CHAPTER 14

Learning in ex-vivo developing networks of cortical neurons

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Abstract: This contribution describes the use of multi-site interaction with large cortical networks in the study of learning. The general physiological properties of the network are described, and the concept of learning is mapped to the experimental network preparation. Learning is then analyzed in terms of exploration (defined as changes in the configuration of associations within the biological network) and recognition (the stabilization of “worthy” associations).

Motivation

This contribution describes the use of multi-site interaction with large cortical networks in the study of learning. It is a “structure-less” neural system, from an anatomical point of view; no cortical layers, no columnar organization and no input from remote anatomical modules. Yet the system possesses two major features common to all mammalian neural systems that learn; these are: (i) an extensive heterogeneous functional connectivity that enables a large repertoire of possible responses to stimuli; and (ii) sensitivity of the functional connectivity to activity, allowing for selection of adaptive responses. One may ask why bother with a “structure-less” neural system that possesses only the primitives of actual systems? We believe that the variance in the structures of neural systems within and between species, on the one hand, and the constancy of basic behavioral phenomena of learning, across individuals and species on the other, implies that learning is governed by a set of underlying universal neural principles. These universals are realized in many different ways, in many different forms of neuroanatomy. At present, the major effort of experimental neurobiology emphasizes specific realizations, such as particular forms of molecular machineries (e.g., receptor mediated intracellular signaling cascades) and specially arranged structures (e.g., the role of the hippocampus in learning). Indeed, descriptions of specific realizations, both microscopic and macroscopic, are invaluable, especially for diagnostic and treatment-oriented purposes. This is true even when the action of underlying universals is unknown. Yet, as far as comprehensive understanding is concerned, collecting facts about specific realizations is by itself insufficient. The complexity of neural systems suggests that accumulation of such facts may lead the field astray rather than offering a coherent large picture. We submit that to understand how neural substrates give rise to learning one must understand the underlying universals and their action in an environment common to all neural systems that learn. Thereafter, hypotheses regarding specific realizations and their constraints become tenable.

The network preparation

Of the various alternatives, large, random, cortical networks developing ex-vivo are most appropriate experimental model systems for studying the general questions of learning and memory at the population
An extensive survey of the properties of large random cortical networks developing ex-vivo may be found in recent reviews (Corner et al., 2002; Marom and Shahaf, 2002). The networks are relatively free of predefined constraints and intervening variables, yet the electrophysiological, biochemical, and pharmacological properties of their neurons are by and large identical to neurons in-vivo (Huettner and Baughman, 1986; Habets et al., 1987; Baughman et al., 1991; Muramoto et al., 1993; Higgins and Banker, 1998; Nakanishi and Kukita, 1998). The proportions of different cell types are practically identical to those found in-vivo (Eckenstein and Thoenen, 1983; Neale et al., 1983; Huettner and Baughman, 1986; Nakanishi and Kukita, 2000). These networks are free to develop in response to experimental manipulations; in other words, they are free to expose their developmental and adaptation potential (Van Huizen et al., 1985; Van Huizen and Romijn, 1987; Van Huizen et al., 1987a, b; Ramakers et al., 1990; Corner and Ramakers, 1991, 1992). Unlike slice preparations, the ex-vivo developing networks are not cut out of a larger system to which their structures are particularly fitted, and in the absence of which they function aberrantly. Indeed, alternative models, such as acute cortical slices and cultured slices allow one to explore what-is-there, but not how-it-got-to-be-there. The latter question is tightly related to development, and slices have a limited capacity to develop. The ex-vivo developing model system enables extensive, multi-site sampling and manipulating of the relevant variable, that is, electrical activity (e.g., Gross, 1979; Gross et al., 1982; Meister et al., 1994; Stenger and McKenna, 1994; Marom and Shahaf, 2002). While many things can be measured in a neural system, electrical activity is most relevant to the organization and function of networks. The ex-vivo developing cortical network system enables measurement procedures that interfere little with the action of universal factors. Moreover, it allows for study over wide range of timescales (milliseconds to months) (e.g., Huettner and Baughman, 1986; Gopal and Gross, 1996; Potter and DeMarse, 2001).

