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Neurofisiologia da predição baseada em memórias sobre regularidades passadas

Neurophysiology of prediction based on memories of past regularities

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RESUMO

SILVA, D. G. **Neurofisiologia da predição baseada em memórias sobre regularidades passadas**. 2022. Tese (Doutorado em Ciências) – Instituto de Biociências, Universidade de São Paulo, São Paulo, 2022.

O sistema nervoso monitora o ambiente continuamente, comparando previsões geradas por memórias sobre regularidades passadas e informações sensoriais atuais. Quando o conteúdo previsto corresponde à informação sensorial, o comportamento em curso continua sem interferência. Porém, quando o conteúdo previsto difere da informação sensorial, a ação em andamento é interrompida e uma atividade exploratória é gerada para investigar a origem da discrepância. Isso possibilita obter mais informações para criar novas memórias, resultando em melhores previsões no futuro. O sistema septo-hipocampal compara estímulos presentes com informações previstas. As informações atuais são recebidas por aferências neocorticais, via córtex entorrinal, e as informações previstas são fornecidas por um sistema gerador de previsões, formado pelo subículo, corpos mamilares, tálamo anteroventral e córtex cingulado. A tarefa de extrapolação a partir de padrões seriais de estímulos parece permitir a avaliação de respostas antecipatórias. Porém, restrições dessa tarefa estão relacionadas ao número de sessões de treinamento necessárias para que os sujeitos possam gerar uma previsão. Assim, o objetivo desse trabalho foi aprimorar a tarefa de extrapolação a partir de padrões seriais de estímulos, tanto para reduzir a fase de treinamento, quanto para aumentar a magnitude dos efeitos da previsão. Visto que a citocromo C oxidase é uma enzima mitocondrial da cadeia de transporte de elétrons e seu aumento indica maior atividade celular, um objetivo adicional foi avaliar a hipótese de que a expressão do citocromo C oxidase aumentaria no subículo e no tálamo anteroventral de sujeitos treinados na tarefa de extrapolação a partir de padrões seriais de estímulos, em comparação a controles não-treinados. Ratos Wistar machos, foram treinados a correr em uma pista reta para receberem reforço ao seu final. Em cada sessão (uma por dia), os animais correram 4 tentativas sucessivas, recebendo quantidades diferentes de sementes de girassol em cada tentativa. No padrão monotônico os sujeitos receberam 14, 7, 3 e 1 sementes de girassol, enquanto os sujeitos expostos ao padrão não-monotônico receberam 14, 3, 7 e 1 sementes de girassol. Os animais foram treinados ao longo de 20 sessões. Na 21ª sessão do experimento, uma quinta tentativa, nunca antes experienciada pelos animais, foi adicionada à sessão. Como controle, um grupo adicional, não exposto ao treinamento, foi usado na avaliação de expressão de citocromo C oxidase. A evolução do desempenho dos sujeitos expostos aos padrões monotônicos e não-monotônicos, ao longo de vinte sessões de treinamento, bem como na sessão de teste, corroboram dados de estudos anteriores relatando extrapolação após um número maior de sessões de treinamento. Isso indica que a modificação do aparato experimental e no procedimento de treinamento para realizar a tarefa foram efetivos. Ainda, análise da expressão de citocromo C oxidase mostrou aumento da atividade do tálamo anteroventral e redução da atividade especificamente no subículo dorsal, no grupo não-monotônico e o inverso no grupo monotônico. Em conclusão, esses dados sugerem que o tálamo anteroventral pode estar envolvido em processos de aprendizagem de informações posteriormente utilizadas na previsão, e que o subículo dorsal pode estar envolvido na recuperação de informações necessárias para a geração de previsão.

Palavras-chave: Comportamento Antecipatório. Padrões Seriais de Estímulos. Tálamo Anteroventral. Subículo. Citocromo C Oxidase.

ABSTRACT

SILVA, D. G. **Neurophysiology of prediction based on memories of past regularities**. 2022. Tese (Doutorado em Ciências) – Instituto de Biociências, Universidade de São Paulo, São Paulo, 2022.

The nervous system continuously monitors the environment, comparing predictions generated by memories of past regularities and current sensory information. When the predicted content matches the sensory information, the ongoing behavior continues without interference. However, when the predicted content differs from the sensory information, the ongoing action is interrupted and an exploratory activity is generated to investigate the source of discrepancy. This makes it possible to obtain more information to create new memories, resulting in better predictions in the future. The septo-hippocampal system compares present stimuli with predicted information. The current information is received by neocortical afferents, via the entorhinal cortex, and the predicted information is provided by a generator of predictions system, composed by the subiculum, mammillary bodies, anteroventral thalamus and cingulate cortex. The extrapolation of serial stimulus patterns task seems to allow the evaluation of anticipatory responses. However, serious restrictions on this task are related to the number of training sessions required for subjects to generate a prediction. Thus, the objective of this work was to improve the extrapolation of serial stimulus patterns task, both to reduce the training phase and to increase the magnitude of the prediction effects. Since cytochrome C oxidase is a mitochondrial enzyme of the electron transport chain and its increase indicates greater cellular activity, an additional objective was to evaluate the hypothesis that cytochrome C oxidase expression would increase in the subiculum and anteroventral thalamus of subjects trained in the extrapolation of serial stimulus patterns task, compared to untrained controls. Male Wistar rats were trained to run on a straight alleyway to receive reinforcement at the end. In each session (one per day), the animals ran 4 successive trials, receiving different amounts of sunflower seeds in each trial. In the monotonic pattern subjects received 14, 7, 3 and 1 sunflower seeds, while subjects exposed to the non-monotonic pattern received 14, 3, 7 and 1 sunflower seeds. The animals were trained over 20 sessions. In the 21st session of the experiment, a fifth trial, never experienced before by the animals, was added to the session. As control, an additional group, not exposed to training, was used in the evaluation of cytochrome C oxidase expression. The evolution of the performance of subjects exposed to monotonic and non-monotonic patterns, over twenty training sessions, as well as in the test session, corroborates data from previous studies reporting extrapolation after a greater number of training sessions. This indicates that the modification of the experimental apparatus and the training procedure to perform the task were effective. Furthermore, analysis of cytochrome C oxidase expression showed increased activity in the anteroventral thalamus and reduced activity specifically in the dorsal subiculum, in the non-monotonic group and the opposite in the monotonic group. In conclusion, these data suggest that the anteroventral thalamus may be involved in learning processes of information later used for prediction, and that the dorsal subiculum may be involved in retrieving information necessary for prediction generation.

Keywords: Anticipatory Behavior. Serial Stimulus Patterns. Anteroventral thalamus. Subiculum. Cytochrome C Oxidase.

Introduction

One of the most remarkable characteristics of the nervous system is its ability to anticipate relying on memories of past regularities. The nervous system is constantly comparing present sensory stimuli with information stored in memory, in order to generate predictions. Such capacity allows generating behaviors modulated by pending events, making it one of the fundamental characteristics of intentional behavior (Campos, Santos & Xavier, 1997). It is interesting to note that once the individual behaves in an anticipatory way, he is adapting his present behavior to deal with situations that may occur in the future (Poli, 2010). It is, then, an extremely important mechanism, the result of the evolution of the nervous system, which allowed to direct attention to relevant aspects of the environment (Helene & Xavier, 2003).

Therefore, anticipation is a widely studied ability, especially in biology and neuroscience. For instance, Pavlov (1927) already mentioned anticipatory behavior in his studies on conditioning. By repeatedly pairing a conditioned stimulus, such as light, to an unconditioned stimulus, such as food, the animal will begin to anticipate the presentation of food, as soon as it receives the light. That is, light will become an anticipatory signal for the food. Not only that, but Krushinsky (1990) also studied the ability to generate prediction in a wide range of wild and laboratory animals. The method used by the author consisted in the animal determining the future direction of a food that moved in a straight rail at a constant speed. At a given moment, the food leaves the animal's sight, and the subjects would need to define the place where this food would appear again. The author demonstrated that animals such as rodents, dogs and crows were able to determine the future and unknown direction of the food, based on the known trajectory that they saw before (Krushinsky,1990).

There is also a wide range of studies demonstrating anticipatory ability in rodents. In contrast of incentive gain, fasting rats learn to decrease consumption of a first presented solution containing 0.15% saccharin, by anticipating the presentation of a second preferred solution, containing 30% sucrose, minutes later. Interestingly, when the animals were part of a group in which they also received 0.15% saccharin as a second solution minutes after the first one, they do not show the same decrease in ingestion of the first solution (e.g., Flaherty & Checke, 1982; Onishi & Xavier, 2011). In addition, several studies involving serial stimulus patterns were able to demonstrate the predictive capacity of rodents. In these studies, rodents abstracted rules out of sequences of stimuli and from them predicted not only the reappearance of constant stimuli, but also the outcome of stimuli never seen before (Fountain & Hulse, 1981; Kundey & Fountain, 2011).

