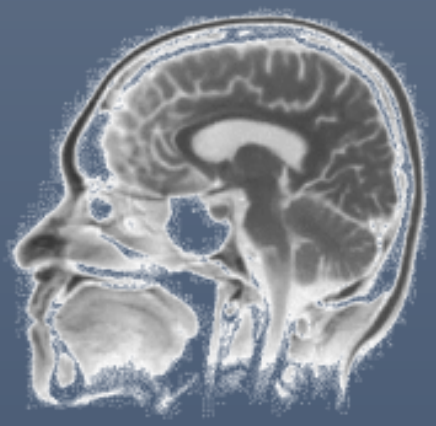
Xzistor LAB

August 2022



Functional Validation Report Homeostasis Mechanism – Thirst (Early DRAFT)

FUNCTIONAL VALIDATION REPORT – THIRST

XZISTOR LAB

NEURO-ROBOTICS LABORATORY

Functional Validation Report Homeostasis Mechanism – Thirst

1. Introduction

This Functional Validation Report Homeostasis 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 Thirst homeostasis.

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 Thirst homeostasis in the manner described by the Xzistor Concept brain model.

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

3. Scope

This Validation Report is limited to presenting evidence to support the fact that the biological brain provides the same type of mechanisms that would be both necessary and sufficient to provide the functions prescribed by the Xzistor Concept to model Thirst homeostasis. 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.

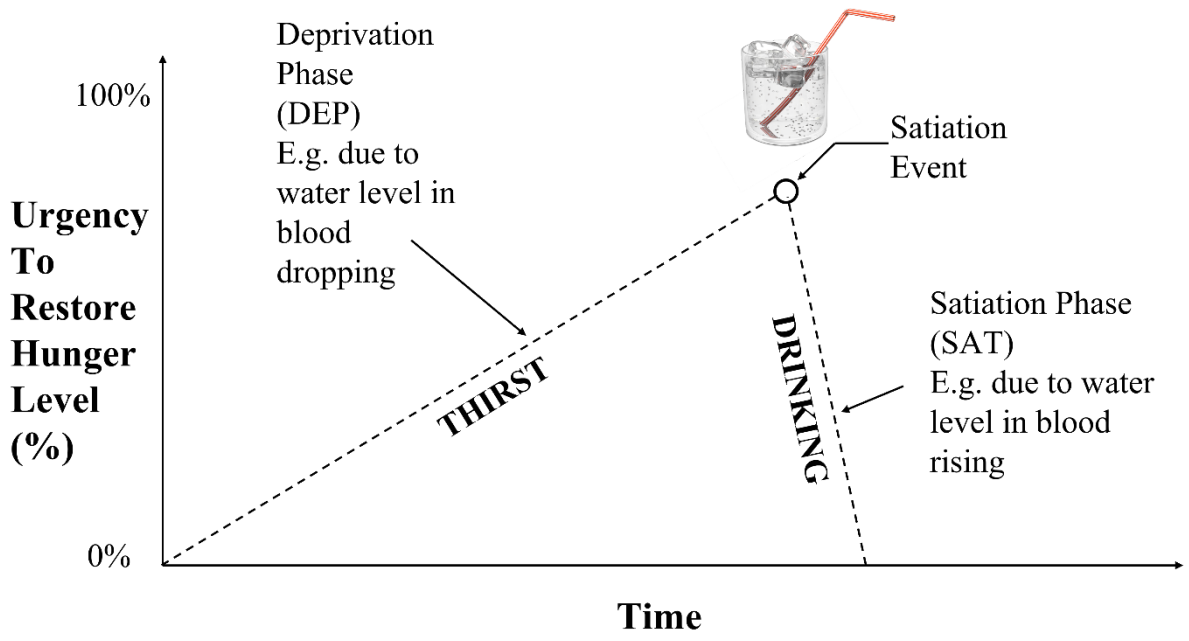
6. The Thirst Homeostasis Mechanism as defined by the Xzistor Concept

To achieve a simple homeostasis Thirst 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.

To add a Thirst homeostasis mechanism to an artificial Xzistor brain a hydration-related marker is normally required which, when the aim is to model a human (mamalin) brain, 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 still emulate Thirst just to demonstrate the mechanism.

As the artificial agent (robot) becomes Thirstier over time, meaning the simulated water level in the blood 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) 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 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 over the ‘activation threshold’. The model will also use the increasing UTR value during the Deprivation phase to generate an increasing ‘intra-abdominal’ pseudo-sensory ‘feeling’ state in the somatosensory cortex equivalent area of the model - for robots this is normally a simplified ‘homunculus’ or ‘bodymap’ area just to demonstrate the principle - of which the robot is also constantly aware of and which will also grow in strength as Deprivation increases. These two sensory states will create the subjective sensation of Thirst during the Deprivation episode as well as the more general negative (-) emotion which 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’.

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 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 be simply be defined 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 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 a ‘pursue’ state with the word ‘good’.

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 operand 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 (this applies to Hunger homeostasis too). The Xzistor Concept therefore requires that a successful contact (first taste) of the Thirst reward source by the agent could be used to trigger the Satiation process preemptively. This will allow for learning about the role of the Thirst reward source in restoring Thirst homeostasis, and the further process of learning to navigate to it in future. 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 expansion of the 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.

Validation Questions and Answers

Question 1

Can substantive evidence be provided that a Thirst homeostasis mechanism has been identified / described in the human (or mammalian) brain?

Answer 1

Yes.

Numerous documented scientific studies provide evidence of a Thirst homeostasis mechanism having been identified in the human (mammalian) brain. A selected number of references are provided below.

References:

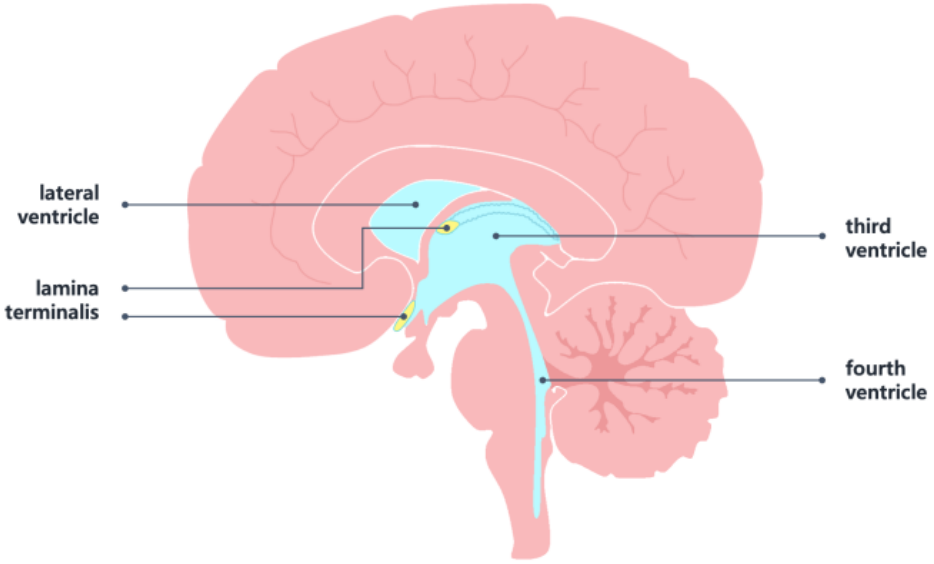
See [1][2][6] in Appendix A.

Question 2

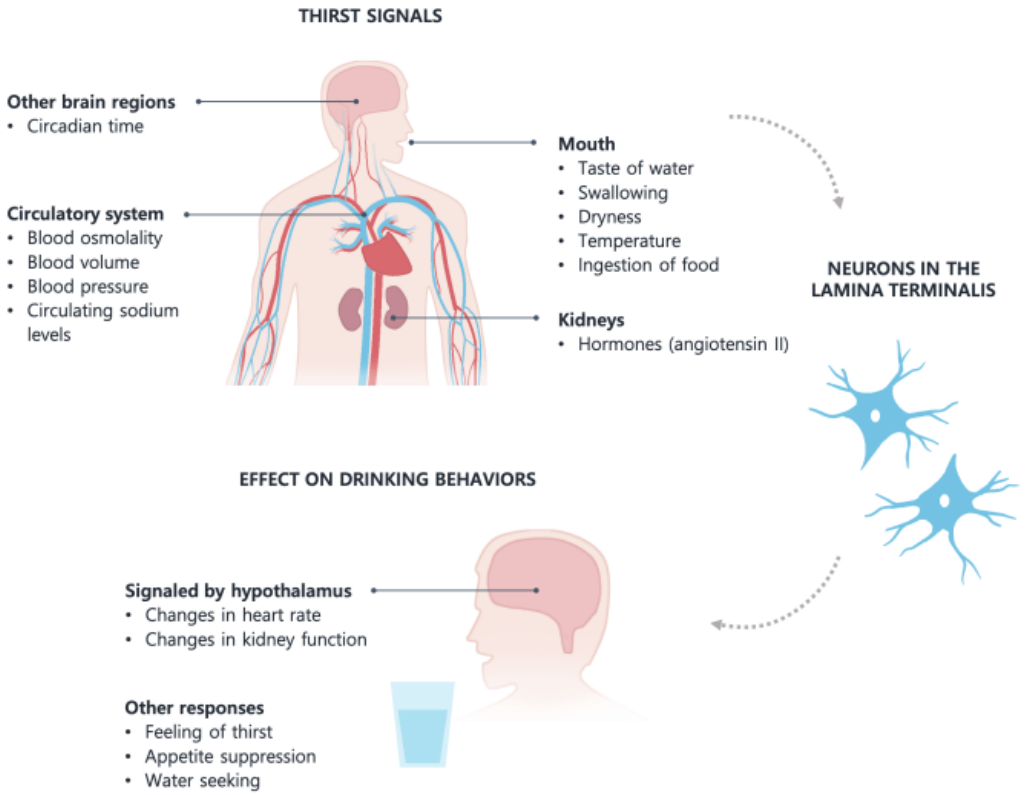
Provide a concise high-level summary of the Thirst homeostasis mechanism in the human (mammalian) brain focusing only on the aspects required to validate the equivalent Xzistor Concept brain model functionality. Use diagrams if required.