On the more functional side, these networks demonstrate extensive (yet experimentally controllable) connectivity and a multitude of mechanisms that make the connectivity sensitive to activity e.g., (Ramakers et al., 1990, 1991; Corner and Ramakers, 1991, 1992; Kamioka et al., 1996; Jimbo et al., 1998, 1999; Maeda et al., 1998; Turrigiano et al., 1998; Desai et al., 1999; Shahaf and Marom, 2001; Eytan et al., 2003).

Mapping the concept of learning to the network preparation

Once the aim is to study neural mechanisms of learning, it is important to be clear about what exactly one means by “learning.” This is a loaded term. Strictly speaking, learning is a behavioral concept that, for the relevant schools of psychologists, means a change in sequences of movements. We extend the concept in such a manner to fit any behaving system. The following definition of learning, extracted from Krippendorff’s dictionary of cybernetics, is particularly appropriate in that sense:

[Learning is] “A process of growing success in a fixed environment. E.g., mastering the violin, acquiring linguistic skills, increasing the accuracy of guesses, driving safer. Thus learning is not the same as acquiring knowledge through reception of information even though this often precedes manifest improvements. Learning is also different from problem solving which involves making decisions of how to bridge the gap between a present and a desired state and adaptation which implies changes in response to a changing environment not necessarily of growing success. One can only speak about learning when behavior noticeably increases the efficiency with which information is processed so that desirable states are reached, errors are avoided, or a portion of the world is controlled. Consciousness may or may not be involved. Learning by trial and error is a process by which feedback on errors prevents unsuccessful behavior from reoccurring thus increasing success.” (Krippendorff’s Dictionary of Cybernetics, http://pespmc1.vub.ac.be/ASC/LEARNING.html).
Many points deserve attention in this definition, we mention two: First, it is important that the growing success be in a fixed environment, marking an important distinction between learning and adaptation, the latter is a change in response to a changing environment. In that respect, LTP, LTD, and related processes are adaptations and should not be treated as synonyms to learning, as often occurs in the literature. The second point concerns increased efficiency with which information is processed, “so that desirable states are reached, errors are avoided, or a portion of the world is controlled”; this necessitates closing a loop with the world; one cannot speak of learning in an open loop context.

With the above definition in mind, we map the concept of learning to the network preparation: The behavior, we assume, may be represented by temporal structures described in terms of associations between neuronal activities. The network is required to modulate associations between neuronal activities such that it noticeably increases the efficiency with which an input stimulus is processed and a desirable spatiotemporal firing pattern is reached.

It is convenient to rephrase the experimental problem of learning in a network in terms of two population-level processes — exploration and recognition. Usually these terms serve higher-level language; for our purpose, exploration in the course of learning corresponds to changes in the configuration of associations within the network; recognition is the stabilization of worthy ones. Since “the mode of genesis of the worthy and the worthless seems the same” (James, 1890), these are two categorically different processes; in other words, there is nothing within the process of exploration that entails recognition and there is nothing within the process of recognition that entails exploration. In what follows we describe our observations in the study of both exploration and recognition.

**Exploration**

“When two elementary brain-processes have been active together or in an immediate succession, one of them, on reoccurring, tends to propagate its excitement into the other.” James, 1890.

“Now there is a basic law of association by simultaneity, ... — the quantitative cathexis of a neuron, A, passes over to another, B, if A and B have at some time been simultaneously cathected from elsewhere.” Freud, 1895.

Exploration, defined as changes in the configuration of associations within the network, naturally brings to mind the various forms of the basic law of association by simultaneity. While familiar to present-day scientists as “Hebb’s Law” (Hebb, 1949), others explicitly defined simultaneity by association, as read above, many years ago. This basic law translates to monosynaptic processes of activity-dependent change in synaptic efficacy, processes that are most notably related to the timing of electrical activities in the pre- and postsynaptic membranes. There is a substantial amount of data suggesting that the efficacy of a synapse will increase when a presynaptic cell A is activated before the postsynaptic cell B within a time window of few tens of milliseconds. The inverse occurs when B is active before A. These observations agree with key aspects of the law of association by simultaneity. In real life, however, the distance between input neuron(s) and output neuron(s), in terms of synaptic stations, can be quite significant; in the neocortex, the number of synapses and pathways involved in propagating a signal through several synaptic stations is very large. What happens when A and B are connected through tens and maybe hundreds of synaptic stations and alternative pathways? Hebb’s logic suggests that even in such a case his postulate should hold. Yet, it is not at all intuitive that Hebb’s postulate will survive the complex spatial and temporal dynamics involved in the transition of a signal from A to B through tens and hundreds of dynamic neurons and synapses in a highly connected network, with the resulting reentrance loops. Do long-range associations follow “laws” while changing in response to input?