1.1. Serial stimulus pattern

Learning from serial stimulus patterns involves abstracting and applying identifiable rules from sequences of stimuli. Being able to learn these rules is beneficial for an individual's survival, as it can guide actions through time in an organized manner, even in unprecedented circumstances (Vassena *et al*., 2014; Garlick, Fountain & Blaisdell, 2017; Geddes, Li & Jin, 2018), preparing better and responding faster and in a more refined way to upcoming stimuli. The importance of serial stimulus learning is even seen in areas of intelligent systems, such as inference, planning, reasoning, robotics, natural language processing, speech recognition, time series prediction and financial engineering (Sun & Giles, 2001).

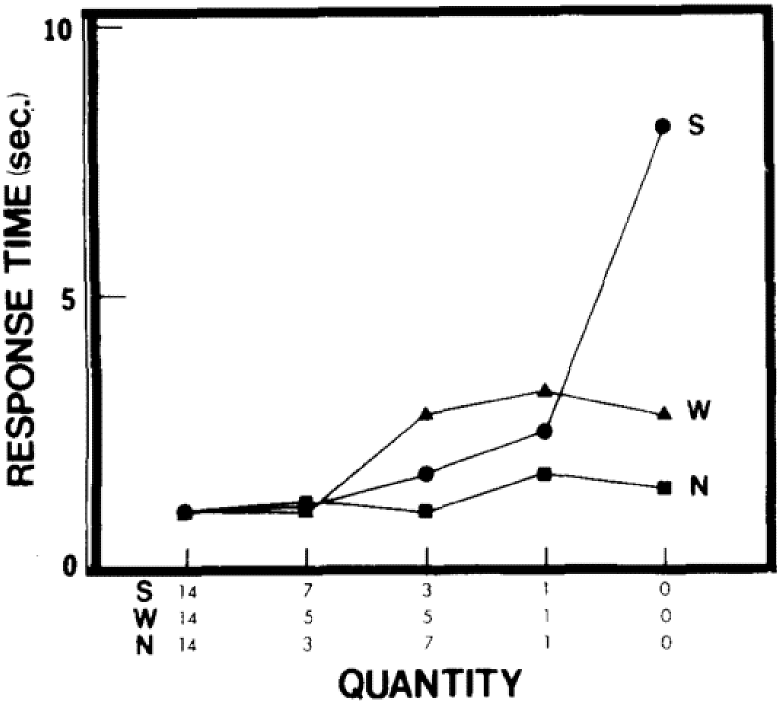
Human beings tend to abstract rules to facilitate the understanding of sequences of stimuli as a strategy (Fountain, 1990; Loffing, Stern & Hagemann, 2015). Thus, humans can divide a long sequence of stimuli, therefore more complex, into smaller subcomponents by applying simple rules to aid their learning (a process known as *chunking*) (Wallace, Rowan & Fountain, 2008; Muller & Fountain, 2016). Humans benefit from this strategy to create lyrics, write speeches (which require generating a logical series of words to make sense), or memorize and reproduce serial numbers such as telephone numbers (Garlick, Fountain & Blaisdell, 2017). Learning of serial stimulus patterns has also been observed in many other groups of animals (Sun & Giles, 2001; Rowan *et al*., 2001; Fountain, 2008; Rowan, Fountain & Kundey, 2021). Such learning seems similar to those seen in humans (Sands & Wright, 1982; Terrace & McGonigle, 1994; Fountain, 2006), being found in rodents (Fountain, 1990; Murphy, Mondragón & Murphy, 2008; Kundey *et al.,* 2019; Caglayan, Stumpenhorst & Winter, 2021), cetaceans (Mercado *et al*., 2000) and pigeons (Blaisdell & Cook, 2005; Garlick, Fountain & Blaisdell, 2017), for instance.

By learning the rules that identify a sequence of stimuli, the individual is able to predict when each item will likely occur again and generate behavioral responses in accordance with the serial pattern. Predicting a given item in the repetitive sequence of stimuli is known as anticipation (Haggbloom & Brooks, 1985; Fountain, 1990). Furthermore, these animals are able to extend the rules of a learned sequence and predict events never experienced before – as long as they are congruent with the original sequence – a process called extrapolation (Krushinsky, 1990; Poletaeva, Popova & Romanova, 1993; Poletaeva & Zorina, 2015). Extrapolating demands complex cognitive performance, as the organism uses past experiences to predict the possible consequences of novel events, never experienced before, constituting an adaptive advantage (Guigon, 2004). Therefore, it is not surprising that extrapolation has been reported not only in humans (Srinivas & Schwoebel, 1998; Schlag *et al*., 2000; Murphy, Mondragón & Murphy, 2008), but in lemurs (Merritt *et al*., 2011), dogs (Sjölander, 1995), rodents (Fountain & Hulse, 1981, Silva & Xavier, 2021), corvids (Wilson, Mackintosh & Boakes, 1985) and bees (Howard *et al*., 2017), among others.

Fountain and Hulse (1981) showed that rats are able to extrapolate from serial stimulus patterns. According to these authors, the subjects abstract and apply rules that describe the sequence of stimuli. These authors trained rats to run through a straight alleyway to receive different amounts of reward at the end of each of four consecutive trials. Independent groups of subjects were exposed to serial patterns involving 4 items presented in defined sequences. One of the groups, the Strongly Monotonic ("S") received 14, 7, 3, and 1 food pellets along 4 trials, respectively. Note that this group was exposed to a decreasing amount of food pellets from trial to trial (i.e., 14-7, 7-3, and 3-1). A second group, the Weakly Monotonic ("W") received 14, 5, 5 and 1 food pellets. In this group there are two decreasing transitions (14-5 and 5-1) and one transition without any change in the amount of food pellets (5-5). A third group, the non-monotonic ("N") received 14, 3, 7 and 1 food pellets. That is, for this group there are two decreasing transitions (14-3 and 7-1) and one increasing transition (3-7). On the first day of training, the animals were exposed to two training sessions. From days two to thirteen they were exposed to four sessions per day, each session with 4 trials. Along training the animals expressed their ability to anticipate the next item in the sequence by running faster on trials that provided greater reinforcement and slower on trials with smaller reinforcement. On day fourteen, the animals were exposed to a regular training session followed by an additional session that included a fifth trial just after the fourth trial. Note that this fifth trial had never been experienced by any of the groups. The speed of the animals on the fifth trial was consistent with the logically possible extrapolation from the serial stimulus pattern. That is, the animals exposed to the S pattern substantially reduced their running speeds on the fifth trial, as if they were expecting an amount of food pellets smaller than the one received in the last fourth trial **(Figure 1)**. Animals exposed to the W pattern exhibited running speeds consistent with the expectation of 1 reinforcement. Finally, animals exposed to the N pattern exhibited running speeds congruent with the expectation that they would receive a greater amount of reinforcement as compared to the last trial **(Figure 1)**.

As the fifth trial was new for all subjects and the total amount of food pellets received in the previous trials within the session was the same for all groups, differences in running speeds could not be ascribed to either novelty or motivation. Thus, the authors ascribed this result to the extrapolation relying on the serial pattern to which each group of subjects was exposed to. The authors' interpretation for the running times in the fifth trial by subjects of the S group was that they identified a simple "less than rule". Data of the N subjects were interpreted as “lack of extrapolation”. That is, subjects would have not been able to learn the rule of the serial pattern they were exposed to, because it would have been more complex (i.e., a decreasing transition, an ascending and another decreasing one).

Figure 1. Mean of running times (sec) of the subjects exposed to the Strongly monotonic (S), Weakly monotonic (W) and Non-monotonic (N) serial patterns along the five trials of the testing session, as a function of the amount of food pellets received in corresponding trials of previous sessions and along trials in the present session (Quantity).



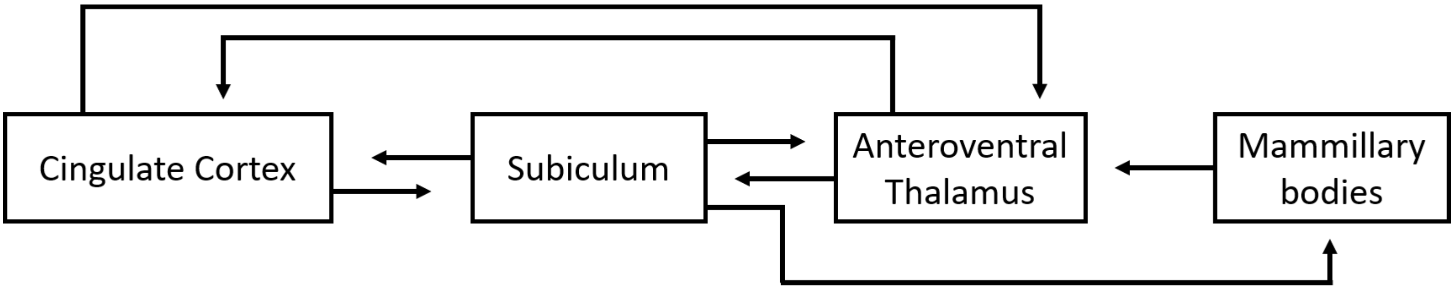
Source: Fountain & Hulse, 1981.

