

The Search for Neurophysiological Mechanisms of Configural Learning

B. V. Chernyshev,^{1,2,3} V. L. Ushakov,^{2,4,5} and L. A. Poznyak³

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Configural learning is a form of associative learning in which the conditioned stimulus is an overall complex of stimulus elements rather than individual stimuli or their isolated properties. Overall analysis of the entire configuration as a whole is required for successful solution of the challenges of this type of associative learning. The ability to analyze not only the individual physical aspects of a stimulus or the individual objects of a visual scene, but also their overall combination, provides significant evolutionary advantages, as configurations often have significantly greater predictive power than the individual elements or features of a stimulus. Furthermore, the ability to analyze integrated combinations of elements or features of a stimulus field can be seen as an initial primitive manifestation of consciousness. This review considers the history of the development of the concept of configural learning, the main methodological research approaches, and currently available neurophysiological data on the putative neuronal basis of this phenomenon. The most interesting studies appear to be those addressing configural learning processes in humans using modern neuroimaging methods, as these provide an opportunity to gain insight into the operation of the whole brain. In conclusion, this review determines which problems in existing research need to be overcome in the future to provide a more complete understanding of the neurophysiology of the phenomenon of configural learning.

Keywords: associative learning, configural learning, gestalt, functional magnetic resonance imaging, electrophysiology, electroencephalography, magnetoencephalography.

Introduction. Sensory processes allow living organisms to receive information which they go on to use to construct and correct internal models of their environment. These models support appropriate behavior, thereby ensuring survival [Friston, 2010]. During evolution and the influence of natural selection, many groups of animals moved towards increasingly complex nervous systems, giving them the opportunity to perform more complicated processing of information coming from their sensory systems and, thus, to create more complex models of the environment

with greater predictive power; this, in turn, yielded great advantages in the process of natural selection. The nervous system also has another important property, i.e., neuroplasticity, which is the physiological basis of learning and memory. This property allows acquired models to be saved for future use, allowing the organism to implement appropriate behavior in subsequent encounters with similar stimuli and their combinations. The conditioned reflex is the basic concept of the physiology of higher nervous activity and can be seen as a fundamental manifestation of memory for the meanings of stimuli, converting a stimulus into a signal for anticipatory triggering of a behavioral reaction.

The ability to develop conditioned reactions to relatively simple stimuli, which arose very early in evolution, was clearly preserved as the nervous system became more complex. However, increases in the complexity of the nervous system during evolution opened up new possibilities. At the level of higher vertebrates, for example, it is difficult to imagine that the search for food, protection from ene-

¹ Department of Higher Nervous Activity, Lomonosov Moscow State University, Moscow, Russia; e-mail: b_chernysh@mail.ru.

² Institute for Advanced Brain Studies, Lomonosov Moscow State University, Moscow, Russia.

³ Center for Neurocognitive Research (MEG Center), Moscow State University of Psychology and Education, Moscow, Russia.

⁴ National Research Nuclear University MEPhI, Moscow, Russia.

⁵ Alekseev Psychiatric Clinical Hospital No. 1, Moscow City Health Department, Moscow, Russia.

mies, and other important behavioral functions could occur without the ability to perceive integral objects and complex contexts whose identification requires the analysis of complexes of multiple features.

Conditioned reflex theory initially addressed simple stimuli, as the analytical task consisted of studying the very phenomenon of acquiring a conditioned reaction. Nonetheless, researchers started to approach the issue of the development of reflexes to complex stimuli at the very beginning of the development of conditioned reflex theory [Zeliony, 1910; Palladin, 1906; Perel'tsveig, 1907]. Pavlov himself described the ability to develop a conditioned reflex as a manifestation of the synthetic activity of the brain [Pavlov, 1949].

Razran, working in the late 1930s, carried out a systematic analysis of the data available at that time on the development of conditioned reflexes to complex stimuli, which he termed configural conditioning; the work was based on review of the large quantities of experimental data already obtained, including in the works of Pavlov, Krasnogorsky, Ivanov-Smolenskii, Beritashvili, Bekhterev, and other Russian authors [Razran, 1939].

Razran interpreted configural conditioning as a gestalt process [Razran, 1939]. Furthermore, developing Pavlov's ideas about the synthetic activity of the brain, Razran postulated that the ability to achieve configural learning is a sign of the presence of liminal consciousness in an animal [Razran, 1971]. A hypothesis was again put forward in the literature, more recently, to the effect that the ability to develop a conditioned reflex to a complex stimulus is the earliest manifestation of consciousness and a factor in its further evolution [Bronfman et al., 2016; Feinberg and Mallatt, 2016; Ginsburg and Jablonka, 2019]. In particular, Ginsburg and Jablonka conducted a systematic analysis of the conventional features of consciousness, on the basis of which they proposed using associative learning of new complex stimuli as a positive marker indicating the presence of a minimal level of consciousness in animals [Bronfman et al., 2016; Ginsburg and Jablonka, 2019].

What Configural Learning Is and How to Study It.

Integrative information processing is inherent to many aspects of brain function. The following discussion will not dwell on sensory processes of pattern recognition, such as, for example, the identification of faces in visual percepts of images. These processes are also called configural, as the overall processing of the perceived image (assembling individual elements into a gestalt) occurring in this case is oriented towards analyzing the configuration of the elements (see, for example, the review by Piepers and Robbins [2012]). However, in these cases we are dealing with specialized sensory networks and even entire areas of the brain which, using innate and/or acquired functions, search for and process statistically probable and frequently occurring configurations of elements of the sensory field. This is precisely the case with the visual face recognition

area [Kanwisher et al. 1997] or the visual word form area [Cohen et al., 2000] – given that the former of these functions has an innate basis and the latter is probably acquired in the course of individual experience. These processes are extremely complex and of great importance, but they are usually highly automated and are carried out only as an integral component of sensory processes (although there may be exceptions to this rule [Kozunov et al., 2020]).

This review will consider those configural phenomena in which the configuration involved is not highly probable on a priori grounds and the subject learns to navigate the configurations of the elements in the course of the experiment while performing some particular task.

It is clear that stimulus situations such as this, where there is a need to remember a certain configuration and respond to it in a certain way, are common in life. For example, as a pedestrian, we learn to respond to traffic light signals consisting of little green and red men, but we ignore green and red signals shaped as circles or arrows. When learning to drive a car, conversely, we learn to respond to green and red colors in combination with round and arrow signal shapes. In all these cases, it is only the conjunction of shape and color that has signal value for us, not the color or shape separately.

Formation of a contextual conditioned reflex is often also a form of configural learning, and a large amount of literature is devoted to it (for example, see [Kubie et al. 2020; Maren et al., 2013; Rudy, 2009; Urcelay and Miller, 2014]). The characteristic feature of this type of learning in natural conditions is that the environment (context) is usually a complex combination of many elements, so this can definitely be regarded as a form of configural learning. Many studies of configural learning are methodologically based on the contextual paradigm (see below). However, it must be noted that experimental studies of contextual learning often vary only one property of the context for the sake of simplifying behavioral and neurophysiological analysis, potentially allowing an animal or person to perform a task without actually involving the mechanisms of configural learning. We will further consider contextual learning only insofar as the performance of an experimental task requires analysis of configuration.

This review will mainly address studies analyzing complex stimuli composed of relatively small and controlled numbers of elements, where the experimental procedure uses only certain conjunctions of elements and/or certain relative arrangements of elements in space which are designated as significant (having signal value).

Animal experiments, including the seminal works of Rudy (see below), make wide use of the negative patterning task, this being the simplest task for configural learning, in which each of the stimuli presented separately is reinforced, while the combined presentation of the same stimuli is not reinforced (A+, B+, AB–). If element-by-element learning occurs for each of the stimuli separately, then the reaction to

the simultaneous presentation of both stimuli will most likely be stronger than the reactions for each alone, but no less than that for each alone, because the effects of two developed reflexes with the same conditioned reaction can only be summed. And suppression of the reaction to a complex consisting of two stimuli requires precisely that same configural processing of information, allowing the complex of stimuli to be perceived as an independent stimulus and not simply the sum of two other stimuli. This class of problems also includes the positive patterning task, the transverse patterning task, and other related problems built on the interdependencies of multiple stimuli presented separately and simultaneously (for a description and comparison of problems in this class, see the review by Rudy and Sutherland [1995]).

