neurons during specific epochs in behavior/bodily physiology (22, 70, 94, 95) could test the conclusions made from the observational studies. Moreover, activity-dependent tagging and manipulation of functionally defined InsCtx neuronal ensembles have powerfully demonstrated the InsCtx’s role in immune function (63). Finally, recent advances in holographic optogenetic activation now allow activation of specific spatio-temporal activity patterns (96-98). As such, specific InsCtx population activity patterns could be artificially induced to test their effects of behavior and bodily physiology.

Finally, we stress the much needed use of the proposed experimental and analytical approach across multiple behavioral and sensory contexts. This includes consummatory behaviors, sexual behaviors, social behaviors, as well as assays for anxiety, depression, and stress. Comparing activity patterns across diverse behavioral contexts will reveal whether and how the InsCtx contributes to all of these through one canonical computation. Studies of this type may also reveal if the InsCtx’s role in

emotions, cognitive processing, and related pathologies, is merely a reflection of the representation of related physiological aspects, or whether emotions and cognitive processes have distinct InsCtx neuronal representations of their own.

What is the implication for understanding pathological conditions?

Aberrant InsCtx activity has been implicated in multiple pathological conditions, from obesity and eating disorders to addiction, anxiety, and depression (10, 31, 34-36). However, the involvement of the InsCtx in these conditions is still unclear. Answering the three outstanding questions presented in the previous section will help clarify the InsCtx's involvement. We propose that using the experimental and analytical approach outlined above will help answer these questions and elucidate the InsCtx's role in diverse pathologies.

From the perspective of population activity patterns and empirically-defined axes of activity, we identify several key questions related to the involvement of the InsCtx in various pathologies. For example, previous human neuroimaging studies have shown stronger responses to food cues in obese patients that are insensitive to satiation (35, 52, 99). Additionally, bulimia nervosa patients also exhibit stronger responses to food cues (100, 101), while anorexia nervosa patients show weaker responses to food cues after eating (102, 103). Beyond feeding and energy balance, this conceptual framework could generalize to cardiovascular and respiratory function and their involvement, for example, in anxiety disorder. The following questions pertain to these examples.

Is pathology rooted in a dysfunction of specific components of the interoceptive predictions?

By using the conceptual framework of different axes of needs, the root cause of the pathology could potentially be identified. Do enhanced responses to food predicting cues in the InsCtx reflect an incorrect identification of the current physiological state (e.g., the level of caloric deficiency), or an overestimation/underestimation of the predicted physiological change that the cue predicts, or both? Specific experiments aimed at teasing apart these aspects will be needed to resolve these issues.

Is the set point (or settling point) changed, resulting in stronger/weaker cravings?

Using the term “homeostasis” usually assumes there is a “set point” that the system aims to achieve. However, the term “settling point” is likely more appropriate. A settling point will reflect the steady state achieved after addressing a homeostatic deficits, but will rarely reflect an optimal state in which all bodily needs are fully fulfilled (104). In bulimia nervosa or obesity, repeated overconsumption could become the new settling point. Similarly, in anorexia nervosa, repeated restriction and underconsumption could create a new settling point (Fig. 3A,B).

Are new “axes” created in newly developed “needs”, such as in drug addiction?

Within the framework in which physiological needs are represented by changes in InsCtx population activity, which can be formally described as axes in population activity space, what happens when there are new needs? For example, abstinence from drugs of abuse is experienced as a “need” for the drug. Seeing as InsCtx is heavily implicated in drug addiction and drug cravings (31), we propose that these needs could be represented as new axes in population activity space (Fig. 3C). Using animal models with the experimental and analytical approach we proposed above, will reveal the structure of newly formed “need axes”. Furthermore, it will reveal the relationship between different axes, both preexisting and new ones (e.g., overlap, orthogonality, etc.).

If new axes are created, what happens during conflict with pre-existing axes? (e.g., hunger)

This question arises as a follow-up question, derived from the previous one. Nevertheless, we highlight it here due to its important clinical relevance, especially for drug addiction. Drug addiction often times causes neglect of other physiological needs such as energy balance. Physiological needs are organized hierarchically, where some dominate others (e.g., thirst trumps hunger and causes “dehydration induced anorexia” (105)). This suggests that the need for the drug of abuse reorganizes this hierarchy to eventually be situated at the apex of it. Understanding mechanistically how this arises during the formation of addiction could have important clinical implications.