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 those associated with positive and negative emotions.

References:

See [2][6] in Appendix A.

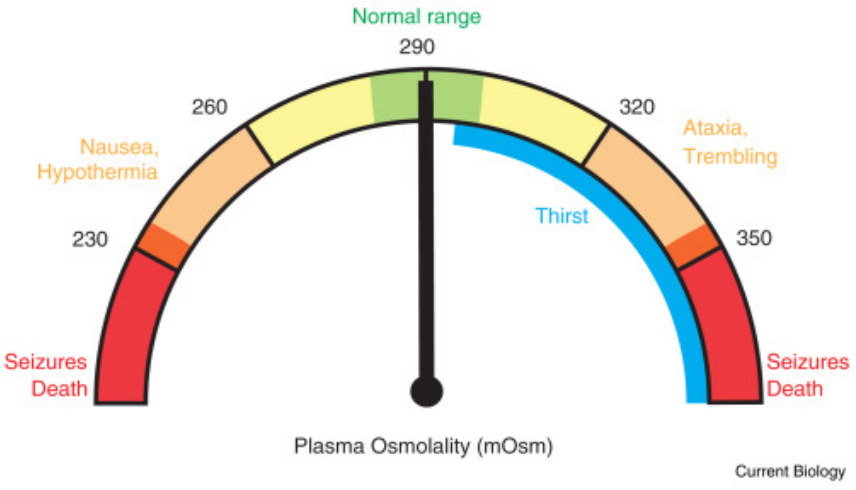
Question 3

What neurological condition / marker in the human (mammalian) brain will act as the utility parameter for the Thirst homeostasis mechanism as defined by the Xzistor Concept? Focus on the most prominent utility parameter if there are more than one.

Answer 3

Plasma osmolality.

Plasma osmolality in humans is maintained between 280 and 295 mOsm/kg H2O, representing one of the most highly regulated parameters of body physiology.



Plasma osmolality will be used as the utility parameter equivalent in this validations study.

References

See [9] in Appendix A.

Question 4

Does the mechanism provide the human (mammalian) brain with an indication (information) that can be interpreted as a state of Deprivation within the Thirst homeostasis mechanism as defined by the Xzistor Concept brain model?

Answer 4

Yes.

The brain can interpret an increase in osmolality above the homeostasis level of 290 as a state of Deprivation within the Thirst homeostasis mechanism.

References

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

Question 5

Does the mechanism provide the human (mammalian) brain with an indication (information) that can be interpreted as the **level** of Deprivation within the Thirst homeostasis mechanism as defined by the Xzistor Concept brain model?

Answer 5

Yes.

*An increase in osmolality above the homeostasis level of 290 can be interpreted by the brain as the **level** of Deprivation within the Thirst homeostasis mechanism.*

References

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

Question 6

Can substantive evidence be provided to prove that the biological Deprivation 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 6

Yes.

Activity in the anterior cingulate cortex(ACC) has been shown to correlate especially well with the feeling of thirst in functional magnetic resonance imaging (fMRI) studies in humans (see [9]).

Studies were also performed to identify the reported plasma osmolality threshold, in dehydrated subjects, for the sensation of thirst, as measured on a visual analogue scale. Trial participants reported thirst intensity (using a visual analogue scale, ranging from 100 mm long to 180 mm long) over the course of the dehydration challenge. Participants would mark the intensity of their subjective sense of thirst on these scales, and the distance from the zero point defined the degree of thirst intensity.

Full journal publication was required. Participants were of any age, with no condition directly affecting their sense of thirst.

Trials included were required to assess thirst intensity as a function of plasma osmolality, and employ linear regression to define the threshold value of pOsm for the sensation of thirst. This allows for both averaging of the thirst response across a range of dehydration severity and identifies the threshold more precisely than a subject reporting their onset of thirst.

Tabulated data were extracted from the trials directly into spreadsheets to become the input for our statistical analysis. The primary variable sought was the pOsm threshold for thirst. Secondary variables, analysed where available, included pOsm threshold for the release of arginine vasopressin (AVP), the rates at which thirst score and AVP concentration varied with increasing pOsm, and linear correlation coefficients of both the thirst and AVP response to pOsm. Each value extracted was accompanied by a measure of variation, being either

standard deviation, standard error or 95% confidence intervals. Data relating to the rate of increase in thirst were normalised to account for differences in size of the visual analogue thirst scales between the studies.

Data on the thirst threshold were available in all included trials. The value ±95% C.I. for the pOsm threshold for thirst sensation was found to be 285.23 ± 1.29 mOsm/kg (n = 167). There was evidence of significant heterogeneity between studies (I2 = 0.73, τ = 4.53). None of the secondary outcome measures were present in all studies. Above this threshold, thirst intensity as a function of pOsm was found to have a mean ± SEM slope of 0.54 ± 0.07 cm/mOsm/kg (n = 143). The mean correlation coefficient of each individual linear regression was 0.91 (n = 120), indicating that above the threshold for sensation, the increase in thirst with pOsm is linear.

References

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

Question 7

Does the mechanism provide the human (mammalian) brain with an indication (information) that can be interpreted as a state of Satiation within the Thirst homeostasis mechanism as defined by the Xzistor Concept brain model?

Answer 7

Yes.

The brain can interpret a decrease in osmolality as a state of Satiation within the Thirst homeostasis mechanism.

References

See [2] in Appendix A.

Question 8

Does the mechanism provide the human (mammalian) brain with an indication (information) that can be interpreted as the **level** of Satiation within the Thirst homeostasis mechanism as defined by the Xzistor Concept brain model?

Answer 8

Yes.

*The rate at which the osmolality decreases can be interpreted by the brain as the **level** of Satiation within the Thirst homeostasis mechanism.*

References

See [2] in Appendix A.

Question 9

Can substantive evidence be provided to prove 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 9

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 10

Is there evidence in the human (mammalian) brain of a Satiation Event (i.e. an operand learning event) that takes place when water (fluid) is first ingested as proposed by the Xzistor Concept brain model?

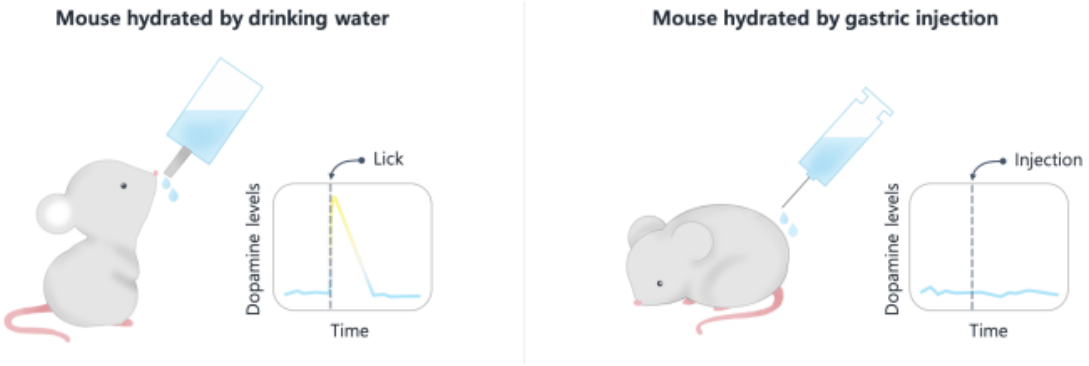
Answer 10

Yes.

The relationship between Thirst Satiation dopamine release and reinforcement learning is well documented in numerous scientific study reports (see references below).[Need more?]

[Is this answering another question?] Researchers at Caltech conducted a study to see why animals find water rewarding. By using a special kind of sensor that glows in the presence of the rewarding molecule dopamine, they could see what kinds of liquids caused dopamine release. They recorded large spikes of dopamine release when thirsty mice drank both water and salty saline solutions, indicating that mice found both of these liquids rewarding. When researchers injected water directly into the guts of thirsty mice, though, they found no

changes in dopamine levels, even though the injected water would also hydrate the thirsty animals.



The fact that the learning event (dopamine spike) takes place when water (fluid) is first experienced and not when body fluid levels start to move towards homeostasis (several minutes later) ensures that the actions around engaging the Thirst reward source are reinforced (stored to memory) and not arbitrary actions which might be performed when the body fluid level starts to move towards homeostasis tens of minutes later.