One popular method of studying configural learning in animal experiments consists of developing a conditioned freezing reflex to a complex conditioned stimulus consisting of several simultaneously presented stimuli of different sensory modalities (usually auditory and visual) in rats [Debiec et al., 2013; Jones et al., 2013] and mice [Yadav et al., 2013; Ivashkina et al., 2020].

Studies on humans based on presentation of images of rooms in which furnishings (tables, chairs, sofas, cabinets, floor lamps, televisions, etc.) are placed in different combinations and in different relative spatial arrangements are common [Baeuchl et al., 2015; Stout et al., 2019; Stout et al., 2018]. Variation of the relative arrangement of elements or exclusion of one element from the scene create conditions for configural processing of visual information. Another situation that can be regarded as close to configural learning is generalization of a context to a single capacious concept, such as a geographic location (easily identifiable by a well-known landmark in a photograph): in this experiment, the participant was required to develop associations between photographs of famous people and famous places (e.g., [Ison et al., 2015], see below). In addition, experiments on humans have used images made up of abstract graphic elements combined in various ways to form a drawing [Duncan et al., 2018], which addresses configural learning in its pure form, without any contextual components. Below, we will consider in more detail how elemental and configural learning are related.

The Difference between Elemental and Configural Learning. Imagine that many different stimuli are continuously arriving from the environment, sometimes separately and sometimes overlapping in time, and your task is to learn to predict the consequences associated with them. In the general case, your brain can try to orient itself either to the stimuli individually or to the combination, as you do not know in advance which is correct. In other words, development of a conditioned reflex in a complex environment, for example on acquisition of a contextual reflex, can involve two processes: elemental learning and configural learning [Rudy, 2009; Rudy et al., 2004]. Element coding implies that associative learning involves only one representation of a single element

or a single property of a sensory stimulus [Rudy et al., 2004; Urcelay and Miller, 2014], such as the pitch of a sound or the color of a shape, regardless of other characteristics of these stimuli. In contrast to elemental learning, configural learning is based on the formation of a representation of the entire complex of stimuli and their properties as a whole, taking into account their mutual arrangement in space and other relationships [Rudy, 2009]. The relationship between elemental and configural processes largely determines which path the learning process will take [Maren et al., 2013].

In general, elemental learning can be more effective if the stimulus components are not interconnected with each other and configural learning can be more effective if the environment includes interdependencies such that the outcome of presenting one stimulus can be different depending on the presence and location of other stimuli. In general, it is more characteristic for humans to focus on stimulus configurations than on individual elements [Kimchi, 1994]. This is probably because in many cases, combinations of stimuli have greater predictive power than individual elements. However, the particular path that learning will take in any particular case depends on many factors, including, for example, previous history: if a rat has previously been trained in a task requiring configural processing of information, then in the future the rat will transfer the principle of configural processing to a new task, even if the new task requires elemental processing [Alvarado and Rudy, 1992].

It is important that learning at the configural level leads to results which are different from those due to learning at the elemental level, and a conditioned reflex to a set of stimuli is not equivalent to the sum of reflexes to the individual stimuli [Pearce, 1987; Rudy and Sutherland, 1995]. A conditioned reflex to a complex configural stimulus is more difficult to extinguish [Jones et al., 2013], while it is important to note that extinction of a reflex to an isolated component of the complex can lead to extinction of the response to the entire complex; in addition, generalization can occur between the components of the complex [Goldfarb et al., 2021]. Of particular interest is the fact that presentation of one element of a complex can result not only in extinction but also in reconsolidation of the entire complex [Debiec et al., 2013]. Differences can be seen not only in behavior, but also at the level of patterns of brain activity [Duncan et al., 2018].

Impaired formation of reactions to complex stimuli may underlie a number of pathological conditions in humans, of which post-traumatic stress disorder is the most often mentioned in the literature. The causes of this disorder may be associated in part with an imbalance between the two forms of learning, with a predominance of elemental learning [Acheson et al., 2012; Bisby et al., 2020; Gilbertson et al., 2007]. Presumably, in this disorder, individual elements of the traumatic experience begin to evoke a fear response regardless of the context, resulting in the generalization of the fear response to completely irrelevant contexts [Goldfarb et al., 2021]. With configural learning,

the occurrence of a fear response to an individual element is less likely, as a fully fledged reaction develops only on coincidence of the entire configuration as a conjunction of its elements [Acheson et al., 2012; Maren et al., 2013].

The Hippocampus Is Critical for Configural Learning. Rudy and Sutherland put forward the configural association theory, whereby the hippocampus is involved in the formation of configural representations of complex stimuli [Rudy and Sutherland, 1995; Sutherland and Rudy, 1989]. For example, one early study showed that rats with hippocampal damage displayed impaired performance on a negative patterning task critically dependent on the ability to remember configurations. However, the ability to form associations in and of itself was not impaired: despite lesioning of the hippocampus, rats successfully coped with simple conditioned reflex differentiation, which does not require configural processing [Alvarado and Rudy, 1995].

Numerous subsequent pharmacological and optogenetic studies confirmed that damage to the hippocampus impairs both configural learning itself and the corresponding memory retrieval processes [Albasser et al., 2013; Anagnostaras et al., 2001; Chang and Liang, 2017; Corcoran and Maren, 2001; Dumont et al., 2007; Kheirbek et al., 2013; Sanderson et al., 2006]. Immunohistochemical mapping of the protein product of the *c-fos* immediate early gene in the hippocampus showed that hippocampal field CA1 is activated during retrieval of the associative memory of a complex conditioned signal, but not on retrieval of its components [Ivashkina et al., 2020]. There are also reports of impaired configural learning in humans with hippocampal damage [Hannula et al., 2006; Watson et al., 2013].

Configural association theory is based on the concept that the memory function of the hippocampus operates by integration of information from multiple sources into a unique overall configuration; on the basis of a large body of relevant literature, it is now generally accepted that configural learning is critically dependent on the hippocampus [Aggleton et al., 2007; Baeuchl et al., 2015; Eichenbaum, 1999; Eichenbaum, 2004; Fanselow, 2000; Stout et al., 2019; Stout et al., 2018; Sutherland and Rudy, 1989]. In other words, the hippocampus provides multimodal binding of elements including the relative locations of stimulus elements [Eichenbaum and Cohen, 2014; Monti et al., 2015].

It is assumed that when a conditioned reflex with negative reinforcement develops, the representation of a configural conditioned signal of this type is passed from the hippocampus to other structures, for example, the amygdala, where association of this configuration with electrocutaneous reinforcement actually takes place [Fanselow and Poulos, 2005; Rudy, 2009]. The hippocampus also has an indirect output to the prelimbic cortex in rodents (a homolog of the dorsal anterior cingulate cortex in humans), which then projects to the amygdala and other structures involved in mediating fear responses during defensive conditioned reflexes [Knapska et al., 2012; Maren et al., 2013].

Elemental associations, unlike configural associations, do not depend on the hippocampus [Gluck and Myers, 1993; Sutherland and Rudy, 1989]. Closure of a conditioned reflex between sensory representations and electrocutaneous reinforcement does not require participation by the hippocampus and occurs directly at the level of the amygdala; thus, this process is characterized in the literature as amygdala-dependent [Davis and Whalen, 2001; LeDoux, 2000; Urcelay and Miller, 2014].

