Xzistor LAB

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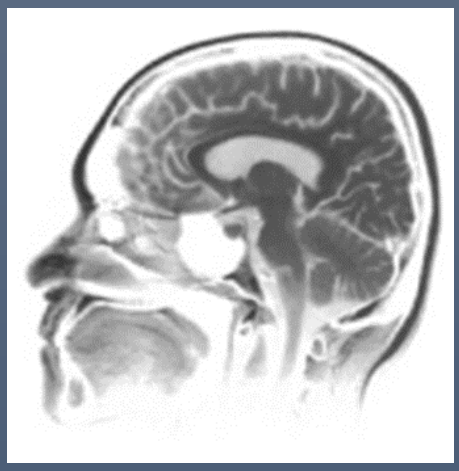


Functional Validation Report: Control Mechanism – Thirst (DRAFT)

FUNCTIONAL VALIDATION REPORT – THIRST

XZISTOR LAB

NEURO-ROBOTICS LABORATORY

Functional Validation Report: Control Mechanism – Thirst

1. Introduction

This Functional Validation Report: Control Mechanism – Thirst ('Validation Report') presents evidence of biological brain structures that provide the same type of functional mechanisms as proposed by the Xzistor Concept brain model to achieve the control of Thirst.

2. Purpose

The aim of this report is to document the evidence collected by the validation team to prove that the biological brain provides the type of functions that would be necessary and sufficient to achieve the control of Thirst in the manner described by the Xzistor Concept brain model.

Whilst the biological brain offers many complex ancillary mechanisms and control functions integrated within the biological Thirst control mechanism, the scope of this project is specifically limited to proving that a set of minimum viable functions provided by the biological brain is both necessary and sufficient to constitute a legitimate instantiation of the Xzistor Concept brain model.

3. Scope

This Validation Report is limited to presenting evidence to support the fact that the biological brain provides the same type of control mechanisms prescribed by the Xzistor Concept to model to achieve the control of Thirst. The Xzistor Concept only aims to explain the biological brain in a 'principal' manner, and the claim is never made that the model can replicate the brain's full complexity.

4. Validation Team

The validation project reported on here was performed by a team of suitably qualified and experienced validators (including holders of PhD degrees in neurology and brain modelling – see Appendix C for short resumes). Whilst during the drafting phase of the report any number of scientific papers could be pulled into the report to act as a temporary central repository of evidential information, the final report will only contain verified references

and will be approved by the Lead Validator. If the report is marked DRAFT it should be handled as work in progress.

5. Copyright

As the report enters the final draft phase a formal audit of final references will be performed to ensure compliance to all applicable copyright rules. While all those collaborating on the project are still collating evidence of scientific research that will support the validation process of the Xzistor Concept, this report will be marked DRAFT to indicate that it should be kept internal to the team.

6. The Thirst Control Mechanism as defined by the Xzistor Concept

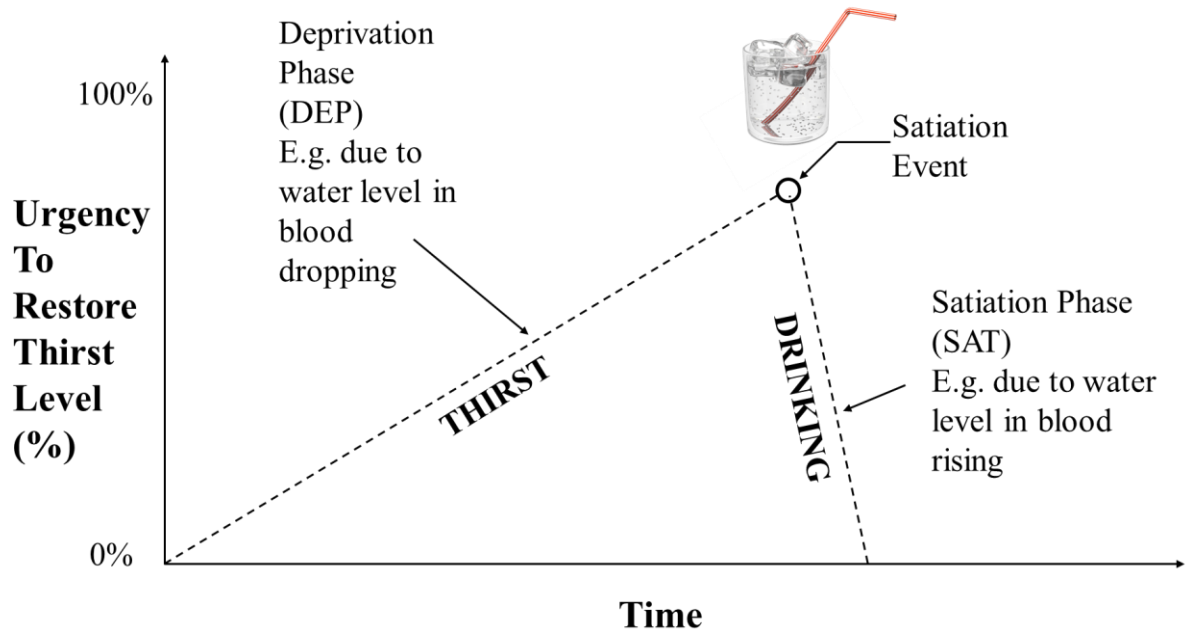
[In the text below, capitalised words e.g. 'Thirst' will always refer to the Xzistor Concept explanation of that term, whilst the uncapitalized version e.g. 'thirst' will denote any other definition that is not specific to the Xzistor Concept brain model.]

To achieve a simple Thirst control mechanism which is 'principally' equivalent to the biological brain, the Xzistor Concept brain model defines a theoretical construct called an Urgency To Restore (UTR) mechanism. The UTR mechanism calculates an 'urgency' for a specific homeostasis utility parameter that has gone out of balance to be corrected and expresses it as a % value. This % value could be derived from when the utility parameter is in optimal homeostasis (no urgency to restore the UTR value = 0%) or to when it is severely out of balance and could damage the system (critically urgent to restore the UTR value = 100%). This provides a way for the model to compare the urgency to restore of all the different UTRs and decide which UTR to prioritise for the restoration of homeostasis. This UTR will be referred to as the Prime UTR.

To add a Thirst control mechanism to an artificial Xzistor brain, a hydration-related marker is required. When the aim is to model a human (mamalin) brain, this could be a simulated utility parameter (e.g. water level in blood, or a derivative marker like NaCL representing plasma osmolality). The Thirst Urgency To Restore (UTR) mechanism can then be defined as a function of the utility parameter. A typical fluctuation of the UTR value as a % over time - first moving out of balance and then being restored - is shown in the graph below). Of course, if actual thirst is not relevant to the embodiment, like for a physical robot, we can

choose a utility parameter like battery level of charge or simulate Thirst just to demonstrate the principle.

As the artificial agent (robot) becomes Thirstier over time, meaning the simulated water level in the blood (or another derivative marker) is effectively dropping, the agent will enter the Deprivation phase of the Thirst UTR curve. When the agent tries to drink something, it will be apparent that the fluid is a legitimate reward source if the simulated water level in the blood suddenly increases (or the derivative marker shows a similar trend) and the UTR value suddenly starts to drop as indicated by the Satiation phase of the UTR curve. This will signify that a Satiation Event (see the apex of the curve) had taken place.



It is crucial for the agent's survival in its environment to learn from the Satiation Event when the simulated fluid (water) reward was encountered for the first time. The model will prominently flag this Satiation Event at the moment it takes place and save all available information around it for future use. What UTR was it trying to restore? What did the water source look like? How did it feel to the touch? Where was it found? How was it retrieved and manually handled? This will be important information for the agent's survival in future and stored a set of associations as part of learning. The Xzistor agent will learn based on the

reward state generated by consuming the simulated fluid, to navigate back to this reward source when Thirsty in future.

It is important to note that the Xzistor Concept brain model will use the increasing UTR value during the Deprivation phase to generate a sensory Thirst state - a variable indicator based on the Deprivation level - that the artificial brain will be constantly be aware of while the Deprivation level remains above the 'activation threshold'. The model will also use the increasing UTR value during the Thirst Deprivation phase to generate an increasing 'intra-abdominal' pseudo-sensory 'feeling' state in the somatosensory cortex equivalent area of the model of which the robot is also constantly aware of and which will also grow in strength as Deprivation increases (for robots this is normally a simplified 'homunculus' or 'bodymap' area). These two aversive sensory states will collectively create a.) the subjective sensation of Thirst during the Deprivation episode as well as b.) the 'intra-abdominal' pseudo-sensory 'feeling' state in the somatosensory cortex (robot equivalent) which will be what the Xzistor model defines as a negative (-) emotion. The latter subjective sensory state will be stored to memory and re-evoked when the agent recalls the Thirst episode in future. Both these sensory states will be 'avoidance' states which means in terms of the Xzistor definition that the robot will 'learn to avoid' these states by operand learning (also called operant conditioning). The Xzistor model explains how, through continued learning and given enough time, the artificial agent could theoretically reach a level where it will be able to associate an avoidance state with the word 'bad' or 'negative'.

