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Anorexia Lowers GFAP+ in the Valuation and Choice Circuit of Decision Making: A Two-Layered Diffusion Model Rat Hippocampus Cell Density

Irtysh Joe*

Department of Cell, Developmental, and Cancer Biology, Oregon Health and Science University, Germany

Abstract

In neurobiology, a circuit of alternative evaluation and selection is regarded as an accurate model. The significant literary contributions on this subject are included. This study uses a two-layered network of computational cells to model the evaluation and selection of a decisional process during a Two-Alternative Forced-Choice (TAFC) problem, where information gathering and processing advance via nonlinear diffusion dynamics. Two linked diffusive modules (2LDM), which reflect the neuronal populations engaged in the valuation-and-decision circuit of decision making, are thus used to describe the evolution of the response-to-stimulus map. Diffusion models are ideally suited to explain the gradual accumulation of data over time. Under the ex-Wald distribution hypothesis, this enables the estimation of the response times (RTs) in valuation and choice. The two layers' activities are integrated using a nonlinear transfer function. The 2LDM is consistent with the reinforcement learning strategy thanks to the input-output map built on the infomax principle. The activity-dependent modulatory component of the effective connection between the neuronal populations may be explained by 2LDM, according to the results of simulated likelihood time series. The 2LDM's compliance with the neurobiology of DM is further supported by the rhythmic variations of the estimate gain functions in the delta-beta bands.

A common eating disorder among young women is anorexia nervosa. Although the neurobiology of the condition is unknown, recent magnetic resonance imaging studies on anorexic patients revealed a volume reduction of the hippocampus. A mouse model called dehydration-induced anorexia (DIA) mimics the main characteristics of this illness, including dramatic weight loss brought on by voluntarily reducing food intake. It is unknown if anorexia affects the density of the astrocytes, which mediate the energy supply to the brain. Therefore, the purpose of this study was to calculate the GFAP+ cell density in the major hippocampal regions using the DIA model. A common eating disorder among young women is anorexia nervosa. Our findings revealed that, with the exception of CA1, the density of GFAP+ cells were dramatically decreased (20%) throughout the whole hippocampus. It's interesting to note that DIA dramatically decreased the ratio of GFAP+ cells to nuclei in the CA2 (by around 23%) and dentate gyrus (by about 48%). The decrease in GFAP+ cell density correlated with a decrease in GFAP protein expression. The expression of nestin and vimentin, two intermediate filaments, was also elevated in anorexia. As a result, anorexia more than doubled the amount of reactive astrocytes in CA2 and the dentate gyrus. We find that anorexia decreases the number of GFAP+ cells in the hippocampus region while increasing vimentin and nestin expression.

Keywords: Anorexia; Nervosa; Neuronal; Neurobiology; Hippocampus

Introduction

Even basic decisions require more complex cognitive processes that take into account noisy sensory input, prior knowledge, and the costs and rewards of potential actions based on their potential occurrence times. The cortical circuitry of neural pools accumulates noisy information as part of the decision-making (DM) process. This procedure takes a lot of time, especially when the information is of low quality and there are numerous potential solutions that can be weighed against one another. There is broad agreement in the research of DM to conform to a phase of evidence accumulation before making a decision, meaning the decision maker is expected to continue accumulating data until the evidence is sufficient in favour of one of the options. Thus, the performance of the responses improves for slower response times, and the costs of collecting additional information are constrained by the speed-accuracy tradeoff that results from the stochastic integration of information up to a specific threshold. Due to their ability to pinpoint the precise moment at which a decision is made, responses times (RTs) to stimuli characterise the speed-accuracy trade-off in this context [1]. RT studies have focused on the application of diffusive models for describing decisional behaviours and the identification of the neuronal regions related to the decisional activity. Diverse parts of the brain are used in the DM process.

These sections include the basal ganglia (BG), which is thought to function as a central switch in gating behavioural requests, and the cortical areas that are intended to absorb evidence supporting alternative actions. Although the decision-making process itself takes place in other regions, such as the prefrontal cortex and posterior parietal cortex, it is known that neurons in the middle temporal area (MT) encode motion stimuli. A delay between the stimulus and the saccadic movement allowed researchers to link the selective activation of neurons in the lateral intraparietal region (LIP) with perceptual choice and response time. These experiments were conducted on primates [2]. This suggests that neither a motor signal nor a sensory input can cause the LIP neurons to fire.