Even though different species can learn rules embedded in sequences of stimuli and generate predictions relying on them, little is known about the neural substrates underlying generation of predictions. Gray (1982) proposed that the nervous system continuously monitors the environment, comparing predictions generated from memories of past regularities in the same context of current sensory information (Henke, 1982; Stolar *et al*., 1989; Brod, Werkle-Bergner & Shing, 2013). When the predicted content corresponds to the sensory information, monitoring continues without interference of the ongoing behavior. However, when the predicted content differs from sensory information, the action in progress is interrupted and exploratory activity is generated to investigate the possible origin of the discrepancy. This renders possible to obtain new information and to create new memories, resulting in better predictions in future occasions.

1.2. Neural Substrates Underlying Generation of Predictions

According to Gray (1982), part of the hippocampal system, specifically the subiculum, would compare the content of predictions and present sensory information. Present information would be received from neocortical afferents, via entorhinal cortex, and predicted information would be provided by a generator of prediction system (GPS), constituted of both (1) a long loop, including the subiculum, mammillary bodies, anteroventral thalamus (AVT) and cingulate cortex, and (2) a short loop, involving direct and reciprocal projections between the subiculum and the AVT **(Figure 2)**. Thus, the GPS would have access to current sensory information, information stored in memory and the motor plans of the individual **(Figure 3)**. The subiculum would also be the comparator in both loops.

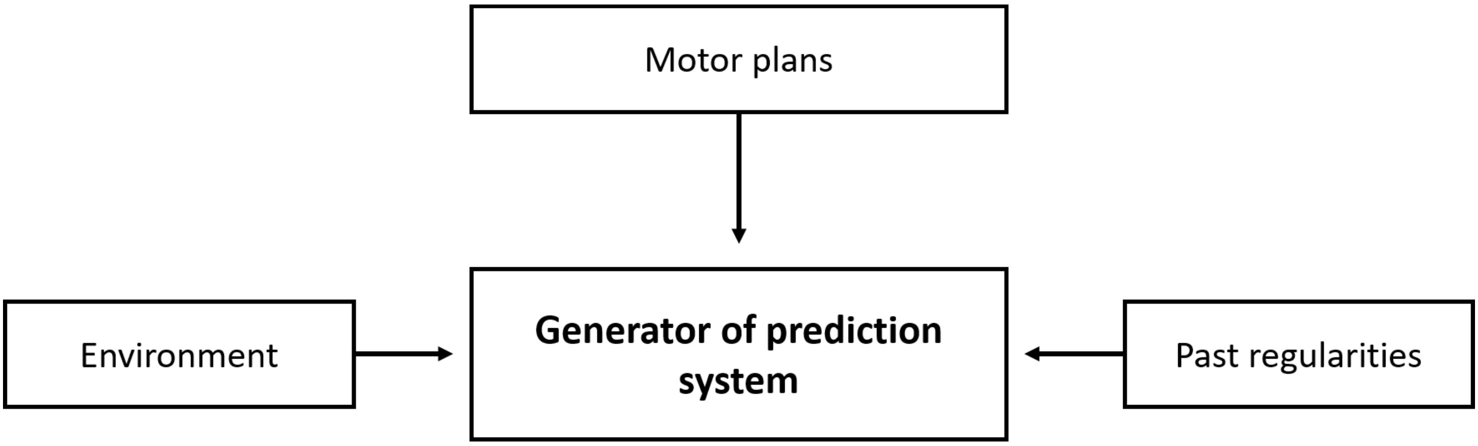
Figure 2. Schematic representation of the structures and projections that form the Generator of Prediction System (GPS).



Source: Gray, 1982.

From the experimental point of view, among the structures that participate in the GPS, the AVT is in a strategic position to investigate this hypothesis. First because it would participate in both the long and the short loops. Second, because it is relatively far from the other structures postulated to be involved in the system, thus rendering possible, for instance, to induce damage in it without reaching other constituents of the system. Furthermore, there have been reports that the AVT plays an active role in the processing information coming from the subiculum (Vinogradova, 2001), as it receives direct and indirect projections from this structure (Dillingham *et al*., 2015; Aggleton & Christiansen, 2015; Christiansen *et al*., 2016). In addition, the AVT receives indirect projections from the CA1 subfield, bringing processed current sensory information from the entorhinal cortex (Gray *et al*., 1991; Gigg, 2006). Finally, according to Stolar and colleagues (1989), the AVT reacts to the probability of pending stimuli. Together these data emphasize the key position of the AVT to investigate this postulated GPS.

Figure 3. Schematic representation of the basic functioning of the Generator of Prediction System (GPS).

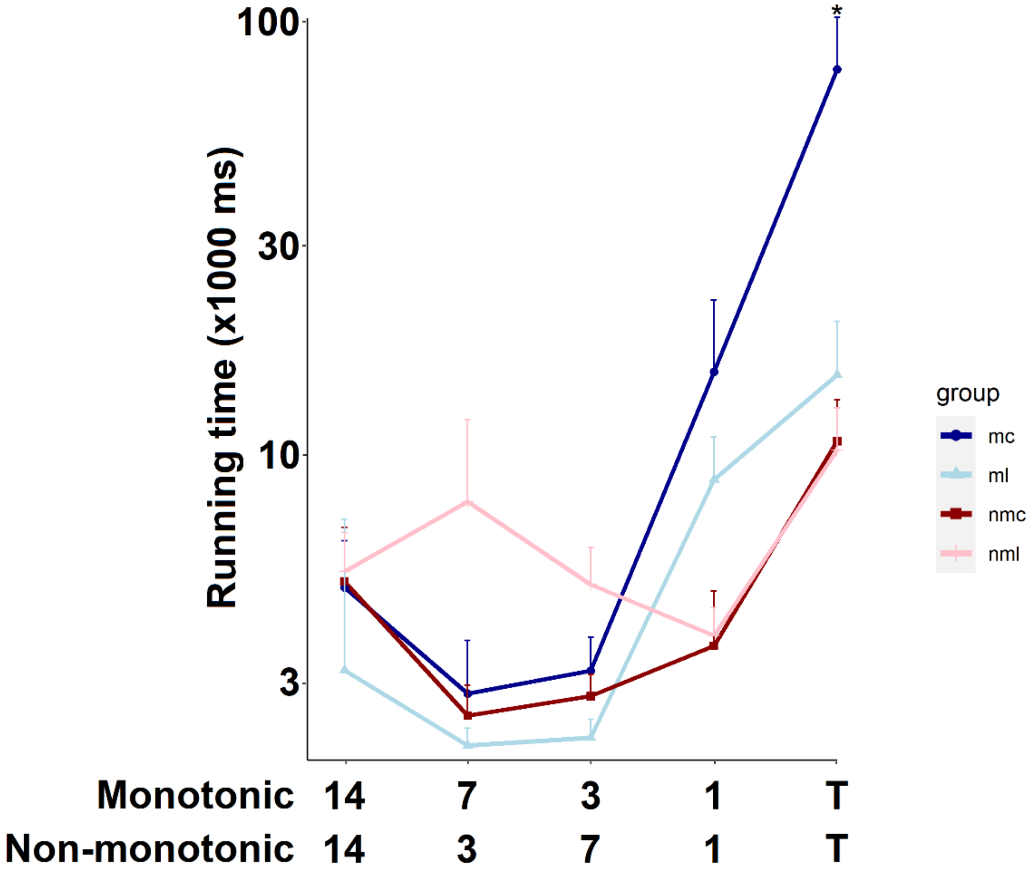


Source: Gray, 1982.

Silva and Xavier (2021) submitted rats with selective damage in the AVT (L Group) and respective sham-operated controls (C Group) to an extrapolation of serial stimulus pattern task. Part of the subjects in each group was trained using a strongly monotonic schedule (hereafter referred to as monotonic - M) and the other part using a non-monotonic schedule (NM). Therefore, there were four groups: LM, LNM, CM and CNM. The subjects were trained along 31 sessions in their respective serial patterns, one session per day. On the 32nd day, a never experienced fifth trial was added to the session soon after the fourth trial. As expected, the running times in the fifth trial of control animals exposed to the monotonic pattern (CM) were substantially longer when compared to control animals exposed to the non-monotonic pattern (CNM), indicating the occurrence of extrapolation **(Figure 4)**. In contrast, lesioned subjects exposed to the monotonic pattern did not exhibit such increase in latency (LM), indicating that these animals did not extrapolate **(Figure 4)**. These results indicate that extrapolation is impaired following selective lesion of the AVT, corroborating Gray's proposal (1982) about the participation of this neural structure in a GPS. Silva and Xavier (2021) report constitutes the first consistent demonstration that the AVT integrity is required for generating predictions, thus stimulating further investigation of the subiculum and AVT involvement in a GPS, as postulated by Gray (1982).