As a first step towards answering such questions, we present here our attempts to describe activity-dependent changes occurring at the population level; while much work is still required, as shown below these data provides the phenomenological base upon which closed-loop learning experiments may be built.
The underlying assumption is that associations between neuronal activities, or some trivial extension of such, are the neurophysiological building blocks of overt, behavioral associations. In our experimental setup (Shahaf and Marom, 2001; Marom and Shahaf, 2002; Eytan et al., 2003), there are tens of thousands of heterogeneously interconnected cortical neurons. The network is laid upon a substrate in which an array of 60 extracellular electrodes is embedded. These electrodes serve for seamless recording of spike activities and focal stimulation. Each of the electrodes may pick signals from 1 to 3 neighboring neurons, signals that can be sorted for cellular origins using standard algorithms. Using this experimental arrangement, one may approach the problem of activity-dependent change in the association of identified neurons (“units”) embedded in a large population of neurons. Operationally, we define pairs of diachronically associated spikes, denoted here as activity pairs, in terms of an action potential $A$ that is followed by another action potential $B$ with a precise time delay $\tau \pm \Delta t$ ms between the two (thus, for instance, for $0 < \tau < 150$ ms, $\Delta t = 2.5$ ms, there are total of 30 activity pairs for a given $A \rightarrow B$). $A$ and $B$ may be action potentials recorded from the same or from different electrodes; in each network we identify thousands of such pairs. In some instances, we use an external stimulation as the first element of a pair in which case we denote the pair as $S \rightarrow R$ (instead of $A \rightarrow B$). For each activity pair, with a time delay $\tau \pm \Delta t$ ms between the elements of the pair, we define functional association strength ($C_\tau$) as the number of occurrences in which action potential $A$ was followed by action potential $B$ within $\tau \pm \Delta t$, divided by the number of occurrences of $A$ measured within a time period. The functional association strength is related to a correlation measure (with a time lag of $\tau$) between two neuronal activities. This measure can be intuitively interpreted as the efficacy of $A$ in predicting the activity of $B$. Thus defined, each diachronically associated pair of spikes represents a different subset of pathways in the network (Abeles, 1991); pairs become representatives of activation paths.

We collect single unit activities over half an hour in which the network is spontaneously active, calculate the association strengths of all the possible pairs in the data and plot the distribution of their values (Fig. 1).

Note the exponential decay of the distribution, with a characteristic value of $\sim 0.02$. The distribution remains stable over many hours of spontaneous activity, as well as under electrical perturbations; the fact that such perturbations do cause significant changes at the level of individual associations (data shown below) implies that there is some normalization mechanism at the population level that keeps the totality of connections stable. A possible mechanism at the single neuron level may involve activity-dependent scaling of quantal amplitude where single cortical neurons, in this same preparation, normalize the totality of their inputs (Turrigiano et al., 1998). Another possible explanation to the stability of the distribution of association strengths is that it results from the large number of associations involved. Focal stimulation of the network through a pair of electrodes may result in a reverberating wave of activity. The characteristics of this evoked activity are described elsewhere (Marom and Shahaf, 2002). When such stimuli are delivered at a rate of $\sim 1$ s$^{-1}$, associations tend to change their strengths. A most robust result we obtain under such circumstances is that there is an inverse correlation between the strength of association before the stimuli are applied, and the direction of the observed change. Associations that are weak before the stimuli are applied tend to increase their strengths; associations that are strong before the stimulation is applied tend to become weaker. The phenomenon is seen in pairs in which the first element is the stimulation itself ($S \rightarrow R$) (Fig. 2) as well as in pairs of two evoked spikes ($A \rightarrow B$) (data not shown).

Another important property of these networks, in relation to exploration, is the nonmonotonous nature of the changes observed at the level of individual
associations. We are used to think of associations changing in terms of the Hebbian postulate, implying that when a pair is changing it is expected to continue changing in the same direction until saturation. This is evidently not the case when associations are observed in the network preparation. While the deviations observed in different trajectories of association strengths are partially correlated, significant local departures from the correlation are often observed. Do these deviations reflect statistically originated fluctuations OR real plastic changes? This question is critical in the context of selective learning in neural networks. Our preliminary data suggest that the variations reflect true plastic changes in the entailment strength of a pair. We know that this is the case because when we shift from an intense frequent stimulation regimen to a sporadic one, we observe substantially fewer deviations. This is demonstrated in Fig. 3 (top), where the fate of two pairs with a similar history is shown to be sensitive to the last values just before moving to the sporadic stimulation regimen. Figure 3 (bottom) shows the sensitivity to recent changes in association strength at the population level. More experiments and analyses are required in order to establish a firm interpretation of this potentially important phenomenon.