Similarly, the Xzistor Concept brain model will use the decreasing UTR value during the Satiation phase to generate a sensory Thirst Satiation state - a variable indicator based on the rate at which the UTR value is declining - that the artificial brain will be constantly aware of while the UTR value remains over the 'activation threshold'. The model will also use the decreasing UTR value during the Satiation phase to generate an 'intra-trunk' pseudo-sensory 'feeling' state in the somatosensory cortex (robot equivalent) area of the model, of which the robot is also constantly aware of and which will also vary based on Satiation strength. These two sensory states (if computer code is used these can simply be defined as variable values) will create the subjective sensation of Thirst Satiation during the 'drinking' phase as well as the more general positive (+) emotion which will be stored to memory and re-evoked when the agent recalls the Thirst Satiation experience in future. Both these

sensory states will be 'pursue' states which means in terms of the Xzistor definition that the robot will 'learn to pursue' these states by operant learning. The Xzistor model explains how through continued learning, and given enough time, the artificial agent could theoretically reach a level where it will be able to associate a 'pursue' state with the word 'good' or 'positive'.

It is important to note that the Xzistor Concept will inhibit some UTRs (like Hunger) and some Reflexes (like Playing) to allow the agent to drink enough to set the Thirst UTR back to 0% before lifting this inhibition (the Xzistor model effectively models an oesophagus delay). Pain and Fear will not be inhibited and will be able to override the Thirst UTR during drinking to become prioritised as the Prime UTR when strong Pain or Fear is experienced.

For the Satiation Event to be effective as an operant learning opportunity, the event must take place when the simulated Thirst reward source (e.g. fluid from faucet) is first sensed and not when the agent starts to sense Thirst Satiation after the oesophagus delay (as this can typically be ten minutes later). The Xzistor Concept therefore requires that a successful contact (first taste) of the Thirst reward source by the trigger the Satiation process preemptively. This will allow for learning about the role of the Thirst reward source in restoring homeostasis *in situ*, and the further process of learning to navigate to it in future through the Xzistor process of reward-backpropagation. The Xzistor Concept does however acknowledge that as fluids move through the theoretical digestive tract there could be further reinforcement learning opportunities based on secondary reward states (but this will require an addition to the current model).

7. Instructions to the validation team

Please send validation sources (papers) where substantive evidence is provided to answer the questions below to **project@xzistor.com**. To manage the amount of information within the strategy provided in the Validation Project Plan, please look carefully at the validation question(s) and make sure the evidence provided addresses the question and that the sources are reputable (preferably peer-reviewed and from international journals). Validation material from internationally acclaimed experts in the field will also help to strengthen the case. Thank you in advance for your contribution.

8. Validation

The validation process will constitute a set of questions and answers. The answers will rely on documented evidence from scientific research (journal published papers) mostly authored by recognised academics in the field and from reputable academic institutions. *Important: It must be emphasised that the sole objective of the Xzistor Validation Project is to provide evidence of functional mechanisms in the human (mammalian) brain that perform the same functions as prescribed by the Xzistor Concept brain model.*

Validation Questions and Answers

Question 1

Does a homeostasis mechanism that result in the subjective perception of thirst exist in the human or mammalian brain?

Answer 1

Yes.

Numerous documented scientific studies provide evidence of a mechanism that controls body fluid homeostasis and leads to the subjective perception of thirst. A selected number of references are provided below.

References:

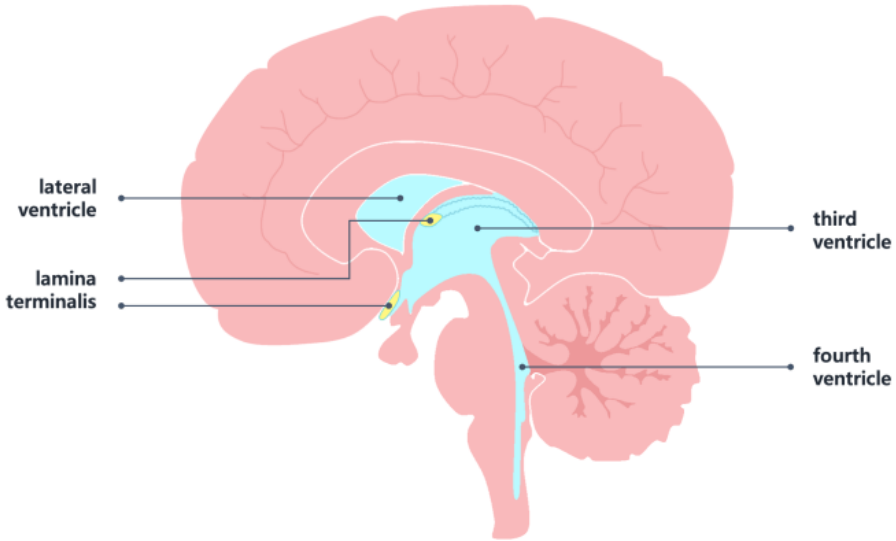
See [2][3][6][8][9][14] in Appendix A.

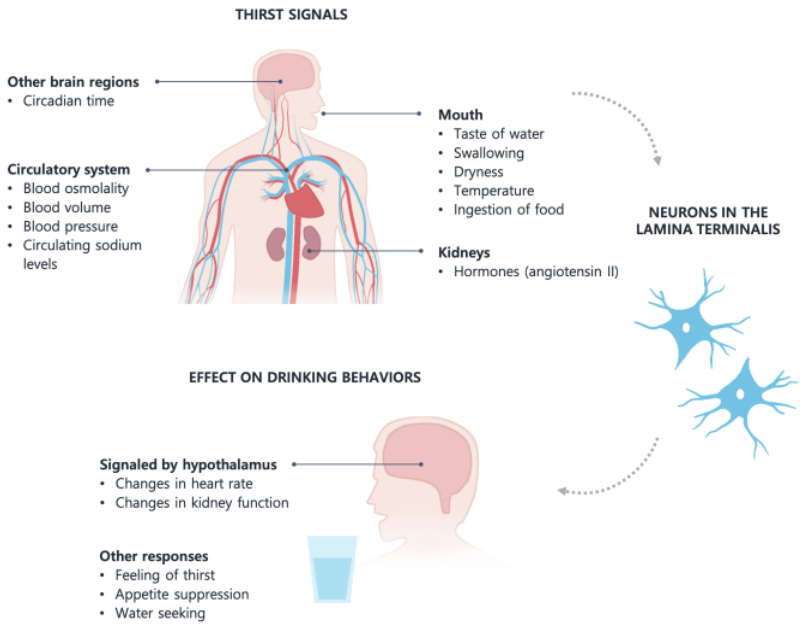
Question 2

Provide a concise high-level summary of the homeostasis mechanism in the human (mammalian) brain focusing only on the aspects required to validate the equivalent Xzistor Concept brain model functionality. Use diagrams if required.

Answer 2

The lamina terminalis (yellow) is a series of interconnected brain structures that act as a central hub to control fluid levels in the body.





Thanks to the location of the lamina terminalis next to ventricles in the brain, they can directly sense key indicators of water needs like sodium levels and osmolality (the ratio of salt particles to a given amount of liquid). They also receive information about what time of day it is from another brain region, as well as cues from the mouth and kidneys.

Neurons in the lamina terminalis can pool all of this information to determine whether the body needs more or less water. If it needs more, the lamina terminalis can trigger feelings of thirst and appetite suppression. If it needs less, the brain will send signals telling you to stop drinking. The lamina terminalis also sends messages to a brain region called the hypothalamus. In turn, the hypothalamus can affect heart rate or urge the kidneys to retain more or less water. The lamina terminalis also projects signals to many other areas of the brain, including the ACC (see [1]) and the insula (see[1][9]) associated with autonomic nervous system responses and also positive and negative emotions. The level of neuronal activation in the ACC (also the insula and MnPO) corresponds directly (linearly) with drinking behaviour in animals and reported thirst perception in humans.

References:

See [1][2][3][6][9][14] in Appendix A.

Question 3

What neurological condition / marker in the human (mammalian) brain will act as the utility parameter to base homeostatic control on as performed by the Thirst Control Mechanism defined by the Xzistor Concept brain model? Focus on the most prominent utility parameter if there are more than one.

Answer 3

ACC activation.

