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Review

Behavioral facilitation after hippocampal lesion: A review

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HIGHLIGHTS

- Hippocampal damage cannot only lead to deficits but also to behavioral facilitation.
- Such facilitatory lesion effects can be attributed to the loss of interference between hippocampal and basal ganglia mechanisms.
- Facilitatory lesion effects are typical for tasks dependent on implicit or procedural information processing.

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ABSTRACT

When parts of the brain suffer from damage, certain functional deficits or impairments are the expected and typical outcome. A myriad of examples show such negative consequences, which afford the daily tasks of neurologists, neuropsychologists, and also behavioral neuroscientists working with experimental brain lesions. Compared to lesion-induced deficits, examples for functional enhancements or facilitation after brain lesions are rather rare and usually not well studied. Here, the mammalian hippocampus seems to provide an exception, since substantial evidence shows that its damage can have facilitatory behavioral effects under certain conditions. This review will address these effects and their possible mechanisms. It will show that facilitatory effects of hippocampal lesions, although mostly studied in rats, can be found in many mammalian species, that is, they are apparently not species-specific. Furthermore, they can be found with various lesion techniques, from tissue ablation, to neurotoxic damage, and from damage of hippocampal structure itself to damage of fiber systems innervating it. The major emphasis of this review, however, lies on the behavioral effects and their interpretations. Thus, facilitatory effects can be found in several learning paradigms, especially active avoidance, and some forms of Pavlovian and instrumental conditioning. These will be discussed in light of pertinent theories of hippocampal function, such as inhibition, spatial cognition, and multiple memory systems theories, which state that facilitatory effects of hippocampal lesions may reflect the loss of interference between hippocampal spatial and striatal procedural cognition. Using the example of the rat sequential reaction time task, it will also be discussed how such lesions can have direct and indirect consequences on certain behavioral readouts. A final note will advocate considering possible functional facilitation also in neurologic patients, especially those with hippocampal damage, since such a strategy might provide new avenues for therapeutic treatments.

Contents

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1. General introduction

This review will focus on the phenomenon of functional facilitation after hippocampal lesion. It consists of the following parts: After a brief overview of hippocampal anatomy and its presumed functions, brain lesions as such will shortly be addressed regarding their general role in neuroscience, as well as critical limitations, which have to be considered when trying to interpret their outcomes. Then, facilitatory effects, mainly from humans, will shortly be addressed with respect to lesions outside the hippocampus, followed by a historical account of hippocampal lesion effects. In more detail, the roles of species, lesion techniques, and behavioral tests will be outlined and discussed in light of prevalent theories of hippocampal function. Here, active avoidance will receive special attention, since tests of active avoidance learning have provided the classical facilitatory effects. Other Pavlovian and instrumental tests will then be described, showing that facilitatory effects can actually be found in rather different paradigms, which makes it difficult to relate the consequences of hippocampal lesions to a unique mechanism. Special emphasis will be given to our own work with an instrumental serial reaction time task in rats, where we studied facilitatory effects of hippocampal lesions in detail, addressing factors such as instrumental versus sequential learning, post-reinforcement pauses, extinction, and action-outcome relationships. Compared to the rich evidence obtained in experimental animals, similar knowledge in human subjects is almost entirely lacking. Nevertheless, the facilitation issue might deserve more clinical attention in the future, since some facilitated function, possibly due to enhanced impacts of undamaged and learning-relevant brain structures (such as in the basal ganglia), might also be useful to help compensate for hippocampal losses in humans.

2. Brief introduction into hippocampal structure and function

Since this review anatomically focusses on the hippocampus, some basic knowledge of it will be presented in the following:

In the current scientific literature, the term “hippocampus” is used in a somehow inconsistent way. Classically, it refers to the three layers of the cornu ammonis, namely CA1, CA2 and CA3, which are often summarized as hippocampus proper. However, it has become rather popular to embrace several brain areas under the term hippocampus, namely hippocampus proper, dentate gyrus, subiculum, and entorhinal cortex, all of which are also termed “hippocampal formation” (for details see [6]). In the present review, the term hippocampus will be used in the more popular sense that is, including hippocampus proper and the adjacent structures mentioned above. Also, one can differentiate between different major parts of the hippocampus proper. In rats, it has a rather bent shape, with a dorsal, intermediate, and ventral part. Since most of the studies reviewed here were done with rats, these terms (especially dorsal) will continue to be used.

Regarding its basic circuitry, the hippocampus, mainly via the entorhinal cortex, receives inputs from various neocortical regions. Through the perforant pathway, projections from entorhinal cells reach the dentate gyrus. Its granule cells send axons (termed mossy fibers) to innervate the pyramidal cells of the CA3, which send projections (termed Schaffer collaterals) to the CA1. These, in turn, project to the subiculum (and entorhinal cortex), and from there to structures outside the hippocampus, especially cortical ones. Also, several fiber bundles funnel information to and from, and within or between the hippocampi of both hemispheres (for details see [1]). Out of these, only the fimbria-fornix pathway will receive specific attention in this review, which connects the hippocampus with areas in the brainstem, thalamus, hypothalamus, septum, and nucleus accumbens.

Regarding its functions, the hippocampus has undergone several stages and levels of interpretation, depending on methodological developments, critical experiments and findings (for older examples [70,119,138]). Discussing these complex issues in great detail goes far beyond the scope of this review, but the reader can be referred to an excellent paper by Morris [107]. Nevertheless, some theoretical hallmarks have to be provided which are of relevance here: Currently, the prevailing theories state that the hippocampus plays a critical role in memory, especially its formation. Here, one major research line, originally based on findings in humans with brain lesions, emphasizes its role in declarative memory [147,153], especially events and facts that can be consciously recalled. Although such kind of conscious memory cannot be tested directly in non-human animals, several monkey or rodent tests are considered to somehow model declarative memory [29,148], especially recognition memory, like the rodent object place-recognition test [58], which is often taken as a tool to measure episodic memory [154]. The other major research line, which apart from various brain manipulation techniques and the development of specific behavioral tests (e.g. [110,111], is largely based on cell recordings in rodents, emphasizes the hippocampal role in spatial cognition and memory, that is, the formation and use of spatial maps [63,120]. Somehow related theories [30,75,150] state that the hippocampus is important to form and use stimulus configurations and relations, and examples for that are space, context and their details. Also, it was suggested that the hippocampus may resolve conflicts between competing approach and avoidance tendencies, that it processes novelty, or regulates stress via control of the HPA-axis (e.g. [69,70]). Regarding functional localization, the major anatomical parts along the hippocampal longitudinal axis have been associated differentially with behavioral functions, since spatial learning and memory has been linked primarily to the dorsal

hippocampus, compared to anxiety-related functions attributed to its ventral part [8,113].

Other, and mostly older theories, state that the hippocampus plays a critical inhibitory role, like in a classical Pavlovian sense, in ongoing behavior, or in attention [71,91,for refinements see 25,36]. Douglas [46] wrote that hippocampal lesion "*produces a unitary deficit*" which "*consists of an ability to withhold a prepotent response whether learned or unlearned*". In general, he assumed that "*hippocampectomized animals excel over the normal in tasks in which a disruptive inhibitory tendency is present, are normal on tasks in which no inhibition is involved, and are inferior . . . on tasks demanding an inhibitory tendency*". Kimble [91] suggested that "*an animal with hippocampal damage would be less able to inhibit or alter its responses to initially prepotent environmental stimuli and consequently would display less flexible and less adaptive behavior*". Simonov [147] concluded that "*the hippocampus is concerned with responses to signals having low probability of reinforcement*" so that "*following destruction of the hippocampus, the neocortex gives preference to signals with high probability of reinforcement*" and that "*an animal with destroyed hippocampus . . . is free of 'doubt and hesitation*"'. More recently, Cameron & Glover [22] stated that subjects with hippocampal lesions hold onto "*hypotheses*", and that such lesions can "*maximize persistence in the face of partial reward*".