Beyond the between session changes in association strengths, a decrease in response of the entire network is observed within a session of stimulation at frequencies higher than \( \sim 0.1 \text{s}^{-1} \) (Fig. 4). It is important to note that the stimulation frequency is not synonymous with the neuronal firing frequency; each stimulus evokes a reverberating network response, in which some of the neurons may fire at instantaneous rates as high as several hundreds of spikes per second. As shown in Fig. 4, at stimulation frequencies lower than \( \sim 0.1 \text{s}^{-1} \), there is enough time for the effects of responses to relax, and no accumulation of inactivation occurs. The stimulation frequencies shown here to induce declined network response are in accord with reports by others, using
this preparation. For example, Maeda et al. (1998) used a stimulation frequency of 1/15–1/30 s to allow recovery from response decline over time; Jimbo et al. (1993) reported that the networks cannot follow periodic stimulation separated by less than 3 s. Shahaf and Marom (2001) reported that at stimulation frequencies higher than 1 s the networks usually inactivate after a few pulses. While decreased responsiveness is seen also at the level of the single isolated neurons in this preparation (Tal et al., 2001), using two-site stimulation experiments (Eytan et al., 2003) we show that cellular excitability does not seem to be a key player in this network phenomenon; rather, inactivation of association strength is due to changes in synaptic transmission.

It is important to know, before trying to apply learning in these networks, how sensitive is the network to the location of stimulation; can the network tell one stimulation site from another? In order to answer this question we have conducted a series of experiments in which the network is stimulated from two different sites (Eytan et al., 2003). Figure 5 shows the cumulative fraction of units responding to either site 1 OR site 2 as a function of time after stimulation delivery (Black line), as well as the cumulative fraction of units responding to site 1 AND site 2 (Gray line). Beyond ~25 ms following a stimulus, the two different stimulation sources largely activate the same neurons. From Fig. 5 we learn that each path may roughly be divided into two segments; an early segment, which is unique to each of the paths, and a later segment, in which some overlap between the two paths, exists. We have shown that the segregation of path can have significant implications for selective modulation of association strengths in such a way that a unit may differentially change its association with upstream neuronal activations from different sources (Eytan et al., 2003). This observation further supports the data mentioned earlier in this section regarding pair-specific plastic variations in association strength.

Recognition

"And how will you enquire, Socrates, into that which you do not know? What will you put forth as the subject of enquiry? And if you find what you want, how will you ever know that this is the thing which you did not know?" Plato, ~383 BC.

In recent years, considerable experimental and theoretical effort has been directed towards identification of neural structures and mechanisms that are responsible for rewarding adaptive behaviors (Schultz, 1998, 2000; Kalivas and Nakamura, 1999; Spanagel and Weiss, 1999; Gisiger et al., 2000; Schultz and Dickinson, 2000). Underlying these endeavors is an attempt to map the behavioral concept of reward to neural processes that change the...
functionality of a subset of neurons, based on past performance of the system. Another approach to the concept of reward is found in general learning theories that were advocated by behaviorists such as Clark Hull and Edwin R. Guthrie over 50 years ago (Hull, 1943; Guthrie, 1946) and even earlier by Freud (1895). These psychological theories, which we collectively refer to as Drive Reduction principle, stress the effect of the reward on the driving stimulus. Specifically, the reward acts to reduce the driving stimulus, precluding the acquisition of any new stimulus–response associations. No separate neural rewarding entity is postulated or needed for shaping behavior.