Note: ACC activation is the result of the integration of information on plasma osmolality, blood volume, blood pressure, certain hormones and nutrients and circadian cycles. ACC activation is also influenced by inputs from visceral structures like the pharynx and oesophagus during swallowing and water ingestion [27].

ACC activation can therefore be used as the biological equivalent of a utility parameter as defined by the Xzistor Concept.

References

See [9] in Appendix A.

Question 4

Can an increase in ACC activation act as an indicator for the human (mammalian) brain to generate the equivalent of a Deprivation phase of a Thirst Urgency To Restore (UTR) function as defined by the Xzistor Concept brain model? Note: This question refers to urgency to restore utility parameter value only, and not the subjective perception of thirst which will be discussed later - see Question 6.

Answer 4

Yes.

An increase in ACC activation can act as an adequate indicator for the human (mammalian) brain to generate the equivalent of a Deprivation phase (rising Urgency To Restore) as part of a Thirst Urgency To Restore (UTR) function as defined by the Xzistor Concept brain model.

The human (mammalian) brain can interpret an increase in ACC activation as a state of Deprivation within the thirst homeostasis mechanism.

References

See [2][3][6][9][14] in Appendix A.

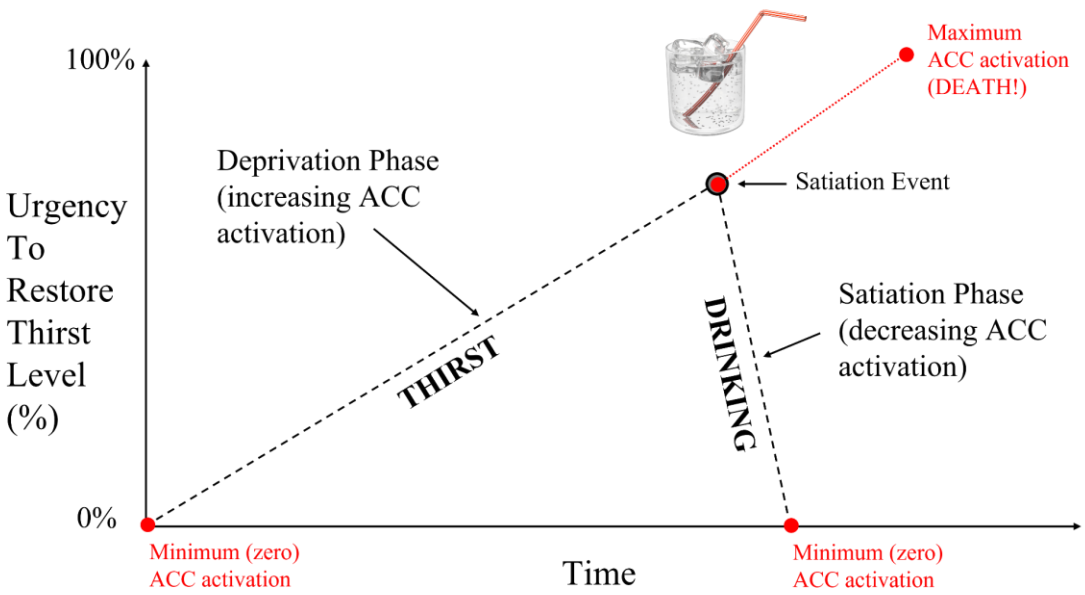
Question 5

Can a continuous rise in ACC activation act as an indicator that can be used by the human (mammalian) brain to interpret as the Thirst UTR's **level** of Deprivation as defined by the Xzistor Concept brain model? Note: This question refers to the level of urgency to restore utility parameter value only, and not the subjective perception of thirst which will be discussed later - see Question 6.

Answer 5

Yes.

*A continuous rise in ACC from zero activation to maximum activation can act as an adequate indicator for the human (mammalian) brain as to the **level** of Deprivation within the biological thirst homeostasis mechanism as shown in the figure below.*



The biological brain can for example start at an Urgency To Restore value of 0% (zero ACC activation) and linearly (approximately) increase to an Urgency To restore value of 100% (at maximum ACC activation).

***Note:** Other parts of the biological brain, namely an area in the insula and also the MnPO have also been shown to proportionally increase activity in concert with the ACC, and a*

decrease during drinking behaviour. For validation of the Xzistor Concept however, a rise in ACC activity offers an adequate biological equivalent of the Deprivation phase as part of a Thirst UTR as shown in the figure above.

References

See [2][6][9][14] in Appendix A.

Question 6

Can it be proven that the biological Deprivation state levels mentioned in Question 5 above are presented to the human (mammalian) brain as a subjective (conscious) perception that the brain will immediately and constantly be aware of once over the thirst awareness threshold?

Answer 6

Yes.

Activity in the anterior cingulate cortex (ACC) has been shown to correlate especially well with the subjective (reported) feeling of thirst in functional magnetic resonance imaging (fMRI) studies in humans [9]. Activity in the ACC has been shown to proportionally increase with an increase in osmolality, and a decrease during drinking behaviour.

References

See [4][9][13][14] in Appendix A

Question 7

The Xzistor Concept brain model calculates a UTR value as a % based on the value of the utility parameter. This means the strength of different UTRs (%) at any given point in time can be compared to determine which UTR is the most urgent to restore. What neurally equivalent metric / measure of UTR strength does the human (mammalian) brain use?

Answer 7

The biological brain will translate the osmolality level (and other related inputs) into the level of neuronal activity in the ACC. Neuroimaging studies have shown that the anterior cingulate cortex (ACC) is consistently activated by thirst [10]. Studies where rates were injected with different concentrations of saline (increased osmolality) showed strong ACC neuronal activation in the form of increased number of c-Fos-positive neurons [10]. Increased firing rates of putative ACC pyramidal neurons preceded drinking behaviour and positively correlated with both the total duration of drinking and the total amount of water consumed. Chemogenetic inhibition of ACC pyramidal neurons changed drinking behaviour from an explosive and short-lasting pattern to a gradual but more persistent pattern, without affecting either the total duration of drinking or the total amount of water consumed. Together, these findings support a role of the ACC in modulating the affective-motivative dimension of hyperosmolality-induced thirst [10].

Discussion by Rocco Van Schalkwyk

The anterior cingulate cortex (ACC) and the insula play key roles in integrating multimodal information important for sensorimotor, emotional, allostatic/homeostatic, and cognitive functions including pain, temperature, sensual touch, itch, visceral sensations, thirst, and hunger [26]. Since the biological brain predominantly acts only on one of these, normally the strongest at any given point in time, the assumption is made that these brain structures neurally compare the activation levels of UTR equivalent mechanisms to identify the strongest (most urgent) UTR to act on.

References

See [10][26]

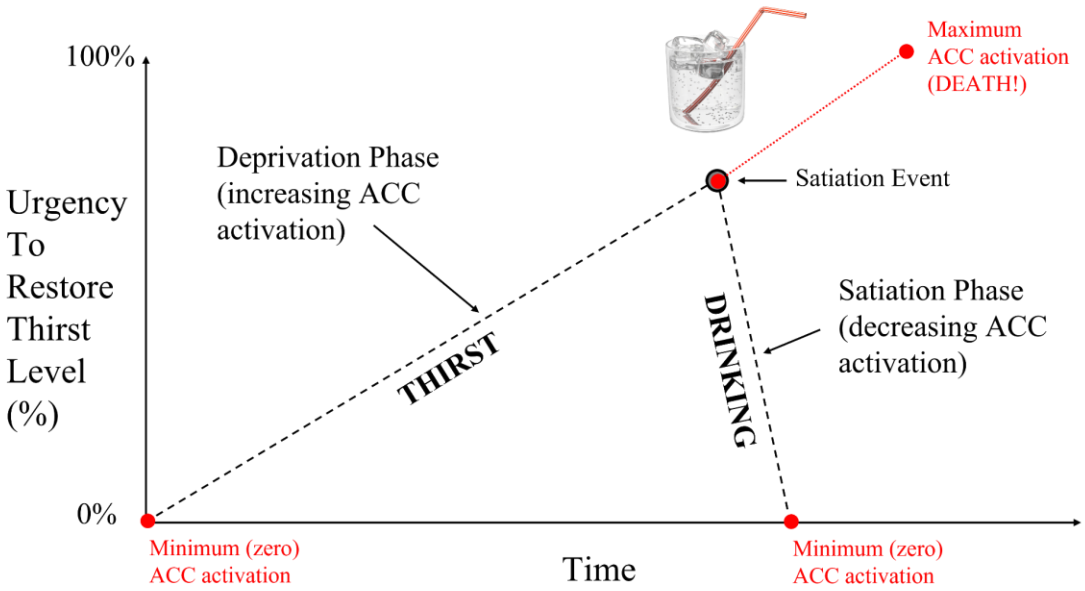
Question 8

Can a decrease in ACC activation act as an indicator that can be used by the human (mammalian) brain to generate the equivalent of a Satiation phase as defined for the Thirst Urgency To Restore (UTR) function (see graph in Section 6) by the Xzistor Concept brain model? Note: This question refers to a decline in urgency to restore utility parameter value only, and not the subjective perception of the satiation of thirst which will be discussed later - see Question 10.