The AVT is one of the components of the anterior thalamic nuclei (ATN). The ATN include two other nuclei (Aggleton *et al*., 2010), namely, the anterodorsal thalamus (AD) and the anteromedial thalamus (AM). Evidence in scientific literature shows that the AD is related to the propagation of signals from Head Direction Cells (HDC) (Clark & Taube, 2011), the AVT would act as a return loop that modulates theta rhythm (Vertes *et al*., 2001), thus, assisting spatial and non-spatial functions in the hippocampus (Buzsaki, 2005), and the AM would form a connection network between hippocampal-diencephalic and prefrontal areas (Jankowski *et al*., 2013). In fact, evidence shows that the ATN helps in distinct components of learning. Not surprising, humans with ATN injury or atrophy show symptoms similar to those seen in Korsakoff syndrome (Harding *et al*., 2000; Tsivilis *et al*., 2008; Carlesimo *et al*., 2011; De Lima, Baldo & Canteras, 2017).

Figure 4. Mean (+ S.E.M.) of the running times (x 1000 ms) of control (C) and lesioned (L) subjects exposed to training either with the monotonic (M) or the non-monotonic (NM) serial patterns, and subjected to Testing (T) by introducing a fifth trial (never experienced before) in the 32nd session.



Source: Silva and Xavier (2021).

Vinogradova (2001) reported that signals from the subiculum reach structures of the limbic system through the fornix. Such structures constitute the ATN, mainly the AVT (Aggleton *et al*., 2010; Christiansen *et al*., 2016), the mammillary bodies (Irle & Markowitsch, 1982; Christiansen *et al*., 2016), through its direct and reciprocal projections with the subiculum (Vann & Aggleton, 2004), and the cingulate cortex (mainly its posterior area) (Irle & Markowitsch, 1982; Wolff & Vann, 2019). It is interesting to note that Vinogradova (2001) emphasized that information coming from the subiculum receives additional processing when passing through these structures. In turn, the mammillary bodies have extensive connections with the AVT, through the mammillothalamic tract (Vann & Aggleton, 2004). As for the posterior region of the cingulate cortex in rats, designated retrosplenial cortex, because it does not have the equivalents of the areas 23 and 31 of primates, is the cortical target of the ATN, specially the AVT (Shibata, 1993; Van Groen & Wiss, 1995; Wolff *et al*., 2008; Vann, Aggleton & Maguire, 2009; Shibata & Honda, 2015). In fact, rodent with ATN lesions exhibit disruption of activity in the retrosplenial cortex (Dupire *et al*., 2013; Aggleton & Nelson, 2015). Wolff and Vann (2019) called attention to the functional relationship involving the ATN, the hippocampal formation – of which the subiculum is part – and the retrosplenial cortex, where the ATN would play a role in synchronizing these areas and updating representations of existing information (Corcoran *et al*., 2016; Eichenbaum, 2017).

The current literature refers to the structures integrating Gray's (1982) GPS system as "extended hippocampal system" (Aggleton & Brown, 1999, 2006; Wright *et al*., 2013; Carlesimo *et al*., 2015). Differently, however, the extended hippocampal system has been related to learning and memory, including spatial memory in rodents and episodic memory in humans (Byatt & Dalrymple-Alford 1996; Aggleton *et al*., 2010; Jankowski *et al*., 2013; Marchand, *et al.,* 2014; Dillingham *et al*., 2015; Dumont *et al*., 2015; Milczarek & Vann, 2020).

Conejo and colleagues (2010) trained rats in the Morris water maze and accompanied the evolution of both the hippocampal system and limbic structures activities using cytochrome C oxidase. The authors reported that distinct groups of rats trained for one, three or five days in the water maze exhibited greater neural activity of the AVT in the first day of training, while hippocampal formation structures presented activity from day 1 of the spatial memory task up to day 5. The authors interpreted these results in terms of the contribution of the “extended hippocampal system” for spatial learning and memory.

Although it seems clear that the structures composing the “extended hippocampal system” play a critical role in spatial learning and declarative memory, one should not ignore evidence that they are not restricted only to this role (e.g., Carlesimo *et al*., 2015; Wolff *et al.,* 2015). For example, it has been shown that these structures participate in attentional set-shifting (Wright *et al.,* 2015; Bubb *et al.,* 2021), contextual fear memory (Dupire *et al*., 2013; Marchand *et al*., 2014) and fear conditioning promoted by predator threats (Carvalho-Netto *et al.,* 2010; De Lima, Baldo & Canteras, 2017).

In discriminative avoidance conditioning task, rabbits learned to avoid a shock by moving in a wheel at a specific moment, electrophysiological recordings of the subiculum and AVT were performed during the task. The data showed that the subiculum exhibited greater activity in the early learning stages of the task, in other words, aiding to gather information that the animals will need to predict when they should move in the wheel, in order to avoid the shock. On the other hand, the AVT was more active during more advanced stages of the behavioral acquisition, guiding behavior after the information about the task rule had already been well acquired (Gabriel, Sparenborg & Stolar, 1987).

1.3. Possible neural changes associated with generation of prediction

Cytochrome C oxidase (COX – also known as Complex IV) is an enzyme that forms the last step in the mitochondrial electron transport chain to produce ATP (Wong-Riley, 2012). Measurement of COX activity can be obtained by histochemistry, acting as a marker of neural metabolism by revealing the energy demand of neurons. Highly metabolic brain regions usually show high expression of COX activity in histochemical assays and vice versa (Mendelez-Ferro *et al*., 2013). For instance, COX histochemistry helped to understand the functional organization of parallel visual pathways in primates (Peres *et al*., 2019), and provided evidence for delineating boundaries of cortical neurons in layers and areas (Balaram, Young & Kaas, 2014), and allowed identification of human visual area 1 (V1) cortical areas related to processing of information from the left and the right eyes (Lingley *et al*., 2018). Furthermore, COX marking helped to reveal that the primate second-order visual area (V2) shows compartmental organization based on bands that run orthogonal to the limits between V1 and V2 (Wong-Riley & Carroll, 1984; DeYoe & Van Essen, 1985; Zeki & Shipp, 1989; Gattass *et al*., 1990). These studies helped to understand how the modular architecture of areas V1 and V2 is associated with parallel pathways originating in the retina and relayed through the lateral geniculate nucleus (Levitt, Kiper & Movshon, 1994; Gattass *et al*., 1997; Federer *et al*., 2009).

Expression of COX has aided to identify energy demand of neurons during prolonged stimulation or repetitive performance of behavioral tasks (Luo, Hevner & Wong-Riley, 1989; Gonzalez-Lima & Cada, 1994), reflecting the degree of neural activity of cells involved in the task performance (Divac *et al*., 1995). For this reason, it has been used in studies involving learning and memory (Poremba, Jones & Gonzalez-Lima, 1997; Conejo *et al*., 2004; Conejo *et al*., 2007). Furthermore, it is notable that results obtained through COX reflect a stable state of metabolic capacity of the neurons of interest, which occurs over hours (Conejo *et al*., 2010). Thus, the use of COX seems interesting in prospective approaches to the study of the neural circuitry underlying a given function. In other words, given that the use of COX histochemistry was successful in the aforementioned behavioral systems and tasks, it seems plausible to assume that it is adequate to evaluate the activity of structures comprising the GPS during performance of serial learning, anticipation and extrapolation tasks.

1.4. Rational for the proposed experiments

The extrapolation of serial stimulus pattern task may help to investigate the GPS because it allows revealing at least two different forms of predictions. One can evaluate anticipation relying on "reconstruction from memory", that is, when within the same situation involving a sequence of events, the subject predicts the next event relying of its previous memories for that experience, like it occurs along training in this task. One can also evaluate extrapolation of a novel (never experience before) event relying on the memories of past regularities, like it occurs during the fifth trial of the testing session.

It seems important to emphasize that although the extrapolation of serial stimulus patterns task usually produce clear results, it demands too many training sessions, but allows only one convincing extrapolation testing session, where the individual generates an extrapolation relying on the rules learned previously. Such a long experimental design can be risky, since if something goes wrong in the testing session this part of the experiment could be lost. Thus, to amplify scores expressing anticipatory effects during performance of this task, a longer straight alleyway with higher walls was employed. Because performance of the task is evaluated based on running times in each trial, a longer alleyway should amplify possible differences. On the other hand, higher walls should avoid possible distracting extra-maze stimuli thus helping the subject to focus on the performance of the serial learning task. These changes aimed at fewer training sessions for learning the rule to be used to generate a prediction in the testing session.

In addition, independent groups of subjects exposed to training using either the Monotonic or the Non-monotonic serial patterns provided brains for COX histochemistry, in order to evaluate COX expression in the AVT and subiculum, critical brain structures involved with the GPS.

Objectives

The present study aimed at improving the behavioral task for studies of extrapolation of serial stimulus patterns in order to both reduce the training phase and increase magnitude of the extrapolation effects.

An additional aim was to evaluate the hypothesis, directly derived from Gray’s (1982) proposal, about the brain structures involved in the GPS, that the COX activity in the subiculum and the AVT in subjects trained in the extrapolation of serial stimulus pattern task would be increased as compared to that seen in control untrained subjects.