3. Some general remarks on brain lesions as research tools

Since the research reviewed in the following is almost exclusively based on experimental brain lesions, this research strategy should shortly be addressed before. Trying to understand neural function through studying the effects of brain lesions, be they experimental, accidental, or therapeutic, is probably one of the oldest neuroscientific appoaches [16,96]. Like any other manipulative method, brain lesioning has critical pitfalls and limitations, which have to be considered when trying to interpret their behavioral and cognitive sequelae. These include the following aspects (see also [12,151]: Did the lesion destroy the entire structure of interest or only parts of it? Did the lesion also encompass adjacent structures? Can one attribute functional changes to cells within the structure or to axons which belong to (perhaps distant) brain areas passing through it (fibers-of passage-problem)? Is the functional change due to damage/dysfunction of brain sites innervating/innervated by the damaged structure, e.g. trans-neuronal degeneration? Is the functional change a direct consequence of brain damage, or is it due to compensatory brain mechanisms, or to the subject having to deal with a functional loss? Is the functional change observed only acutely or permanently? Is a given loss due to a more general deficit (like in overall performance), which might prevent more specific processes to become effective, or is it due to a loss of a specific cognitive process? What functions are preserved? Can one dissociate lesion effects between certain brain areas? What are appropriate controls: intact subjects, those with sham lesions (and how is sham operationalized), animals with lesions of structures surgically situated on the way to the structure of interest (which is especially relevant in case of the dorsal hippocampus covered by neocortical structures)? Finally, a general, and sometimes overlooked problem has to be addressed, namely the danger of a logical fallacy, that is, when a "positive" function is deduced from the negative features of a symptom and this "positive" function is simply localized to the site of lesion. In case of the hippocampus, over-simplistic application of the "*behavioral inhibition*" theory [91] may be such an example. As also outlined below, one outcome of hippocampal lesions is that the animal may be hyperactive and seems to have problems stopping certain kinds of behaviors in response to changing environmental demands, especially when well-trained (see also [46]). Based on such findings, it was assumed that a major function of the hippocampus is inhibitory, which may explain some but not all outcomes of hippocampal lesions (for a more in-depth discussion see [25,36].

The typical and intuitively plausible outcome of a brain lesion is an impairment or even loss of some kind of function, which might be sensory, motor, emotional, motivational, attentional, executive, mnestic, and so on (like aphasia, agnosia, paresis, amnesia). In case of the hippocampus, a myriad of papers exists showing such deficits, especially in the area of spatial and declarative learning and memory (for review see [109]. Nevertheless, there are cases of brain lesions where a certain function (or better a performance measure from which a function is derived) is not only preserved but even improved (for review see [86–88], which has often been termed a paradoxical facilitatory lesion effect. Such effects have not only been found in experimental animals but also human patients. These include enhanced performance in problem-solving tasks in patients with frontal lesions [129], certain kinds of perceptual performance in visual object agnosia [112], visual search in semantic dementia [155], facial processing in aphasia [59], recall of visual or tactile arrays [114], and reduced false positives in amnesias [77,135]. These studies cannot be addressed in detail here, but some conclusions should be mentioned regarding amnestic patients (see also [88]: In some learning tasks, it may be helpful to forget associations from previous trials, since these have now become irrelevant; here, the forgetfulness of amnesic patients may be helpful [116]. In other tasks, there may be a competition between implicit and explicit processing, although the task can be mastered efficiently implicitly. Again, amnesic patients may be superior under such implicit conditions [24,115], whereas they fail when explicit processing is required.

Overall, the above mentioned human literature on facilitatory lesion effects is more or less anecdotal, lacks consecutive research, and often cannot be related to specific brain sites, like in the case of amnesia, where brain damage and dysfunction is often rather widespread. Interestingly, however, facilitatory lesion effects are rather typical in the case of animal hippocampal brain damage and there are now quite a number of papers available, including reviews [13,52], which show the effects in different species with different types of brain lesion and different behavioral tests. These papers will be reviewed in the following starting with a brief retrospect.

4. Brief history of facilitatory lesion effects

Evidence for facilitation of performance after brain lesions dates back to the famous work of Karl Lashley [96], who studied the effects of massive neocortical lesions in rats using a box problem and a brightness discrimination task. He found superior acquisition performance after lesion, for example, in terms of trials to criterion. Lashley concluded that lesion-induced motor deficits ("paresis") were somehow advantageous given the specific behavioral requirements of his tasks, and that lesion and control animals were actually equal in their learning abilities. This study also included some subjects with additional hippocampal lesions, and these showed similar performance as animals with only neocortical damage.

An early experiment showing a facilitatory effect of a hippocampus lesion was that of Allen [5], who found that dogs with hippocampal lesions were somewhat superior compared to controls in the acquisition of a conditioned olfactory response. Thereafter, about another two decades elapsed until further substantial evidence for facilitatory lesion effects was published, and the then appearing papers (see below) were probably initiated by the study of Isaacson et al. [78]. These authors used a tone-signaled active-avoidance paradigm in rats and found a facilitatory effect of hippocampal/neocortical ablations as compared to controls with only neocortical ablations. The effect was measurable in terms of

trials to criterion and in terms of latencies; besides, a deficit in subsequent extinction was observed. The authors interpreted their findings with respect to the role of the hippocampus in memory and argued that the hippocampus may not be required for all types of recent memories, a conclusion which was later substantiated by theories advocating multiple memory systems [31,75,80,120].

5. Functional facilitation after lesions: species

In all mammalian species investigated so far, evidence of facilitatory lesion effects after hippocampal (or related) damage was obtained. In most cases, rats of various outbred strains were used (e.g. [14,18,50,54,78,81,97,100,123,164], but similar evidence, albeit with different tests (see below) was found in mice [37,65,66,134], rabbits [126,141], cats [17], dogs [5], monkeys [12,47,95,132], and even humans [128], including the famous amnesic patient H.M., who besides his severe anterograde deficits in declarative memory showed facilitation of perceptual identification by priming [104].

6. Functional facilitation after lesions: lesion types and sites

The techniques used to damage hippocampal or related brain structures varied substantially between studies largely due to technical developments during the historical course of this now almost centennial 'lineí of research. Thus, in the older studies, ablation techniques were applied usually by means of aspiration (e.g. [17,78,143] or transection [21,95,169], followed by electrolytic and radiofrequency lesions (e.g. [54,55,65,100,121]. Often, these lesions, especially the ones implemented by means of tissue aspiration, had limited specificity, like substantial brain damage outside the hippocampus. Also, lesion size and location were not always documented in great detail.

This situation changed substantially with the introduction of techniques to microinject neurotoxins into the hippocampus, especially the excitotoxic ones, like NMDA [26,80,84,132,134], and ibotenic acid [12,37,50,64,124,142,19,20], or the catecholaminergic neurotoxin 6-OHDA [64,65]. Furthermore, an electrical stimulation technique was used which led to a loss of certain CA layers within the hippocampus [164]. Compared to these various permanent lesion approaches, studies with temporary inactivation techniques trying to replicate facilitatory performance effect induced by brain lesion are sparse, for example, by means of local anesthetic infusion (but see [145,158].

In the bulk of publications, the lesions were aimed directly at the hippocampus; however, facilitatory effects on behavior were also observed in the case of lesions aimed at the entorhinal cortex, which serves as an interface between the hippocampus and various neocortical sites [62,65,66,121,166], or lesions of the fornix, that is, fiber tracts providing a major hippocampal output [20,54,55,95,100,123,169].