Answer 8

Yes.

A decrease in ACC activation (while water is being ingested) can act as an adequate indicator for the human (mammalian) brain to generate the equivalent of a Satiation phase, in effect reducing the urgency to restore for the biological thirst neural correlate of the Thirst Urgency To Restore (UTR) function as defined by the Xzistor Concept brain model - see graph below.



When thirst level is increasing, and water is suddenly ingested, the biological brain will register this (through mainly viscerosensory afferents from the oral cavity and pharynx / oesophagus) and start to decrease the activity in the ACC. If drinking continues, the

equivalent of a Satiation phase will ensue where the thirst urgency to restore will decrease gradually over time.

References

See [14] in Appendix A.

Question 9

Can a continuous decrease in ACC activity act as an indicator that can be used by the human (mammalian) brain to interpret the **level** of Satiation as defined by the Xzistor Concept brain model? Note: This question refers to urgency to restore utility parameter value only, and not the subjective perception of the satiation of thirst which will be discussed later - see Question 10.

Answer 9

Yes.

*A decrease in ACC activation can act as an adequate indicator for the human (mammalian) brain as to the **level** of Satiation within the biological thirst homeostasis mechanism as shown in the figure in Answer 8.*

According to the Xzistor Concept definition, Satiation (%) refers to the rate of decrease (Satiation = abs|∂UTR/∂t| where ∂UTR/∂t < 0) and the biological brain will have to detect the decline in Thirst UTR as a function of time to generate the neural equivalent of a Satiation value (%).

When the thirst level is increasing, and water is suddenly ingested, the brain will register this change via the ACC activation level. The ACC activity will start to decrease, mainly through inputs from viscerosensory afferents from the oral cavity and pharynx / oesophagus. Plasma osmolality will take longer (tens of minutes) to change due to water ingestion and will only later contribute to signals inhibiting the ACC activity. If drinking continues, the equivalent of a Satiation phase will ensue where the thirst urgency to restore will decrease gradually over time. In the theoretical construct of the Xzistor model, the Urgency To Restore Satiation phase allows the UTR to decrease linearly, but in real life different UTRs will be Satiated at different rates, depending on the rate of ingestion[], the hydrating quality of the fluid[] and how the ACC activation level will be affected by these.

References

See [2][6][9][14] in Appendix A.

Question 10

Can it be proven that the biological Satiation state levels mentioned in Question 5 are represented to the human (mammalian) brain as a subjective (conscious) sensation that the brain will immediately and constantly be aware of once over the thirst awareness threshold?

Answer 10

Yes.

Scientific studies have shown that administering small amounts of water to dehydrated subjects will systematically (again almost linearly) decrease their sense of thirst.

ILLUSTRATION OF THE INTRA-TASK THIRST RATINGS (MEAN ± SEM). Each time bin represents an interval of 10 trials, i.e., the ingestion of 100 ml of water.

References

See [8][14] in Appendix A.

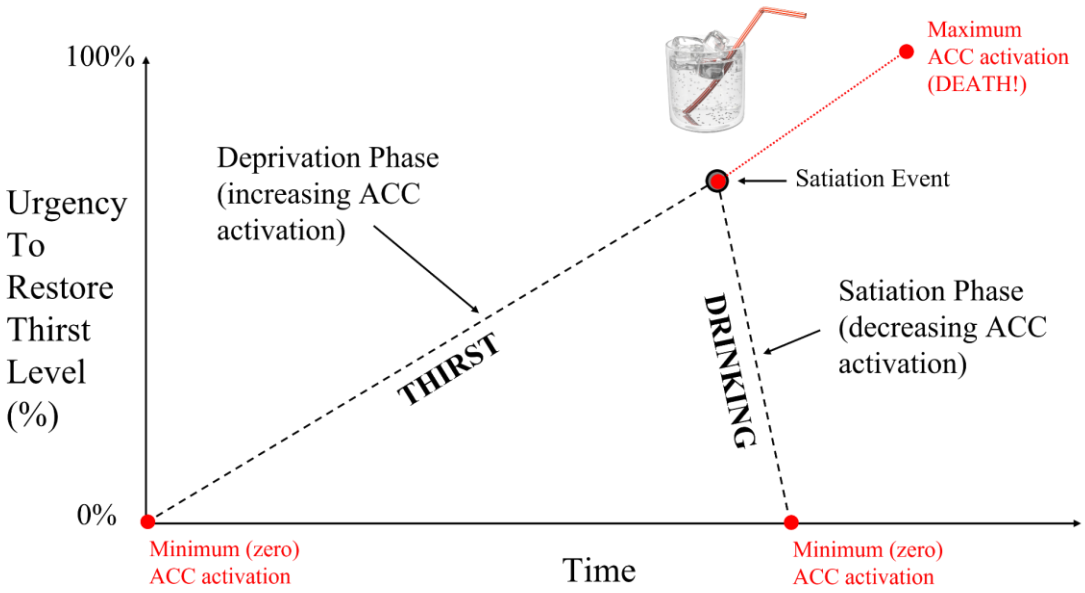
Question 11

Is there evidence in the human (mammalian) brain of a Satiation Event (i.e. an operant learning event) that takes place when water (fluid) is first ingested as proposed by the Xzistor Concept brain model? This question only relates to operant learning, not the subjective 'pleasant' perception during the Satiation Event.

Answer 11

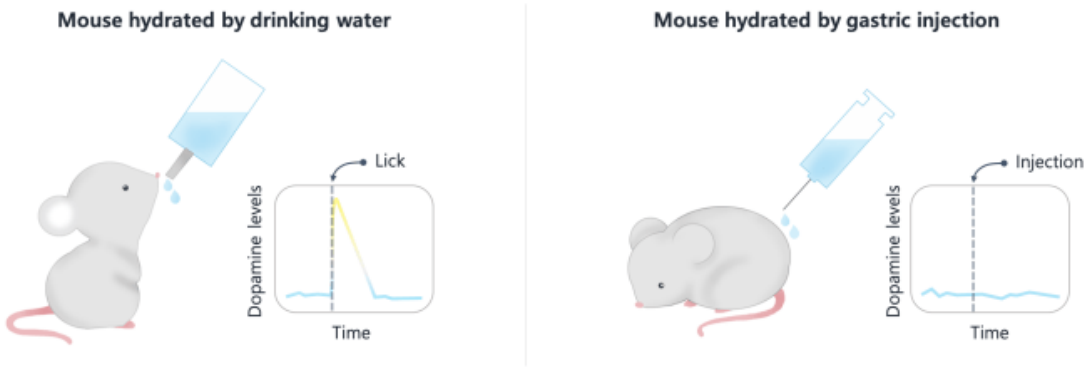
Yes.

The Xzistor Concept brain model defines a Satiation Event as an operant learning event that takes place on the moment the UTR curve changes from the Deprivation phase to the Satiation phase (at the apex of the curve) - see below.



According to the Xzistor Concept, the effector actions that facilitated (and preceded) the successful access to the reward source (water) will be stored to memory as part of operant learning for future use. By rewarding actions that reduce or eliminate the thirst Deprivation state (and lead to Satiation), the Deprivation state will be turned into an 'avoidance' state in the artificial brain. By the Xzistor Concept definition the reinforced effector actions will become a 'mental instruction' to avoid the Thirst Deprivation state.

The psychological phenomenon of operant conditioning is well documented. By using a special kind of sensor that glows in the presence of dopamine, researchers from Caltech found that dopamine was released when thirsty mice drank both water and salty saline solutions [2]. Interestingly, it is the instantaneous physical action of drinking water that releases the dopamine and not simply re-hydration (change in osmolality). This was noticed when oral ingestion was replaced by gastric injections (see image below).



There is ample evidence of mice quickly learning to push a lever to access a reward (e.g. food, water) - see the 'Skinner Box' experiment [15]. This is proof that the effector actions performed to elicit the reward are written to memory and re-evoked when next thirst is experienced and the mouse is in the vicinity of the lever that produced the water. This is functionally the same as the Xzistor Concept using the transition from Thirst Deprivation to Thirst Satiation (the Satiation Event) to form a special association linking important states present in the artificial brain at that specific moment e.g. the presence of the Thirst UTR as the Prime UTR, sensed information about the environment, the effector motions performed during and leading up to the accessing of the reward source, etc. In this way the agent will repeat the effector motions that lead to accessing the reward source when next it experienced Thirst Deprivation in that environment.