This does not mean that dopamine is only released upon first encounter with the Thirst reward source. Dopamine is released at different brain sites in a way that tracks the passage of nutrients and fluids through stages of ingestion from the mouth to gastrointestinal tract to blood (see [5] below), and a cluster of veins in the liver has been discovered which is thought to report the actual body fluid hydration level (dilution of nutrients) to the brain.

The strong dopamine spike upon first contact with fluid when Thirsty however provides evidence of the functionality that is equivalent to the Xzistor Concept mechanism for a Satiation Event.

References

See [2][5] in Appendix A.

Question 11

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 11

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 12

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?

Answer 12

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

1.) A utility parameter (plasma osmolality)

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. operand 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 13

Is there substantive evidence available to show that the biological Deprivation state mentioned above could be represented to the human (mammalian) brain as a pseudo-tactile sensory state or other 'body internal' sensory state?

Answer 13

Yes.

The pseudo-sensory 'intra-abdominal' state defined by the Xzistor Concept brain model is created by the biological brain during a Thirst Deprivation event by means of the biological mechanisms described below.

Acute dehydration will cause a steep rise in osmolality which will activate the ACC. The ACC will in turn trigger strong sympathetic nerve activity (SNA) driven by glutamatergic activation of the hypothalamic paraventricular nucleus (PVN)[1]. The SNS will release adrenaline and

cortisol into the bloodstream which will create a characteristic sensory pattern that will be subjectively experienced ('felt') in the abdominal area and normally associated with a 'fear' situation (also called the Fight-or-Flight reflex). While adrenaline contracts most of the gut wall to slow digestion, it relaxes a specific gut muscle called the "external anal sphincter". This neurally mediated vasoconstriction (constriction of the veins) causes a reduction in blood flow through the GI tract and produces the typical "butterflies" feeling in the pit of the stomach. The GI tract senses the shortage of blood, and oxygen, through the stomach's own sensory nerves. This unpleasant sensation is described by some as a feeling of 'stress' or 'anxiety' and can lead to nausea and vomiting in extreme cases. The vagus nerve contains more than 600 million neurons (more than the spine). Approximately 80% of the ascending signals from the GI vagus nerve to the brain are sensory signals []. These 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). Visceral and somatosensory inputs converge on the same neurons [158.] at different stages (spinal cord, NTS). As described in Figure 2, the brainstem nuclei directly influence both serotonergic (dorsal Raphe nucleus) and noradrenergic (locus coeruleus) pathways, and act as relays for direct thalamocortical pathways. From the thalamus numerous cortical areas receive visceral inputs: ***primary and secondary somatosensory cortex*** *[159., 160.],* ***insula*** *[161.], ventromedial* ***prefrontal cortex*** *[162.], cingulate motor regions [163.]. The hippocampus also receives inputs from the NTS via a multi-synaptic pathway [164.]. In addition, the NTS and PBN reach various subcortical structures, the* ***hypothalamus****, the cerebellum, the* ***amygdala****, and the striatum, structures that in turn project to several other cortical areas.*

We thus see evidence that Thirst Deprivation will cause a subjective need (compulsion) to drink in the ACC, but also, via the vagus nerve, create a representation state in the primary and secondary somatosensory cortex. This is in effect a body-sensory state that will depend on the level of Thirst Deprivation akin to how the Xzistor Concept defines a pseudo-sensory 'intra-abdominal' state which, when turned in an 'avoidance' state through reinforcement learning (operant conditioning), will qualify as a negative (-) emotion (see Understanding Emotions: For designers of humanoid robots).

The fact that this pathway always involves the insular cortex is important. It plays a role in a variety of homeostatic functions related to basic survival needs, such as taste, visceral

sensation, and autonomic control. The insula controls autonomic functions through the regulation of the sympathetic and parasympathetic systems.[45][46]

The insular cortex, in particular its most anterior portion, is also considered a limbic-related cortex. The insula has increasingly become the focus of attention for its role in body representation and subjective emotional experience. In particular, Antonio Damasio has proposed that this region plays a role in mapping visceral states that are associated with emotional experience, giving rise to conscious feelings. This is in essence a neurobiological formulation of the ideas of William James, who first proposed that subjective emotional experience (i.e., feelings) arise from our brain's interpretation of bodily states that are elicited by emotional events.

Another important fact is the effect of the adrenaline release on long-terms memory. It has been proven that adrenergic hormones, such as adrenaline, can produce retrograde enhancement of long-term memory in humans. The release of adrenaline due to emotionally stressful events, which is endogenous adrenaline, can modulate memory consolidation of the events, ensuring memory strength that is proportional to memory importance (this supports the Xzistor Concept approach where we see adrenaline is involved in the (-) emotion event and then also ensures the (-) emotion memory of the episode is saved proportionally to the emotional intensity via the Impact Factor).

Post-learning adrenaline activity also interacts with the degree of arousal associated with the initial coding.[48] There is evidence that suggests adrenaline does have a role in long-term stress adaptation and emotional memory encoding specifically (as claimed by the Xzistor Concept). Evidence indicates that epinephrine (EPI) modulates memory consolidation for emotionally arousing tasks in animals and human subjects.[49] This provides the function defined by the Xzistor Concept that will ensure this unpleasant Thirst episode is 'emotionally reinforced' into long-term memory by the effect of adrenaline in the manner that the Xzistor's Impact Factor mechanism explains i.e. episode with strong emotional value will be more prominently stored and easier (preferentially) retrieved in future.

This provides a clear path from homeostasis to emotion as suggested by the Xzistor Concept and explains why thinking about a bad Thirst episode (e.g. 4 days in the desert) will evoke an 'unpleasant' feeling by triggering the SNS (adrenaline) again, but not regenerate an actual

feeling of Thirst Deprivation (i.e. the desire to drink) as generated by the ACC during high osmolality states.

References

[Rocco: Confirm references above]

See [11] in Appendix A.

Question 14

Is there evidence to show that the 'body internal' sensory state above is different for different **levels** of Deprivation?

Answer 14

Thirst will cause a 'body internal' sensory state as per Answer 13. Note that this is not the sensation of Thirst itself. The Deprivation phase of the Thirst UTR will generate the Thirst sensation. But it will also generate, via the sympathetic nervous system, an additional sensory state in the visceral (vagus) area. These two sensory states are not the same. When we recall a drastic Thirst episode (lost in the desert), thinking back will not re-evoke a feeling of Thirst (we will not get Thirsty), but it will evoke from memory an unpleasant feeling. The magnitude of this unpleasant feeling will depend on how high the Thirst Deprivation was at the time. The amygdala would have attached this negative emotion to the memories formed during the extreme Thirst episode, and the punceate will be instrumental in re-evoking these negative sensations when the memories are recalled. This negative sensation meets the definition of negative (-) emotion as defined by the Xzistor Concept brain model.

Reference [8]

Question 15

Is there evidence that shows the state / brain area above plays a role in Negative Emotions?

Answer 15

Sympathetic NS – links to Negative Emotions (Stress / Anxiety)

Emotional expression, which depends greatly on the sympathetic nervous system, is controlled by regions of the cerebral hemispheres above the hypothalamus and by the midbrain below it (Brittanica).]

Question 16

Is there substantive evidence to show that the biological Satiation state mentioned above could be represented to the human (or mammalian) brain as a pseudo-tactile sensory state or linked to another 'body internal' sensory state?

Answer 16

Yes.

Decreased osmolality [Na+] will trigger the parasympathetic nervous system (steady on Rocco! Evidence?). The autonomic response to water drinking is rather unusual, consisting of simultaneous sympathetic and vagal activation [11]. CONTRADICTION!!! Or is this pleasant state driven by dopamine??? Limbic system??

75% of PNS signals go to to the vagus nerve system. 90% signals from the vagus nerve go to the brain. Will be consciously 'felt' along the GI tract from the anus to the ears! This is for PNS not SNS. The vagus nerve represents the main component of the parasympathetic nervous system, which oversees a vast array of crucial bodily functions, including ***control of mood****, immune response, digestion, and heart rate*

The relaxing / resting effect (and subjective feeling) caused by the parasympathetic nervous system is well documented. The parasympathetic nervous system will therefore create a body state (this might be mild) that will be sensed in the vagus area and experienced as a 'body internal' sensory state by the brain. It will become an 'pursue' state as the brain learns how to pursue this state. Learning happens during Satiation Events when actions leading to this sensation are strongly rewarded and stored as the actions to pursue in future when this state is experienced.

Question 17

Is there evidence to show that the 'body internal' sensory state is different for different **levels** of Satiation?

Answer 17

Thirst will cause a 'body internal' sensory state as per Answer 13. Note that this is not the sensation of Thirst Satiation itself. The Satiation phase of the Thirst UTR will generate the Thirst Satiation sensation. But it will also generate, via the parasympathetic nervous system, an additional sensory state in the visceral (vagus) area. These two sensory states are not the same. When we recall an intense Thirst Satiation (quenching) event, thinking back will not re-evoke a feeling of quenching, but it will evoke from memory a pleasant feeling. The magnitude of this pleasant feeling will depend on how high the Thirst Satiation was at the time. The amygdala would have attached this positive emotion to the memories formed during the intense Thirst Satiation event, and the punceate will be instrumental in re-evoking these positive sensations when the memories are recalled. This positive sensation meets the definition of positive (+) emotion as defined by the Xzistor Concept brain model.