In natural settings, a range of sensory cues produce various options, necessitating the assessment of several possible responses,

***Corresponding author:** Irtysh Joe, Department of Cell, Developmental, and Cancer Biology, Oregon Health and Science University, Germany E-mail: joe@hytrihealth.port

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or various actions. In other words, a selection question also appears, forcing the person's motor system to be controlled by the (probability) distribution of the right answer. A dispute among the brain's decisional centres would then be resolved by the choice of action. By considering the basal ganglia (BG) as the neurological substrate for that switch, a central switch that takes into account the necessity and possibility of a certain reaction to the stimuli resulting in an ideal solution in computing terms that is physiologically trustworthy [3].

As a result, BG collect information from various parts of the brain and, by transmitting tonic inhibition to brain stem and midbrain targets engaged in motor activities, limit cortical control over these actions.

As a result, the disinhibition of their targets is determined by the inhibition of the neurons in the output nuclei brought on by BG activity, and the actions are subsequently chosen. In other words, by serving as a central switch, BG would assess the available evidence and facilitate the reactions that are most strongly supported.

The main goal of this study was to establish theoretical, neurobiologically sound foundations for representing the two stages of valuation and choice of DM during the Two-Alternative Forced-Choice (TAFC) task in terms of two distinct layers of neuronal populations performing diffusive dynamics (2LDM). This was done under the premise that the lateral prefrontal and parietal cortex integrate the corresponding weighted evidence of the DM among alternative options. Verifying the 2LDM's capacity to account for any potential influence the populations might have on one another was the secondary goal [4]. A Two-Alternative Forced-Choice (TAFC) visual task was therefore simulated using time series that replicated the likelihood of performing motor action (visual aiming). In the two layers of the model, the synchronisation analysis of the instantaneous phases of the activities of the neuronal populations and the power spectrum of the gain functions revealed that the effective connection between the populations was modulated in a manner that was activity-dependent. The experimental context used for DM analysis is frequently defined by the so-called Two-Alternative Forced-Choice (TAFC) task.

A severe loss of weight, osteoporosis, and amenorrhea are all side effects of anorexia nervosa, an eating disorder characterised by drastically reduced calorie intake. 90–95 percent of instances of anorexia nervosa occur in girls, and it typically begins between puberty and adolescence.

The neurobiology of anorexia nervosa is complicated, making it difficult to understand, although studies utilising magnetic resonance imaging revealed decreased hippocampus volume. The hippocampus is important in cognition, anxiety management, and spatial learning. There have been reports of changes in these cognitive abilities in anorexia patients and experimental models [5]. Murine models of anorexia such as dehydration-induced anorexia (DIA) or activity-based anorexia (ABA) mimic the characteristic weight loss and reduced food intake observed in anorexic patients.

Hippocampal volume may have decreased in anorexic patients due to cellular structural abnormalities. Reduced cell proliferation in the dentate gyrus and lessened dendritic branching in the stratum radiatum of CA1 were two alterations in the hippocampus seen in the ABA model. A vitamin and electrolyte imbalance can occur as a result of excessive physical activity, which changes how food is absorbed [6]. Therefore, a calorie deficit that impairs the brain's ability to get the energy it needs could lead to changes in hippocampal shape and function. We investigated whether hippocampal astrocyte density and intermediate filament expression are impacted by anorexia because astrocytes, one of the major populations of cells in the central nervous system, are essential for delivering energy to neurons.

Materials and Methods

Animals and Housing

The UNAM Institute of Neurobiology's Institutional Animal Care and Use of Laboratory Animals Committee gave its approval to all of the research protocols. In compliance with the National Institute of Health's Guide for the Care and Use of Laboratory Animals, animals were handled. Wistar female rats (weighing 160–190 g) were maintained separately in a controlled environment with a 12-hour/12-hour light/dark cycle and access to unlimited food and water.

Dehydration-Induced Anorexia

The procedure was carried out as previously mentioned. In a nutshell, animals were separated into three groups of four for each of the two distinct experimental series, each of which contained twelve animals. Water and snacks were freely available to the first group (control). The only liquid provided to the DIA group to drink was a 2.5 percent NaCl solution, and they were given free reign to eat whatever they wanted. The forced food-restricted (FFR) group received the same quantity of food as the DIA animals as well as unlimited access to tap water as a positive control to help distinguish between the effects of dehydration and famine. Body weight and solid food intake for each experimental group were recorded each day at noon for the course of the five-day experiment.

Histology

Following a transcardial infusion of 100 mL of saline and 250 mL of cold 4 percent paraformaldehyde in phosphate-buffered saline (PBS), rats were given a heavy dosage of sodium pentobarbital (100 mg/Kg) to induce a deep state of anaesthesia (pH 7.4). Brains were taken out, postfixed for an overnight period, and then put into a series of sucrose solutions (from 10 to 30 percent). In cryoprotectant solution (30 percent ethylene glycol/20 percent glycerol in PBS), coronal slices (30 m) containing the dorsal hippocampus were cut, collected, and kept at 20°C.