References

See [2][5] in Appendix A.

Question 12

Is there evidence in the human (mammalian) brain that the Satiation Event is experienced as a 'subjectively' pleasant (reward) state as proposed by the Xzistor Concept brain model?

Answer 12

Yes.

Scientific studies have shown that administering small amounts of water to dehydrated subjects will systematically (again almost linearly) decrease their sense of thirst.

ILLUSTRATION OF THE INTRA-TASK THIRST RATINGS (MEAN ± SEM). Each time bin represents an interval of 10 trials, i.e., the ingestion of 100 ml of water.

References

See [8] in Appendix A.

Question 13

Based on the above, can it be concluded that the human (mammalian) brain has a mechanism that will provide the functionality of the Thirst Urgency To Restore (UTR) as defined by the Xzistor Concept brain model? Provide an indicative UTR curve.

Answer 13

Yes, we see biological evidence of all the functional components required for the Xzistor Concept UTR mechanism, including:

1.) A utility parameter (ACC activation)

2.) A biological equivalent to the UTR Deprivation phase that shows an increase in ACC neuronal activity and an associated increase in reported thirst (basically linearly) in individuals as their plasma osmolality increases.

3.) A biological equivalent to the UTR Satiation phase that shows a decrease in ACC neuronal activity and an associated decrease (almost linearly) in reported Thirst as fluid is ingested.

4.) A biological equivalent of the Satiation Event as the spike in dopamine (i.e. operant learning) occurs exactly with the first lick of water as recorded in the mouse brain.

References

See [1] [2][3][4] and [8] in Appendix A.

Question 14

Is there substantive evidence to show that the biological Deprivation state mentioned above, apart from creating a subjective thirst perception, also creates a pseudo-tactile sensory state or other 'body internal' sensory state in the human (mammalian) brain that can be used as an avoidance state or 'negative emotion' as defined by the Xzistor Concept brain model?

Answer 14

Yes.

Evidence will be provided below of a mechanism in the human (mammalian) brain providing a clear circuit from the lamina terminalis (LT) to the somatosensory cortex (S1). How the state created in S1 can be turned into a 'negative emotion' will also be discussed.

Activity in the ACC has been shown to correlate especially well with the subjective feeling of thirst in functional magnetic resonance imaging (fMRI) studies in humans [9]. As per the rat brain diagram (Fig 14.1 below), signals from the LT will activate areas of the ACC via the thalamus in response to thirst. In addition, signals from the OVLT (in the LT) to the hypothalamic paraventricular nucleus (PVN) will also activate the sympathetic nervous system [17].

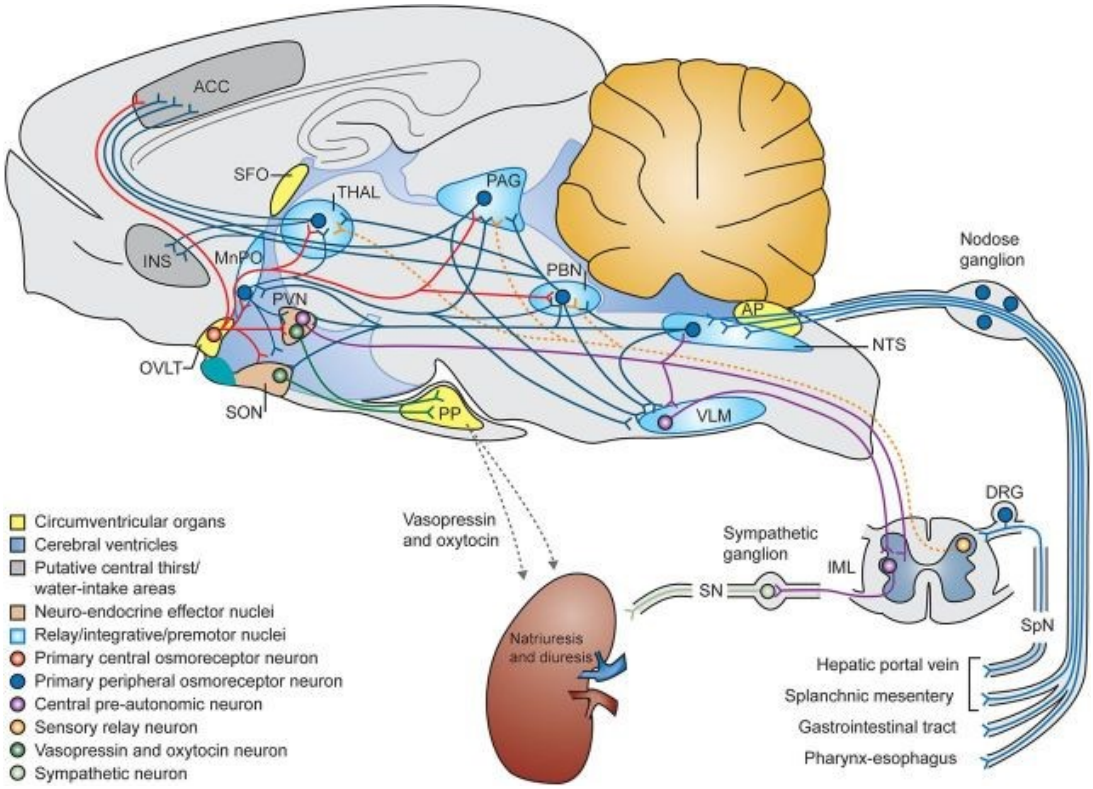


Figure 14.1 - Thirst Descending and Ascending Pathways [18]

The PVN is also the main driver of hypothalamic-pituitary adrenal (HPA) responses producing epinephrine, norepinephrine and cortisol [19]. The physiological effects of the SNS activation on the GIT will include contracting the gut wall, gallbladder, urethral sphincter and relaxing the detrusor muscle and the external anal sphincter [20].

Vasoconstriction causing a reduction in blood flow (and lowered oxygen) in the GI tract, will create a subjectively experienced sensory patterns ranging from e.g. a 'mild fluttering or butterflies in the stomach" to abdominal numbness, nausea (even vomiting)[21]. These subjective feelings are sensed by the GI tract sensory neurons - part of the approximately 500 million neurons of the vagus nerve.

The vagus nerve is the principal component of the parasympathetic nervous system, and is a mixed nerve composed of 80% afferent and 20% efferent fibres[22]. These exteroceptive signals will travel through spinal or cranial nerve (mostly vagal but also glossopharyngeal) pathways, to brainstem nuclei (nucleus tractus solitarius, NTS; and parabrachial nucleus, PBN) [13]. The NTS projects to the thalamus which in turn radiates to the cortical regions

associated with viscerosensory perception, including the somatosensory cortex(S1), insula, medial prefrontal cortex, striatum, nucleus accumbens, hippocampus, and amygdala. Viscerosensory signals have been proven to reach and activate the somatosensory cortex (S1) in humans [23], squirrel monkeys [24] and rats [25].

The study in humans identified a wide pattern of cortical areas that process ano-rectal sensation, including areas involved in spatial discrimination (S1 and S2) and those involved in processing affective and cognitive aspects of sensation (ACC, insula and prefrontal cortex). The results for the squirrel monkey suggest that the squirrel monkey's S1 area is involved in the processing of visceral information [24]. The rat S1 contains a region representing general visceral information, topographically located as if the visceral organs protruded from the mouth[25].

The fMRI scans of human visceral stimulation in the S1 is shown below[23]

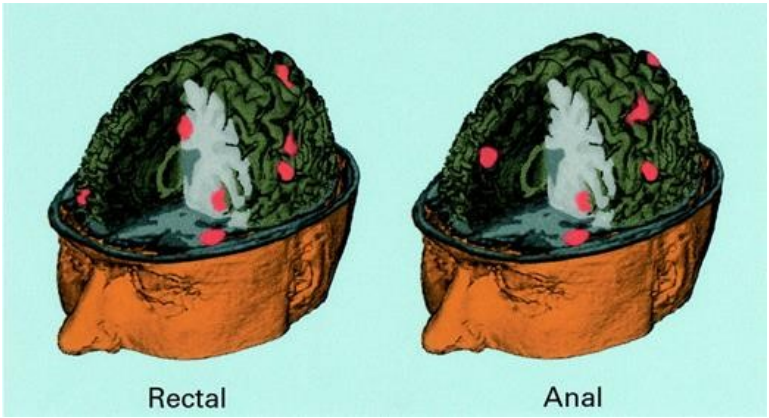


Figure 14.2 - 3D rendered MRI brain scans showing rectal and anal stimulation in S1.