Reference [8]

Question 18

Is there evidence that shows the state / brain area above plays a role in Positive Emotions?

Answer 18

*Parasympathetic NS (get evidence Rocco!) – links to vagus nerve links to Pos Emotions (Reduce Stress / Anxiety)??? The vagus nerve represents the main component of the parasympathetic nervous system, which oversees a vast array of crucial bodily functions, including **control of mood**, immune response, digestion, and heart rate.*

Question 19

What are the main regions of the human (or mammalian) brain involved in providing the Thirst homeostasis functions required by the Xzistor Concept? Provide a simple diagram if possible.

Answer 19

Now we can show a diagram of the areas we have nominated to provide the key functions we have identified.

Question 20

Is there evidence that learning (association-forming) occurs within the human (or mammalian) brain during a Thirst Satiation Event?

Answer 20

Dopamine release = learning. Emotions linked to memories by amygdala

Question 21

Is there evidence of a 'competition' function/ mechanism that will compare the Thirst UTR's strength with the strengths of other UTRs?

Answer 21

Check thalamus, amygdala, etc.

Question 22

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 22

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 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

[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] From How Does the Brain Sense Osmolality?

Joseph G. Verbalis

JASN December 2007, 18 (12) 3056-3059; DOI: https://doi.org/10.1681/ASN.2007070825

[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 2005https://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/

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

[B3] 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)

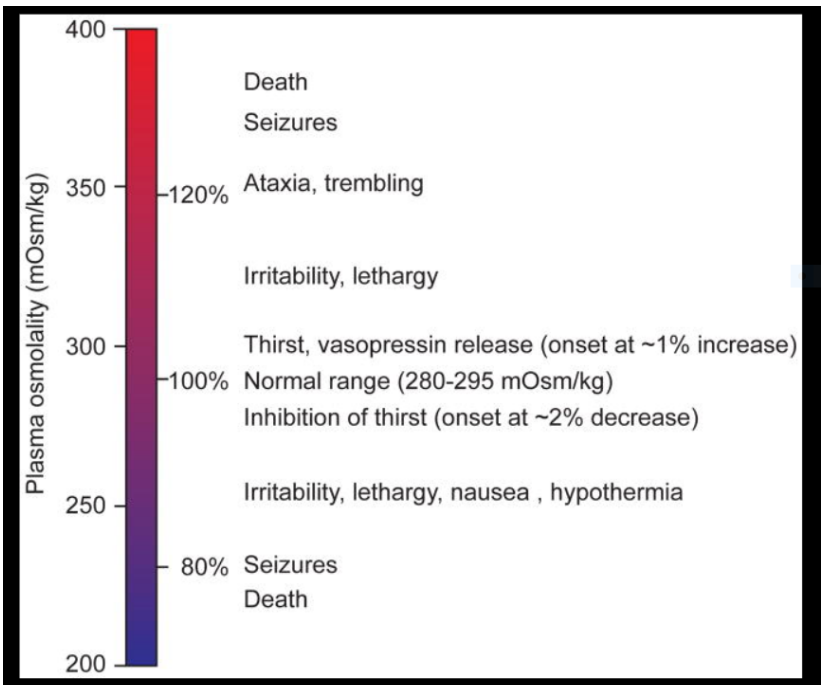
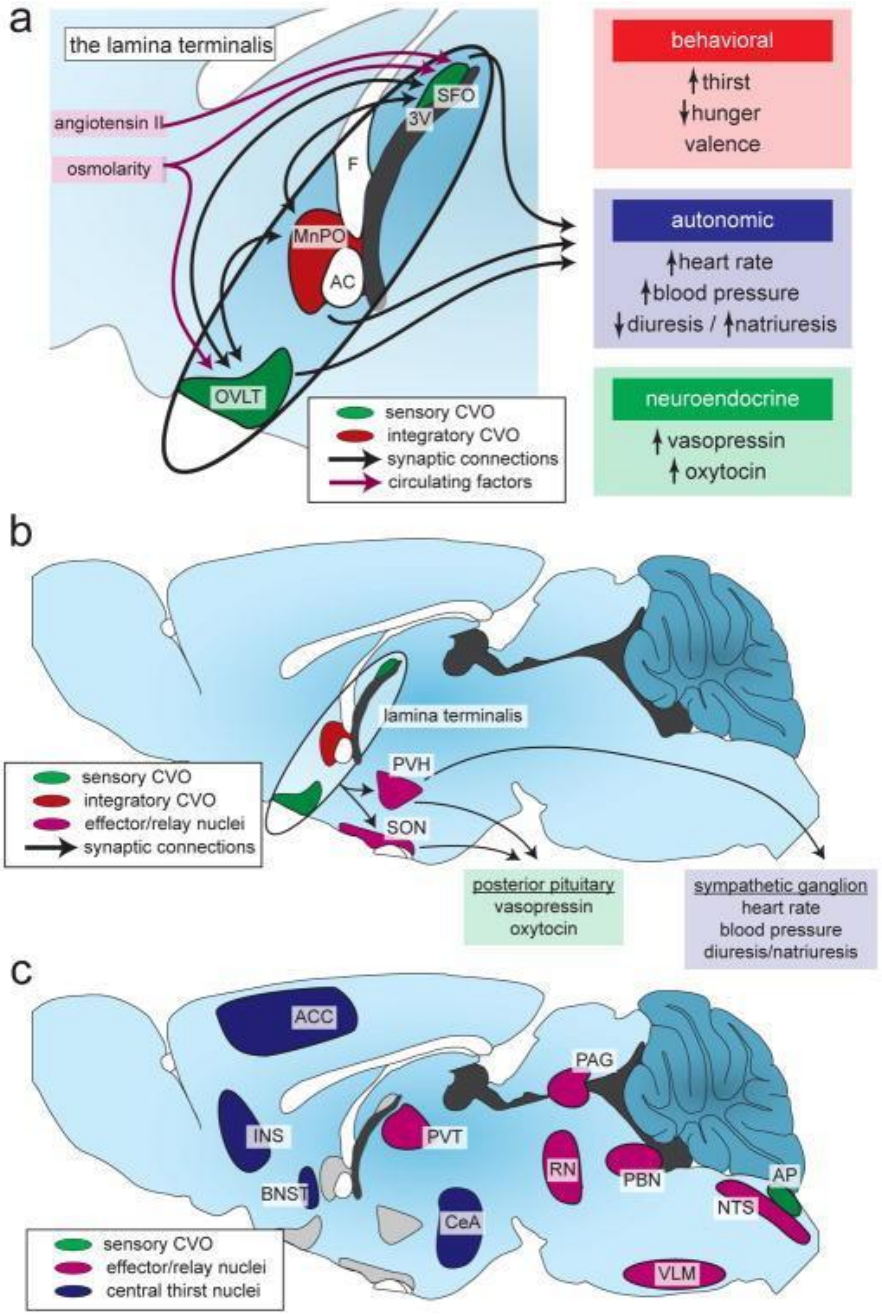


Figure 1 Physiologic effects of deviations in plasma osmolality


a
the lamina terminalis
angiotensin II
osmolarity
SFO
3V
F
MnPO
AC
OVLT
sensory CVO
integratory CVO
synaptic connections
circulating factors
behavioral
thirst
hunger
valence
autonomic
heart rate
blood pressure
diuresis / natriuresis
neuroendocrine
vasopressin
oxytocin
b
lamina terminalis
PVH
SON
sensory CVO
integratory CVO
effector/relay nuclei
synaptic connections
posterior pituitary
vasopressin
oxytocin
sympathetic ganglion
heart rate
blood pressure
diuresis/natriuresis
c
ACC
PAG
INS
PVT
RN
PBN
AP
NTS
BNST
CeA
VLM
sensory CVO
effector/relay nuclei
central thirst nuclei

[B4] The limbic system

Queensland Brain Institute

https://qbi.uq.edu.au/brain/brain-anatomy/limbic-system

From paper [B4}

*The limbic system is the part of the brain involved in our behavioural and **emotional** responses, especially when it comes to behaviours we need for survival: **feeding**, reproduction and caring for our young, and fight or flight responses.*

*You can find the structures of the limbic system buried deep within the brain, underneath the cerebral cortex and above the brainstem. The **thalamus**, **hypothalamus** (production of important hormones and regulation of **thirst**, hunger, **mood** etc) and basal ganglia (reward processing, habit formation, movement and learning) are also involved in the actions of the limbic system, but two of the major structures are the **hippocampus** and the **amygdala**.*

[Rocco: For the thalamus and hypothalamus to be able to generate the appropriate hormones to regulate thirst it needs to either first generate the information needed to choose the correct hormones, or receive this information from somewhere else.]