Regarding rodent hippocampal lesions, most studies aimed at the dorsal part, whereas dorsal plus ventral lesions are comparably sparse in this research field (but see [80,102,156–158]. Since the multitude of studies with dorsal lesions showed facilitatory effects, one can conclude, that ventral hippocampal lesions are not required for the phenomenon (for further details regarding such hippocampal subareas see [60]), although the results by Wang et al. [158] imply that dorsal plus ventral lesions are required, at least to facilitate active avoidance performance (see below). With respect to the dorsal lesions themselves, most of them were more or less complete tissue resections, which is obvious in case of the earlier aspiration studies; however, regarding the more selective excitotoxic lesions, one often finds that such chemical lesions also lead to a rather complete loss of the dorsal hippocampus (see for example [18,19,50,158].

Although technically available, there are only few examples in this research field with lesion approaches aiming at certain components within the hippocampal formation. One exceptional example is the electrical stimulation technique of the perforant pathway, which is used as a model of medial temporal lobe epilepsy [119]. This technique leads to a retarded development of seizures, which are preceded by widespread neuron loss in areas CA3 and CA1 but sparing of CA2 and granule cells (termed classic hippocampal sclerosis), paralleled by a facilitatory effect in a sequential reaction time task ([164], see also below). Clearly, further studies using selective manipulations within the hippocampal formation are needed to figure out, which of its anatomical elements are linked to facilitatory lesion effects, which will be reviewed in the following.

7. Functional facilitation after lesions: test paradigms, findings and interpretations

7.1. Avoidance tasks

As outlined above, the pioneering finding on behavioral facilitation after hippocampal lesion was published by Isaacson et al. [78], who used a tone-signaled active avoidance paradigm, that is, a test which involves Pavlovian and instrumental conditioning. They found a facilitatory effect of combined hippocampal/neocortical ablations, which was not induced by neocortical ablations alone. The effect was characterized by faster attainment of the learning criterion and slower extinction thereafter (for similar results see [73,74,93,121,127,153,159]). Regarding the roles of dorsal and ventral hippocampus, Wang et al. [158] recently found a trend for facilitated acquisition when both hippocampal parts were destroyed but no effect of excitotoxic dorsal or ventral lesions alone. In contrast to active avoidance, inhibitory (passive) and one-way avoidance were not affected by hippocampal lesions [65,66,79,90,121].

The facilitation in active avoidance was generally discussed in terms of lesion-induced hyperactivity, perseveration, and loss of inhibition. Thus, Kimble [90] interpreted the slowed extinction as a deficit of an ability to inhibit previously rewarded behavior and to adapt to changing reward contingencies. Lesion-induced hyperactivity, which was often but not always found, may be attributed to an upregulation of dopamine transmission in the ventral striatum/nucleus accumbens, due to the loss of its hippocampal afferents [107,163]. Since ventral striatal dopamine is critical, among others, for locomotor activity, such an effect may determine hyperactivity induced by hippocampal lesion, and thereby enhance active avoidance performance.

The critical role of hyperactivity is not fully clear, however. Thus, Green et al. [73], on the one hand, found enhanced inter-trial activity after relatively large hippocampal lesions, possibly due to less freezing. When testing smaller hippocampal lesions, in contrast, the avoidance learning effect was replicated, but without enhanced activity, indicating that hyperactivity might not be necessary for the avoidance effect. Blanchard & Blanchard [14] exposed rats with dorsal plus ventral hippocampal lesions to a cat and found superior escape responses from this threatening stimulus. They assumed that the effect might be due to a lesion-induced reduction in unconditioned freezing, whereas Pentkowski et al. [124] who compared dorsal and ventral hippocampal lesions in a similar test, showed that ventral, but not dorsal, lesions seem to be critical for such freezing responses. Therefore, improved active avoidance after dorsal hippocampal lesions might not generally be attributable to deficits in freezing or simple hyperactivity (see also [158]).

Regarding alternative explanations, Olton & Isaacson [121], who also ruled out general activity effects to explain changes in avoidance behavior, argued that enhanced performance in case of two-way avoidance is due to reduced avoidance of places paired with aversive experiences, since subjects with hippocampal lesions may be impaired to associate the aversive stimulus with the environment where is was experienced. This is critical in case of two-way avoidance, where a given spatial part is temporarily either safe or unsafe, and where it is critical to use the cue, which signals coming shocks, to shuttle between these spaces. Similar conclusions were drawn in a review by Black et al. [13]: They argued that the facilitatory effects of hippocampal lesions in avoidance tasks are due to a deficit in spatial information processing, so that the animals cannot use spatial strategies to avoid or escape, but that they can use cue strategies. In avoidance paradigms like the two-way avoidance test, spatial strategies may be disadvantageous: The intact subject may initially process an environment with shock experience as an inescapable place leading to freezing which is incompatible with escape, thereby hindering subsequent avoidance learning. Animals with hippocampal lesions, in contrast, are spared from such a relatively maladaptive spatial interference. Such subjects rather rely on relevant cues allowing them better avoidance performance in such tasks.

7.2. Pavlovian conditioning

Concerning aversive Pavlovian conditioning paradigms, the nictitating membrane response, the eyelid response, and fear conditioning were used. It was found that hippocampal lesions can lead to either deficits or to facilitation. Anatomically, deficits in aversive Pavlovian conditioning seem to be more typical in case of ventral hippocampal manipulations as compared to dorsal ones [8,10,130]. Furthermore, aspects of the given conditioning paradigm are critical: In older studies, with rather gross lesion sites, Schmaltz & Theios [143] found faster acquisition of a rabbit conditioned nictitating response (delay conditioning) followed by an extinction deficit. This deficit was explained according to Klüver [94], namely that "*the temporal lobe limbic areas are important for an animal's coping with 'shifting and fluctuating phenomena' of the environment*". Port et al. [126] reported that facilitatory lesion effects depend on the inter-stimulus interval. Later studies also showed that lesion effects in the conditioned nictitating membrane response critically depend on the kind of conditioning (trace vs. delay) and its procedural details. In short, deficits after hippocampus lesions are considered most likely in case of trace conditioning and a trace interval of 500 ms (for review see [160]). Why hippocampal lesions can lead to enhanced conditioning under certain procedural conditions was not addressed any further. Lee & Kim [97] used delayed eye blink conditioning in rats with lesions of the dorsal hippocampus, amygdala, cerebellum, or sham-controls, and found facilitated acquisition in case of hippocampal lesions, in contrast to impaired acquisition with amygdala lesions, or complete losses with of cerebellar lesions. They argued that the dorsal hippocampus might not be required for simple eye blink conditioning, but for more complex ones. The facilitatory lesion effect was discussed in term of interference between hippocampal and cerebellar information processing, i.e. contextual processing in the hippocampus and CS-US associations in the cerebellum. In case of simple eye lid conditioning, contextual hippocampal information processing is not required and may even interfere with more basic associations processed in the cerebellum. Similar conclusions were drawn in a study with a discriminative fear conditioning paradigm with specific contexts and tone CS [37], where a facilitatory effect was mainly observed during the CS phases. The authors assumed that normal subjects use two competing strategies in such tasks, one that relies on contextual information, and the other on distinct cues. Hippocampus lesions may impair use of the context information, but may improve that of the CS (see also [165]).

In other studies, odors were used to allow discrimination of appetitive or aversive stimuli. Regarding aversive conditioning, Schmajuk & Isaacson [139] used a 2-odor discrimination paradigm, where odors signaled foot shocks with different probabilities. They found that rats with hippocampal lesions showed better learning than controls when odors partially or perfectly predicted the contingencies. They assumed that the hippocampal animals are actually more sensitive to such contingencies than normal animals. Ferry et al. [62] used odors to signal delayed aversion induced by LiCl injection. They found that entorhinal lesions facilitated learning in case of longer delays and they explained this effect by assuming that the lesion might have led to a longer persistence of the odor trace, thus allowing associations with the aversive US even in cases of rather delayed appearance.