The MRI diagrams above provide representations of the group mean activations for rectal and anal stimulation displayed on a 3D rendered MRI brain scan with the left frontal lobe removed to show the insular and anterior cingulate activations. This shows the similarities in activations in SII, insular and peri-orbital cortex, with the difference in position of the SI activation.[23]

Further evidence of how visceral signals shape brain dynamics and cognition is provided in [27] - see Figure 14.3 below.

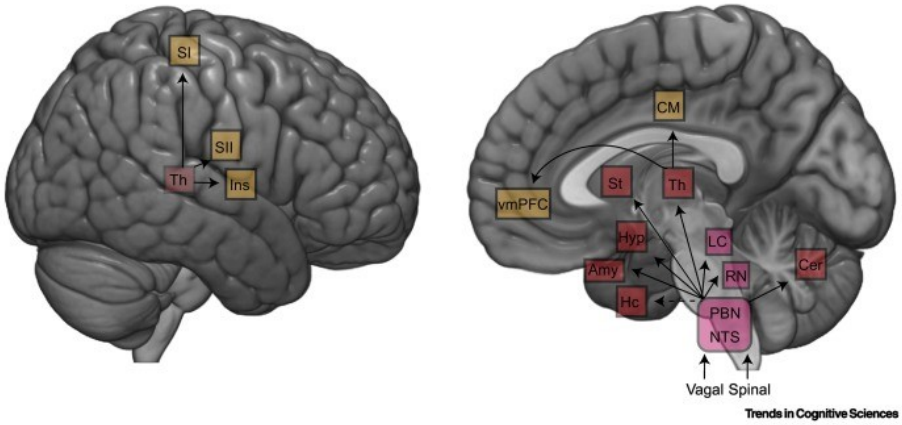


Figure 14.3 Central Targets of Visceral Signals.

Visceral inputs reach the brain via vagal and spinal pathways which target NTS and PBN brainstem relay nuclei (purple). These in turn project to noradrenergic (LC) and serotonergic (RN) nuclei in the brainstem, and to subcortical (red) and cortical (yellow) regions. Note that this schematic representation does not highlight differences between species. Abbreviations: Amy, amygdala; Cer, cerebellum; CM, cingulate motor regions; Hc, hippocampus; Hyp, hypothalamus; Ins, insula; LC, locus coeruleus; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; RN, raphe nucleus; SI, primary somatosensory; SII, secondary somatosensory; St, striatum; Th, thalamus; vmPFC, ventromedial prefrontal cortex.

Turning the state created in S1 into a 'negative emotion'.

Discussion by Rocco Van Schalkwyk.

The sensory state created in S1 due to Thirst Deprivation activating the sympathetic nervous system (SNS) will become an 'avoidance' state because operant learning (i.e. rewarding actions that cause a move away from this S1 state) will 'mentally instruct' the brain to 'avoid' this state in future. [Note: This is not the Thirst Deprivation state which we have based on neuronal activation in the ACC, which will also become an 'avoidance' state. The viscerosensory intra-abdominal state in S1 will be tagged to many Deprivation states generated by different homeostatic control mechanisms. It will also become tagged to all the associations (memories) formed in its presence. And when these memories are recalled (e.g. due to recognition), this 'avoidance' state in S1 will be re-evoked as part of the association

and regenerate the same visceral sensation in the abdomen via the SNS (sympathetic activation), telling the brain that it is sensing (recognising) something or thinking about something that should best be avoided based on prior experience. This S1 'avoidance' state, generated via the SNS during thirst Deprivation or when recalling a tagged association (memory), will be the 'negative emotion'. This 'negative' emotion will be experienced subjectively in the 'intra-abdominal' area of S1 and generated / recalled in a similar fashion for all other UTRs.

The above completes the answer for Question 13.

***Note**: The insular cortex might seem the obvious location for the visceral avoidance state, but sensory representations in the insula are part of the UTR mechanisms in the brain where homeostasis of utility parameters get evaluated for Deprivation and Satiation - this will 'lead' to generating/re-evoking the emotion states in S1 rather than 'being' the emotion states. The Xzistor model explains this very simply in that the insula works with 'control parameters' (utility parameters requiring homeostasis control) while the S1 cortex creates tactile-type sensory representational states (exteroceptive and interoceptive) based on 'parameters' that only serve to inform the brain about environment and body internal conditions and not to assess so-called motivational 'valence'.*

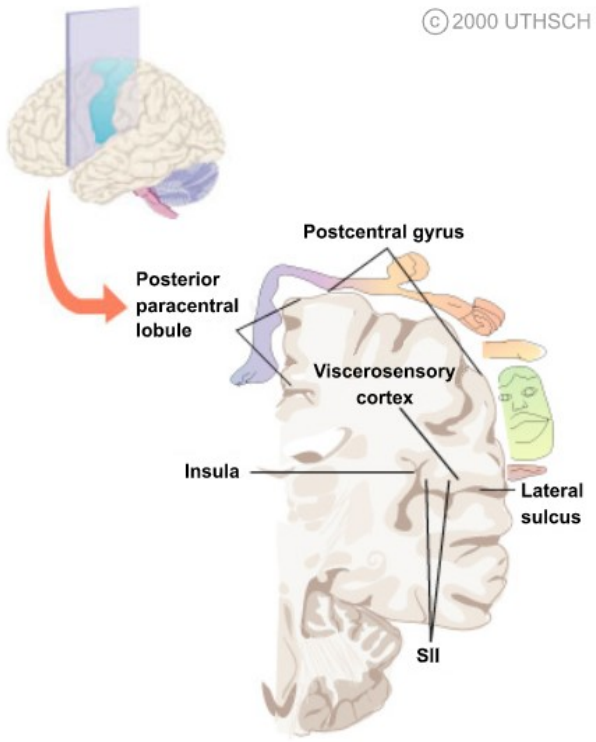


Figure 5.4
The somatotopic representation of the body and face in the postcentral gyrus and posterior paracentral lobule. The somatotopic map was developed from reports of the sensation and the location of the sensation from conscious patients whose cortices were electrically stimulated during neurosurgery.

Figure 14.4 - The 'Intra-abdominal' or viscerosensory cortex in S1 (from [22]).

At the time of this answer the exact locations in the brain that receive viscerosensory inputs are still being debated. Because the Xzistor Concept aims to only provide a 'principal' explanation of the brain, it is adequate (based on the pathways identified above) to choose the S1 intra-abdominal state because it has been established that tactile sensory states in S1 are brought into consciousness. As such it can be claimed that the brain is immediately and constantly aware of these 'emotions' created / regenerated in S1 and that the brain is constantly conscious of these subjective avoidance states - challenging the Chalmers 'hard problem'.

The somatotopic architecture of the intra-abdominal area in the cortical homunculus (see Figure 13.4 above) shows that it links the adjacent parts of the whole GI tract (mouth to anus) that will allow the brain to experience it as an internal 'bodymap' and a sensory

continuum. We do not see the same fidelity in the insula where visceral inputs are viscerotopically organised and integrated. With this assumption, the detailed area in the cortical homunculus (S1) for 'intra-abdominal' sensory representation is given important purpose.

References

References included in text above - see Appendix A.

Question 15

Is there substantive evidence to show that the biological Satiation state mentioned above, apart from creating a subjective thirst Satiation perception, also creates a pseudo-tactile sensory state or other 'body internal' sensory state in the human (mammalian) brain that can be used as an pursual state or 'positive emotion' as defined by the Xzistor Concept brain model?

Answer 15

Yes.

As the ACC activation level starts to decrease during drinking behaviours (e.g. swallowing and ingestion of water), the activation of the sympathetic nervous system via the ACC will also decrease. This inhibition of the SNA will be executed by the vagus nerve - the main way in which the parasympathetic nervous system is activated. In effect this will reverse or 'calm' the sympathetic nervous system and the conscious viscerosensory effects it created. Because of the fact that this calming happens as the 'avoidance' state is being reduced, the activation of the parasympathetic nervous system via the vagus nerve becomes a 'pursual' state - making this intra-abdominal body sensation a positive emotion by the definition of the Xzistor Concept.

The process is in effect the reverse of the one described in some detail in Answer 14, and during the Satiation Event (dopamine release), the 'avoidance' of the sympathetic nervous system viscerosensory effects is reinforced while 'pursual' of the parasympathetic nervous system viscerosensory effect are reinforced.

This reinforcement will lead to the brain effectively become 'mentally instructed' (programmed) to feel a strong compulsion to avoid thirst or bad thirst recollections (indeed leading to a psychophysiological explanation for the word 'bad') and to feel a strong compulsion toward ' pursuing' thirst satiation or good thirst recollections (leading to a psychophysiological explanation for the word 'good').