Conclusions and future outlook

In this review, we described the InsCtx’s potential role in interoceptive predictions. We argue that achieving a deeper understanding of the underlying mechanism of the creation, or computation, of these predictions could have important implications for many health conditions, ranging from metabolic diseases to psychiatric disorders. We have outlined an approach, which could bring us closer to this goal. As the InsCtx and brain-body interactions fields are growing, the scientific tools and approaches therein also diversifying in many ways. We believe that, as these fields grow, it will be important for different researchers from different disciplines to keep communicating through a common conceptual infrastructure. This way, we will together enhance our understanding of InsCtx function and related pathologies.

Figure legends

Figure 1: The proposed function of the InsCtx

A. Schematic of some of the different organs and systems that provide direct or indirect sensory information to the InsCtx (highlighted in red): mouth and tongue, stomach, intestines, liver, pancreas, blood, kidneys, heart, and lungs. Note that several additional relevant organs, such as the esophagus are not shown.

B. Illustration of how the InsCtx integrates internal and external sensory information to compute interoceptive predictions that regulate bodily physiology. The sight and smell of the cupcake (external information) will be integrated with bodily signals of energy deficit (internal information). The resulting prediction will trigger a command to the digestive system, causing anticipatory changes such as digestive juice and insulin release.

Figure 2: A proposed experimental and analytical approach for studying the role of the InsCtx in physiological needs

A. Schematic of the proposed approach. *Left:* Activity of large populations of InsCtx neurons are recorded concomitantly with various physiological and behavioral parameters. *Middle:* These physiological and behavioral parameters are then used to define distinct physiological states, and average population patterns are then empirically defined for each physiological state. *Right:* Population activity pattern dynamics are then projected onto the empirically defined axes. This gives a moment-to-moment description of activity patterns in the space of physiological states.

B. Left: Within multi-dimensional neuronal activity space, activity can move along many different axes of physiological deficit. Here we consider two axes of activity: caloric and fluid deficit. *Right:* Similar plot, but for short time-scale activity. During caloric or fluid deficit, cue-driven consumption of a small food/water reward transiently drives activity patterns along the relevant deficit axis towards the sated state. This potentially reflects a transient prediction of the future satiety state that will be reached in 1-2 hours following repeated consumption of such rewards.

C. Experimental data supporting the model in ‘B’. During caloric deficit, cue-driven consumption of a very small food reward (0.1% of the amount needed for satiety) transiently drives activity patterns towards the sated state on the axis between caloric deficit and repletion. Modified with permission from Livneh et al., 2020.

Figure 3: Components of interoceptive predictions that are potentially compromised in various pathologies

A. Schematic demonstration of how the satiety “settling point” can change for pathological conditions such as Anorexia Nervosa (middle) and obesity (bottom).

B. Due to the shift in settling point (shown in ‘A’), responses to food predicting cues (e.g., food logos, or the smell of food) will either decrease or increase, as has been shown in multiple human neuroimaging studies.

C. Schematic illustration of how multiple physiological parameters can be used to define physiological need axes. Once a new need is created (e.g., in drug addiction during abstinence), a new axis may be created based on a unique combination of physiological parameters.

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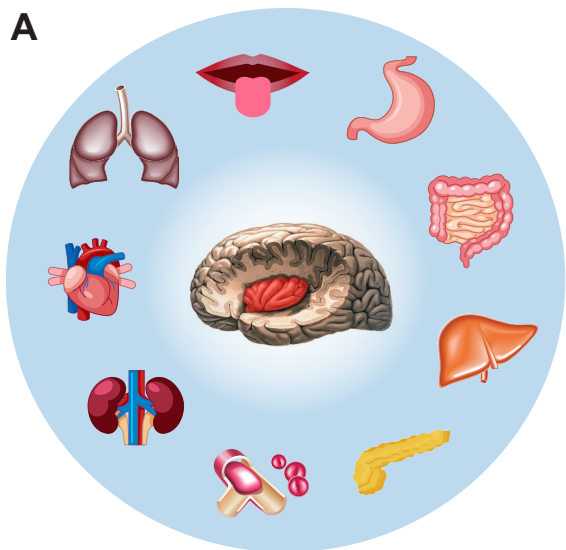
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