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Effects of early life stress on rodent hippocampal synaptic plasticity: a systematic review

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Early life stress shapes brain development and animal behavior. Neurophysiological properties such as signal transmission and synaptic plasticity are thought to underlie the animal's behavioral performance. We carried out a systematic review to determine how early life stress relates to neurophysiology in rodents. We specifically discuss effects on basal transmission and long-term potentiation in the hippocampus, as this brain area undergoes strong developmental changes during the first postnatal weeks. In general, basal transmission does not appear to be affected by early life conditions. Long-term potentiation is mainly increased by mild stress, while it is impaired by more severe early life stressors. The dentate gyrus shows stronger effects than the CA1 area. These changes may impact on hippocampus-dependent behavior. We conclude that rodent early life stress models provide important insights in stressor-dependent effects after human childhood adversity.

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Introduction

The early postnatal period is characterized by extensive brain development. During this time, external factors have a large impact on brain development and functioning which may last throughout life [1]. One of these influential external factors is early life stress (ELS): ELS in humans is known to affect cognitive function and increases the risk for psychiatric disorders such as depression, anxiety disorders and schizophrenia [2]. Cognitive function as well as behavior is often found to be altered by ELS in rodents too, as measured by their performance in memory tasks or other behavioral paradigms. For example, social memory as well as object recognition are impaired by prolonged maternal separation, whereas anxiety in the elevated plus maze is reduced by 15 min neonatal handling [3••]. Knowledge of the underlying mechanisms causing behavioral alterations after ELS is essential for the development of targeted behavioral or pharmaceutical therapies.

There is a large variation in rodent ELS models, which parallels the many types of early life adversities that children are subjected to. Since the dam is often the only caregiver in laboratory mice and rats, most ELS models in these species are based on disruption of the mother-pup interaction (by temporal removal of the dam or stressing the dam otherwise). The most commonly used rodent ELS protocols are maternal separation (MS, separating pups from dam daily for a specified number of hours), maternal deprivation (MD, single 24 hours separation of pups and dam), limited nesting/bedding (dam placed on a metal grid in the cage and provided with limited nesting material) and low licking and grooming (low LG, naturally occurring variation in maternal care). The variation in ELS models is reflected by the variety in behavioral outcomes: mild or brief ELS are thought to increase brain functioning, while more prolonged severe models are more likely to cause impairments [3••,4••,5]. These effects are seen both at the behavioral level and the underlying neurophysiological parameters [6•].

Neurophysiological studies focus on synaptic transmission and plasticity. Well-studied forms of synaptic plasticity are long term potentiation (LTP) and long term depression (LTD), processes that are essential for memory formation [7]. Changes in either basal transmission or synaptic plasticity are thought to drive the behavioral consequences of ELS and are therefore important to investigate.

In the current study, we report the results of a systematic review of the effects of different rodent ELS models on neurophysiological properties. We focused our discussion on basal transmission and LTP in the hippocampal

formation, as this brain area (especially the dentate gyrus (DG)) is strongly developing during the first postnatal weeks [1] and therefore is most commonly investigated in ELS research.

Materials and methods

Search strategy, in- and exclusion criteria

We developed a comprehensive search strategy for PubMed, Web of Science and EMBASE on effects of early life stress on neurophysiology in rodents. The search strategy consisted of three specific components, addressing: (1) early life stress models, (2) neurophysiological parameters and (3) rodent studies. Thesaurus and EMTREE terms were included in the query (see supplemental methods for complete search strings per database). No language restrictions were applied.

Searches were conducted in all three databases on the 4th of August 2016. Duplicates/triplicates were both automatically and manually removed. All studies were screened by title and abstract and in- or excluded according to predefined criteria (see supplemental methods for list of criteria). Reviews and conference abstracts were not included. Correct inclusion of all relevant studies was verified by an independent assessor.

Study characteristics & risk of bias assessment

From the included articles we extracted data on bibliography (*e.g.*, authors, title, year of publication), animal models (*e.g.*, species, strain, sex, age), ELS protocol (*e.g.*, type of stress, frequency, duration and age), additional interventions and outcome characteristics (*e.g.*, type of recording, age of assessment, brain area studied). We used an adapted version of the Risk of Bias assessment tool for animal studies developed by Hooijmans *et al.* [8] to assess the methodological quality of the included studies and thereby the reliability of the included results. All papers were scored on randomization, blinding, adequate handling of missing data and selective outcome reporting.

Data synthesis

All extracted outcome measures regarding baseline synaptic transmission and synaptic plasticity were listed by ELS model and brain area. Baseline synaptic transmission included all parameters that did not involve high-frequency stimulation (*e.g.*, input–output functions, spontaneous transmission (mEPSC amplitude and frequency), AMPA/NMDA ratios, EPSC rise time and decay, *etc.*).