Immunohistofluorescence

Floating sections underwent glial fibrillary acidic protein (GFAP) staining. In a nutshell, coronal slices were treated with 3% hydrogen peroxide for 10 minutes, three PBS rinses, and a 6–8 minute incubation with 1.0 percent sodium borohydride to decrease free aldehydes. The blocks (5 percent horse serum albumin/1 percent Triton X-100 in PBS) were incubated on the sections for 1 hour. Polyclonal rabbit anti-GFAP antibody was incubated on the sections for 48 hours [7]. Alexa 594 conjugated goat anti-rabbit secondary antibody was used to identify the main antibody after washing. Vectashield H-1000 was used to mount the sections after they had been counterstained with DAPI.

Western Blot

As previously mentioned, the hippocampus was cut out. For each experimental group (control, DIA, and FFR), three distinct rats' hippocampi were homogenised in ice-cold lysis buffer (200 mM glycine, 150 mM NaCl, 50 mM EGTA, 50 mM EDTA, and 300 mM sucrose) with a protease inhibitor (Sigma-Aldrich, USA). The homogenate was centrifuged at 10,000 g for 15 min at 4 °C, and the supernatants were divided up and kept at 80 °C. Bradford's technique was used to estimate the protein concentration of each sample. Electrophoresis on 10% polyacrylamide gel was used to separate a

protein sample with an identical concentration (30 g) (PAGE). The proteins were electrophoretically transferred to PVDF membranes, and the membranes were subsequently blocked for 3 hours at room temperature with 5% non-fat dry milk in TBS-T. (RT). Membranes were incubated with one of the primary antibodies listed below overnight at 4°C: (a) polyclonal rabbit anti-GFAP antibody (dilution 1: 2000, Dak Cytomation, Fort Collins, CO, USA); (b) polyclonal rabbit anti-vimentin antibody (dilution 1: 2500, Cell Signaling, Danvers, MA, USA); (c) monoclonal mouse anti-nestin antibody (dilution 1)

Results

The dentate gyrus (DG), CA1, CA2, and CA3 hippocampal areas were used to determine the effects of DIA and FFR on the density of astrocytes and nuclei. For the DG, observations were made in the hilus, whereas all observations encompassed the stratum radiatum and stratum oriens, where astrocytes are favoured locations.

The chance of visual targeting in the resampled time series at the final chosen image ranged from [0.3827: 0.7427], with mean = 0.5853 and SD = 0.095. Mean = 0.6630 and SD = 0.0951 were the values for the initial likelihood data series. The rates of the populations' activity variables N1 and N2 were compared using a paired-samples t-test. Between the rates of N1 (mean = 0.2775, SD = 0.001) and N2 (mean = 0.1891, SD = 0.0009), there was a statistically significant difference ($t(99) = 649.85$, $P = 0.00001$). Higher components were visible in the power spectrum of the gain function in P2 than in P1 up to the (lower bound of) beta-band.

The Hilbert-transform of the rates of the populations' activity variables N1 and N2 was used to calculate the degree of synchronisation between the instantaneous phases (1, 2), and the result was expressed in terms of correntropy coefficients. Phase locking is indicated by departures from zero values. The vector of correntropies (sur) between the surrogate instantaneous phases (sur1, sur2) was used as a proxy for the null hypothesis in order to test the asynchronous state hypothesis. It was anticipated that the distance between and sur would follow a Weibull random variable distribution with shape and scale parameters of a = 0.3752 and b = 1.5661.

We discovered that the test statistic, mean (distance)/S.E.(distance) = 15.323, was substantially different from zero (P = 0.00012) based on the Weibull-like distribution.

The distance between and sur is distributed cumulatively. With parameters a = 0.3752 and b = 1.5661, the cumulative distribution function of the variable reflecting the difference between the correntropy coefficients and sur is distributed as a Weibull-like random variable.