Amygdala

*The amygdala's name refers to its almond-like shape. Located right next to the hippocampus, the left and right amygdalae play a central role in our emotional responses, including feelings like pleasure, fear, anxiety and anger. The **amygdala also attaches emotional content to our memories**, and so plays an important role in determining how robustly those memories are stored. Memories that have strong emotional meaning tend to stick.*

[Rocco: Perfect for our validation of Xzistor association forming]

The amygdala doesn't just modify the strength and emotional content of memories; it also plays a key role in forming new memories specifically related to fear. Fearful memories are able to be formed after only a few repetitions. This makes 'fear learning' a popular way to investigate the mechanisms of memory formation, consolidation and recall.

Hippocampus

The hippocampus, like many other structures in the brain, comes as a pair, one in each hemisphere of the brain. It resembles the shape of a curvy seahorse (and is named after its scientific genus) and is essentially the memory centre of our brains. Here, our episodic memories are formed and catalogued to be filed away in long-term storage across other parts of the cerebral cortex.

Connections made in the hippocampus also help us associate memories with various senses (the association between Christmas and the scent of gingerbread would be forged here). The hippocampus is also important for spatial orientation and our ability to navigate the world.

The hippocampus is one site in the brain where new neurons are made from adult stem cells. This process is called neurogenesis, and is the basis of one type of brain plasticity. So it's not surprising this is a key brain structure for learning new things.

[B5] Think Twice: How the Gut's "Second Brain" Influences Mood and Well-Being

https://www.scientificamerican.com/article/gut-second-brain/

This multitude of neurons in the enteric nervous system enables us to "feel" the inner world of our gut and its contents.

"A big part of our emotions are probably influenced by the nerves in our gut," Mayer says. Butterflies in the stomach—signaling in the gut as part of our physiological stress response, Gershon says—is but one example. Although gastrointestinal (GI) turmoil can sour one's moods, everyday emotional well-being may rely on messages from the brain below to the

brain above. For example, electrical stimulation of the vagus nerve—a useful treatment for depression—may mimic these signals, Gershon says.

[Rocco: Well aligned with Xzistor 'intra-abdominal' representation of Deprivation i.e. negative emotion.]

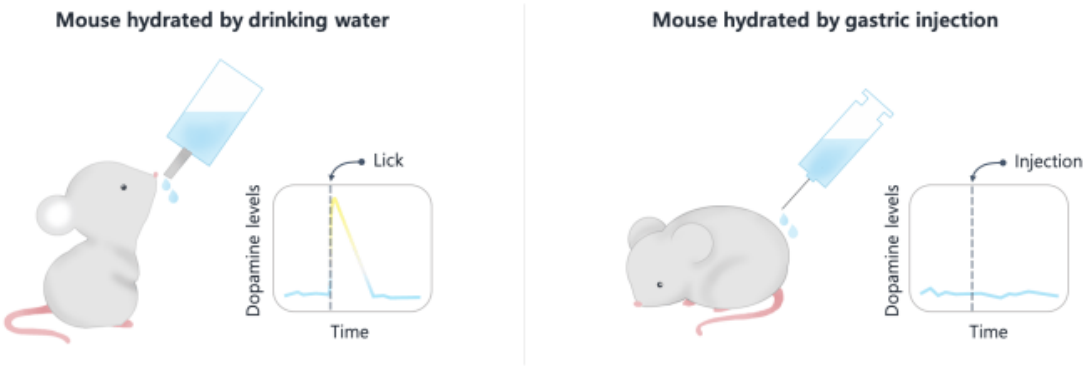
[B6] Temporally and Spatially Distinct Thirst Satiation Signals

https://www.cell.com/neuron/fulltext/S0896-6273(19)30396-4?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0896627319303964%3Fshowall%3Dtrue

NOTES

Yes.

Figure below: Drinking water is rewarding. Researchers in Yuki Oka's group at Caltech conducted a study to see why animals find water rewarding. By using a special kind of sensor that glows in the presence of the rewarding molecule dopamine, they could see what kinds of liquids caused dopamine release. They recorded large spikes of dopamine release when thirsty mice drank both water and salty saline solutions, indicating that mice found both of these liquids rewarding. When researchers injected water into thirsty mice, though, they found no changes in dopamine levels, even though the injected water would also hydrate the thirsty animals.



Model Developer Comment: This phenomenon might seem contradictory at first but is elegantly explained by a concept defined by the Xzistor Concept brain model as a Satiation Event (see above: Section 6. The Thirst Homeostasis Mechanism as defined by the Xzistor Concept). The Satiation Event explains that any reward provided to the brain after the correct drinking behaviour had been performed (e.g. 10 minutes later) will reinforce the wrong behaviours – not the moving to the faucet and sipping/swallowing sequence. Therefore the biological brain has no choice but to reward the 'swallowing' behaviour (assuming it will lead to hydration) and assign no reward to the actual restoration of hydration into the blood stream that is expected to happen a few minutes later. The biological brain's effective UTR curve will still broadly look like the XC curve, except that the Satiation Event is moved to an earlier (pre-emptive) point and triggered by a swallow sequence rather then a lowering of osmolality. Some mammals will closely resemble the XC curve while other mammals like mice, humans, etc. will required the Satiation Event to be

moved earlier and triggered by the 'swallow sequence' to ensure learning and 'valuing' of this behaviour as important for survival.

This revealed that dopamine is released at different brain sites in a way that tracks the passage of nutrients and fluids through stages of ingestion (from the mouth to gastrointestinal tract to blood.

"The inhibitory signals we discovered are only active during the drinking action," Oka says. "However, the feeling of satiety indeed lasts much longer. This indicates that the MnPO inhibitory neurons cannot be the only source of thirst satiety. This will be the subject for future study."

RVS: Add vein cluster in liver.

Thirst circuitry mapped in the brain

https://www.nih.gov/news-events/nih-research-matters/thirst-circuitry-mapped-brain

References

See [2] in Appendix A and [8][10][23] in Appendix B.

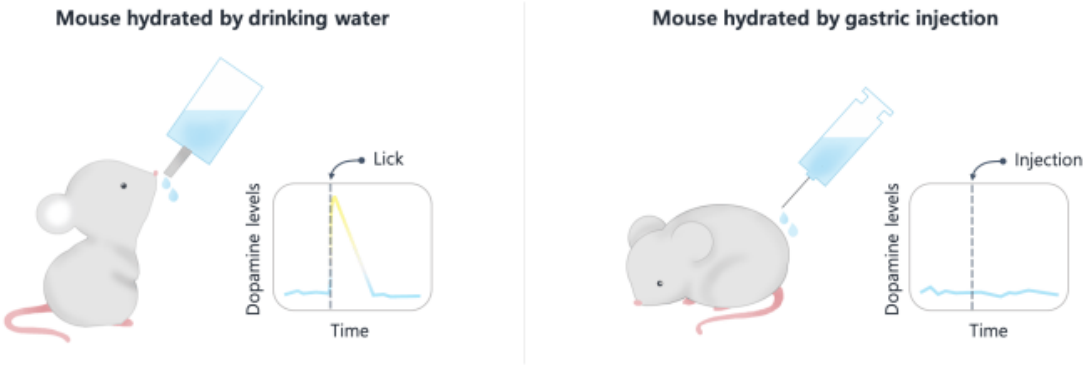
Question 7

Does the mechanism provide the human (or mammalian) brain with an indication (information) that can be interpreted as the **level** of Satiation within the Thirst homeostasis mechanism as defined by the Xzistor Concept brain model?

Answer 7

Yes.

The dopamine graph on the left indicates how dopamine (and therefore Satiation level if we choose the base our Satiation mechanism on dopamine) will spike at first intake of water and then reduce as water is ingested.



Research also shows that different liquids will have different reward levels and that mice will quickly learn to navigate to the better tasting fluid. This links level of learning (reinforcement) with dopamine – what the Xzistor Concept calls the Satiation Event.

This suggests that LH-GABA neurons are the source of the signal that informs VTA-DA (dopamine) neurons about fluid balance (Fig. 3a).[5]

Question 8

Based on the above, can it be concluded that the human (or 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?

Answer 8

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

1.) A utility parameter (plasma osmolality)

2.) A biological equivalent to the UTR Deprivation phase that increases reported thirst in individuals as their plasma osmolality increases. This suggests that LH-GABA neurons are the

source of the signal that informs VTA-DA (dopamine) neurons about fluid balance (Fig. 3a).[5] Strengthens as a function of osmolality?

3.) A biological equivalent to the UTR Satiation phase that shows reduction as fluid is ingested as their dopamine level decreases.

4.) A biological equivalent of the Satiation Event as the spike in dopamine occurs exactly with the first lick of water. (We will later prove that this encouraged a Satiation Event (or learning event) as defined by the Xzistor Concept). This release of dopamine can work to dissolve the Deprivation state generated.

References

See [1] [2][3] and [4] in Appendix A and [8][10][23] in Appendix B.

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.[5]

Dry mouth sensation? Cooling liquid effect.

We should now see that the circuits head back towards the 'always on' workspace like the hypothalamus to ensure information is 'factored in' into behaviours. We know it needs to follow the memory pathway to later recall water / juices that can be navigated to. Could be deceptive because XC nor necessarily expect animals to think like this.