Eichenbaum & co-workers used appetitive odor tasks in several studies (for review see [53]). For example [54], they compared fornix, amygdala, or combined lesions and found normal learning in all of them when the task required successive discrimination of two odors, whereas deficits were obtained when the same types of stimuli had to be discriminated simultaneously [55], that is, when direct comparisons among stimuli were required. In a subsequent reversal test, only the fornix group (which otherwise had the expected deficit in a spatial delayed alternation task) easily learned the reversal. The authors concluded that these rats processed the reversal condition like a new discrimination task, that is, there was apparently no interference from previously learned odor associations which normal animals have to unlearn. Facilitated acquisition was also found with successive odor discrimination in case of entorhinal lesions [122], and it was assumed that the lesion-induced facilitation may not be due to a disinhibitory lesion effect (because several task aspects require inhibition) or a deficit to inhibit attention to task-irrelevant stimuli. Rather, the deficits in the case of simultaneous stimulus presentation and facilitation in the case of successive stimulus presentation were interpreted as such that simultaneous comparisons are processed within the hippocampus, whereas successive processing may occur outside of it, namely via habit and reward association systems in the striatum and amygdala (for more details see [52]). In the latter case, stimuli and their meanings may be encoded individually, which may prevent explicit comparisons between different stimuli due to temporal separation. Furthermore, it was assumed that the hippocampus, which processes relations between stimuli, either normally overrides other brain areas, which encode stimuli individually and in a non-relational way, or competes with them regarding control over behavioral options.

Together, facilitations after hippocampal lesions can be found, both in case of aversive and appetitive Pavlovian conditioning paradigms. These outcomes depend critically on specific task requirements, which in turn, seem to reflect differential involvement of hippocampal or extra-hippocampal brain structures. If a test does not require hippocampal, i.e. contextual, spatial, or relational information processing, but relies on associative mechanisms processed largely by brains structures like neostriatum, amygdala, or cerebellum, it is possible that it can be mastered even in a superior way when the hippocampus is damaged.

7.3. Instrumental tasks

Encouraged by their earlier active avoidance results [78], Wickelgren & Isaacson [162] used running for food in food-deprived rats, to test whether hippocampal lesion effects might also have facilitatory effects on appetitive behavior. Using a measure of approach latencies, they found evidence that the lesion group "*seemed to acquire the response more rapidly than did the control groups*"; however, only descriptive data were presented in support of this

statement (see [51] for similar results in rats with fornix lesions). Furthermore, Wickelgren & Isaacson [162] found that hippocampal animals, unlike controls, were not distracted when irrelevant tactile stimuli were placed on the runway floor. The findings were interpreted in terms of the then predominant inhibition theory, that is, animals with hippocampal lesions may either be able to detect changes in the environment, but cannot inhibit the previously acquired, dominant response, or that they are less able to pay attention or orient towards novel and distracting stimuli. Brown et al. [17] trained cats to displace a block in order to obtain food, and found that cats with hippocampal lesions learned better to withhold a response during non-rewarded trials, which is not compatible with the inhibition hypothesis. Also, they found that their lesion subjects were more resistant to extinction, which is consistent with the perseveration hypothesis. In an object discrimination task, which was solvable either by tactile or visual means, monkeys with fimbria-fornix transections showed normal learning in the tactile mode, but had enhanced performance compared to controls in the visual mode [169]; the reasons for this selective facilitation effect remained unclear.

In subsequent studies, bar pressing, usually for food, was mostly used. However, facilitatory lesion effects are not restricted to food-reinforced behavior, since similar hippocampal lesion effects were also found in case of reinforcing electrical brain stimulation [108,168]. Thus, Zimmermann et al. [168] found higher rates of lateral hypothalamic self-stimulation in rats with ibotenic acid lesions of the CA1 region, and they concluded that this outcome was indicative of a lesion-induced disinhibition of a reinforcement system located outside the hippocampus.

Regarding the more prevalent studies using food-reinforced behavior, these can be classified according to the schedules of reinforcement (for details see [45]) being used, as outlined below.

7.4. Continuous reinforcement (CRF)

Regarding CRF, results are equivocal. Ehrlich [51] found that rats with fornix lesions were slightly impaired or unimpaired (see also [28,142]), whereas Means et al. [102] tested rats with dorsal plus ventral hippocampal ablations through aspiration (plus cortex overlying the dorsal part) and found that these needed less training to reach a certain criterion of reinforced responses per time under CRF conditions (see also [64,65] for entorhinal lesions in mice), whereas Clark & Isaacson [28] found that hippocampal rats responded less under CRF conditions. The inconsistencies in these outcomes cannot be explained, especially since these study differ in many critical methodological aspects, like lesion type or task details.

7.5. Ratio schedules

Similar to CRF schedules, reinforcement in ratio schedules depends on the number of instrumental responses displayed, that is, the higher the response rate, the higher the number of reinforcements. If the ratio is fixed (FR), like pellet delivery after each 10th bar press (termed FR-10), the number of necessary responses is predictable and the subjects typically increase response rate close to the end of each ratio and show a short period of not responding after subsequent reinforcement delivery, termed post reinforcement period (PRP). In variable ratio (VR) schedules, the exact response rate per ratio is not predictable, and with such schedules, subjects usually show very high and steady rates of responding; however, VR schedules have apparently not received attention in the present context.

In contrast to CRF schedules outlined above, Ehrlich [51] showed clearly higher response rates after lesion when a FR schedule was used. This held up to FR-144, that is, although the amount of work for food reward was steadily increased. No such effect was observed when water was used as the reward. Unfortunately, this interesting differentiation between the two reward types was not further addressed. Schmelzeis & Mittleman [144] tested rats with excitotoxic hippocampus lesion under conditions of increasing work demands, that is, either by using progressive ratio schedules or by using elevated levers, different drive states, and different rewards. As a major finding, they found higher breakpoints in the lesion group, and argued that hippocampal lesions enhanced activational properties or hedonic effects of food rewards. Also, the impacts of environmental stimuli, which might serve as positive incentives, may have been increased after hippocampal lesion. As shown by others [107,163], both kinds of effects might be mediated by dopaminergic mechanisms in the ventral striatum/nucleus accumbens, which is no longer under hippocampal control, and which may invigorate instrumental responding.

7.6. Interval schedules

In these schedules, responses are only reinforced when they are displayed after a certain time has elapsed since the previous reinforcement, and this interval can again either be fixed (FI) or variable (VI). Response rates in interval schedules are usually lower than in ratio schedules, since appropriate response timing, rather than high rates, leads to optimal reinforcement, that is, performance in interval schedules depends on the subject's timing accuracy [45]. Like in the case of ratio schedules, VI schedules lead to rather steady response rates, whereas FI schedules produce higher response rates proximal to reinforcement followed by PRPs thereafter.

Most studies using FI schedules obtained evidence for lesion-induced facilitation, except [56], where a fixed interval schedule of 1 min was used. Thus, Means et al. [102], who trained with a fixed interval schedule (FI-2) in alternating go- and no-go trials, found that hippocampal rats were superior to controls (see also [156]), both in terms of more responding during go-phases and suppression during no-go phases. These findings again argue against a hippocampal response inhibition hypothesis. Also, the authors suggested that hippocampal destruction cancelled out or compensated for deficits induced by damage of the overlying neocortex, since this alone led to impaired responding. The lesion-induced facilitation was replicated [157], plus that the same lesion led to impairment when introducing longer inter-trial intervals within go or no-go trials. The authors assumed that the longer inter-trial intervals might have led to a memory deficit of the preceding trial, or that the animals were not able to inhibit attention to irrelevant stimuli during such phases. Others [82] trained rats to bar press for food under a FI-40 schedule with an inactive and a cued active lever. Subjects with largely dorsal hippocampal lesion showed faster response rates and shorter PRPs than controls or rats with neocortical lesions. The hippocampal lesion effect was not substantially discussed in this paper, probably since its emphasis lay on the effects of neocortical damage.