Discussion

Female adolescents frequently develop anorexia nervosa, which has one of the highest death rates among psychiatric diseases (10–20 percent), even surpassing depression. Due to a fast spike in hormone levels that impact the hippocampus throughout puberty, mood swings and anxiety are frequent. The hippocampus has also been found to undergo structural and functional changes in the activity-based anorexia model (ABA), which are accompanied by symptoms of anxiety. However, little research has been done on how anorexia affects astrocyte density. Astrocytic density was indeed regionally reduced in the DIA model, but cell proliferation was decreased with the ABA model in earlier investigations in the rat corpus callosum. The dentate gyrus hippocampus cell proliferation was similarly found to be lowered in the ABA investigation. According to the study's findings, anorexia decreased the density of astrocytes in the CA2, CA3, and DG regions, whereas CA1 did not see any discernible changes. In consequence, c-Fos expression was reduced in the dentate gyrus and CA3 area of the hippocampus in anorexia mutant mice (anx/anx), but not in CA1. On the other hand, the expression of GFAP protein was decreased as a result of the reduction in GFAP+ cell density. Three different intermediate filament proteins are expressed by astrocytes: GFAP, vimentin, and nestin. Nestin and vimentin are the major intermediate filaments in immature astrocytes, whereas vimentin and GFAP are present in maturing and adult astrocytes.

It's interesting to note that anorexia enhanced nestin and vimentin expression, which is similar to reactive astrocytes seen following damage. In anorexia, vimentin+/nestin+ cells may thereby fill in for the absence of GFAP+ cells. Nestin reexpression has been seen after experimental hippocampal injuries as well as in human pathologies like multiple sclerosis, providing evidence in favour of this theory. Additionally, forced food restriction and anorexia increased the number of reactive astrocytes, showing that GFAP+ cells respond to extreme caloric restriction. Another thing to think about is that female animals that experience prolonged stress or starvation halt their reproductive cycles, which prevents them from being exposed to hormones that could influence astrocyte density and morphology. Furthermore, in the ABA model, hippocampal gliogenesis but not neurogenesis is diminished.

As a result, even in the adult brain, astrocytes have varied degrees of differentiation and maturation and can transition between these stages. The same is true for the gliotransmitters and growth factors secreted by astrocytes, which are essential for synaptic plasticity, synaptogenesis, and neurogenesis. Accordingly, a decreased density of GFAP+ cells may have an impact on the hippocampal gliotransmission of d-serine, a gliotransmitter required for neuronal NMDA-mediated transmission and long-term potentiation. Dendrites in the adult hippocampus need growth factors like BDNF in order to maintain long-term synaptic plasticity. Dendrite branching, notably in the stratum radiatum, was found to be lessened in an ABA model, nevertheless. Our findings indicated that anorexia reduces the number of GFAP+ cells and the expression of GFAP. Similar outcomes were noted in a rat model of depression, where there was a decrease in GFAP expression. Thus, we draw the conclusion that anorexia has an impact on GFAP+ cells and intermediate filament expression. The structural alterations in the hippocampus seen in anorexic mouse models are now better understood thanks to our findings.

Conclusions

The model proposed in this paper posits that the trajectories of an observable variable (y) caused by the TAFC.decision making task are conditional to the final state (x), and therefore they trace the information processing ***[8]***. According to this hypothesis, it is possible to explore the relationship between the end state of the decisional process, which is controlled by the y path, and the creation of a decision by taking into account the fact that populations of neurons control neuronal responses to stimuli. Here, it is proposed that the probability series ($y \mid x$) are formed by the sequential activation of two neural populations P1 and P2, and that the decision-making process results from the accumulation of activity by a pool of neuron populations.

The gathered evidence would develop a diffusive dynamic as a result. As a result, the proposed model, known as the 2LDM, to some part implements the two-stage circuitry of valuation and decision, which is computationally trustworthy in terms of both neurobiology and Bayesian theory [**9**].

According to its diffusive activation mechanisms, likelihood is ultimately dependent on commutations between internal representations. Since both models rely on nonlinear diffusive dynamics, there is a theoretical connection between the 2LDM and the well-known integrate-and-fire attractor network model. The primary difference is in the dynamics of the basal ganglia involved in decision-making, which we predicted to be nonlinear rather than linear. Additionally, the 2LDM becomes an entropy when the input-output map is described using the infomax principle. If the distribution of the residuals is not Gaussian and is heavy-tailed, exhibiting substantial skewness and kurtosis, improvement in the optimization of the 2LDM parameters is anticipated by taking different error functions instead of RMSE. The implementation of additional layers for the investigation of the potential subcircuits involved in the valuation or choosing stage of DM (such as the direct and indirect routes in BG) would be a difficult undertaking [**10**]. Last but not least, the application of 2LDM to a particular cognitive experimental task would provide insight into how speed and accuracy performance may change depending on a psychometric or behavioural smoothing parameter.

This latter viewpoint appears to be supported by our observation of enhanced beta activity in the second neuronal population, which would choose the best alternative, even though it was at the lower bound of the beta frequency range.

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Conflict of Interest

The author has no known conflicts of interested associated with this paper.

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