If hippocampal function is impaired, then complex information, including contextual information, can be represented in the brain almost exclusively at the level of elemental learning [Maren et al., 1997; Maren et al., 2013]. In particular, on acquisition of a conditioned reflex with negative reinforcement, the conditioned stimulus evokes a fear response regardless of the context in which it is presented, and this may be one of the mechanisms for the development of post-traumatic stress disorder [Acheson et al., 2012; Bisby et al., 2020; Gilbertson et al., 2007].

The Overlapping Memory Engram Theory. In understanding the role of the hippocampus in configural learning, a unique series of studies conducted by Quiroga et al. using experiments in which single-neuron activity was recorded in humans is of great importance [Quiroga, 2012]. These experiments used electrodes implanted for medical reasons in patients with epilepsy. Quiroga et al. identified neurons located in the medial temporal lobe (parahippocampal cortex, perirhinal cortex, and amygdala) which were extremely selective for certain people or landmarks, such as Jennifer Aniston, Luke Skywalker, the Sydney Opera House, or the Leaning Tower of Pisa. Quiroga termed these neurons “concept cells.” the authors noted that these cells responded specifically to combinations of features and therefore encoded abstract concepts characterized by these features. For example, one of the first experiments of this kind identified a neuron in the hippocampus which responded to a photo of actress Jennifer Aniston but did not respond to pictures of any other famous people, animals, or places. However, a subsequent experimental session showed that the same neuron also responded to a photo of Lisa Kudrow, who starred in a popular TV show with Jennifer Aniston. The authors subsequently studied this issue in more detail and concluded that the occurrence of neurons in the medial temporal lobe responding to more than one concept indicated that these concepts were associated with each other in one way or another [Rey et al., 2018]. Thus, although neurons in the medial temporal cortex, including the hippocampus, are capable of encoding abstract concepts based on a combination of features, they are not “grandmother neurons” [Gross, 2002], i.e., they encode complex combinations of features rather than specific unique objects.

An important next step was that they were able to trace the formation of “concept cells” during associative learning [Ison et al., 2015]. Participants in the experiments developed associations between a photo of a specific person and a spe-

cific place. Neurons sensitive to only one component of the association began to respond to both components after training, though learning outcome was highly specific, i.e., these neurons did not respond to any other visual stimuli (i.e., similar photos of other people and other places) presented during the experiment but not associated with them. The effect developed quite quickly, requiring only a small number of combinations. The results of experiments of this type and computational modeling led to the development of “overlapping memory engram theory” [Gastaldi et al., 2022]. According to this theory, “concept neurons” responding to two different concepts (and, accordingly, simultaneously belonging to two different neuron ensembles representing each concept separately) provide the basis for the association between two initially isolated concepts. Using attractor neural network modeling, the authors convincingly showed how this overlap between ensembles of neurons has the result that presentation of one concept (person, place, etc.) can lead to activation of another concept – provided that these concepts were associated at some time in the past.

In addition to “concept cells,” each of which invariantly encodes a specific concept, another type of neuron with a direct relationship to configural learning was identified later. These neurons, also found in recordings from the human hippocampus (but not from the parahippocampal cortex), were called episode-specific neurons. During both the encoding and retrieval of episodic memory, these cells responded exclusively to the conjunction of all the elements that made up the configuration of a specific episode but did not respond to presentation of the individual elements that were part of the episode [Kolobius et al., 2023].

In comparing the studies with recording of single neurons in the human medial temporal lobe described in this section with other studies of configural learning, it is important to note that no reinforcement was used in these experiments to develop an association between relatively neutral stimuli. This is probably a much more correct approach, as it allows configural learning to be studied in its pure form, without the accompanying autonomic and behavioral components of conditioned reflexes with biologically significant unconditioned stimuli.

Systemic Consolidation: Hippocampus vs. Neocortex.

The studies discussed above provide a convincing picture of the involvement of the hippocampus in configural learning. This mechanism could potentially be sufficient to close a conditioned reflex. However, in the case of animals with a more developed cerebral cortex and complex behavior, especially humans, it is difficult to imagine that certain cortical associative processes would not be taking place in the neocortex during learning in addition to hippocampal plasticity.

According to the classical point of view regarding systemic consolidation,¹ configural associations form first in the hippocampus, and they are transmitted to the cortex only much later and in some as yet unclear way [Squire and Alvarez, 1995; Squire et al., 2015]. An influential mod-

ern formulation of the concept of systemic consolidation is known as the “multiple trace theory” put forward by Moscovitch et al. [Moscovitch and Gilboa, 2022; Nadel and Moscovitch, 1997]. This theory, like others, recognizes that the hippocampus is necessary for configural learning, but makes an important clarification: while it was previously believed that the process of systemic consolidation involves complete transfer of memory from the hippocampus to the cortex, with the hippocampus then becoming unnecessary for memory retrieval [Squire and Alvarez, 1995; Squire et al., 2015], this approach argues that there is an indefinite need for the hippocampus to participate in episodic memory. One way or another, these theories postulate that in the early stages, learning is mediated exclusively by the hippocampus and not by the neocortex. The process of systemic consolidation is quite slow and can stretch out over several days or even weeks, going through several different phases during this time [Fiebig and Lansner, 2014].

Thus, this scheme suggests that the hippocampus plays a critical role in the process of configural learning and that the neocortex probably joins in with memory retrieval only much later. However, recent work has shown that plastic rearrangements in the neocortex (specifically, in the medial prefrontal cortex) can occur from the very beginning of the formation of associations, though they are initially latent and it is only after the process of systemic consolidation that they are fully formed and evident [Tonegawa et al., 2018].

Do any significant neuroplasticity processes occur in this way in the neocortex of the cerebral hemispheres directly during the development of an association? This issue clearly remains little studied, given that the ideas noted above regarding systemic consolidation contradict a number of other works. It is known that cortical plasticity can develop almost immediately, i.e., it does not in fact require systemic consolidation lasting, for example, a day or more. Moreover, cortical plasticity occurs even when it may seem unnecessary within the framework of the methodological paradigm used. For example, it is known that the closure of a classical conditioned fear reflex (assessed in terms of heart rate, especially in conditions of stereotaxic fixation of the animal as opposed to free behavior) to simple single sound tones with electrical pain reinforcement in rodents occurs at the subcortical level: the representation of the sound comes to the amygdala from the medial geniculate body of the thalamus and the corresponding conditioned autonomic reactions are then mediated via the amygdala [LeDoux, 2000]. However, auditory cortex neurons undergo marked plastic restructuring, which can

¹ A clear distinction needs to be made between systemic consolidation, which occurs at the systems level in the whole brain on a time scale of days and weeks, and synaptic consolidation, which takes place at the level of an individual neuron and requires much less time, on a scale of hours rather than days. These concepts originate from the general psychological view of memory consolidation processes, though they have completely different neurophysiological mechanisms.

be observed immediately after the association is developed (see, for example, [Weinberger, 2004]).

Furthermore, if we consider not only the simplest unconscious autonomic indicators of the formation of associations, but also more complex manifestations, including declarative memory (after all, the participants in many experiments perform explicit behavioral responses such as pressing buttons), it becomes clear that the hippocampus probably does not have the requisite organization or outputs to executive structures to perform functions which in mammals are inherent almost exclusively to the neocortex, which contradicts data suggesting exclusive involvement of the hippocampus. For example, a number of fMRI studies of the development of associations between new unfamiliar pseudowords and the meanings assigned to them [Davis and Gaskell, 2009; Gaskell and Dumay, 2003; Rodríguez-Fornells et al., 2009] showed that immediately after learning, an association effect was detected exclusively in the hippocampus, with no manifestations of association being found in the neocortex. The corresponding effects in the neocortex could be detected only the next day, i.e., after a night's sleep, which, as the authors suggest, is required for systemic consolidation processes (for more details, see the review by Razorenova et al. [2020]). Results such as these are in good agreement with classical concepts of systemic consolidation. However, it is important to understand that the participants in these experiments were well trained to make explicit conscious behavioral responses on the very first day. This raises the question: how could an acquired association be realized in complex voluntary and conscious human behavior without the neocortex being involved? Presumably, this is not a question of the complete non-participation of the neocortex immediately after development of the association, but more a question of whether the recording methods have sufficient sensitivity to allow effects in the neocortex to be detected. Indeed, magnetoencephalography studies identified the cortical effects of associative plasticity immediately after the development of an association between pseudowords and the meanings assigned to them [Razorenova et al., 2020]. Similar experiments involving learning the meanings of words are based on the auditory-verbal analysis of sound stimuli in the brain, and it is clear that in this case, the brain analyzes the configurations of phonemic compositions, i.e., in essence, processes close to configuration learning take place.