A deficit in FI performance, on the other hand, was found in mice with excitotoxic dorsal hippocampal lesions [167], which were tested with two levers, each associated with a specific FI schedule. Interestingly, these animals became superior to controls when the lever assignments were subsequently reversed; an effect which was not specifically explained.

Jarrard [83] used variable interval schedules (up to 2 min) and found increased bar pressing for food in case of hippocampal lesions. In additional tests, he could rule out enhanced food motivation as a cause and, similar to others, suggested that the lesion may have led to a deficit in "*inhibiting well-learned responses*". Finally, Gallagher & Holland [64] tested lever-pressing (VI-1) for sucrose solutions in a configural discrimination task, where, for example, a light indicated the availability of sucrose when paired with a tone, but not when paired with noise. Rats with ibotenic

hippocampus lesions, which spared some of the dorsal hippocampus, were impaired in a spatial water maze task, but were better than controls in the discrimination task, especially during its acquisition. Gallagher & Holland took these findings as evidence against the hypothesis [150], that deficits after hippocampal damage reflect impairment in general configural learning, since there are instances, as tested here, where some configural processing is apparently preserved.

7.7. Differential reinforcement of low rate (DRL)

With such a schedule, reinforcement is delivered only after a given behavior has occurred at a specified rate within a specified time interval. Importantly, this rate is lower than a previously determined baseline rate, that is, DRL schedules maintain a low rate of responding and can therefore be viewed as a kind of response-inhibition task.

In contrast to Ellen et al. [57], Clark & Isaacson [28] found enhanced DRL responding after hippocampal lesions compared to controls. This effect led to fewer reinforcements and was taken as the result of a deficit to inhibit bar pressing and greater resistance to extinction, especially when having undergone substantial CRF training before (see also [140,141]). Thus, hippocampal rats may be able to provide the temporal discriminations necessary in a DRL schedule, but may be impaired to extinguish a now inappropriate premature response, given it had been well-trained before [140]. In a subsequent study [141], however, the authors concluded that hippocampal lesions do not necessarily lead to an increased resistance to extinction.

7.8. Others

When delaying reinforcement after the appropriate instrumental responses, Cheung & Cardinal [26] found that rats with excitotoxic hippocampus lesions, which were slightly slower than controls in case of no delays, now became superior. In contrast, when having to decide between smaller immediate vs. larger delayed rewards, they preferred the small immediate reward, which was not preferred when small vs. immediate rewards were obtainable without delay. The authors discussed their findings in terms of competitions, here between context-reinforcer and response-reinforcer associations, with the former normally hindering the latter. Hippocampal lesions may improve learning by reducing this facilitation in favor of action-outcome associations which may be more relevant in case of delayed reinforcement. Alternatively, the lesion may have affected temporal perception (see also [167]), that is, it may have increased the speed of an internal clock, which, among others, might have made delays less aversive.

Devenport [38] tested rats with septal or hippocampal lesions, which received food pellets every 100 s irrespective of any behavior and found that such animals started to display superstitious behavior, that is, bar-pressing or other repeated behaviors directed at certain parts of the testing environment. Since these behaviors ceased when reward was withheld, the lesion effect could not be attributed to an impairment to inhibit responding. The authors suggested that the hippocampus integrates information regarding response-reinforcer relationships, which in intact subjects permits superfluous behavior to be eliminated. Basically similar effects were obtained when rats with hippocampus lesions were yoked to other rats bar pressing for food [39,40]. Devenport & Holloway [40] argued that the hippocampus "*permits the control of behavior by contingency and that without the structure, operant behavior is guided by simple response-reinforcer contiguity*".

Furthermore, the work of Corbit, Balleine and coworkers [33,34] has to be addressed, although they did not find facilitated behavior after hippocampal lesion. These authors performed several experiments, varying in lesion technique and several instrumental aspects. Using two levers providing different nutritional rewards (termed outcomes), they found that rats with hippocampal lesions performed similar to controls, that is, they learned the tasks rather normally and achieved similar performance levels thereafter [33]. In a subsequent test, one of the outcomes was devalued by providing sufficient access to it prior to testing. Hippocampal rats responded to this outcome devaluation like controls, indicating that rats without a hippocampus can basically process action-outcome associations. In a subsequent test, however, they degraded the contingencies by providing one outcome irrespective of the animal's behavior, and found that hippocampal rats, unlike controls, respond inappropriately to this contingency degradation, as if they were not sensitive to the consequences of their instrumental behavior. Furthermore, Corbit & Balleine [33] argued that such non-contingent reinforcers can be predicted by the context, which is processed by the hippocampus; thus, their lesion animals may have failed to associate context with outcome. In subsequent studies with modified lesion techniques, Corbit et al. [34] obtained evidence indicating that their previous hippocampal lesion effects were actually due to damage of fibers of passage, which seem to originate in the retrohippocampal entorhinal cortex and pass through the alveus.

7.9. Spatial versus response

The following studies are specifically driven by the multiple-memory hypotheses (especially hippocampus and striatum; [30,31,75,120]), and the ideas of how different memory-related systems may interact during cognitive processing in a given situation, for example, in cooperation, competitively, or even in interference. In the perhaps first study of this kind, Packard et al. [123] used a radial maze baited with food and tested rats with either fimbria/fornix or dorsal striatal lesions. Importantly, they examined their subjects either under win-shift or win-stay conditions. In the win-stay condition, a cue light indicated those arms where food was available, whereas in the win-shift condition, all arms were baited initially and the rats had to learn, not to re-enter arms where they had already consumed the bait. They found that rats with fimbria-fornix lesions learned the win-stay task faster than intact controls, whereas an intact hippocampus was necessary for spatial win-shift performance, for which rats may be predisposed according to the authors (see also [103] for similar results and conclusions in a genetic mouse model for Alzheimer's disease). Since rats with striatal lesions were impaired in the win-stay version, a double dissociation of striatal and hippocampal mnemonic functions was postulated with hippocampal function required for spatial processing, and striatal mechanism for stimulus/response relationships [99,106,123].

Similar results, namely enhanced acquisition after hippocampal lesions in a response-based task, but impaired learning in a spatial task was found by Compton et al. [32] in a Greek Cross version of the water maze. Also, Sanderson et al. [134] tested mice in a T-maze discrimination task and found facilitated discrimination in case of hippocampal lesions. They assumed that hippocampal lesions enhance learning in non-spatial tasks as used here, since control animals might persist in incorrect spatial strategies, which are not available in case of hippocampal lesions. Gallagher & Holland [64] tested rats with excitotoxic hippocampus lesions in the Morris water-maze. These had to master the maze either by distal spatial cues or by a local one (here visibility of the rescuing platform). As expected, the lesion group had a severe impairment in the spatial version, but was superior to controls in the cue version where "*the inability to acquire place learning may have provided an advantage due to explicit cue training*". Also using the water maze,

McDonald & White [100] tested rats with either fornix or dorsal striatal lesions. In several test versions, they found that rats with fornix lesions easily learned to swim to the rescuing platform, when it was visibly detectable, but failed to do so, when it had to be located by spatial cues in the environment. When the visible platform was moved to a new location, they again swam directly to it, while controls swam either to it or to the place where it been before. Based on the general hypothesis that different brain substrates acquire different types of information in parallel, McDonald & White [100] suggested that animals with fornix lesions (that is, devoid of a functioning hippocampus), which cannot rely on spatial information, are very efficient when they can rely on stimulus-response relationships governed by the dorsal striatum. Similar conclusions were drawn by Schroeder et al. [145], who used transient inactivation of the hippocampus through local hippocampal infusion of an anesthetic drug after training (i.e. post-trial). This manipulation impaired acquisition of a place version of a water plus-maze task, but enhanced it in case of a response version (i.e. a specific body turn). The authors assumed that it is sufficient to inactivate the hippocampus during the phase of memory consolidation in order to impair place and enhance response learning. Again, this may have been due to prevention of interference between different memory systems, here in case of memory consolidation.