Conclusion

Rodents are capable of using past experience to generate predictions about pending events. Such predictions may involve both recurring events, named anticipation, and never experienced events predicted by the application of rules relating serial patterns, named extrapolation.

Studies on generation of predictions are limited by the availability of tasks that provide unequivocal measures of anticipation. Extrapolation of serial stimulus patterns seems to allow evaluation of anticipatory responses about both recurrent and novel events.

Serious constraints involving the use of this task relate to the number of training sessions required for the subjects to anticipate events and the fact that extrapolation is evaluated in a single testing session.

One of the aims of this study was to modify the experimental apparatus and training procedure in order to perform the extrapolation testing after a smaller number of training sessions, whilst ensuring abstraction of the serial pattern rules and thus extrapolation. The evolution of performance by the subjects exposed to M and NM serial patterns, along twenty training sessions, as well as their performance in the extrapolation testing session, confirmed data of previous studies reporting extrapolation following a greater number of training sessions (Fountain & Hulse, 1981; Silva & Xavier, 2021). This indicates that the present version of the task allowed achieving that aim.

Another aim of the present study was to gather evidence that brain structures included in a postulated generator of predictions system, particularly the AVT and the subiculum (see Gray, 1982), would exhibit changes in their activity, as revealed by COX histochemistry, following training and testing in the extrapolation of serial stimulus pattern task. In general, results showed (1) increased AVT and AD activity and (2) reduction of dorsal subiculum activity, in both cases in NM subjects, but not in M subjects. These figures, in association with relevant literature, suggests that the AVT may be involved in learning processes of information latter used in extrapolation, and that the dorsal subiculum may be involved in retrieval of information required for predicting.

Bibliographic references

AGGLETON, J. P.; BROWN, M. W. Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. **Behavioral and brain sciences**, v. 22, p. 425 – 489, 1999.

AGGLETON, J. P.; BROWN, M. W. Interleaving brain systems for episodic and recognition memory. **Trends in Cognitive Sciences**, v. 10, p. 455-463, 2006.

AGGLETON, J. P.; CHRISTIANSEN, K. The subiculum: the heart of the extended hippocampal system. **Progress in Brain Research,** v. 219, p. 65 – 82, 2015.

AGGLETON, J. P.; NELSON, A. J. D. Why do lesions in the rodent anterior thalamic nuclei cause such severe spatial deficits? **Neuroscience and Biobehavioral Reviews,** v. 54, p. 131–144, 2015.

AGGLETON, J. P.; O'MARA, S. M.; VANN, S. D.; WRIGHT, N. F.; TSANOV, M.; ERICHSEN, J. T. Hippocampal-anterior thalamic pathways for memory: uncovering a network of direct and indirect actions. **European Journal of Neuroscience,** v. 31, p. 2292-2307, 2010.

BAKER, R.; *et al*. Learning to predict: Exposure to temporal sequences facilitates prediction of future events. **Vision Research**, v. 99, p. 123-133, 2014.

BALARAM, P.; YOUNG, N. A.; KAAS, J. H. Histological features of layers and sublayers in cortical visual areas V1 and V2 of chimpanzees, macaque monkeys, and humans. **Eye Brain,** v. 6, p. 5 – 18, 2014.

BASSET, J. P.; *et al*. Passive Movements of the Head Do Not Abolish Anticipatory Firing Properties of Head Direction Cells. **Journal of Neurophysiology,** v. 93, p. 1304-1316, 2005.

BEIN, O.; DUNCAN, K.; DAVACHI, L. Mnemonic prediction errors bias hippocampal states. **Nature Communications**, v. 11, p. 3451, 2020.

BLAIR, H. T.; LIPSCOMB, B. W.; SHARP, P. E. Anticipatory Time Intervals of Head-Direction Cells in the Anterior Thalamus of the Rat: Implications for Path Integration in the Head-Direction Circuit. **Journal of Neurophysiology,** v. 78, p. 145 – 159, 1997.

BLAIR, H. T.; SHARP, P. E. Anticipatory head direction signals in anterior thalamus: evidence for a thalamocortical circuit that integrates angular head motion to compute head direction. **Journal of Neuroscience,** v. 15, p. 6260 – 6270, 1995.

BLAISDELL, A. P.; COOK, R. G. Two-item same-different concept learning in pigeons. **Learning & Behavior,** v. 33, n. 1, p. 67–77, 2005.

BOUSSARD, A.; *et al*. Brain size does not predict learning strategies in a serial reversal learning test. **Journal of Experimental Biology**, v. 223, p. 1-8, 2020.

BROD, G.; WERKLE-BERGNER, M.; SHING, Y. L. The influence of prior knowledge on memory: a developmental cognitive neuroscience perspective. **Frontiers in Behavioral Neuroscience,** v. 7, p. 1 – 13, 2013.

BUBB, E. J., *et al*. Chemogenetics Reveal an Anterior Cingulate–Thalamic Pathway for Attending to Task-Relevant Information. **Cerebral Cortex**, v. 31, p. 2169–2186, 2021.

BUBIC, A.; VON CRAMON, D. Y.; SCHUBOTZ, R. I. Prediction, cognition and the brain. **Frontiers in human neuroscience,** v. 4, n. 25, 2010.

BUCKNER, R. L.; CARROLL, D. C. Self-projection and the brain. **Trends in Cognitive Sciences**, v. 11, p. 49–57, 2007.

BUTLER, W. N.; *et al.* The head direction signal plays a functional role as a neural compass during navigation. **Current Biology**, v. 27, p. 1259-1267, 2017.

BUZSAKI, G. Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. **Hippocampus**, v. 15, p. 827–840, 2005.

BYATT, G.; DALRYMPLE-ALFORD, J. C. Both anteromedial and anteroventral thalamic lesions impair radial-maze learning in rats. **Behavioral Neuroscience,** v. 110, n. 6, p. 1335-1348, 1996.

CAGLAYAN, A.; STUMPENHORST, K.; WINTER, Y. Learning Set Formation and Reversal Learning in Mice During High-Throughput Home-Cage-Based Olfactory Discrimination. **Frontiers in Behavioral Neuroscience**, v. 15, p. 1-12, 2021.

CAMPOS, A.; SANTOS, A. M. G.; XAVIER, G. F. A consciência como fruto da evolução e do funcionamento do sistema nervoso. **Psicologia USP**, v. 8, n. 2, p. 181-226, 1997.

CAPALDI, E.J.; MILLER, R. M. Serial learning vs. reward schedules: What is learned? **Learning and Motivation**, v. 34, p. 127-147, 2003.

CAPALDI, E. J.; VERRY, D. R.; DAVIDSON, T. L. Memory, serial anticipation pattern learning, and transfer in rats. **Animal Learning & Behavior,** v. 8, p. 575-585, 1980.

CAPALDI, E. J.; VERRY, D. R. Serial order anticipation learning in rats: memory for multiple hedonic events and their order. **Animal Learning & Behavior**, v. 9, p. 441-453, 1981.

CARLESIMO, G. A.; LOMBARDI, M. G.; CALTAGIRONE, C.; BARBAN, F. Recollection and familiarity in the human thalamus. **Neuroscience & Biobehavioral Reviews**, v. 54, p. 18-28, 2015.

CARLESIMO, G. A.; LOMBARDI, M. G.; CALTAGIRONE, C. Vascular thalamic amnesia: a reappraisal. **Neuropsychologia**, v. 49, p. 777–789, 2011.

CARVALHO-NETTO, E. F.; *et al*. Evidence for the thalamic targets of the medial hypothalamic defensive system mediating emotional memory to predatory threats. **Neurobiology of Learning and Memory**, v. 93, p. 479–486, 2010.

CHRISTIANSEN, K.; DILLINGHAM, C. M.; WRIGHT, N. F.; SAUNDERS, R. C.; VANN, S. D.; AGGLETON, J. P. Complementary subicular pathways to the anterior thalamic nuclei and mammilary bodies in the rat and macaque monkey brain. **European journal of neuroscience,** v. 43, p. 1044 – 1061, 2016.

CLARK, B. J.; TAUBE, J. S. Intact landmark control and angular path integration by head direction cells in the anterodorsal thalamus after lesions of the medial entorhinal cortex. **Hippocampus,** v. 21, p. 767 – 782, 2011.

CONEJO, N.; GONZALEZ-PARDO, H.; GONZALEZ-LIMA, F.; ARIAS, J. Spatial learning of the water maze: Progression of brain circuits mapped with cytochrome oxidase histochemistry. **Neurobiology of Learning and Memory,** v. 93, n. 3, p. 362 – 371, 2010.

CONEJO, N. M.; GONZALEZ-PARDO, H.; VALLEJO, G.; ARIAS, J. L. Changes in brain oxidative metabolism induced by water maze training. **Neuroscience,** v. 145, p. 403 – 412, 2007.

CONEJO, N. M.; GONZALEZ-PARDO, H.; VALLEJO, G.; ARIAS, J. L. Involvement of the mammillary bodies in spatial working memory revealed by cytochrome oxidase activity. **Brain Research,** v. 1011, p. 107 – 114, 2004.