A person is able to learn to associate a configural stimulus with negative reinforcement extremely quickly, and learning is evident simultaneously in terms of both autonomic indicators (for example, galvanic skin response) and explicit behavior in the form of pressing buttons [Stout et al., 2019; Stout et al., 2018]. It is clear that an explicit conscious response made by a person must immediately involve the corresponding areas of the cerebral cortex, i.e., even before the onset of systemic consolidation. In fact, a number of studies addressing configural learning in humans

using modern visualization methods have demonstrated reliable manifestations of acquired associations not only in the hippocampus, but also in the neocortex of the cerebral hemispheres, and immediately after learning; these studies will be discussed below in further sections.

The involvement of the neocortex directly during or immediately after learning (i.e., before systemic consolidation) has also been confirmed indirectly by the fact that during associative learning, complex bidirectional oscillatory interactions can be seen between the hippocampus and cortical areas, such as the prefrontal cortex, at θ , α , and β frequencies [Brincat and Miller, 2015].

In which areas of the cortex can we expect associative effects to be apparent during configural learning? First among these are clearly the high-level associative areas which support the synthesis of different representations, including those at the intermodal level, and the formation of rules and action programs. Below, we will consider what data have been obtained regarding the cerebral cortex to date.

It is important to note that, contrary to popular belief, even low-level sensory areas have cross-modality properties (for review see [Ghazanfar and Schroeder, 2006]) and therefore already have the necessary sensory inputs for mediating associative plasticity, which combines individual stimuli and stimulus characteristics into a memorized integral configuration.

There is also a significant body of work in the literature showing that clear indicators of cortical associative effects can be recorded in EEG and MEG investigations in conditions of binding of stimulus features by humans (see, for example, [Novikov et al., 2015; Razorenova et al., 2020]).

We will now consider the main works on studies of configural learning in humans using modern neuroimaging methods, returning to animal studies from time to time as necessary.

Functional Magnetic Resonance Imaging Studies of Configurative Learning. Studies of contextual learning with negative reinforcement in humans using current neuroimaging methods have demonstrated the involvement of a considerable number of brain structures, including the amygdala, hippocampus, medial prefrontal cortex, anterior cingulate cortex, dorsolateral and ventrolateral prefrontal cortex, and insular cortex [Alvarez et al., 2008; Andreatta et al., 2015; Marschner et al., 2008]. It should be noted that these experiments used fairly simple background contexts, which could be distinguished based on single properties or elements rather than configurations. Thus, the role of configural coding overall remained unclear from the results of these studies [Glenn et al., 2018].

The idea that the hippocampus has a critical role in configural learning (see above) has been supported by all recent fMRI studies of configural learning known to us, which have demonstrated that the hippocampus is indeed involved; we will consider these studies below. Unfortunately, none of the studies known to us investigated the dynamics of systemic consolidation: recording was performed only on the

day of training, and repeat studies a few days later were not undertaken.

Even the first study [Baeuchl et al., 2015] specifically attempting to investigate contextual learning using controlled configurations of stimulus field elements (with electrical pain reinforcement) consistently revealed activation in the hippocampus and amygdala, along with bilateral activation in the anterior insular cortex, the medial part of the superior frontal gyrus (dorsomedial prefrontal cortex), the caudate nucleus, the inferior parietal lobule, and the inferior frontal gyrus (including the opercular, triangular, and orbital parts). The authors noted, however, that no activation was detected in the anterior cingulate cortex, a structure typically involved in fear conditioning [Sehlmeyer et al., 2009]. The involvement of these areas is not strictly unique to conditions of configural learning and has been previously found in other studies of contingent learning with negative reinforcement in humans (e.g., [Alvarez et al., 2008; Büchel et al., 1998; Lang et al., 2009; Marschner et al., 2008; Pohlack et al., 2012; Pohlack et al., 2012]).

The work already cited [Baeuchl et al., 2015] also found functional connectivity between the hippocampus and some cortical regions, namely the posterior cingulate cortex, superior parietal lobule, and postcentral gyrus.

Another study using similar stimulus material specifically sought to compare configural and elemental learning [Stout et al., 2018], though the stimuli for the configural and elemental conditions in this study were, unfortunately, significantly different, which ultimately prevented the authors from making a direct comparison between these types of learning. An effect was observed in the hippocampus on configural learning, but not in the amygdala. Conversely, activation was found in the amygdala during elemental learning, but not in the hippocampus.

This methodological shortcoming of the earlier studies was corrected in a subsequent study by the same authors [Stout et al., 2019] – the stimulus material was now designed in such a way that it allowed for direct comparison of cerebral activity between the configural and elemental learning conditions. This new study showed that both the hippocampus and the amygdala are involved in configural learning with negative reinforcement, while the posterior hippocampus was specifically active in connection with configural learning as opposed to elemental learning, i.e., this appears to be the central structure for the formation of configural representations. Analysis of whole-brain activity revealed multiple brain structures, including neocortical regions, to be involved in configural learning, including the posterior cingulate cortex, anterior and posterior insular cortex, supplementary motor area, paracentral gyrus, supramarginal gyrus, dorsolateral and dorsomedial prefrontal cortex, parietal cortex, caudate nucleus, periaqueductal gray matter, and thalamus.

Of particular note is a study reported by Duncan et al. (2018). This is greatly different from the fMRI studies not-

ed above in terms of a number of important methodological features. First, the authors completely abandoned the contextual learning paradigm: the experimental participants had to distinguish between combinations of elements making up various complex figures. Second, there was no physical negative reinforcement at all in these experiments – only visual feedback informing the participant whether or not he or she had responded correctly to the figures. In addition, the experiment was not designed to be a dull presentation of a small number of stimuli, but was delivered as a complex computer game in which participants had to predict the weather in response to presentation of a large number of diverse composite figures. The task provides a perfect opportunity to compare configural and elemental learning both on the basis of the factor structure of the task itself and on the basis of identifying individual strategies for each participant. However, as in the earlier experiments described above, recordings were made on the day of training and systemic consolidation was not studied. A characteristic feature of configural learning was found to be the involvement of the hippocampus and ventral striatum (nucleus accumbens), along with functional connectivity between them. Thus, the crucial role of the hippocampus in configural learning was again confirmed. The involvement of the ventral striatum (rather than the amygdala, posterior insular cortex, anterior cingulate cortex, or periaqueductal gray) may be due to the fact that no physical negative reinforcement was used (in fact, positive reinforcement was provided for correct responses). As regards the neocortex, the paper mentions only that the lateral occipital complex in the occipital cortex had a greater level of involvement during elemental learning, and no other effects in the neocortex were reported.

Thus, all the fMRI studies of configural learning in humans over the past 10 years of which we are aware have demonstrated hippocampal involvement on the day of learning. These studies also show that several cortical areas are involved, most notably the prefrontal and posterior parietal areas, which are high-level areas involved in decision-making and implementing task rules in behavior. Unfortunately, none of these studies recorded brain activity from their human subjects after the period of systemic consolidation. However, it seems extremely important that several studies revealed specific effects of configural learning in the neocortex immediately after learning, i.e., before the period of systemic consolidation. At the same time, the clearly insufficient total number of studies on this topic and the significant methodological shortcomings in several of them do not currently allow us to construct a clear or complete picture of the physiological basis of the process; they only indicate the need for further research.