Information about plasma sodium enters the circuit through specialized aldosterone-sensitive NTSHSD2 neurons, which promote salt appetite and project to the pre-LC, PBN, and BNSTvl. Arch, archaerhodopsin; AVP, vasopressin; BNSTvl, ventrolateral part of the bed nucleus of the stria terminalis; ChR2, channelrhodopsin-2; MnPO, median preoptic nucleus; NTS, nucleus of the solitary tract; OVLT, organum vasculosum of the lamina terminalis; OXT, oxytocin; PBN, parabrachial nucleus; PP, posterior pituitary; pre-LC, pre-locus

coeruleus; PVH, paraventricular hypothalamus; SCN, suprachiasmatic nucleus; SFO, subfornical organ;

SNA, sympathetic nerve activity; SON, supraoptic nucleus.

EXAMPLES. Physiological changes induced by the sympathetic nervous system include accelerating the heart rate, widening bronchial passages, ***decreasing motility of the large intestine****, dilating the pupils, and causing perspiration.13 Aug 2020*

decreasing motility of the large intestine (hollow / empty feeling or butterflies in the stomach) *caused by abnormalities of the* ***enteric nerves***

he ***enteric nervous system*** *or intrinsic nervous system is one of the main divisions of the autonomic nervous system and consists of a mesh-like system of neurons that governs the function of the gastrointestinal tract*

Researchers are finding evidence that irritation in the gastrointestinal system may send ***signals to the central nervous system (CNS) that trigger mood changes.***

Gut Issues and Mood (John Hopkins Medicine)
https://www.hopkinsmedicine.org/health/wellness-and-prevention/gastrointestinal-issues-whats-your-brain-have-to-do-with-it

The brain-gut connection is evident when we experience butterflies in our stomachs, typically when we're excited, in love or scared. Strong emotions can cause people to experience GI symptoms.

Nail down this emotional connection with the GI tract.

Science is beginning to understand the process behind this link, which ultimately relates to hormones released from different parts of our brain — yes, they are in your head, as well as other places — when we are particularly stressed or excited.

Chemicals circulating in the bloodstream affect the sensitivity and function of nerves in the wall of the gut, which can be collectively referred to as the ***enteric nervous system.***

There is also a lesser known part of our body's nervous system located in our gut. It's called the enteric nervous system. The enteric nervous system's network of nerves, neurons and neurotransmitters extends along the entire digestive tract – from the esophagus, through the stomach and intestines, and down to the anus.

Emotions, feelings of excitement, or nervousness can cause the familiar churning in the stomach – the so-called "butterflies in your stomach" feeling. The gut-brain connection works in both directions too. For example, GI problems can create anxiety and stress.

https://my.clevelandclinic.org/health/treatments/16358-gut-brain-connection

So the lT neurons can send signals to the GI track neurons to create a state akin to butterflies or nausea or just and unwanted state (avoidance) that might not be butterflies or nausea, but an avoidabce state that will be felt in the stomach area.

See 'homeostatic emotion' hypothesis by A. D. Craig 78. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nature Rev Neurosci. *2002;3:655–666. [PubMed] [Google Scholar] [Ref list]*

The medial PFC network receives input from a lateral PFC and orbitofrontal cortex (OFC) network that provides integrated multisensory information about the representation of complex homeostatic body states, including those related to gut homeostasis, food intake and visceral pain

Outputs from subregions of the medial network, ***amygdala and hypothalamus are integrated*** *into distinct motor patterns within the mesencephalic PAG18. The most caudal component of the central autonomic networks is represented by pontine and medullary nuclei, including the serotonergic raphe nuclei, the locus coeruleus complex (including Barrington's nucleus) and the dorsal vagal complex. This system of parallel outflows from cortico–limbic–pontine networks, which* ***is engaged by distinct homeostatic states****, has been referred to as the* ***emotional motor system (EMS)*** *and consists of integrated motor autonomic, neuroendocrine and* ***pain modulatory*** *components*

Gut responses to nociceptive stimuli typically involve spinal and supraspinal reflexes, engaging ***strong emotional*** *and autonomic responses.*

Gut to brain signalling during homeostasis

There are between 200 and 600 million neurons in the human ENS, which is equal to the number of neurons in the spinal cord1. They have been classified on the basis of their morphology, electrophysiological properties and chemical coding into distinct classes of functional specific neurons, including several classes of afferents1,42. The size and complexity of the ENS is not surprising when considering the challenges posed by the interface of the organism with its luminal environment: it interfaces closely with our largest body surface (the intestinal surface area, which is approximately 100 times larger than the surface area of the skin), with the largest population of commensal microorganisms of all body surfaces (100 trillion microorganisms from 40,000 species with 100 times the number of genes in the human genome43), with the gut-associated immune system (containing two-thirds of the body's immune cells) and with thousands of enteroendocrine cells (containing more than 20 identified hormones). These unparalleled relationships between the gastrointestinal tract and the brain, with multiple bidirectional and often interacting interoceptive communication systems, emphasize the importance of this system in the ***maintenance of homeostasis****.*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3845678/ [7]

Reference

See [7]

**Add question for Satiation Event!*

A lot of what the Xzistor Concept does in terms of UTRs, Prime UTR and emotions seems to be associated with the: ***Anterior Cingulate Cortex: Unique Role in Cognition and Emotion***

https://neuro.psychiatryonline.org/doi/10.1176/jnp.23.2.jnp121

*The anterior cingulate cortex is **implicated in emotion**, because it is involved in **linking reward and punishment information, which elicit emotional responses**, to behaviour, and, in particular, to actions. The subgenual cingulate cortex (area 25) may link rewards and punishers to autonomic output*

*Evidence is provided for a new conceptualization of the connectivity and functions of the cingulate cortex in emotion, action, and memory. The anterior cingulate cortex receives information from the orbitofrontal cortex about reward and non-reward outcomes. The posterior cingulate cortex receives spatial and action-related information from parietal cortical areas. It is argued that these inputs allow the **cingulate cortex to perform action–outcome learning**, with outputs from the midcingulate motor area to premotor areas. In addition, because the **anterior cingulate cortex connects rewards to actions, it is involved in emotion; and because the posterior cingulate cortex has outputs to the hippocampal system, it is involved in memory.** These apparently multiple different functions of the cingulate cortex are related to the place of this proisocortical limbic region in brain connectivity.*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6875144/

Drinking initiates a feedback; an avalanche of neural

inflow derives from mouth sensation, including alleviation of

dry mouth, and this flows up the fifth cranial nerve, taste by the

chorda tympani included in the seventh nerve, pharyngo-esophageal

impulses metering volume swallowed by the ninth nerve, and lower

esophageal and gastric sensation—including distension—by the

10th cranial nerve. This "gestalt" of inflow from drinking determined by thirst reduces the central intention to drink to the

point of its obliteration, and a state of satiation ensues.

A conspicuous feature is that the drinking stops well before

blood changes reflect significant absorption from the gut. Rapid

intake of water consequent upon thirst, or of a salt solution when…

Regional brain responses associated with drinking

water during thirst and after its satiation

https://www.pnas.org/doi/pdf/10.1073/pnas.1403382111

As a result of investigations using functional brain imaging techniques, the insula and anterior cingulate cortex, as well as several other cortical sites, have been implicated in the ***conscious perception of thirst*** *and hunger in humans.* ***Viral tracing techniques show that the anterior cingulate cortex and insula receive neural inputs from thirst-related neurones in the subfornical organ and OVLT****, with hunger-related neurones in the area postrema having polysynaptic efferent connections to these cortical regions.* ***For thirst, initially, the median preoptic nucleus and, subsequently, the thalamic paraventricular nucleus and lateral hypothalamus have been identified as likely sites of synaptic links in pathways from the subfornical organ and OVLT to the cortex****. The challenge remains to identify the links in the neural pathways that relay signals originating in sensory CVOs to cortical sites subserving either thirst or hunger.*

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

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

During the first scan, the volunteers drank water to quench their thirst, and during a second scan, they were told to keep drinking water even though their thirst was quenched. The volunteers reported that drinking to satisfy their thirst felt pleasurable, whereas drinking excess water felt unpleasant.

In the scans taken while the participants drank water to quench their thirst, their brains lit up with activity in the ***anterior cingulate cortex and the orbitofrontal cortex — regions that play a role in emotional decision-making.***

This is an additional Individuals have reported their subjective thirst level and this was confirmed to be a functions of plasma osmolality. Cite papers. Find objective evidence.

The cingulate cortex and insula are among the neural structures whose activations have been modulated in functional imaging studies examining discrete states of thirst and drinking to satiation. Building upon these findings, the present study aimed to identify neural structures that change their pattern of activation elicited by water held in the mouth in relation to the internal body state, i.e., proportional to continuous water consumption. Accordingly, participants in a thirsty state were scanned while receiving increments of water until satiety was reached. As expected, fluid ingestion led to a clear decrease in self-reported thirst and the pleasantness ratings of the water ingested.

gut motility slow and ENS – ***nausea****.*

See Emotional valence [16] Lammel S, Ion DI, Roeper J, Malenka RC Projection-specific modulation of dopamine neuron synapses by aversive and rewarding stimuli. Neuron*. 2011, 70:855–62. [PMC free article] [PubMed] [Google Scholar] [Ref list]*

Can this be regarded as an emotional response?