Question 16

Is there evidence that indicates that other researchers have speculated that the following two 'avoidance' states are experienced as 'negative emotions' as proposed by the Xzistor Concept brain model

a.) The subjective feeling reported during thirst related ACC activation.

b.) The subjective feeling in S1 reported upon reflecting on a severe thirst experience.

Answer 16

Response to a.)

Over the years many researchers have chosen to classify the subjective thirst and thirst satiation (quenching) experiences as emotions. Some examples are discussed below [Need to add form our list].

Add here.

Response to b.)

There is obviously a difference between 'feeling' thirsty and 'thinking' about thirst. But both of these mental states could lead to negative emotions (or generate 'avoidance' states in Xzistor speak). Thinking about an unpleasant thirst episode does not evoke a 'feeling' of thirst (desire to drink water), but will generate a negative emotion. There is less evidence available of researchers who have offered explanations / theories of how 'thinking' about thirst could evoke negative memories. Some isolated references are listed below.

Add here.

Question 17

Summarise the main regions of the human (or mammalian) brain involved in providing the equivalent of the Thirst homeostasis control functions defined by the Xzistor Concept? Provide a simple diagram if possible.

Answer 17

Thirst

Discussion by Rocco Van Schalkwyk

All body/brain parameters to inform thirst level are consolidated in the LT (OVLT, SFO and MnPO). This leads to an increase in activity of the ACC which will create a strong subjective 'desire to drink water'. The ACC activates the sympathetic nervous system via the PVN causing the typical 'stress' body sensation. The viscerseneoty state in the gut is sent to the brainstem, thalamus and on to the somassnory cortex where a dedicated area for the 'intra-abdominal' somatotopic representation will be activated. This will be a conscious state and form a negative emotion (by the Xzistor Concept definition). Memories of the environment will be created linked to this thirst context and associated negative emotions. These memories can be recalled in future which will revoke the same negative emotions (not the actual thirst sensation).

Thirst Satiation

Discussion by Rocco Van Schalkwyk

Many body/brain parameters will inform thirst level originating in the LT (OVLT, SFO and MnPO), but thirst satiation will be triggered by swallowing behaviours and ingesting water (ahead of plasma osmolality changes). This leads to a decrease in activity of the ACC which will create a strong subjective 'quench' sensation. The reduction in ACC activation is achieved by the parasympathetic nerdy systems (mainly situated in the vagus nerve) which will send signals via the brainstem to the thalamus, and from there to the somatosensory area in the brain where the 'intra-abdominal' states are represented. This will be a consciousness state and form a positive emotion (by the Xzistor Concept definition). Memories of the environment will be created linked to this thirst satiation context and associated positive

emotions. These memories can be recalled in future which will revoke the same positive emotions (not the actual thirst 'quench' sensation).

The learning (dopamine) during an actual thirst episode will aid in memorising reward sources and navigation routes to reward sources when the Thirst UTR is active and the prime UTR.

The learning (adrenaline) during an actual thirst episode will aid in memorising reward sources and navigation routes to reward sources when the Thirst UTR is not active and not the prime UTR. This will allow 'avoidance' and 'pursual' planning or prediction even when thirst is not actively being experienced. It will also attach 'avoidance' and 'pursual' context (meaning) to all environmental objects / conditions /routes that could potentially lead to the thirst and thirst satiation situations in future.

Question 18

Discuss any specifics / peculiarities that may be relevant to the manner in which the Thirst homeostasis mechanism in the human (or mammalian) brain is achieved versus the functional description provided by the Xzistor Concept brain model.

Answer 18

Name brain areas.

Add references.

1.) Pre-emptive quenching (oesophagus delay)

2.) Too much water intake can also be fatal and the body has homeostasis mechanisms to avoid this too (compare with hunger / nausea system)

3.) Dopamine Sat reduced over time / not constant for thirst, hunger, etc.

Model still works well with the constant Satiation level approximation.

4.) We probed the function of these signals using a behavioural paradigm that uncouples the oral and systemic effects of ingested fluids, which revealed that post-ingestive rehydration alone can drive robust learning and that this requires VTA-DA neurons. This exposes an organisational logic whereby ingestion of food and water and their subsequent effects on internal state are differentially represented in the dopamine system and used for learning.

https://www.nature.com/articles/s41586-022-04954-0

Validation Questions and Answers

- END HERE -

Validation Statement by Independent Validator 1

Add statement as to quality of evidence presented. Areas of strength / weakness. Clearly state if the provided evidence make the case for a mechanism in the biological brain that can provide the functionality required by the Xzistor Concept brain model.

Validation Statement by Independent Validator 2

Add statement as to quality of evidence presented. Areas of strength / weakness. Clearly state if the provided evidence make the case for a mechanism in the biological brain that can provide the functionality required by the Xzistor Concept brain model.

Assessment by Developer

Add statement as to quality of evidence presented. Areas of strength / weakness. Clearly state if the provided evidence make the case for a mechanism in the biological brain that can provide the functionality required by the Xzistor Concept brain model.

Final Validation Statement by Validation Lead

Add statement as to quality of evidence presented. Areas of strength / weakness. Clearly state if the provided evidence make the case for a mechanism in the biological brain that can provide the functionality required by the Xzistor Concept brain model.

Appendix A – Main Validation Sources (Maximum 20 papers)

(Paste copies of referenced validation sources (papers) here.)

[1] How Does the Brain Sense Osmolality?

Joseph G. Verbalis

Professor of Medicine and Physiology, Georgetown University School of Medicine, Washington, DC

SCIENCE IN RENAL MEDICINE www.jasn.org

J Am Soc Nephrol 18: 3056 –3059, 2007. doi: 10.1681/ASN.2007070825

https://doi.org/10.1681/ASN.2007070825

[2] The Neuroscience of Thirst: How your brain tells you to look for water

SEPTEMBER 26, 2019

BLOG, SPECIAL EDITION: WATER

https://sitn.hms.harvard.edu/flash/2019/neuroscience-thirst-brain-tells-look-water/

Michelle Frank is a PhD Candidate in Neurobiology at Harvard Medical School.

[3] Thirst-associated preoptic neurons encode an aversive motivational drive

William E. Allen, Laura A. DeNardo, Michael Z. Chen, Cindy D. Liu, Kyle M. Loh, Lief E. Fenno, Charu Ramakrishnan, Karl Deisseroth, Liqun Luo

www.science.org (Neuroscience)

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5723384/

[4] The sensitivity of the human thirst response to changes in plasma osmolality: a systematic review

Fintan Hughes , Monty Mythen and Hugh Montgomery*

Hughes et al. Perioperative Medicine (2018) 7:1

DOI 10.1186/s13741-017-0081-4

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5763530/pdf/13741_2017_Article_81.pdf

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5763530/

[5] Dopamine subsystems that track internal states

JamesC.R.Grove1,2,3, LindsayA.Gray4, NaymalisLaSanta Medina4, NillaSivakumar4, JamieS.Ahn4,TimothyV.Corpuz4, JoshuaD.Berke3,5,6, AnatolC.Kreitzer1,3,5,6,7 & ZacharyA.Knight1,2,3,4,6 ✉

https://doi.org/10.1038/s41586-022-04954-0

Received: 30 March 2021

Accepted: 8 June 2022

Published online: 13 July 2022

Here we show that individual dopaminergic neurons in the VTA respond to detection of nutrients or water at specific stages of ingestion. A major subset of dopaminergic neurons tracks changes in systemic hydration that occur tens of minutes after thirsty mice drink water, whereas different dopaminergic neurons respond to nutrients in the gastrointestinal tract. We show that information about fluid balance is transmitted to the VTA by a

hypothalamic pathway and then re-routed to downstream circuits that track the oral, gastrointestinal and post-absorptive stages of ingestion.

https://www.nature.com/articles/s41586-022-04954-0.pdf

[6] Neural circuits underlying thirst and fluid homeostasis

Christopher A. Zimmerman, David E. Leib, and Zachary A. Knight

Department of Physiology, Kavli Institute for Fundamental Neuroscience, and Neuroscience Graduate Program, University of California, San Francisco, San Francisco, California 94158, USA

Published in final edited form as:

Nat Rev Neurosci. 2017 August ; 18(8): 459–469. doi:10.1038/nrn.2017.71.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5955721/pdf/nihms965777.pdf

[7] Gut feelings: the emerging biology of gut–brain communication

Emeran A. Mayer

Center for Neurobiology of Stress, Division of Digestive Diseases, Departments of Medicine, Physiology and Psychiatry, David Geffen School of Medicine at University of California, Los Angeles, CHS 47-122 10833 Le Conte Avenue, Los Angeles, California 90095-7378, USA

Published in final edited form as:

Nat Rev Neurosci. ; 12(8): . doi:10.1038/nrn3071.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3845678/pdf/nihms523424.pdf

[8] From Thirst to Satiety: The Anterior Mid-Cingulate Cortex and Right Posterior Insula Indicate Dynamic Changes in Incentive Value

ORIGINAL RESEARCH article

Front. Hum. Neurosci., 11 May 2017

Sec. Sensory Neuroscience

https://doi.org/10.3389/fnhum.2017.00234

https://www.frontiersin.org/articles/10.3389/fnhum.2017.00234/full#:~:text=The%20cingulate%20cortex%20and%20insula,thirst%20and%20drinking%20to%20satiation.