CORCORAN, K. A.; *et al*. Analysis of coherent activity between retrosplenial cortex, hippocampus, thalamus, and anterior cingulate cortex during retrieval of recent and remote context fear memory. **Neurobiology of Learning and Memory**, v. 127, p. 93–101, 2016.

DE LIMA, M. A. X.; BALDO, M. V. C.; CANTERAS N. S. A role for the anteromedial thalamic nucleus in the acquisition of contextual fear memory to predatory threats. **Brain Structure and Function**, v. 222, p. 113–129, 2017.

DEYOE, E. A.; VAN ESSEN, D. C. Segregation of efferent connections and receptive field properties in visual area V2 of the macaque. **Nature,** v. 317, p. 58 – 61, 1985.

DILLINGHAM, C. M.; ERICHSEN, J. T.; O'MARA, S. M.; AGGLETON, J. P.; VANN, S. D. Fornical and Nonfornical Projections from the Rat Hippocampal Formation to the Anterior Thalamic Nuclei. **Hippocampus,** v. 25, p. 977 – 992, 2015.

DIVAC, I.; *et al*. Improved contrast in histochemical detection of cytochrome oxidase: metallic ions protocol. **Journal of Neuroscience Methods,** v. 56, p. 105 – 113, 1995.

DUMONT, J. R.; *et al*. The impact of fornix lesions in rats on spatial learning tasks sensitive to anterior thalamic and hippocampal damage. **Behavioural Brain Research,** v. 278, p. 360 – 374, 2015.

DUNCAN, K.; *et al*, Evidence for area CA1 as a match/mismatch detector: A high-resolution fMRI study of the human hippocampus. **Hippocampus**, v. 22, p. 389–398, 2012.

DUPIRE, A.; e*t al.* A Role for Anterior Thalamic Nuclei in Affective Cognition: Interaction with Environmental Conditions. **Hippocampus**, v. 23, p. 392–404, 2013.

EICHENBAUM, H.; FORTIN, N. J. The neurobiology of memory based predictions. **Philosophical Transactions of the Royal Society B,** v. 364, p. 1183 – 1191, 2009.

EICHENBAUM, H. Prefrontal-hippocampal interactions in episodic memory. **Nature Reviews Neuroscience**, v. 18, p. 547–558, 2017.

EICHENBAUM, H. To Cortex: Thanks for the Memories. **Neuron,** v. 19, p. 418 – 484, 1997.

FEDERER, F.; *et al*. Four projection streams from primate V1 to the cytochrome oxidase stripes of V2. **The Journal of Neuroscience,** v. 29, p. 15455 – 15471, 2009.

FLAHERTY, C. F.; CHECKE, S. Antecipation of incentive gain. **Animal Learning & Behavior,** v. 10, p. 177-182, 1982.

FLAHERTY, C. F.; COPPOTELLI, C.; POTAKI, J. Effect of Chlordiazepoxide on the Response to Repeated Reductions in Sucrose Concentration in Free-Fed Rats. **Physiology & Behavior,** v. 60, p. 1291-1298, 1996.

FLAHERTY, C. F.; ROWAN, G. A. Anticipatory contrast: within-subjects analysis. **Animal Learning & Behavior,** v. 13, p. 2-5, 1985.

FOUNTAIN, S. B.; EVENSEN, J. C.; HULSE S. H. Formal structure and pattern lenght in serial pattern learning by rats. **Animal Learning & Behavior**, v. 11, n. 2, p. 186-192, 1983.

FOUNTAIN, S. B.; HULSE, S. H. Extrapolation of serial stimulus pattern by rats. **Animal learning & Behavior,** v. 9, p. 381 – 384, 1981.

FOUNTAIN, S. B. Pattern structure and rule induction in sequential learning. **Comparative Cognition & Behavior Reviews.** v. 3, p. 66–85, 2008.

FOUNTAIN, S. B.; ROWAN, J. D.; WOLLAN, M. O. Central cholinergic involvement in sequential behavior: impairments of performance by atropine in a serial multiple-choice task for rats. **Neurobiology of Learning and Memory**, v. 106, p. 118–126, 2013.

FOUNTAIN, S. B.; ROWAN, J. Sensitivity to Violations of "Run" and "Trill" Structures in Rat Serial-Pattern Learning. **J Exp Psychol Anim Behav Process**., v. 21, p. 78–81, 1995.

FOUNTAIN, S. B. Rule abstraction, item memory, and chunking in rat serial-pattern tracking. **Journal of experimental psychology: animal behavior processes**. v. 16, p. 96 – 105, 1990.

FOUNTAIN, S. B. The structure of sequential behavior. In WASSERMAN, E. A., & ZENTALL, T. R., (Eds.) **Comparative cognition: Experimental explorations of animal intelligence**, pp. 439–458, 2006.

GABRIEL, M. Discriminative avoidance learning: a model system. In: Vogt BA, Gabriel M, editors. **Neurobiology of cingulate cortex and limbic thalamus, Boston: Birkhäuser,** p. 478 – 523, 1993.

GABRIEL, M.; *et al.,* Anterior Thalamic Lesions and Neuronal Activity in the Cingulate and Retrosplenial Cortices During Discriminative Avoidance Behavior in Rabbits. **Behavioral Neuroscience**, v. 97, p. 675-696, 1983.

GABRIEL, M.; FOSTER, K.; ORONA, E. Interaction of laminae of the cingulate cortex with the anteroventral thalamus during behavioral learning. **Science**, v. 208, p. 1050-1052, 1980.

GABRIEL, M.; SPARENBORG, S. P.; STOLAR, N. Hippocampal control of cingulate cortical and anterior thalamic information processing during learning in rabbits. **Experimental Brain Research,** v. 67, p. 131 – 152, 1987.

GARLICK, D.; FOUNTAIN, S. B.; BLAISDELL, A. P. Serial Pattern Learning in Pigeons: Rule-Based or Associative? **Journal of Experimental Psychology,** v. 43, n. 1, p. 30 – 47, 2017.

GATTASS, R.; ROSA, M. G.; SOUSA, A. P., PIÑON, M. C.; FIORINI JÚNIOR, M.; NEUENSCHWANDER, S. Cortical streams of visual information processing in primates. **Brazilian Journal of Medical and Biological Research,** v. 23, p. 375 – 393, 1990.

GATTASS, R.; SOUSA, A. P. B.; MISHKIN, M.; UNGERLEIDER, L. G. Cortical projections of area V2 in the macaque. **Cerebral Cortex,** v. 7, p. 110 – 129, 1997.

GEDDES, C. E.; LI, H.; JIN, X. Optogenetic Editing Reveals the Hierarchical Organization of Learned Action Sequences. **Cell,** v. 178, n. 1, p. 32 – 43, 2018.

GIGG, J. Constraints on hippocampal processing imposed by the connectivity between CA1, subiculum and subicular targets. **Behavioural Brain Research**, v. 174, p. 265–271, 2006.

GONZALEZ-LIMA, F.; CADA, A. Cytochrome oxidase activity in the auditory system of the mouse: A qualitative and quantitative histochemical study. **Neuroscience,** v. 63, p. 559 – 578, 1994.

GRAY, J. A.; FELDON, J.; RAWLINS, J. N. P.; HEMSLEY, D. R.; SMITH, A. D. The neuropsychology of schizophrenia. **Behavioral and Brain Sciences**, v. 14, p. 1 – 84, 1991.

GRAY, J. A. **The neuropsychology of anxiety: an enquiry into the functions of the septo-hippocampal system.** New York, Oxford University Press, 1982.

GRAY, R. Behavior of college baseball players in a virtual batting task. **Journal of Experimental Psychology: Human Perception and Performance,** v. 28, n. 5, p. 1131–1148, 2002.

GUIGON, E. Interpolation and Extrapolation in Human Behavior and Neural Networks. **Journal of Cognitive Neuroscience,** v. 16, n. 3, p. 382 – 389, 2004.

GUPTA, A. S.; *et al*. Segmentation of spatial experience by hippocampal θ sequences. **Nature Neuroscience**, v. 15, p. 1032–1039, 2012.

HAGGBLOOM, S.; BROOKS, D. Serial anticipation and pattern extrapolation in rats as a function of element discriminability. **Animal Learning & Behavior,** v. 13, n. 3, p. 303–308, 1985.

HARDING, A.; *et al*. Degeneration of anterior thalamic nuclei differentiates alcoholics with amnesia. **Brain**, v. 123, p. 141–154, 2000.

HELENE, A. F.; XAVIER, G. F. Building attention from memory. **Revista Brasileira de Psiquiatria**, v. 25, p. 12-20, 2003.

HENKE, P. G. Septal Lesions and Incentive Expectancies in Rats. **Canadian Journal of Psychology,** v. 36, n. 3, p. 388 – 401, 1982.

HERMAN, J. P.; MULLER, N. K. Role of the ventral subiculum in stress integration. **Behavioural brain research**, v. 174, p. 215-224, 2006.

HOWARD, S. R.; *et al.* Free-flying honeybees extrapolate relational size rules to sort successively visited artificial flowers in a realistic foraging situation. **Animal Cognition,** v. 20, p. 627 – 638, 2017.