Later! Yes, negative emotions (e.g., anger) result in parasympathetic withdrawal and sympathetic activity (McCraty, Atkinson, Tiller, Rein, & Watkins, 1995) whereas positive emotions result in altered autonomic nervous system activity, characterised by increased parasympathetic nervous system activity.

Spinal nerves T1-L2 carry sympathetic innervation for the trunk wall, as well as participate in comprising the splanchnic nerves for innervation of the abdominopelvic viscera. The stress / anxiety effect (and subjective feeling) caused by the sympathetic nervous system is well documented. The sympathetic nervous system will therefore create a body state (this might be mild) that will be sensed in the vagus area (adrenal glands, cortisol) and experienced as a 'body internal' sensory state by the brain. It will become an 'avoidance' state as the brain learns how to reduce or diminish this state. Learning happens during Satiation Events when actions reducing or eliminating this sensation are strongly rewarded and stored as the actions to pursue in future when this state is experienced.

Dopamine is a neurotransmitter made in your brain. It plays a role as a "reward center" and in many body functions, ***including memory, movement, motivation, mood, attention*** *and more*

Dopaminergic neurons are found principally in the VTA of the midbrain, the substantia nigra pars compact, and the arcuate nucleus of ***hypothalamus****. The axons of these neurons project to different areas of the brain through major pathways known as mesocortical, mesolimbic, and nigrostriatal pathways [12]. The mesolimbic pathway connects the VTA to the nucleus accumbens. The somata of the neurons originate in the VTA, and, from there, DA is transported to the nucleus accumbens through the* ***amygdala and the hippocampus****. The nigrostriatal pathway joins the substantia nigra with the neostriatum. The neuronal somata are located in the substantia nigra, and the axons of these neurons are ramified into the caudate nucleus and putamen. This pathway is also connected to the basal ganglia motor loop. All of the innervations originating from these pathways explain many of the effects produced when the DA system is activated [13]. For instance, the VTA and the nucleus accumbens connected through the mesolimbic pathway are central to the brain reward system [14].*

**The emotions might be GUT related as the ENS runs all the way from the oesophagus to the anus – soe emotions maybe not in the somasenssor cortex.*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4684895/

Dopamine can provide an intense feeling of reward.

Dopamine is most notably involved in helping us feel pleasure as part of the brain's reward system. Sex, shopping, smelling cookies baking in the oven — all these things can trigger dopamine release, or a "dopamine rush." [RVS smelling cookies will make the case for associations having an emotions state (Impact Factor) linked to them as per XC]

This feel-good neurotransmitter is also involved in reinforcement [RV This is the satiation event]. That's why, once we try one of those cookies, we might come back for another one (or two, or three). The darker side of dopamine is the intense feeling of reward people feel when they take drugs, such as heroin or cocaine, which can lead to addiction.

Dopamine also plays a role in these functions:learning and attention, mood, movement, heart rate, kidney function, blood vessel function, sleep, pain processing, lactation

https://www.health.harvard.edu/mind-and-mood/dopamine-the-pathway-to-pleasure

Yes.

As a result of investigations using functional brain imaging techniques, the insula and anterior cingulate cortex, as well as several other cortical sites, have been implicated in the conscious perception of thirst in humans. Viral tracing techniques show that the anterior cingulate cortex and insula receive neural inputs from thirst-related neurons in the subfornical organ and OVLT. For thirst, initially, the median preoptic nucleus and, subsequently, the thalamic paraventricular nucleus and lateral hypothalamus have been identified as likely sites of synaptic links in pathways from the subfornical organ and OVLT to the cortex. The challenge remains to identify the links in the neural pathways that relay signals originating in sensory CVOs to cortical sites subserving either thirst or hunger.

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

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

[This could be the link: We also describe mechanisms in the brain by which [Na+] increases in body fluids activate the sympathetic neural activity leading to hypertension.]

The pleasantness of drinking when thirsty is associated with activation in the anterior cingulate cortex and orbitofrontal region. These brain regions were identified using Fos mapping studies in rodents and fMRI/PET mapping studies in humans (see reference 9 below). The anterior cingulate cortex is responsible for a host of cognitive functions, including emotional expression, attention allocation, and mood regulation.

Anterior Cingulate Cortex: Unique Role in Cognition and Emotion

https://neuro.psychiatryonline.org/doi/10.1176/jnp.23.2.jnp121

The anterior cingulate cortex (ACC) has connections to both the "emotional" limbic system and the "cognitive" prefrontal cortex. Thus, the ACC likely has an important role in integration of neuronal circuitry for affect regulation.

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

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

Neuroimaging studies have shown that the anterior cingulate cortex (ACC) is consistently activated by thirst and may underlie the affective motivation of drinking behaviour demanded by thirst

Thirst is the basic instinct to drink water. Previously, it was shown that neurons in several circumventricular organs of the hypothalamus are activated by thirst-inducing conditions1. Here we identify two distinct, genetically separable neural populations in the subfornical organ that trigger or suppress thirst. We show that optogenetic activation of subfornical organ excitatory neurons, marked by the expression of the transcription factor ETV-1, evokes intense drinking behaviour, and does so even in fully water-satiated animals. The light-induced response is highly specific for water, immediate and strictly locked to the laser stimulus. In contrast, activation of a second population of subfornical organ neurons, marked by expression of the vesicular GABA transporter VGAT, drastically suppresses drinking, even in water-craving thirsty animals. These results reveal an innate brain circuit that can turn an animal's water-drinking behaviour on and off, and probably functions as a centre for thirst control in the mammalian brain.

https://www.nature.com/articles/nature14108

Homeostatic Emotion

Derick Denton includes sexual desire in this class[5] and distinguishes two classes of feelings: these primordial emotions ("imperious states of arousal and compelling intentions to act" driven by activation of interoceptors and involving ancient, lower brain regions such as the medulla, midbrain and hypothalamus), and the classic emotions such as anger, fear and love, driven by distance receptors (vision, hearing, olfaction) and mediated by higher, more recently evolved brain regions.[6]

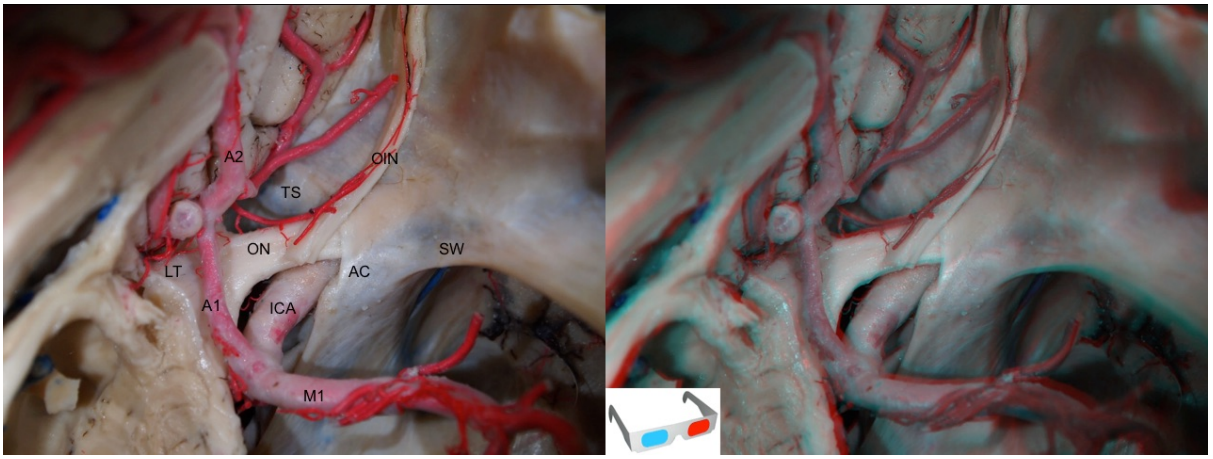
Jaak Panksepp called this class of feelings "homeostatic affect." He recognised it as one of three primary classes of affect: sensory affect (e.g., touch, warmth), homeostatic affect (e.g., thirst, fatigue) and emotional affect (e.g., anger, fear).[7]

[Rocco: Xzistor differ asToo Warm and Too Cold will also be Hom Affetc as well as anger, fear, sex, etc - all modlled through UTRs]