Consider, for instance, a thirsty monkey undergoing a training procedure. In order to be rewarded by juice, the monkey is required to touch a defined area within a grid that is projected on a touch-screen. Initially, the monkey explores, performing many “wrong” touches. As long as this is the situation, the monkey is not rewarded by juice. Once the monkey performs as required, the rewarding juice is given. Now, according to the “reward as a strengthening entity” class of theories, the juice causes some uniquely defined neural entity to affect a subset of synapses in the brain thus increasing the chance of a similar behavior when the same circumstances are encountered in the future. According to the Drive Reduction principle, the reward abolishes the stimulus (thirst) and therefore the exploratory behavior of the monkey ceases; the last associations that were made between thirst and the experimental environment are left unaltered. No neural reward entity is required and no active strengthening of synapses occurs after performance of the appropriate movement.

While not mutually exclusive, the two classes of theories, in relation to reward, imply different cellular and synaptic mechanisms. The “reward as a strengthening entity” theories imply that there is a substance (neuromodulator) released by some neural reward entity that is capable of modulating the efficacy of a given synapse after it has been activated. Accordingly, recently active synapses should be in some fashion selectively available for modulation by the rewarding neuromodulator. In contrast, the Drive Reduction principle advocates that neural connectivity changes are due to the persistence of a driving stimulus and proceed under the direction of activity dependent rules: an exploration process. If the output of the system changes the driving stimulus by its removal, there is no longer a drive for further connectivity change and the system is “frozen” in its last conformation; no specific cellular and synaptic reward mechanism needs be postulated. In that respect, the notion of reward under the Drive Reduction principle is more primitive, whereas the “reward as a strengthening entity” might be considered an evolved, or unique version. In what follows we relate to a demonstration of the feasibility of the primitive Drive Reduction principle, base it on the phenomenological data on exploration brought above, and provide data concerning the possible involvement of dopamine, a neuromodulator implicated in the learning process.

Two observations on exploration in these networks make it quite trivial to obtain learning curves in our preparation, using a Drive Reduction procedure. The first and most important is exemplified in Fig. 2 showing that weak association strengths tend to increase upon repetitive stimulation; the second, required when selective learning is attempted, is exemplified in Fig. 3 showing that variations in changes of association strengths are plastic and pair-specific. The design of closed loop experiments becomes straightforward: the idea is to choose a “target” (R) recording site that have a relatively weak S → R association strength to a focal input (S), and use a closed loop arrangement in which increased S → R association ceases the stimulation. The statistical criteria for cessation of the stimulation are related to the result of Fig. 2. We have demonstrated that such a procedure may result in the production of learning curves (Shahaf and Marom, 2001). The results are summarized in Fig. 6 and detailed in (Shahaf and Marom, 2001; Marom and Shahaf, 2002). Note the sharp transitions seen in individual curves, as opposed to the smoothness of the averaged curves; the smoothness and monotonicity of averaged learning curves may lead to a mistaken interpretation that invokes a progressive approach towards an a priori known solution; this however is not the case in our networks; see insightful commentary on this issue by Guthrie (1946). The results of Shahaf and Marom (2001) imply that it is not necessary to assume a separate mechanism for the biological realization of a reward; the behavioral
concept of reward might well be considered as a change in (or removal of) the drive underlying the exploration of possible modes of response. Drive reduction is an intentionless natural principle to allow adjustment to a rich and unrestricted environment. Interestingly, Hebb criticized Hull’s Drive Reduction principle saying that:

“What Hull has done, in this modification of Pavlov’s ideas, is to postulate a special class of stimulus that (1) must be present before learning can occur, and (2) must then decline. The decline, and the decline only, determines the occurrence of a new connection. No way is suggested as to how the decrease of stimulation promotes the formation of connection.” The Organization of Behavior, Hebb, p. 178.

But our results suggest that Hebb was not correct in his interpretation of Hull’s postulate; it is not necessary to assume that the decrease (removal) of stimulation promotes the formation of connection. To the contrary; the results brought in the previous