Taken together, these studies show that intact animals can use either place or response strategies. The most effective strategy depends on specific task demands, but rodents may be disposed to preferentially rely on spatial cues if available. Lesions of either the dorsal striatum or hippocampus bias the animal toward the intact system, suggesting a reduction in interference resulting from competing response strategies.

7.10. Serial and sequential tasks

Lesions of the hippocampus have also been studied repeatedly with tests, where the subject has to perform series of actions directed towards slightly different objects, for example, different levers or nose-poke holes, in order to obtain reward. These kinds of tests are often termed serial or sequential tasks. Perhaps the earliest kind of study with hippocampal lesions is that of Kimble & Pribram [92], who tested rhesus monkeys with aspiration lesions, which had to press two panels with specific numerals in succession in order to obtain food. These numerals, for example “6” and “4”, could appear in random positions out of 16 possible ones. Animals with lesions were impaired in this task, but were normal in other more simple visual discrimination tests with inter-trial intervals, indicating that the deficit in the serial task was not due to simple visual or short-term memory deficits. Also, lesion-induced perseveration could be excluded. In a subsequent study [47], a modified procedure was used in the same apparatus, where the subjects had to press two illuminated panels in succession. In contrast to the previous study, the authors now found that monkeys with hippocampal lesions learned this task faster than controls. The discrepancy to the previous results [92] was attributed to task differences, namely that the two stimuli were presented simultaneously in the earlier study, but successively in the newer one (see also below, [122]). Apparently, the monkeys in Kimble & Pribram [92] could not stop the tendency to press that panel repeatedly, which was followed by reward. This tendency was also found in controls, but these learned to refrain from it with training. The maladaptive lesion effect [92] was in accord with the then prevalent inhibition hypothesis, that is, the hippocampal lesion may have led to a lack of inhibition, either with respect to responding or paying attention to the irrelevant stimulus. According to the authors, intact inhibition in the newer study is probably not task-relevant or may even hinder performance there; for example, it may reduce responses to the 1st stimulus, which in contrast to the 2nd is not followed by reward.

In two subsequent studies, bar pressing for food was tested in rats with hippocampal lesions [81,149]. In one study [81], rats had to alternate their responses between different levers. When a simple left/right alteration was required, lesion rats acquired this alteration faster and showed more correct alterations than controls. In a subsequent experiment with three levers and more complex sequences between them (like 1-2-3 or 1-2-1-2-3), lesion rats again were superior to controls, which failed to acquire more difficult sequence versions. Jackson & Strong [81] suggested that the hippocampal rats were better in this task since they might have displayed less other activities (like rearing or grooming). Unfortunately, no specific data were provided to support this hypothesis (but see [19]). Response alterations were also tested [149] using a set-up, where the correct lever was either not cued or signaled by a light stimulus. In a first experiment, hippocampal rats showed faster learning and reached better performance levels thereafter when a cue was provided, which appeared somehow more distal from the lever (around 9.5 cm above it) or when it appeared in random locations; this advantage was lost when no cue was provided or when the cue was spatially identical with the response (by using press panels, which could be illuminated). The authors excluded lesion-induced hyperactivity, perseveration, or enhanced stimulus tracking as critical factors, and suggested that the lesion animals may be superior in attending to slightly remote stimuli, which may have supported their performance.

7.11. Functional facilitation after hippocampal lesions in the rat SRTT

With the aim to provide a rat version of the human sequential reaction time task (SRTT), which since its first introduction in 1987 [118] has been of substantial importance in psychological, neurological, and basic neuroscientific research (e.g. [7,89]), we developed an instrumental rat equivalent [41; for review see 146]. In this task, rats have to respond to visual stimuli by nose-poking into one of four spatial locations in order to obtain food reward. In the current version (e.g. [18,19,43]), the rat has to respond under a fixed ratio schedule (FR-13) to a repeating sequence of 12 singly lit locations (3–2–4–1–3–4–2–1–2–3–1–4) until it is rewarded. This is a so-called second-order sequence since at least two consecutive items are necessary to predict the next one. Such rather complex sequences are also common in human research, that is, this feature of the rat test has substantial face validity for human research. Since the human literature had shown that learning of such sequences, which is often taken as a type of procedural learning, is critically dependent on fronto-striatal circuits and striatal dopamine (e.g. [72]), our early studies with the rat SRTT were aimed at striatal dopamine, which we studied by testing the effects of systemic dopaminergic antagonists [42] and 6-OHDA lesions of ventral striatal or neostriatal dopamine [44,48,49]. As expected, impairing dopamine function led not only to general impairments in instrumental behavior, but also to specific deficits in sequential learning and performance, the details of which depended on time (pre- vs. post-training), and the degree and site of lesion (dorsal vs. ventral striatal).

In contrast to striatal mechanisms, evidence for hippocampal involvement in procedural, especially sequential learning is somehow equivocal. Following the theory that striatal mechanisms are critical for procedural learning and memory, and hippocampal mechanisms for declarative learning and memory, hippocampal damage should not have substantial effects on sequential learning, at least when it remains implicit. Accordingly, older studies with patients suffering from brain damage including hippocampal tissue reported preserved (Morbus Korsakoff [118]; hypoxia [76]; mild cognitive impairment [117]; but see [61]) or even enhanced sequential learning (amnesia [128]). Given the lack of anatomical

specificity and the partial and variable degrees of damage within the hippocampus, such human cases cannot provide decisive evidence for or against a hippocampal role in sequential learning. Neuroimaging studies, on the other hand, have indicated not only striatal but also hippocampal activation during sequential learning and correlations between hippocampal activation and sequential learning [2–4,67,136] which seem to depend on specific task features and learning phases (e.g. [15,23,68,85,131; for review see [4]). Since imaging studies in humans go far beyond the limits of this review (and beyond the skills of its writers), the interested reader is referred to the original publications. Simplified, however, these imaging findings argue for a hippocampal role in sequential learning, at least in correlative terms.

To address this issue in a more manipulative way, we decided to test rats with hippocampal lesions in our SRTT. The lesions were established by means of multiple local ibotenic acid injections [18,19,50], following a procedure suggested by Bast et al. [11]. In our first experiment [50], where the excitotoxic lesions led to complete tissue loss mainly in the dorsal hippocampus, we found a clear and profound enhancement of post-lesion performance in the rat SRTT using FR-13. Importantly, the effect was measurable in terms of both, shorter reaction times **and** a higher percentage of correct responses, that is, the increase in response speed was not at the expense of response accuracy. These same lesions led to a deficit in an object-place recognition task compared to untreated controls, that is, the animals had an expected impairment in spatial episodic cognition (see also [9,18]), but where clearly outstanding in an instrumental sequential task, which is thought to reflect procedural learning. Since performance there is motivated by the reinforcer food, we additionally asked whether the facilitatory lesion effects might be secondary to enhanced food motivation, but could not find evidence in favor of this hypothesis, since lesion rats in a food consumption test, if at all, tended to consume less rather than more food than controls. Also, we tested the animals for possible hyperactivity in the open-field, but found only a trend for more locomotion in the lesion group. Thus, hyperactivity probably did not account for our SRT results, and would also not explain why our lesion rats were not only faster but also more accurate there.

It should be mentioned that others [27], using sequences of 4, 8, or 12 positions, did not find enhanced performance in rats with hippocampal lesions; however, their approach differed in several aspects from ours, namely reward type (food pellets versus electrical stimulation of the medial forebrain bundle), lesion (excitotoxic versus radio-frequency), and a kind of nose-poke arrangement, which probably had a higher spatial load [27].