HULSE, S. H.; CAMPBELL, C. E. “Thinking ahead” in rat discrimination learning. **Animal Learning & Behavior**, v. 3, p. 305-311, 1975.

HULSE, S. H. Cognitive structure and serial pattern learning by animals. In S. H. HULSE, H. FOWLER; W. K. HONIG (Eds.), **Cognitive processes in animal behavior.** Hillsdale, N.J: Erlbaum, 1978.

HULSE S. H.; DORSKY, N. P. Serial pattern learning by rats: transfer of a formally defined stimulus relationship and significance of nonreinforcement. **Animal Learning & Behavior,** v. 7, p. 211-220, 1979.

HULSE S. H.; DORSKY, N. P. Structural complexity as a determinant of serial learning. **Learning and Motivation,** v. 8, p. 488-506, 1977.

IRLE, E.; MARKOWITSCH, H. J. Connections of the hippocampal formation, mamillary bodies, anterior thalamus and cingulate cortex. **Experimental Brain Research**, v. 47, p. 79-94, 1982.

JANKOWSKI, M. M.; *et al*. The anterior thalamus provides a subcortical circuit supporting memory and spatial navigation. **Frontier in systems neuroscience,** v. 7, n. 45, 2013.

JENKINS, T.A., *et al*. Novel spatial arrangements of familiar stimuli promote activity in the rat hippocampal formation but not the parahippocampal cortices: a c-fos expression study. **Neuroscience**, v. 124, p. 43–52, 2004.

KANG, E.; GABRIEL, M. Hippocampal modulation of cingulo-thalamic neuronal activity and discriminative avoidance learning in rabbits. **Hippocampus**, v. 8, p. 491-510, 1998.

KITANISHI, T.; UMABA, R.; MIZUSEKI, K. Robust information routing by dorsal subiculum neurons. **Science advances**, v. 7, p. 1-19, 2021.

KÖRDING, K. P. Decision theory: What "should" the nervous system do? **Science,** v. 318, p. 606–610, 2007.

KRUSHINSKY, L. V. **Experimental Studies of Elementary Reasoning: Evolutionary, Pshysiological and Genetic Aspects of Behavior**. New Delhi, Oxonian Press Pvt. Ltd, 1990.

KUNDEY, S. M. A.; *et al*. Sex differences in serial pattern learning in mice. **Behavioural Processes**, v. 168, p. 103958, 2019.

KUNDEY, S. M. A.; FOUNTAIN, S. B. Irrelevant relations and the active search for pattern structure in rat serial pattern learning. **Animal Cognition**, v. 14, p. 359-368, 2011.

LEE, C. S.; ALY, M.; BALDASSANO, C. Anticipation of temporally structured events in the brain. **eLife**, v. 10, p. 1-15, 2021.

LEVITT, J. B.; KIPER, D. C.; MOVSHON, J. A. Receptive fields and functional architecture of macaque V2. **Journal of Neurophysiology,** v. 71, p. 2517 – 2542, 1994.

LINGLEY, A. J.; *et al*. Mapping of neuron soma size as an effective approach to delineate differences between neural populations. **Journal of Neuroscience Methods,** v. 304, p. 126 – 135, 2018.

LOFFING, F.; STERN, R.; HAGEMANN, N. Pattern-induced expectation bias in visual antecipation of action outcomes. **Acta Psychologica,** v. 161, p. 45-53, 2015.

LUO, X.; HEVNER, R.; WONG-RILEY, M. Double labeling of cytochrome oxidase and gamma-aminobutyric acid in central nervous system neurons of adult cats. **Journal of Neuroscience Methods,** v. 30, n. 3, p. 189 – 195, 1989.

MARCHAND, A.; *et al.* A role for anterior thalamic nuclei in contextual fear memory. **Brain Structure and Function**, v. 219, p. 1575–1586, 2014.

MELO, M. B.; FAVARO, V. M.; OLIVEIRA, M. G. M. The dorsal subiculum is required for contextual fear conditioning consolidation in rats. **Behavioural Brain Research**, v. 390, p. 112661, 2020.

MENDELEZ-FERRO, M.; et al. An accurate method for the quantification of cytochrome C oxidase in tissue sections. **Journal of Neuroscience Methods**, v. 214, p. 156-162, 2013.

MERCADO, E. III.; *et al*. Generalization of 'same-different' classification abilities in bottlenosed dolphins. **Behavioural Processes,** v. 50, p. 79–94, 2000.

MERRITT, D.J.; *et al.* Numerical rule-learning in ring-tailed lemurs (Lemur catta). **Frontiers in Psychology,** v. 2, p. 1 – 9, 2011.

MILCZAREK, M. M.; VANN, S. D. The retrosplenial cortex and long-term spatial memory: from the cell to the network. **Current Opinion in Behavioral Sciences**, v. 32, p. 50-56, 2020.

MULLER, D. M.; FOUNTAIN, S. B. Concurrent cognitive processes in rat serial pattern learning: II. Discrimination learning, rule learning, chunk length, and multiple-item memories. **Journal of the Experimental Analysis of Behavior,** v. 105, n. 1, p. 155 – 175, 2016.

MULLER, M. D.; FOUNTAIN, S. B. Concurrent cognitive processes in rat serial pattern learning: Item memory, serial position, and pattern structure. **Learning and Motivation**, v. 41, p. 252–272, 2010.

MURPHY, R. A.; MONDRAGÓN, E.; MURPHY, V. A. Rules Learning by Rats. **Science,** v. 319, p. 1849–1851, 2008.

O’KEEFE, J.; NADEL L. **The hippocampus as a cognitive map**. Oxford: Clarendon Press, 1978.

O’MARA, S. The subiculum: what it does, what it might do, and what neuroanatomy has yet to tell us. **Journal of anatomy**, v. 207, p. 271-282, 2005.

ONISHI, B. K. A.; XAVIER, G. F. Negative antecipatory contrast: Does it involve anticipation of an impending reward? **Behavioural Processes,** v. 86, p. 263-271, 2011.

PAVLOV, I. P. **Conditioned Reflexes.** London, Oxford University Pres, 1927.

PAXINOS, G.; WATSON, C. **The rat brain in stereotaxic coordinates,** 5. ed. London, Elsevier Academic Press, 2004.

PERES, R.; *et al*. Neuronal response properties across cytochrome oxidase stripes in primate V2. **Journal of Comparative Neurology,** v. 527, n. 3, p. 651 – 667, 2019.

POLETAEVA, I.; POPOVA, N. V.; ROMANOVA, L. G. Genetic Aspects of Animal Reasoning. **Behavior Genetics,** v. 23, n. 5, p. 467–475, 1993.

POLETAEVA, I.; ZORINA, Z. A. Extrapolation Ability in Animals and Its Possible Links to Extrapolation, Anxiety, and Novelty Seeking. **Cognitive Systems Monographs,** v. 25, p. 415 – 430, 2015.

POREMBA, A.; JONES, D.; GONZALEZ-LIMA, F. Metabolic effects of blocking tone conditioning on the rat auditory system. **Neurobiology of Learning and Memory,** v. 68, p. 154 – 171, 1997.

POTVIN, O.; DORÉ, F. Y.; GOULET, S. Contributions of the dorsal hippocampus and the dorsal subiculum to processing of idiothetic information and spatial memory. **Neurobiology of Learning and Memory**, v. 87, p. 669-678, 2007.

QUENT, J. A.; HENSON, R. N.; GREVE, A. A predictive account of how novelty influences declarative memory. Neurobiology of Learning and Memory, v. 179, p. 107382, 2021.

QUINTERO, E.; *et al*. Ventral subiculum involvement in latent inhibition context specificity. **Physiology and Behavior**, v. 102, p. 414-420, 2011.

REDISH, A. D. Vicarious trial and error. **Nature Reviews Neuroscience**, v. 17, p. 147-159, 2016.

ROWAN, J. D. *et al.* A multiple species approach to sequential learning: Are you a man or a mouse? **Behavior Research Methods, Instruments, & Computers,** v. 33, n. 3, p. 435-43, 2001.

ROWAN, J. D.; FOUNTAIN, S. B.; KUNDEY, S. M. A. Rat’s use of hierarchical organization in serial pattern learning. **Behavioural Processes**, v. 192, p. 104490, 2021.

ROY, D. S.; *et al*. Distinct neural circuits for the formation and retrieval of episodic memories. **Cell**, v. 170, p. 1000-1012, 2017.

SANDS, S. F.; WRIGHT, A. A. Monkey and human pictorial memory scanning. **Science**, v. 216, p. 1333-1334, 1982.

SCHACTER, D. L.; ADDIS, D. R. The cognitive neuroscience of constructive memory: Remembering the past and imagining the future. **Philos. Trans. R. Soc. Lond. B Biol. Sci.**, v. 362, p. 773–786, 2007.

SCHLAG, J.; *et al.* Extrapolating movement without retinal motion. **Nature,** v. 403, p. 38 – 39, 2000.