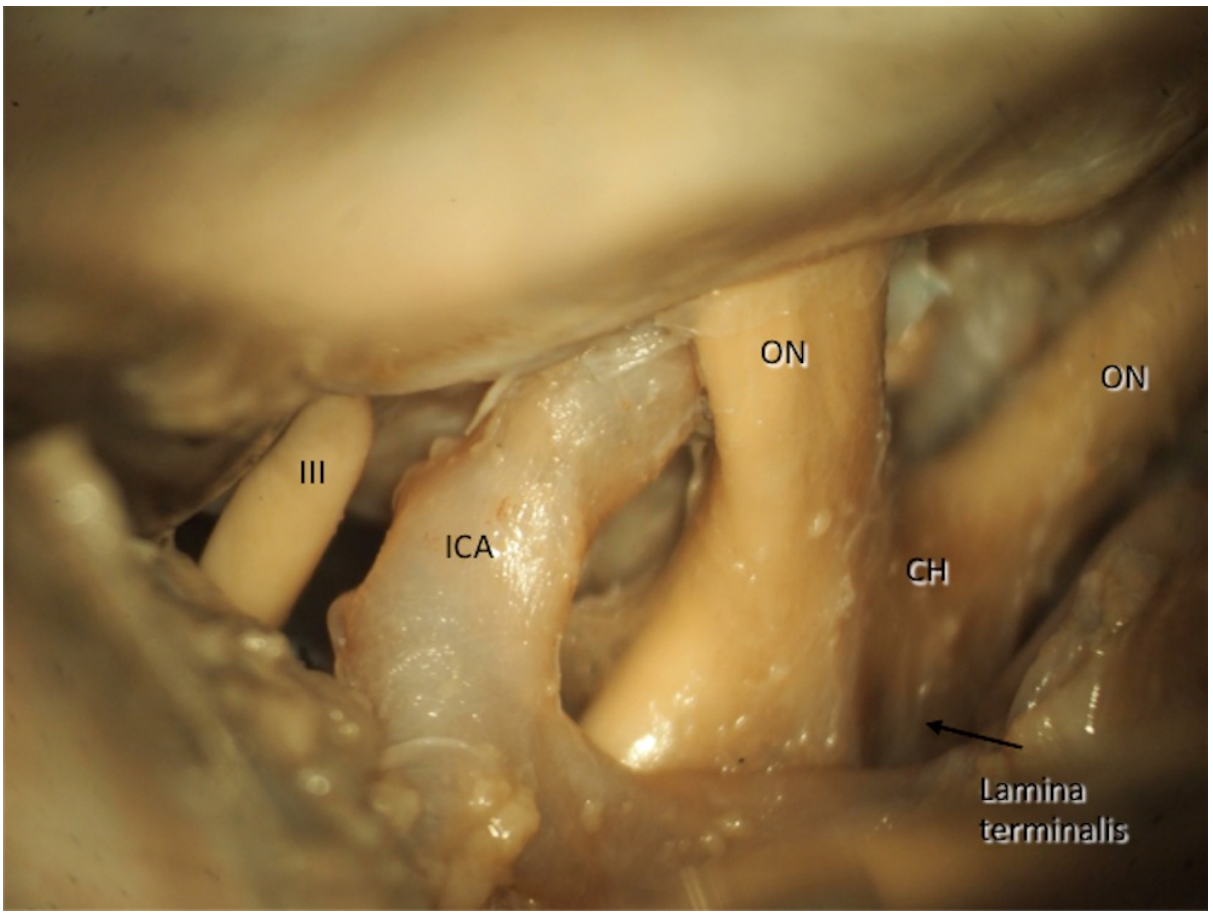
There are two constituents of a primordial emotion—the specific sensation which when severe may be imperious, and the compelling intention for gratification by a consummatory act."[4]

[Rocco: Aligns with Xzistor Deprivation phase and Satiation phase]

Lamina terminalis



AC: anterior clinoid process; ICA: internal carotid artery; LT: lamina terminalis; ON: optic nerve; OIN; olfactory nerve; SW: sphenoid wing; TS: tuberculum sellae; A1: A1 segment of the Anterior Cerebral Artery; A2: A2 segment of the Anterior Cerebral Artery; M1: M1 segment of the Middle Cerebral Artery

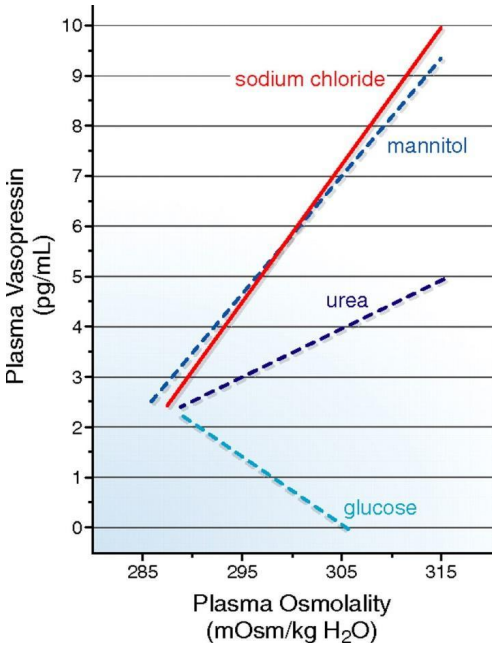


1) ***Komotar RJ, Hahn DK, Kim GH, Starke RM, Garrett MC, Merkow MB, Otten ML, Sciacca RR, Connolly ES Jr. Efficacy of lamina terminalis fenestration in reducing shunt-dependent hydrocephalus following aneurysmal subarachnoid hemorrhage: a systematic review. Clinical article. J Neurosurg. 2009 Jul;111(1):147-54. doi: 10.3171/2009.1.JNS0821. Review. PubMed PMID: 19284236.***

constantly aware of activate the ‘intra-abdominal’ somatosensory cortex as a sensory ‘feeling’ that will become associated with an ‘avoidance state’ (i.e. bad). This feeling is what the Xzistor Concept model defines as negative emotion. The agent therefore feels the Thirst as a pseudo-tactile ‘body’ sensation (negative emotion) and is not aware of the working of the Thirst UTR mechanism. As the Xzistor model only ever claims to offer a ‘principal’ explanation of the brain, the negative emotion generated in the ‘intra-abdominal’ somatosensory cortex is just a one way to explain that the UTR Deprivation state (which the agent is not aware of) is used to create a sensory state (which the agent is constantly aware

of). The sensory state used for the negative emotion becomes an ‘avoidance’ state by the brain rewarding actions leading to this negative emotion being reduced or eliminated (this mechanism will be covered as part of the Functional Analysis Report on Emotions).

Similarly, the Xzistor Concept brain model will use the decreasing UTR value during the Satiation phase to activate the ‘intra-trunk’ somatosensory cortex as a sensory ‘feeling’ that will become associated with a ‘pursue state’ (i.e. good). This feeling is what the Xzistor Concept model defines as positive emotion. The agent therefore feels the Thirst as a pseudo-tactile ‘body’ sensation (positive emotion) and is not aware of the working of the Thirst UTR mechanism. Again, as the Xzistor model only ever claims to offer a ‘principal’ explanation of the brain, the positive emotion generated in the ‘intra-trunk’ somatosensory cortex is just a one way to explain that the UTR Satiation state (which the agent is not aware of) is used to create a sensory state (which the agent is constantly aware of). The sensory state used for the positive emotion becomes a ‘pursue’ state by the brain rewarding actions leading to this positive emotion being created in the brain (this mechanism will be covered as part of the Functional Analysis Report on Emotions).



The lines in the graph above represent the relationship of plasma AVP (Vasopressin) to plasma osmolality in healthy adults during intravenous infusion of hypertonic solutions of different solutes.

Vasopressin (AVP) is a hormone that helps blood vessels constrict and helps the kidneys control the amount of water and salt in the body. This helps control blood pressure and the amount of urine that is made. Vasopressin is made by the hypothalamus and is secreted into the blood by the pituitary gland. It prevents water loss and dehydration.

Note that effective solutes, i.e., those compartmentalised to the extracellular fluid (NaCl and mannitol), are much more effective at eliciting AVP secretion than the non effective solutes, urea and glucose, that distribute across cell membranes into the intracellular fluid as well (adapted from Zerbe and Robertson GL.8)

as pred the [This is just the level of osmolality]

Neurons in the lamina terminalis can pool all the information from different sources in the brain to determine whether the body needs more water,or less water.

Viral tracing techniques show that the anterior cingulate cortex (ACC) and insula receive neural inputs from thirst-related neurons in the subfornical organ and OVLT. It has been proven that the level of ACC neuronal activation correlates with drinking behaviour (i.e. the desire for hydration). The increase in activity can be interpreted as the level of Deprivation as part of the Thirst homeostasis mechanism.

References

See [10] in Appendix A.

Question 7

Does the mechanism provide the human (mammalian) brain with an indication (information) that can be interpreted as a state of Satiation within the Thirst homeostasis mechanism as defined by the Xzistor Concept brain model?

Answer 7

Yes.

The brain can interpret an increase in osmolality as a state of Deprivation within the Thirst homeostasis mechanism.

Neurons in the lamina terminalis can pool all the information from different sources in the brain to determine whether the body needs more water, or less water.

References

See [2] in Appendix A.

Neurons in the lamina terminalis can pool all the information from different sources in the brain to determine whether the body needs more water, or less water.

Viral tracing techniques show that the anterior cingulate cortex (ACC) and insula receive neural inputs from thirst-related neurons in the subfornical organ and OVLT. It has been proven that the level of ACC neuronal activation correlates with drinking behaviour (i.e. the desire for hydration). This will fluctuate down during drinking. The rate of decrease in activity can be interpreted as the level of Satiation as part of the Thirst homeostasis mechanism.

Much progress has been made during the past 30 years with respect to elucidating the neural and endocrine pathways by which bodily needs for water and energy are brought to conscious awareness through the generation of thirst and hunger. As a result of investigations using functional brain imaging techniques, the insula and anterior cingulate

cortex (ACC), as well as several other cortical sites, have been implicated in the conscious perception of thirst in humans (see reference [13]).

References

See [2][4][10][13] in Appendix A.