Fig. 6. (Adapted from Shahaf and Marom (2001)). Top left: two learning curves, differing in their learning kinetics. The response time (i.e., the duration of stimuli series until criterion is fulfilled) is plotted against the number of stimulation cycles (each stimulation cycle consists of ~0.3 Hz stimuli until the network responds “appropriately,” followed by 5 min of nonstimulation periods). Each point depicts the time (seconds) to accomplish the task in one cycle. These learning curves were obtained with simple tasks, where a network is stimulated until spike probability in one predefined network site responds beyond criterion. The criterion in this case was responsiveness to the stimulus within a time window of 50 ms (±10 ms) in a stimulus/response rate > 0.2 s⁻¹. Bottom left: A learning curve of more complicated task; here, the network was required to respond differentially in two different predefined loci. Note the more fluctuating nature of the curves, relative to the simple learning. Right: the averaged control curve, obtained by not removing the stimuli upon fulfillment of predefined criteria, suggests that the exploration in the space of connectivity configurations continues as long as the driving stimulus persists; hence the importance of closed loop monitoring of the network response. Average learning curves of all learning trials are shown, where the stimulus is removed when the “appropriate” responses are obtained. Each point depicts the average time (seconds) to accomplish the task in one cycle. Filled gray circles and filled black squares depict points that are significantly different from averaged control (F-test, p < 0.05). Fitted power function lines are added in order to emphasize the different trends of the curves. Top learning curve (gray) is an average over all the curves obtained in learning experiments (n = 24), including those where the network was unable to accomplish the task; bottom curve (black) is the average of all the successful learning experiments (n = 16).
section (on exploration) suggest that formation and modulation of connections is promoted by stimulation. When the stimulation is removed, the last configuration of connectivity that was formed is “frozen.”

What about the rewarding neuromodulatory entities? Let us examine the dopamine case. The involvement of dopamine in the process of learning, at the cellular and behavioral levels, has been extensively studied in recent years. Within this context, the role of dopaminergic neurons, residing in the ventro-anterior midbrain and projecting to the striatum and the neocortex, is considered central. These neurons are reported to be transiently activated in response to surprising events such as novel stimuli, salient sensory stimuli, unexpected primary rewards, and arbitrary stimuli that are associated with primary rewards, thus reporting an error in the prediction of the stimulus (Redgrave et al., 1999; Horvitz, 2000; Dayan and Balleine, 2002; Schultz, 2002). The activation of dopaminergic neurons is correlated with the learning process, suggesting that dopamine acts as a modulator of functional connectivity in its target tissues. Cellular-level experiments indicate that dopamine has a wide range of effects on synaptic plasticity and cellular excitability. Translation of the cellular-level effects to the behavioral level passes through an in-between level of integration — i.e., the level of neuronal ensembles. Using our network preparation we address the intermediate level of organization, exploring the effects of dopamine on the functional connectivity of neurons separated by many synapses. We ask: how does dopamine affect the functional connectivity between two such neurons? Does it stabilize or destabilize such connections? We approach these questions using multi-site recordings from networks of cortical neurons developing ex-vivo. Our results (Eytan et al., 2004) show that, at the polysynaptic level, dopamine enhances changes in functional connectivity. This effect is differential in the sense that weak associations are more sensitive to dopamine as compared to strong associations (Fig. 7). Pharmacological experiments and controls support this interpretation (data not shown). The effects are in accordance with hypotheses about the role of dopamine in updating functional connectivity upon exposure to salient unpredicted stimuli: the observation that dopamine destabilizes neuronal associations seems reasonable, if one considers the unpredictability of a stimulus as an indication for the inadequacy of an existing association. The preferential strengthening effect of dopamine on weak associations also seems to fit this logic in the sense that poor predictability and weak associations are correlated. Thus, we suggest that the dispersing effects of dopamine naturally fit the presumed role of dopamine in learning: inducing strengthening of rarely occurring associations, if such associations prove to be rewarding. While such extrapolations are inherently limited because of the ex-vivo unnatural context in which the networks are kept (for example, since there are no dopaminergic neurons in these cultures, hypersensitivity to dopamine cannot be excluded), the similarity between key features of the ex-vivo and in-vivo networks in terms of structural, biochemical, physiological, and pharmacological indicates that these results may be very relevant to intact neuronal networks in vivo.

A concluding remark and a caveat

In this chapter we have tried to convey our conviction that studying a structure-less neuronal network may significantly enhance understanding of learning. We show that combining insights from general learning theories, technology of long-term multi-site interaction with the network and population level analyses, provides an infrastructure for in-depth study of principles of learning in neural systems. A caveat however is in place; the caveat, brought in the words of James, relates to our ability to generalize findings...
from the model system presented here to the actual brain-behavior system:

“I trust that the student will now feel that the way to a deeper understanding of the order of our ideas lies in the direction of cerebral physiology... it is only as incorporated in the brain that such schematism can represent anything causal.” James, on Association; p. 593, Principles, 1890.

Acknowledgments

This work is partially funded by research grants from the Israel Science Foundation, the National Institute for Psychobiology, and the Minerva Foundation.

References