Studies of Configural Learning Using Recordings of Local Field Potentials, Electroencephalography, and Magnetoencephalography. The negative patterning task is a frequently used configural learning task in experiments on rats. This is one of the simplest tasks requiring a conjunction

of features and is feasible in experiments on rodents. This operant task reinforces presentations of individual stimulus elements, while the combined presentation of a complex consisting of these same elements serves as a differentiating stimulus and is not reinforced (A+, B+, AB−). Performance of this task is thought to be critically dependent on the hippocampus, disruption of this structure typically leading to impairment of task performance (for review, see [Sakimoto and Mitsushima, 2017]). Recordings captured via implanted electrodes revealed a change in the power of hippocampal θ oscillations during performance of a configural task, as compared with non-configural tasks, with both increases [Sakimoto et al., 2013] and decreases [Sakimoto et al., 2013]. This result appears to be associated with the fact that performance of the negative patterning task requires suppression of responses to the elements, each of which is separately reinforced, i.e., the effect can potentially be inverted. In a separate study, the authors examined the power of hippocampal θ oscillations in a positive patterning task (A−, B−, AB+): the power of θ oscillations in response to a reinforced complex stimulus was greater than that for a sound element presented separately and not reinforced, while no consistent differences were found for the second element, i.e., the visual stimulus [Sakimoto and Sakata, 2015]. Thus, on the one hand, these studies indicate the involvement of hippocampal θ oscillations in configural learning, though at the same time they fail to provide clarity regarding the role of θ oscillations as a mechanism of these processes and do not even clarify the sign of the effect. It is important to take account of the fact that, due to the characteristics of making chronic recordings in animals with training to an operant task, the experimental data were obtained only from well-trained rats at unknown times after training – probably many days or weeks (the exact time periods are not indicated in the publications).

The involvement of θ oscillations in configural learning has been demonstrated not only in the hippocampus, but also in the retrosplenial cortex, which is closely connected to it. A carefully designed study [Yoshida et al., 2021] performed in rats specifically constructed a behavioral task to study configural learning and compare it with elemental learning, using a balanced design of six stimuli – two visual, two auditory, and two complex stimuli – representing combinations of the same auditory and visual stimuli. Local field potentials and single-neuron activity were recorded in the retrosplenial cortex using implanted electrodes. The results showed that the retrosplenial cortex is involved in configural learning at both the θ and single-neuron levels.

As discussed above, fMRI studies of configural learning with negative reinforcement have demonstrated simultaneous involvement of the hippocampus and the amygdala [Stout et al., 2019]. Studies using stereo-EEG with intracranial electrodes implanted in the hippocampus and amygdala in patients with epilepsy showed that successful recognition of visual patterns (photographs of scenes with different emotional valence) was accompanied by a two-way interac-

tion between the hippocampus and amygdala at the frequency of the θ rhythm (3–7 Hz) [Zheng et al., 2019]. Errors in recognizing visual patterns were accompanied by a unidirectional influence of the amygdala on the hippocampus in the α range (7–13 Hz). The results of this study should be interpreted with caution in the context of this review, as the authors did not set out to study configural processes, though there is no doubt that visual pattern discrimination involved configural processes.

Interregional γ synchronization has been shown to transmit sensory information to the hippocampus on memory formation and to represent information from the hippocampus to the cortex during its retrieval [Griffiths and Jensen, 2023].

An extremely interesting series of studies of configural learning was performed with recording of magnetoencephalographic (MEG) brain activity [Cashdollar et al., 2009; Fuentemilla et al., 2010; Poch et al., 2011]. Although the behavioral tasks in these studies were oriented toward studying working memory, they included a configural condition in which images of groups of abstract objects or photographs of rooms differed in their relative positions or the absence of one of the elements: for example, two realistic photographs could show identical scenes of a room with furniture, the only difference being that the ottoman was positioned differently relative to the chairs – in one photo it was between the chairs and in the other it was slightly to the side of both chairs. Non-configural conditions included other options, such as presenting another room with different furniture. Unfortunately, these studies also did not examine systemic consolidation, i.e., they did not make repeat recordings of brain activity a few days or weeks after training.

Cashdollar et al. [2009] analyzed MEG activity in the cerebral cortex during retention of scenes in working memory in configural and non-configural conditions. Analysis of cortical synchronization of θ oscillations in healthy participants and in patients with bilateral hippocampal sclerosis identified two θ synchronization networks. One network, which was critically dependent on the hippocampus, was involved in maintaining configural representations and integrated the occipital and temporal sensors; importantly, this network was not detected in patients with hippocampal damage, and their performance on the configural task was impaired. The other network, which integrated frontal and parietal areas, was independent of the hippocampus and, according to the authors, served only to maintain the visual image as such in working memory.

The next work by the same group [Fuentemilla et al., 2010], applied multivariate pattern classification analysis to β and γ oscillations recorded using MEG to assess the duration of the period of image retention in memory in configural and elemental conditions. The authors found that during the period of image retention in memory, the corresponding patterns could be reproduced (“replayed”), allowing discrimination between the types of scenes being

remembered (photographs taken outdoors or indoors, similar to those in the study noted above), and the moments of replay detected in this work were phase-locked with θ oscillations. Reproduction of the information retained in memory depended on condition: in the configural condition, replay occurred in the frontotemporal areas, while in the non-configural condition replay took place in the fronto-parietal and occipital areas.

The authors then returned to the same data on the retrieval of remembered information during the retention period [Poch et al., 2011] and reanalyzed these data using the beamformer spatial filter algorithms, which locate sources of brain activity in space and provide the ability to examine activity in the hippocampus. This work found that individual differences in the level of performance on the working memory task in the configural condition were associated with the degree of phase synchronization of θ oscillations between the right posterior hippocampus and the right inferior frontal gyrus. Thus, memory reactivation was shown to be tied to the phase of the hippocampal θ rhythm.

A similar study [Olsen et al., 2013], also analyzing MEG data using the beamformer spatial filter, used configurations of three visual objects on a light background (new in each implementation). For memorization, combinations of elements were presented sequentially; then, in the test phase, all three were presented simultaneously in new absolute spatial locations on the screen, either with retention of the mutual relative locations or with one of the objects in an altered position. The power of theta θ oscillations in the hippocampus and medial prefrontal cortex increased during the periods of encoding and retention in memory during the delay, i.e., when the dominant processes was that of linking the relative locations of elements into an overall configuration and its retention. Comparison of spatial relationships during testing was associated with greater θ oscillation power in the right lateral prefrontal cortex and the intraparietal sulcus – in those trials in which element locations changed, as compared with trials in which the element locations did not change. Importantly, memory for configural relationships was positively associated with an increase in θ oscillation power in the hippocampus during the encoding period.

Conclusions. This review sought to present currently available data on the neurophysiological mechanisms of configural learning and the methodological approaches used. An indisputable result of work carried out over the past 30 years has been the understanding that the hippocampus is critically necessary for configural learning, both for memorization and for retrieval from memory.

However, much remains unclear regarding the involvement of the neocortex both at the early stages of learning, i.e., before systemic consolidation, and after its completion. It is difficult to study this issue in animals by making chronic recordings of local field potentials and neural activity because chronic recording usually dictates its limitations: recording is generally carried out on animals which have

already been trained, and the time elapsed from training to recording usually remains unknown. Conversely, studies in humans using modern neuroimaging methods involve convenient and appropriate recording of neocortical activity immediately after formation of an association. However, despite this, none of the neuroimaging studies in humans that we know of have included repeat recording, say, a week after acquisition of an association.

This gap in research into the involvement of the cerebral cortex in the dynamics of systemic consolidation seems very strange. Our current understanding of systemic consolidation, given the consensus on the critical involvement of the hippocampus, does not suggest that the cerebral cortex has any significant involvement on the day of acquisition of a configural association. However, this contradicts some of the experimental data discussed in this review. Clarification of this issue requires carefully designed neuroimaging studies, with recordings obligatorily made before and after the presumptive systemic consolidation.