[9] Thirst

David E Leib 1, Christopher A Zimmerman 1, Zachary A Knight 2

Affiliations expand

PMID: 27997832 PMCID: PMC5957508 DOI: 10.1016/j.cub.2016.11.019

Free PMC article

Author manuscript here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5957508/

(2 x Images below from paper Thirst (Leib, D)

[10] Anterior cingulate cortex modulates the affective-motivative dimension of hyperosmolality-induced thirst

Journal of Physiology

Longyu Ma,Yuqi Zhang,Lupeng Yue,Xueying Zhang,Shuang Cui,Feng-Yu Liu,You Wan,Ming Yi

First published: 07 August 2019 https://doi.org/10.1113/JP278301Citations: 3

Edited by: Ole Paulsen & Yasuhiko Minokoshi

https://physoc.onlinelibrary.wiley.com/doi/full/10.1113/JP278301#:~:text=Neuroimaging%20studies%20have%20shown%20that,drinking%20behaviour%20demanded%20by%20thirst.

[11] Cardiovascular responses to water drinking: does osmolality play a role?

Clive M. Brown, Luc Barberini, Abdul G. Dulloo, and Jean-Pierre Montani

*01 DEC 2005*https://doi.org/10.1152/ajpregu.00205.2005

https://journals.physiology.org/doi/full/10.1152/ajpregu.00205.2005

https://journals.physiology.org/doi/epdf/10.1152/ajpregu.00205.2005

[12] Fluid intake, what's dopamine got to do with it?

Elizabeth G. Mietlicki-Baase,1,2, Jessica Santollo,3,* and Derek Daniels2,4,#*

"Although water rewards are widely used to train animals, attempts to bypass normal drinking and drive operant behaviour with intragastric fluids alone have been unsuccessful. However, we reasoned that changes in fluid balance might be more efficient at driving learning about oral cues such as flavours, since these two modalities are tightly coupled during normal ingestion."

Physiol Behav. Author manuscript; available in PMC 2022 Mar 7.

Published in final edited form as:

Physiol Behav. 2021 Jul 1; 236: 113418.

Published online 2021 Apr 7. doi: 10.1016/j.physbeh.2021.113418

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8900711/

[13] From sensory circumventricular organs to cerebral cortex: Neural pathways controlling thirst and hunger

Michael J McKinley 1 2, Derek A Denton 1 3, Philip J Ryan 1, Song T Yao 1, Aneta Stefanidis 4, Brian J Oldfield 4

Affiliations expand

PMID: 30672620 DOI: 10.1111/jne.12689

https://pubmed.ncbi.nlm.nih.gov/30672620/

[14] Neurons that drive and quench thirst

Claire Gizowski and

Charles W. Bourque

View the article online

https://www.science.org/doi/10.1126/science.aao5574

Permissions

https://www.science.org/help/reprints-and-permissions

www.science.org (Neuroscience)

[15] The Neuroscience of Pleasure

David J. Linden

This piece is an excerpt from David J. Linden's new book, The Compass of Pleasure. He is a professor of neuroscience at The Johns Hopkins University School of Medicine and Chief Editor of the Journal of Neurophysiology.

https://www.huffpost.com/entry/compass-pleasure_b_890342

[16] Dopamine and Noradrenaline in the Brain; Overlapping or Dissociate Functions?

Yadollah Ranjbar-Slamloo1 and Zeinab Fazlali2**

ORIGINAL RESEARCH article

Front. Mol. Neurosci., 21 January 2020

Sec. Molecular Signalling and Pathways

https://doi.org/10.3389/fnmol.2019.00334

https://www.frontiersin.org/articles/10.3389/fnmol.2019.00334/full

[17] Coping with dehydration: sympathetic activation and regulation of glutamatergic transmission in the hypothalamic PVN

Megan E. Bardgett,1 Qing-Hui Chen,3 Qing Guo,1 Alfredo S. Calderon,1 Mary Ann Andrade,1 and Glenn M. Toneycorresponding author1,2.

Am J Physiol Regul Integr Comp Physiol. 2014 Jun 1; 306(11): R804–R813.

Published online 2014 Mar 26. doi: 10.1152/ajpregu.00074.2014

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4042205/#:~:text=Autonomic%20and%20endocrine%20profiles%20of%20chronic%20hypertension%20and,glutamatergic%20activation%20of%20the%20hypothalamic%20paraventricular%20nucleus%20%28PVN%29.

[18] Central vasopressin: dendritic and axonal secretion and renal actions

Daniel G. Bichet1,2

Clin Kidney J. 2014 Jun; 7(3): 242–247.

Published online 2014 May 23. doi: 10.1093/ckj/sfu050

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4377765/

[19] The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress

Sean M. Smith, PhD

Sean M. Smith, Clayton Foundation Laboratories for Peptide Biology, The Salk Institute for Biological Studies, La Jolla, Calif, USA ;

*Wylie W. Vale, PhD**

Wylie W. Vale, Clayton Foundation Laboratories for Peptide Biology, The Salk Institute for Biological Studies, La Jolla, Calif, USA ;

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181830/

[20] Neuroanatomy, Sympathetic Nervous System

Mark N. Alshak; Joe M Das

Last Update: May 14, 2022.

https://www.ncbi.nlm.nih.gov/books/NBK542195/

[21] Explainer: why do we get butterflies in our stomachs?

Bradley Elliott

Lecturer in Physiology, University of Westminster

Published: February 20, 2017 2.06pm GMT

https://theconversation.com/explainer-why-do-we-get-butterflies-in-our-stomachs-72232

[22] Chapter 5: Somatosensory Processes

Patrick Dougherty, Ph.D., Department of Anesthesiology and Pain Medicine, MD Anderson Cancer Center

(content provided by Chieyeko Tsuchitani, Ph.D.)

Neuroscience Online (Open source)

McGovern Medical School

Reviewed and revised 07 Oct 2020

https://nba.uth.tmc.edu/neuroscience/m/s2/chapter05.html

[23] A study of the cortical processing of ano-rectal sensation using functional MRI

David I. Hobday, Qasim Aziz, Neil Thacker, Igor Hollander, Alan Jackson, David G. Thompson

Brain, Volume 124, Issue 2, February 2001, Pages 361–368,
https://doi.org/10.1093/brain/124.2.361

Published: 01 February 2001

https://academic.oup.com/brain/article/124/2/361/402278?login=false

[24] Viscero-somatic neurons in the primary somatosensory cortex (SI) of the squirrel monkey

J Brüggemann 1, T Shi, A V Apkarian

Affiliations expand

PMID: 9187347 DOI: 10.1016/s0006-8993(97)00296-5

https://pubmed.ncbi.nlm.nih.gov/9187347/

[25] Visceral region in the rat primary somatosensory cortex identified by vagal evoked potential

Shin-Ichi Ito

Affiliations expand

PMID: 11835179 DOI: 10.1002/cne.10120

https://pubmed.ncbi.nlm.nih.gov/11835179/

[26] Two systems of resting state connectivity between the insula and cingulate cortex

Keri S. Taylor, 1 , 2 David A. Seminowicz, 1 , 2 and Karen D. Davis

Hum Brain Mapp. 2009 Sep 15; 30(9): 2731–2745.

Published online 2008 Dec 15. doi: 10.1002/hbm.20705

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6871122/#bib3

[27] Visceral Signals Shape Brain Dynamics and Cognition

DamianoAzzalini12IgnacioRebollo12CatherineTallon-Baudry

Trends in Cognitive Sciences

Volume 23, Issue 6, June 2019, Pages 488-509

https://doi.org/10.1016/j.tics.2019.03.007

https://www.sciencedirect.com/science/article/pii/S1364661319300890#bbb0845

Appendix B – Additional Validation Sources

(Paste links to additional validation sources (papers) here.)

[B1] Scientists Can Now Turn off Feelings of Thirst in Mice

They've located the neurons that tell us to reach for the water.

https://www.xzistor.com/validation-of-the-xzistor-concept-against-the-biological-brain/

[B2] Neurons make the sensation of thirst feel unpleasant

Study reveals how the brain prompts mice to drink.

https://www.nature.com/articles/d41586-017-03410-8#:~:text=Thirsty%20animals%20seek%20water