We interpreted our results as supporting the multiple parallel memory hypothesis [161] and in terms of a possible competition or even interference between striatum and hippocampus. Both structures receive inputs from various cortices and project to the prefrontal cortex, where their simultaneous inputs may interfere depending on the demands of the given test situations, that is, spatial (hippocampus) vs. stimulus-response demands (striatum). In a task like our SRTT, where spatial information processing is probably minimal or not required at all, a lack of hippocampal interference due to its destruction may therefore be promotive, resulting in more efficient sequential learning and performance. Compared to complete damage of the dorsal hippocampus [50], similar, albeit smaller facilitatory effects were obtained in a subsequent study [164] where a lesion was tested which did not lead to a complete loss of the hippocampus, but to widespread neuron loss in areas CA3 and CA1 while sparing CA2 and granule cells. This is one of the rare cases in this research field, where a facilitatory effect was obtained in case of a rather selective lesion within the hippocampus (see also [168]).

In both studies [50,164], the daily duration of training was kept constant; therefore, it is possible that the animals with lesions, which were faster than controls already soon after lesion, gained more instrumental experience. Thus, their sequential superiority, which is based on instrumental learning, may have been due to an unspecific training effect. We tested this possible confound in another experiment [18], where we kept the amount of training constant between groups. Now, the lesion group showed shorter reaction times only during the first few days of sequential training, and had no advantage in accuracy. Nevertheless, these animals with dorsal hippocampal lesions completed their daily training sessions substantially sooner than controls. Since shorter session durations were observed in the lesion group throughout the experiment, whereas faster responding or lower error rates disappeared with time, the temporal advantage of the lesion group must have been due to some other factor. Accordingly, we found that these rats showed around 50% shorter PRPs than controls, that is, after obtaining their FR-dependent rewards, they resumed instrumental responding much more rapidly. Since PRPs had not been quantified in our initial study [50], we now re-analyzed those data and found shorter PRPs in rats with hippocampal lesions there as well (for an overview of PRP data from several experiments see Fig. 1). This is in contrast to striatal dopamine lesions, where PRPs tended to be increased [48].

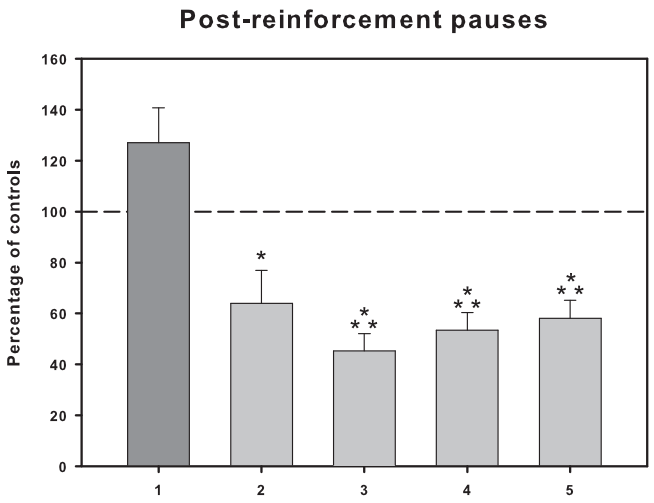

Fig. 1. Post-reinforcement pauses in the serial reaction time task of rats with either neostriatal dopamine lesions or excitotoxic lesions of the dorsal hippocampus. Neostriatal dopamine lesions were induced by local injections of 6-hydroxydopamine (1: Eckart et al., [48,49]), whereas the hippocampal lesions (2–5) were induced locally using ibotenic acid (2: Eckart et al., [50]; 3: Busse & Schwarting [18]; 4: Experiment 1 from Busse & Schwarting [19]; 5: Experiment 2 from Busse & Schwarting [19]). All data were (re)calculated for the present review and are presented as percentages of untreated controls (means + SEM). For that purpose, a single mean PRP was calculated for each animal over all days of testing. The bars 1–3 reflect data from animals tested under sequential conditions, whereas bars 4–5 refer to pseudo-randomly presented stimuli. * $p < 0.05$, *** $p < 0.001$ according to two-tailed *t*-tests. The neostriatal lesion group (1) showed only a trend for a difference compared to control levels ($p = 0.068$).

Thus, one major effect of our dorsal hippocampal lesions seems to be that on PRPs, which is in line with other results [82]. Such an effect can allow that lesion animals receive more training per time. If this effect is not controlled, for example by stratifying the daily amount of training, lesion animals can profit from it and can gain higher performance levels.

Also, since sequential performance in our SRT test is based on instrumental behavior, we recently tested whether the excitotoxic hippocampal lesions would actually have its facilitatory effects primarily on instrumental behavior in general, rather than on sequential behavior, in specific. Thus, the previously found sequential advantages could have been a consequence of an instrumental one. To test this hypothesis, we again trained rats after lesion under

a FR-13 schedule, but now with pseudo-randomly presented stimuli [19], but the lesion animals again needed less time to complete their daily test sessions due to shorter PRPs (see Fig. 1). Thus, in our instrumental studies, the most robust outcome of dorsal hippocampal lesions is a reduction in PRP lengths. The mechanism of this effect is currently not clear, but several factors apart from reinforcement schedules seem to affect PRP length, including hedonic features, frustration, or impulsivity, which could be affected by hippocampal lesions [35,98,101,105,125,137]. Also, the hypothesis that hippocampal lesions can invigorate learned behaviors could serve as an explanation.

In one of our experiments [19], we analyzed various behaviors during the sessions (including PRPs), and found that lesion and control animals usually showed similar amounts of behaviors like rearing, grooming and sniffing during the first day of training. However, these patterns changed substantially thereafter. While the lesion group showed a significant decrease in all three non-instrumental behaviors on the last day of training, the control group showed a decrease in grooming behavior only, while rearing and sniffing behaviors were increased, indicating that the lesion group behaved in a much more task-oriented way than the controls.

In some of our experiments, we also tested for extinction. In Busse & Schwarting [18], we found that rats with hippocampal lesions took longer than controls to cease nose-poking to the no longer rewarded light CSs. In the first experiment of Busse & Schwarting [19], we again tested for extinction, but in contrast to the previous study, food reward was devaluated before by satiating the animals. Descriptively, lesion animals still required more time and responses to extinguish responding under these conditions, but this effect was not significant. Possibly, the motivational state of the hippocampal animal affects its extinction behavior in a different way than in controls.

In the second experiment of Busse & Schwarting [19], we also analyzed a test phase where, after a fixed amount of reinforced FR runs, reward was decoupled from nose-poking by delivering food pellets every 30 s independent of the subject's behavior. These phases were alternating with normal phases of reinforced nose-poking. The tests showed that lesion and control animals displayed their usual patterns of responding under reinforcement conditions and that control animals rapidly learned to cease responding, when reward was decoupled from behavior, whereas lesion animals continued to nose-poke although this behavior was not causal for reward delivery. Several days of such training had to elapse until the lesion group adjusted their behavior in a way similar to that of controls, that is, to reduce their nose poking during the decoupled phases. This result is somehow consistent with the conclusion [33] that the hippocampal lesion made the animals "*insensitive to the causal consequences of their instrumental actions*", yet, after a prolonged period of training, lesion animals became somehow capable to discriminate between the action-outcome-coupled and −decoupled task requirements in our experiment. A possible explanation could be that loss of hippocampal function rendered rats prone to striatum-dependent stimulus-response behavior, but a switch back to response-outcome behavior could still be achieved by prolonged, i.e. repeated exposure to the different task rules.

Together, our hippocampal lesion studies show facilitatory performance effects in the rat SRTT. The gain in sequential performance, which was observed in terms of faster reaction times and higher response accuracy in the initial experiments, is probably due to a facilitation in FR instrumental behavior, which is required for our sequential task. Soon after lesion, the animals seem to establish rather strong stimulus-response relationships which allow rapid and precise responding, and shorter PRPs. If not controlled for, this advantage allows more training, leading to higher performance levels, for example in sequential information processing, which is more complex than the instrumental behavior on which it is based.