Another important requirement for such studies, met in only a few of the studies reviewed above, is an experimental design ensuring careful balancing between experimental conditions in order to produce correct comparison of the elemental and configural learning pathways. Otherwise, the case for involvement of the neocortex is weakened by the possibility that there are alternative interpretations reducing to differences in cortical activation during processes (e.g., sensory processes) irrelevant to the configural task as such.

Another extremely significant shortcoming of virtually all the configural learning studies discussed above is the predominant use of negative reinforcement. This methodological approach is justified when working with rodents, but it is not entirely clear why virtually all human studies have adhered to logic translated from animals to humans and taken so literally. As a result, many of the studies discussed above place significant emphasis on projections from the hippocampus to the amygdala and note activity in other brain structures presumably associated with fear or discomfort, while other mechanisms remain outside the focus of investigation. An important – and virtually the only – exception known to us is the work of Duncan et al. [2018], where the feedback given to the subjects consisted only of abstract messages on the monitor screen. Separate mention should be made of the experiments, noted above, by Quiroga's group [Ison et al., 2015], in which no biologically significant reinforcement was used at all, allowing the phenomenon of configural learning to be studied in pure form. However, the vast majority of studies, even those on people, have used physically unpleasant and painful stimulation. This may be justified if, for example, a study addresses the mechanisms of post-traumatic sensory disorder in humans, though a broader approach to the sign of reinforcement is required for a fundamental understanding of the issue.

In addition, a significant proportion of studies of configural learning has another potential problem: the over-

whelming majority of cases use tasks targeting contextual learning to study configural learning itself. Again, this is true for experiments on both animals and humans, with an important exception in the form of the same work by Duncan et al. [2018]. Although perception of context is often configural in contextual learning, it is essential for future studies to separate these concepts by using configural tasks not requiring contextual learning.

Interest in associative learning is currently not only not decreasing, but even growing. For example, it is currently supposed that learning of speech, i.e., memorizing the meanings of words, is based on the neurobiological mechanisms of associative learning [Pulvermüller, 2005; Pulvermüller, 2018]. It is natural in the case of animals with a highly developed nervous system, especially humans, to focus on complex configurations of stimuli: obviously, this provided significant advantages in the course of natural selection, as it made it possible to identify and use complex patterns in the environment which were inaccessible to animals with more primitive brains.

It was precisely this complication that Pavlov described as a manifestation of the “synthetic activity of the brain” [Pavlov, 1949]. This ability to form associations based on complex configurations of stimuli is in good agreement with current views on the early manifestation of consciousness – the beginning that opened the way to the formation of developed consciousness [Bronfman et al., 2016; Feinberg and Mallatt, 2016; Ginsburg and Jablonka, 2019; Razran, 1971]. Our goal in this review was not only to draw attention to the phenomenon of configural learning, which is so significant in the context of the evolution of the brain and consciousness, but also to outline pathways for its further experimental study.

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REFERENCES

- Acheson, D. T., Gresack, J. E., and Risbrough, V. B., “Hippocampal dysfunction effects on context memory: Possible etiology for posttraumatic stress disorder,” *Neuropharmacology*, **62**, No. 2, 674–685 (2012).
- Aggleton, J. P., Sanderson, D. J., and Pearce, J. M., “Structural learning and the hippocampus,” *Hippocampus*, **17**, No. 9, 723–734 (2007).
- Albasser, M. M., Dumont, J. R., Amin, E., et al., “Association rules for rat spatial learning: The importance of the hippocampus for binding item identity with item location,” *Hippocampus*, **23**, No. 12, 1162–1178 (2013).
- Alvarado, M. C. and Rudy, J. W., “A comparison of ‘configural’ discrimination problems: Implications for understanding the role of the hippocampal formation in learning and memory,” *Psychobiology*, **23**, No. 3, 178–184 (1995).
- Alvarado, M. C. and Rudy, J. W., “Some properties of configural learning: An investigation of the transverse-patterning problem,” *J. Experim. Psychol. Anim. Behav. Proc.*, **18**, No. 2, 145–153 (1992).
- Alvarez, R. P., Biggs, A., Chen, G., et al., “Contextual fear conditioning in humans: cortical-hippocampal and amygdala contributions,” *J. Neurosci.*, **28**, No. 24, 6211–6219 (2008).
- Anagnostaras, S. G., Gale, G. D., and Fanselow, M. S., “Hippocampus and contextual fear conditioning: Recent controversies and advances,” *Hippocampus*, **11**, No. 1, 8–17 (2001).
- Andreatta, M., Glotzbach-Schoon, E., Muhlberger, A., et al., “Initial and sustained brain responses to contextual conditioned anxiety in humans,” *Cortex*, **63**, 352–363 (2015).
- Baeuchl, C., Meyer, P., Hoppstadter, M., et al., “Contextual fear conditioning in humans using feature-identical contexts,” *Neurobiol. Learn. Mem.*, **121**, 1–11 (2015).
- Bisby, J. A., Burgess, N., and Brewin, C. R., “Reduced memory coherence for negative events and its relationship to posttraumatic stress disorder,” *Curr. Dir. Psychol. Sci.*, **29**, No. 3, 267–272 (2020).
- Brincat, S. L. and Miller, E. K., “Frequency-specific hippocampal-prefrontal interactions during associative learning,” *Nat. Neurosci.*, **18**, No. 4, 576–581 (2015).
- Bronfman, Z. Z., Ginsburg, S., and Jablonka, E., “The transition to minimal consciousness through the evolution of associative learning,” *Front. Psychol.*, **7**, 1954 (2016).
- Büchel, C., Morris, J., Dolan, R. J., and Friston, K. J., “Brain systems mediating aversive conditioning: an event-related fMRI study,” *Neuron*, **20**, No. 5, 947–957 (1998).
- Cashdollar, N., Malecki, U., Rugg-Gunn, F. J., et al., “Hippocampus-dependent and -independent theta-networks of active maintenance,” *Proc. Natl. Acad. Sci. USA*, **106**, No. 48, 20493–20498 (2009).
- Chang, S.-D. and Liang, K. C., “The hippocampus integrates context and shock into a configural memory in contextual fear conditioning,” *Hippocampus*, **27**, No. 2, 145–155 (2017).
- Cohen, L., Dehaene, S., et al., “The visual word form area: Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients,” *Brain*, **123**, No. 2, 291–307 (2000).
- Corcoran, K. A. and Maren, S., “Hippocampal inactivation disrupts contextual retrieval of fear memory after extinction,” *J. Neurosci.*, **21**, No. 5, 1720–1726 (2001).
- Davis, M. and Whalen, P. J., “The amygdala: vigilance and emotion,” *Mol. Psychiatry*, **6**, No. 1, 13–34 (2001).
- Davis, M. H. and Gaskell, M. G., “A complementary systems account of word learning: neural and behavioural evidence,” *Philos. Trans. Roy. Soc. Lond. B Biol. Sci.*, **364**, No. 1536, 3773–3800 (2009).
- Debiec, J., Diaz-Mataix, L., Bush, D. E. A., et al., “The selectivity of aversive memory reconsolidation and extinction processes depends on the initial encoding of the Pavlovian association,” *Learn. Mem.*, **20**, No. 12, 695–699 (2013).
- Dumont, J., Petrides, M., and Sziklas, V., “Functional dissociation between fornix and hippocampus in spatial conditional learning,” *Hippocampus*, **17**, No. 12, 1170–1179 (2007).
- Duncan, K., Doll, B. B., Daw, N. D., and Shohamy, D., “More than the sum of its parts: a role for the hippocampus in configural reinforcement learning,” *Neuron*, **98**, No. 3, 645–657 (2018).
- Eichenbaum, H. and Cohen, N. J., “Can we reconcile the declarative memory and spatial navigation views on hippocampal function?” *Neuron*, **83**, No. 4, 764–770 (2014).
- Eichenbaum, H., “Hippocampus: cognitive processes and neural representations that underlie declarative memory,” *Neuron*, **44**, No. 1, 109–120 (2004).
- Eichenbaum, H., “The hippocampus: The shock of the new,” *Curr. Biol.*, **9**, No. 13, R482–R484 (1999).