SCHMIDT, R.; *et al*. Single-trial phase precession in the hippocampus. **The Journal of Neuroscience**, v. 29, p. 13232–13241, 2009.

SHARP, J. L.; *et al*. Serial pattern retention in male and female rats. **Neurobiology of learning and memory**, v. 155, p. 578-582, 2018.

SHETTLEWORTH, S. J. **Cognition, Evolution, and Behavior.** New York, NY: Oxford University Press, 2010.

SHIBATA, H. Efferent projections from the anterior thalamic nuclei to the cingulate cortex in the rat. **The journal of comparative neurology**, v. 330, p. 533-542.

SHIBATA, H.; HONDA, Y. Thalamocortical projections of the anterodorsal thalamic nucleus in the rabbit. **The journal of comparative neurology**, v. 520, p. 2647-2656, 2012.

SHIBATA, H.; HONDA, Y. Thalamocortical projections of the anteroventral thalamic nucleus in the rabbit. **Journal of comparative neurology,** v. 523, p. 726-741, 2015.

SILVA, D. G.; XAVIER, G. F. Anterior thalamic NMDA-induced damage impairs extrapolation relying on serial stimulus patterns, in rats. **Neurobiology of Learning and Memory**, v. 185, p. 107536, 2021.

SINCLAIR, A. H.; et al. Prediction errors disrupt hippocampal representations and update episodic memories. **PNAS**, v. 118, p. 1-12, 2021.

SINCLAIR, H.; BARENSE, M. D. Prediction error and memory reactivation: How incomplete reminders drive reconsolidation. Trends in Neurosciences, v. 42, p. 727–739, 2019.

SJÖLANDER, S. Some cognitive breakthroughs in the evolution of cognition and consciousness, and their impact on the biology of language. **Evolution and Cognition**, v. 1, p. 3 – 11, 1995.

SPETCH, M. L.; FRIEDMAN, A. Recognizing rotated views of objects: Interpolation versus generalization by humans and pigeons. **Psychological Bulletin & Review**, v. 10 (1), p. 135-140, 2003.

SRINIVAS, K.; SCHWOEBEL, J. Generalization to novel views from view combination. **Memory & Cognition,** v. 26, n. 4, p. 768 – 779, 1998.

STEMPOWSKI, N. K.; CARMAN, H.M.; FOUNTAIN, S. B. Temporal phrasing and overshadowing in rat serial-pattern learning. **Learn Motiv**, v. 30, p. 74–100, 1999.

STOLAR, N.; SPARENBORG, S.; DONCHIN, E.; GABRIEL, M. Conditional Stimulus Probability and Activity of Hippocampal Cingulate Cortical, and Limbic Thalamic Neurons During Avoidance Conditioning in Rabbits. **Behavioral Neuroscience,** v. 103, n. 5, p. 919 – 934, 1989.

SUN, R.; GILES, C. L. Sequence Learning: From Recognition and Prediction to Sequential Decision Making. **IEEE Intelligent Systems,** v. 16, n. 4, p. 67 – 70, 2001.

TAUBE, J. S. Head direction cells and the neurophysiological basis for a sense of direction. **Progress in Neurobiology,** v. 55, p. 225 – 256, 1998.

TAUBE, J. S. Head Direction Cells Recorded in the Anterior Thalamic Nuclei of Freely Moving Rats. **The Journal of Neuroscience**, v. 15 (1), p. 70-86, 1995.

TAUBE, J. S.; MULLER, R. U.; RANCK, J. B. Head-direction cells recorded from the postsubiculum in freely moving rats. **Journal of Neuroscience,** v. 10, p. 420 – 435, 1990.

TERRACE, H. S.; McGONIGLE, B. Memory and representation of serial order by children, monkeys, and pigeons. **Current Direction in Psychological Science**, v. 3, p. 180-185, 1994.

THORNTON, A.; LUKAS, D. Individual variation in cognitive performance: developmental and evolutionary perspectives. **Phil. Trans. R. Soc. B.**, v. 367, p. 2773-2783, 2012.

TSANOV, M.; *et al*. Theta-modulated head direction cells in the rat anterior thalamus. **Journal of Neuroscience**, v. 31, p. 9489 – 9502, 2011.

TSE, D.; *et al*. Schemas and Memory Consolidation. **Science**, v. 316, p. 76-82, 2007.

TSIVILIS, D., *et al*. A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. **Nature Neuroscience**, v. 11, p. 834–842, 2008.

VAN GROEN, T.; WYSS, J. M. Projections from the anterodorsal and anteroventral nucleus of the thalamus to the limbic cortex in the rat. **Journal of comparative neurology,** v. 358, p. 584-604, 1995.

VANN, S. D.; AGGLETON, J. P.; MAGUIRE, E. A. What does the retrosplenial cortex do? **Nature Reviews Neuroscience**, v. 10, p. 792-802, 2009.

VANN, S. D.; AGGLETON, J. P. The mammillary bodies: two memory system in one? **Nature Reviews,** v. 5, p. 35-44, 2004.

VANN, S. D.; *et al*. Fos imaging reveals differential patterns of hippocampal and parahippocampal subfield activity in response to different spatial memory tasks. **The Journal of Neuroscience**, v. 20, p. 2711–2718, 2000.

VASSENA, E.; *et al*. Overlapping Neural Systems Represent Cognitive Effort and Reward Anticipation. **Plos One,** v. 9, n. 3, 2014.

VERTES, R. P.; ALBO, Z.; VIANA DI PRISCO, G. Theta-rhythmically firing neurons in the anterior thalamus: implications for mnemonic functions of Papez's circuit. **Neuroscience**, v. 104, p. 619–625, 2001.

VINOGRADOVA, O. S. Hippocampus as Comparator: Role of the Two Input and Two Output Systems of the Hippocampus in Selection and Registration of Information. **Hippocampus,** v. 11, p. 578 – 598, 2001.

WALLACE, D. G.; FOUNTAIN, S. B. What Is Learned in Sequential Learning? An Associative Model of Reward Magnitude Serial-Pattern Learning. **Journal of Experimental Psychology,** v. 28, n. 1, p. 46 – 63, 2002.

WALLACE, D. G.; ROWAN, J. D.; FOUNTAIN, S. B. Determinants of phrasing effects in rat serial pattern learning. **Animal Cognition**, v. 11, p. 199-214, 2008.

WALLIS, J. D.; ANDERSON, K. C.; MILLER, E. K. Single neurons in prefrontal cortex encode abstract rules. **Nature**, v. 411, p. 953-956, 2001.

WILSON, B.; MACKINTOSH, N.; BOAKES, R. Transfer of relational rules in matching and oddity learning by pigeons and corvids. **The Quarterly Journal of Experimental Psychology,** v. 37, p. 313 – 332, 1985.

WOLFF, M.; *et al.* A thalamic bridge from sensory perception to cognition. Neuroscience & Biobehavioral Reviews, v. 120, p. 222–235, 2021.

WOLFF, M.; *et al*. Functional heterogeneity of the limbic thalamus: From hippocampal to cortical functions. **Neuroscience & Biobehavioral Reviews**, v. 54, p. 120–130, 2015.

WOLFF, M.; *et al*. The extended hippocampal-diencephalic memory system: enriched housing promotes recovery of the flexible use of special representations after anterior thalamic lesions. **Hippocampus**, v. 18, p. 996-1007, 2008.

WOLFF, M.; VANN, S. D. The cognitive thalamus as a gateway to mental representations. **The Journal of Neuroscience**, v. 39, p. 3-14, 2019.

WONG-RILEY, M. T. T. Bigenomic regulation of cytochrome c oxidase in neurons and the tight coupling between neuronal activity and energy metabolism. In: KADENBACH, B. editor. Mitochondrial Oxidative Phosphorylation, **Advances in Experimental Medicine and Biology**, v. 748, p. 283-304, 2012.

WONG-RILEY, M. T.; CARROLL, E. W. Quantitative light and electron microscopic analysis of cytochrome oxidase-rich zones in V II prestriate cortex of the squirrel monkey. **Journal of Comparative Neurology**, v. 222, p. 18 – 37, 1984.

WRIGHT, N. F.; *et al.* A Critical Role for the Anterior Thalamus in Directing Attention to Task-Relevant Stimuli. The Journal of Neuroscience, v. 35 (14), p. 5480–5488, 2015.

WRIGHT, N. F.; *et al.* Segregation of parallel inputs to the anteromedial and anteroventral thalamic nuclei of the rat. **Journal of Comparative Neurology,** v. 521, n. 13, 2966-2986, 2013.

POLI, R. The many aspects of anticipation. **Foresight**, v. 12 (3), p. 7–17, 2010.

ZEKI, S.; SHIPP, S. Modular connections between areas V2 and V4 of macaque monkey visual cortex. **European Journal of Neuroscience,** v. 1, p. 494 – 506, 1989.

ZIRKELBACH, J.; STEMMLER, M.; HERZ, A. V. M. Anticipatory neural activity improves the decoding accuracy for dynamic head-direction signals. **The Journal of Neuroscience,** 2019.