8. Which conclusions can be drawn from the behavioral studies?

The evidence reviewed above provides the following patterns:

A.) Although the bulk of evidence has been obtained with rats as experimental subjects, facilitatory behavioral effects after lesion of hippocampal structures have been found in many mammalian species including primates. In the case of humans, there is only some pertinent evidence available, but we do not see any reason, why human subjects should make an exception here. Together, facilitatory lesion effects seem to be a rather general phenomenon of species with mammalian hippocampi.

B.) Facilitatory effects have been found with various kinds of lesions, be they electrolytic, neurotoxic, or by means of aspiration, radiofrequency, or destruction of critical projection systems. Damage of structures outside the hippocampal formation may occur with many of these techniques, like damage of the overlying neocortex in the case of the dorsal hippocampus. Studies, where such damage was controlled for, indicate that facilitation is probably not due to such neocortical damage. Rather there is evidence that neocortical damage itself can lead to a deficit [18,19], which is apparently overcome by the hippocampal lesion. These aspects have to be considered carefully when planning controls for studying facilitatory lesion effects, for example, they may play a role in the case of sham lesions, which produce relatively small damage, also in the target structure itself, and can have behavioral effects on their own (see for example [1,50]).

Also, it has to be clarified whether the lesion outcomes a) merely reflect the absence of the hippocampus, or b) extra-hippocampal neural changes induced by its loss. Here, it has to be pointed out that some temporary inactivation studies of the hippocampus did not find facilitatory findings as obtained with lesions [10,158,but see 145], which argues for more complex explanations than a) and asks for further research. Furthermore, it is not clear yet whether damage of an entire hippocampal part, like the dorsal one, is necessary, or whether loss of specific neural elements within it are sufficient, for example, certain pyramidal or granule cell types (but see [164]). This aspect clearly needs specific experimental attention in the future.

C.) Facilitatory effects of hippocampal lesions have been found in different test paradigms. The early studies often interpreted such lesion outcomes focusing on the loss of a hippocampal function, for example the then prevalent theory of hippocampal inhibition, whereas more recent studies incorporated the possible actions of other structures, like striatum, amygdala, or cerebellum, which according to the interference hypothesis may work more efficiently after hippocampal lesion if task demands are appropriate. For example, in active, but not inhibitory avoidance paradigms, hippocampal lesions typically lead to better performance, for example, faster achievement of a given learning criterion. Several studies indicated that damage of the dorsal hippocampus seems to be sufficient for this effect, but this was questioned more recently [158]. Also, slowed extinction has often been found, possibly indicating stronger stimulus-response relationships. Such effects can reflect a mixture of effects, namely, deficits in hippocampal spatial processing together with enhancement of stimulus-response associations determined by striatal and other sites,

like the amygdala. Thus, a deficit in relating aversion to a specific context in case of active avoidance might allow hippocampal rats to return to a context where they had been punished before, whereas intact animals have to overcome their tendency to avoid it. In contrast, processing the stimulus (e.g. tone), which signals the coming punishment and initiates avoidance, seems not to be impaired in hippocampal rats. In case of Pavlovian conditioning paradigms, the outcomes of hippocampal lesions seem to critically depend on the details of the conditioning procedures, and facilitatory effects, which seem to be the exception rather than the rule, are more typical for delay, but not trace, conditioning. Again, a spatial hypothesis has been favored for this effect, namely that the lesion seems to prevent interference of task-irrelevant spatial information. When conditioning includes a discriminative component, the method of stimulus presentation is important, since hippocampal lesions lead to a discriminatory deficit when stimuli are presented simultaneously, and have to be processed in a relational, that is, hippocampus-dependent way, but lead to facilitation when stimuli are presented successively, and can be processed individually in a stimulus-response fashion, again via the striatum and/or amygdala. These effects are probably not due to deficits of inhibition. Regarding instrumental conditioning, facilitatory lesion effects were found in several paradigms and with different schedules, especially in FR schedules, where high response rates are favorable, and even when these requirements were increased like in progressive ratio schedules. In interval schedules (FI, VI), where high response rates are less favorable, facilitatory lesion effects were also found, whereas in DRL schedules, lesion effects are equivocal. Furthermore, evidence for shortened PRPs and for longer extinction was obtained, whereas there is few substantial evidence that hippocampal lesion might have acted in these tasks by effects on food motivation. These instrumental findings might look compatible with a lesion-induced lack of inhibition or enhanced perseveration. Findings from reversal, delay, or serial alteration tasks, however, argue against this hypothesis, since one would expect impairments rather than facilitation under reversal or delay conditions, which is apparently not the case.

Besides lack of inhibition or enhanced perseveration, one could argue that hippocampal lesions lead to invigorated responding, which could explain not only high response rates, shortened PRPs, and longer extinction, but also effective reversals. Such an invigoration may reflect brain changes outside the hippocampus, here, increased dopamine transmission in one of its efferent targets, the ventral striatum/nucleus accumbens [107,163], which may not just simply lead to behavioral activation, like hyperactivity, but enhanced control of conditioned behavior (e.g. [133,152]).

Also, evidence for lesion-induced superstition was obtained, that is, hippocampal animals may show "instrumental" behavior, although reward delivery is provided irrespective of their behavior. This pattern, which could also account for extinction deficits, might reflect a loss of cognition for causal relationships or contingencies between own behavior and outcomes. Such effects were also obtained in our SRT tasks, together with shortened PRPs and prolonged extinction. There, performance facilitation in terms of shorter reaction times and lower error rates under conditions of sequential stimulus presentation were probably secondary to a more general effect: Since our instrumental SRT task favors high response rates, hippocampal rats, which also have clearly shorter PRPs may especially profit. For example, they can practice more per time, which allows them to become superior under sequential conditions which, in turn, build up on the instrumental basis. Both, instrumental and sequential learning are thought to depend on striatal mechanisms, which according to the interference hypothesis, can work more efficiently without a hippocampus when tested under non-spatial stimulus-response conditions.

Together, the behavioral profile of hippocampal subjects in tests of learning and memory is complex, and cannot easily be explained by a single functional theory. The inhibition hypothesis, which coined the early experiments, may be valid for some facilitatory lesion effects, but clearly not all of them. Other explanations have to be taken into account, like changes in causal cognition, or spatial vs. stimulus/response processing. In some cases, like the sequential example, the effect measured may not be a direct consequence (or readout) of the lesion, but may be secondary to some other change, that is, lesion-induced enhancement of one type of learning may promote some other type of learning which builds on it. Therefore, great care has to be taken when trying to interpret the outcomes of such lesion studies, and inclusion of several control tests is warranted to specify a given lesion outcome. These general problems are well known from the work with lesion-induced deficits, but unquestionably also hold in case of lesion-induced facilitation.

9. Final thoughts on basic research and its possible clinical relevance

The studies outlined above, which almost exclusively depend on experimental lesions in laboratory animals, show that hippocampal lesions can have facilitatory functional effects which depend on certain demands of a given task. The question remains whether it is possible that patients with damage of the hippocampus, despite being deficient in a number of cognitive tasks, may not only be normal, but even superior in some other aspects compared to controls. Which tests should be used to test such a hypothesis? Based on the current literature, a general recommendation could be that such tests should have only few or even no spatial, relational, and explicit requirements, whereas they should rely on procedural aspects, specific cues, and action/outcome relationships. Even if substantial evidence in favor of certain facilitatory effects will be found in patients, the major question will probably remain, namely how such knowledge can be used for the good of the patients. There is currently no answer to this question, but finding one will surely require intense cooperation between neuroscientists working in basic research and clinical practitioners.

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