- Fanselow, M. S. and Poulos, A. M., "The neuroscience of mammalian associative learning," *Annu. Rev. Psychol.*, **56**, No. 1, 207–234 (2005).
- Fanselow, M. S., "Contextual fear, gestalt memories, and the hippocampus," *Behav. Brain Res.*, **110**, No. 1, 73–81 (2000).
- Feinberg, T. E. and Mallatt, J., "The nature of primary consciousness. A new synthesis," *Conscious. Cogn.*, **43**, 113–127 (2016).
- Fiebig, F. and Lansner, A., "Memory consolidation from seconds to weeks: a three-stage neural network model with autonomous reinstatement dynamics," *Front. Comput. Neurosci.*, **8**, 64 (2014).
- Friston, K. J., "The free-energy principle: a unified brain theory?" *Nat. Rev. Neurosci.*, **11**, No. 2, 127–138 (2010).
- Fuentemilla, L., Penny, W. D., Cashdollar, N., et al., "Theta-coupled periodic replay in working memory," *Curr. Biol.*, **20**, No. 7, 606–612 (2010).
- Gaskell, M. G. and Dumay, N., "Lexical competition and the acquisition of novel words," *Cognition*, **89**, No. 2, 105–132 (2003).
- Gastaldi, C., Schwalger, T., De Falco, E., et al., "When shared concept cells support associations: Theory of overlapping memory engrams," *PLoS Comput. Biol.*, **17**, No. 12, e1009691 (2022).
- Ghazanfar, A. A. and Schroeder, C. E., "Is neocortex essentially multisensory?" *Trends Cogn. Sci.*, **10**, No. 6, 278–285 (2006).
- Gilbertson, M. W., Williston, S. K., Paulus, L. A., et al., "Configural cue performance in identical twins discordant for posttraumatic stress disorder: theoretical implications for the role of hippocampal function," *Biol. Psychiatry*, **62**, No. 5, 513–520 (2007).
- Ginsburg, S. and Jablonka, E., *The Evolution of the sensitive Soul: Learning and the Origins of Consciousness*, MIT Press, Cambridge, MA (2019).
- Glenn, D. E., Risbrough, V. B., Simmons, A. N., et al., "The future of contextual fear learning for PTSD Research: a methodological review of neuroimaging studies," in: *Behavioral Neurobiology of PTSD*, Vermetten, E. et al. (eds.), Springer International Publishing, Champaigne (2018), pp. 207–228.
- Gluck, M. A. and Myers, C. E., "Hippocampal mediation of stimulus representation: A computational theory," *Hippocampus*, **3**, No. 4, 491–516 (1993).
- Goldfarb, E. V., Blow, T., Dunsmoor, J. E., and Phelps, E. A., "Elemental and configural threat learning bias extinction generalization," *Neurobiol. Learn. Mem.*, **180**, 107405 (2021).
- Griffiths, B. J. and Jensen, O., "Gamma oscillations and episodic memory," *Trends Neurosci.*, **46**, No. 10, 832–846 (2023).
- Gross, C. G., "Genealogy of the 'Grandmother Cell'," *Neuroscientist*, **8**, No. 5, 512–518 (2002).
- Hannula, D. E., Tranel, D., and Cohen, N. J., "The long and the short of it: relational memory impairments in amnesia, even at short lags," *J. Neurosci.*, **26**, No. 32, 8352–8359 (2006).
- Ison Matias, J., Quiroga, R., and Fried, I., "Rapid encoding of new memories by individual neurons in the human brain," *Neuron*, **87**, No. 1, 220–230 (2015).
- Ivashkina, O. I., Toropova, K. A., Roshchina, M. A., and Anokhin, K. V., "Formation and retrieval of associative memory for a complex signal in mice: specific involvement of neurons in the hippocampal field CA1," *Zh. Vyssh. Nerv. Deyat.*, **70**, No. 3, 327–341 (2020).
- Jones, C. E., Ringue, S., and Monfils, M.-H., "Learned together, extinguished apart: reducing fear to complex stimuli," *Learn. Mem.*, **20**, No. 12, 674–685 (2013).
- Kanwisher, N., McDermott, J., and Chun, M. M., "The fusiform face area: a module in human extrastriate cortex specialized for face perception," *J. Neurosci.*, **17**, No. 11, 4302–4311 (1997).
- Kheirbek M. A., Drew, L. J., Burghardt, N. S., et al., "Differential control of learning and anxiety along the dorsoventral axis of the dentate gyrus," *Neuron*, **77**, No. 5, 955–968 (2013).
- Kimchi, R., "The role of wholistic/configural properties versus global properties in visual form perception," *Perception*, **23**, No. 5, 489–504 (1994).
- Knapaska, E., Macias, M., Mikosz, M., et al., "Functional anatomy of neural circuits regulating fear and extinction," *Proc. Natl. Acad. Sci. USA*, **109**, No. 42, 17,093–17,098.
- Kolibius, L. D., Roux, F., Parish, G., et al., "Hippocampal neurons code individual episodic memories in humans," *Nat. Hum. Behav.*, (2023).
- Kozunov, V. V., West, T. O., Nikolaeva, A. Y., et al., "Object recognition is enabled by an experience-dependent appraisal of visual features in the brain's value system," *NeuroImage*, **221**, 117–143 (2020).
- Kubie, J. L., Levy, E. R. J., and Fenton, A. A., "Is hippocampal remapping the physiological basis for context?" *Hippocampus*, **30**, No. 8, 851–864 (2020).
- Lang, S., Kroll, A., Lipinski, S. J., et al., "Context conditioning and extinction in humans: differential contribution of the hippocampus, amygdala and prefrontal cortex," *Eur. J. Neurosci.*, **29**, No. 4, 823–832 (2009).
- LeDoux, J. E., "Emotion circuits in the brain," *Annu. Rev. Neurosci.*, **23**, 155–184 (2000).
- Maren, S., Aharonov, G., and Fanselow, M. S., "Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats," *Behav. Brain Res.*, **88**, No. 2, 261–274 (1997).
- Maren, S., Phan, K. L., and Liberzon, I., "The contextual brain: implications for fear conditioning, extinction and psychopathology," *Nat. Rev. Neurosci.*, **14**, No. 6, 417–428 (2013).
- Marschner, A., Kalisch, R., Vervliet, B., et al., "Dissociable roles for the hippocampus and the amygdala in human cued versus context fear conditioning," *J. Neurosci.*, **28**, No. 36, 9030 (2008).
- Monti, J. M., Cooke, G. E., Watson, P. D., et al., "Relating hippocampus to relational memory processing across domains and delays," *J. Cogn. Neurosci.*, **27**, No. 2, 234–245 (2015).
- Moscovitch, M. and Gilboa, A., "Has the concept of systems consolidation outlived its usefulness? Identification and evaluation of premises underlying systems consolidation," *Fac. Rev.*, **11**, 33 (2022).
- Nadel, L. and Moscovitch, M., "Memory consolidation, retrograde amnesia and the hippocampal complex," *Curr. Opin. Neurobiol.*, **7**, No. 2, 217–227 (1997).
- Novikov, N. A., Bryzgalov, D. V., and Chernyshev, B. V., "Theta and alpha band modulations reflect error-related adjustments in the auditory condensation task," *Front. Hum. Neurosci.*, **9**, 673 (2015).
- Olsen, R. K., Rondina, I. R., Riggs, L., et al., "Hippocampal and neocortical oscillatory contributions to visuospatial binding and comparison," *J. Experim. Psychol. Gen.*, **142**, No. 4, 1335–1345 (2013).
- Palladin, A., "Formation of artificial conditioned reflexes from the sum of stimuli," *Trudy Obshch. Russ. Vrachei v SPb*, **73**, 393 (1906).
- Pavlov, I. P., *Complete Collection of Works in Five Volumes*, USSR Academy of Sciences, Moscow, Leningrad (1949).
- Pearce, J. M., "A model for stimulus generalization in Pavlovian conditioning," *Psychol. Rev.*, **94**, No. 1, 61–73 (1987).
- Perel'tsveig, I. Ya., *Studies of Conditioned Reflexes. A Dissertation*, St. Petersburg (1907).
- Piepers, D. and Robbins, R., "A Review and clarification of the terms 'holistic,' 'configural,' and 'relational' in the face perception literature," *Front. Psychol.*, **3**, 559 (2012).
- Poch, C., Fuentemilla, L., et al., "Hippocampal theta-phase modulation of replay correlates with configural-relational short-term memory performance," *J. Neurosci.*, **31**, No. 19, 7038–7042 (2011).
- Pohlack, S. T., Nees, F., Liebscher, C., et al., "Hippocampal but not amygdalar volume affects contextual fear conditioning in humans," *Hum. Brain Mapp.*, **33**, No. 2, 478–488 (2012).
- Pohlack, S. T., Nees, F., Ruttorf, M., et al., "Activation of the ventral striatum during aversive contextual conditioning in humans," *Biol. Psychol.*, **91**, No. 1, 74–80 (2012).
- Pulvermüller, F., "Brain mechanisms linking language and action," *Nat. Rev. Neurosci.*, **6**, No. 7, 576–582 (2005).
- Pulvermüller, F., "Neural reuse of action perception circuits for language, concepts and communication," *Prog. Neurobiol.*, **160**, 1–44 (2018).
- Quiroga, R. Q., "Concept cells: the building blocks of declarative memory functions," *Nat. Rev. Neurosci.*, **13**, No. 8, 587–597 (2012).
- Razorenova, A. M., Chernyshev, B. V., Nikolaeva, A. Y., et al., "Rapid cortical plasticity induced by active associative learning of novel words in human adults," *Front. Neurosci.*, **14**, 895 (2020).

- Razorenova, A. M., Skavronskaya, V. V., Tyulenev, N. B., et al., "Can learning new words in the auditory modality lead to rapid formation of plastic restructuring in the cerebral cortex in adults?" *Sovremen. Zarubezhn. Psikh.*, **9**, No. 2, 46–56 (2020).
- Razran, G., "Studies in configural conditioning: I. Historical and preliminary experimentation," *J. Gen. Physiol.*, **21**, No. 2, 307–330 (1939).
- Razran, G., "Studies in configural conditioning: IV. Gestalt organization and configural conditioning," *J. Psychol.*, **7**, No. 1, 3–16 (1939).
- Razran, G., *Mind in Evolution: An East-West Synthesis of Learned Behavior and Cognition*, Houghton Mifflin (1971).
- Rey, H. G., De Falco, E., Ison, M. J., et al., "Encoding of long-term associations through neural unitization in the human medial temporal lobe," *Nat. Commun.*, **9**, No. 1, 4372 (2018).
- Rodríguez-Fornells, A., Cunillera, T., Mestres-Missé, A., and de Diego-Balaguer, R., "Neurophysiological mechanisms involved in language learning in adults," *Philos. Trans. R. Soc. B. Biol. Sci.*, **364**, No. 1536, 3711–3735 (2009).
- Rudy, J. W. and Sutherland, R. J., "Configural association theory and the hippocampal formation: An appraisal and reconfiguration," *Hippocampus*, **5**, No. 5, 375–389 (1995).
- Rudy, J. W., "Context representations, context functions, and the parahippocampal-hippocampal system," *Learn. Mem.*, **16**, No. 10, 573–585 (2009).
- Rudy, J. W., Huff, N. C., and Matus-Amat, P., "Understanding contextual fear conditioning: insights from a two-process model," *Neurosci. Biobehav. Rev.*, **28**, No. 7, 675–685 (2004).
- Sakimoto, Y. and Mitsushima, D., "Hippocampal theta activity during stimulus discrimination task," in: *Electroencephalography*, Sittipraporn, P. (ed.), IntechOpen, Rijeka (2017), pp. 11–22.
- Sakimoto, Y. and Sakata, S., "The transient decline in hippocampal theta power during response inhibition in a positive patterning task," *NeuroReport*, **26**, No. 14, 833–837 (2015).
- Sakimoto, Y., Hattori, M., Takeda, K., et al., "Hippocampal theta wave activity during configural and non-configural tasks in rats," *Exp. Brain Res.*, **225**, No. 2, 177–185 (2013).
- Sakimoto, Y., Okada, K., Takeda, K., and Sakata, S., "Transient decline in hippocampal theta activity during the acquisition process of the negative patterning task," *PLoS One*, **8**, No. 7, e70756 (2013).
- Sanderson, D. J., Pearce, J. M., Kyd, R. J., and Aggleton, J. P., "The importance of the rat hippocampus for learning the structure of visual arrays," *Eur. J. Neurosci.*, **24**, No. 6, 1781–1788 (2006).
- Sehlmeyer, C., Schöning, S., Zwitserlood, P., et al., "Human fear conditioning and extinction in neuroimaging: a systematic review," *PLoS One*, **4**, No. 6, e5865 (2009).
- Squire, L. R. and Alvarez, P., "Retrograde amnesia and memory consolidation: a neurobiological perspective," *Curr. Opin. Neurobiol.*, **5**, No. 2, 169–177 (1995).
- Squire, L. R., Genzel, L., Wixted, J. T., and Morris, R. G., "Memory consolidation," *Cold Spring Harb. Perspect. Biol.*, **7**, No. 8 (2015).
- Stout, D. M., Glenn, D. E., Acheson, D. T., et al., "Characterizing the neural circuitry associated with configural threat learning," *Brain Res.*, **1719**, 225–234 (2019).
- Stout, D. M., Glenn, D. E., Acheson, D. T., et al., "Neural measures associated with configural threat acquisition," *Neurobiol. Learn. Mem.*, **150**, 99–106 (2018).
- Sutherland, R. J. and Rudy, J. W., "Configural association theory: The role of the hippocampal formation in learning, memory, and amnesia," *Psychobiology*, **17**, No. 2, 129–144 (1989).
- Tonegawa, S., Morrissey, M. D., and Kitamura, T., "The role of engram cells in the systems consolidation of memory," *Nat. Rev. Neurosci.*, **19**, No. 8, 485–498 (2018).
- Urcelay, G. P. and Miller, R. R., "The functions of contexts in associative learning," *Behav. Processes*, **104**, 2–12 (2014).
- Watson, P. D., Voss, J. L., Warren, D. E., et al., "Spatial reconstruction by patients with hippocampal damage is dominated by relational memory errors," *Hippocampus*, **23**, No. 7, 570–580 (2013).
- Weinberger, N. M., "Specific long-term memory traces in primary auditory cortex," *Nat. Rev. Neurosci.*, **5**, No. 4, 279–290 (2004).
- Yadav, R., Hillman, B. G., Gupta, S. C., et al., "Deletion of glutamate delta-1 receptor in mouse leads to enhanced working memory and deficit in fear conditioning," *PLoS One*, **8**, No. 4, e60785 (2013).
- Yoshida, M., Chinzorig, C., Matsumoto, J., et al., "Configural cues associated with reward elicit theta oscillations of rat retrosplenial cortical neurons phase-locked to LFP theta cycles," *Cereb. Cortex*, **31**, No. 5, 2729–2741 (2021).
- Zelony, G., *Contribution à l'Analyse des Excitants Complexes des Reflexes Conditionnels*, Institut Impérial de Médecine Expérimentale (1910).
- Zheng, J., Stevenson, R. F., Mander, B. A., et al., "Multiplexing of theta and alpha rhythms in the amygdala-hippocampal circuit supports pattern separation of emotional information," *Neuron*, **102**, No. 4, 887–898 (2019).