For LTP data in the hippocampus, group means and group size were extracted from the papers. We had to estimate the group means from figures in the papers for 7 out of 12 papers for the DG and for 6 out of 19 papers for the CA1. For the other brain areas we determined whether LTP was either increased or decreased, without attempting to determine the exact values. We did not contact authors for original data.

The ratio between the effect in the ELS vs. the control condition was calculated by dividing the mean %LTP in the ELS condition by the mean %LTP of the control group (effect ratio = mean %LTP in ELS group/mean % LTP in controls). If the mean %LTP per group was not provided in the results section, the values were estimated from the paper's figures as accurately as possible. This ratio was plotted against the mean number of animals in the ELS and control group. The resulting funnel plots were used to assess the presence of any publication bias and to determine the mean effects of different ELS models on LTP. If LTP was determined at multiple time points, compared to multiple control groups or when both population spike (PS) and excitatory post-synaptic potential (EPSP) LTP were recorded within the same animals, we only plotted the largest effect to ensure that each data point represents independent groups. In the case of a correlation between % licking and grooming (LG) and %LTP, we divided the data points in three groups and compared the lowest one-third of observations (low LG) with the highest one-third (high LG).

Results

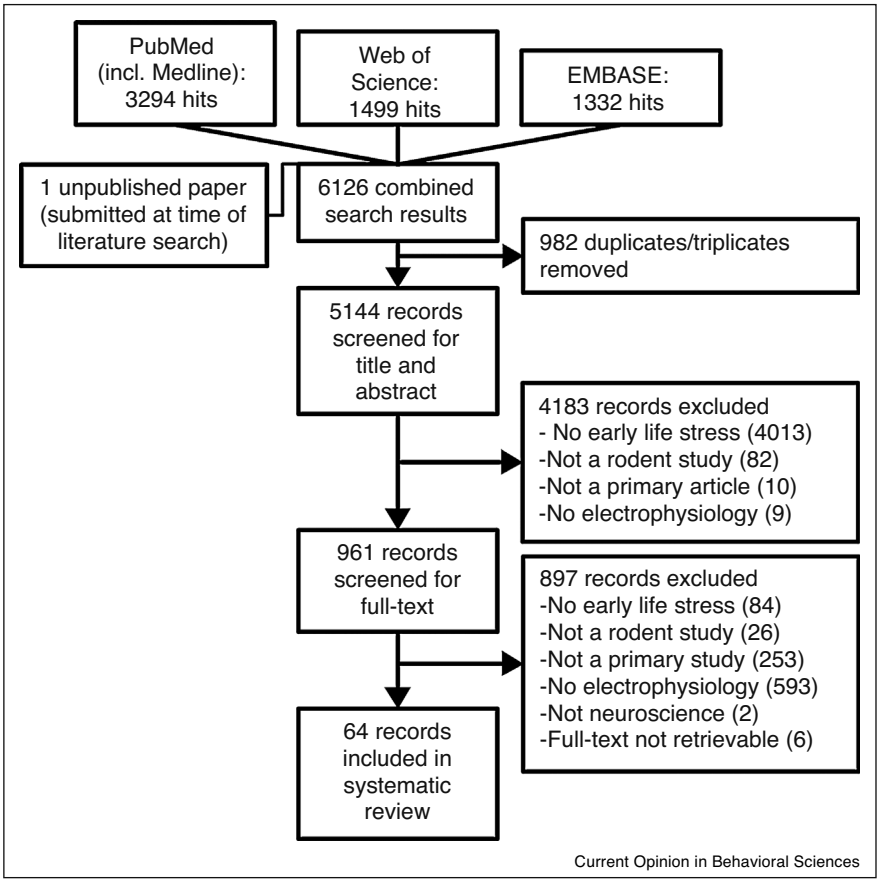
Search strategy & risk of bias assessment

Our search strategy yielded 6126 papers, of which 5144 papers were screened after removal of duplicates. According to the criteria listed in Figure 1, 5074 papers were excluded. An additional six papers were omitted because the full-text was not retrievable. The majority of the included 64 studies was performed in rats (85%), 12% in mice and 3% in other rodents. 68% of studies were performed in males, 3% in females, 8% used mixed sex groups, 10% assessed males and females separately and 11% did not mention the sex of the animals.

The risk of bias assessment indicated a clear lack of methodological descriptions regarding blinding, randomization and data handling (Supplementary Figure 1). Randomized allocation of the ELS condition was reported by 30%, blinding of researchers and animal caretakers to the experimental condition by 6%, random selection of animals for the outcome assessment by 1%, outcome assessor blinding by 7% and the presence and adequate addressing of incomplete data was never mentioned. The assessment of selective outcome reporting was disregarded because it could usually not be determined based on the provided data in the papers.

After data extraction, all papers were listed per ELS model, brain area and outcome measure to determine whether there were trends observable regarding these parameters. Basal transmission and LTP in the DG and cornu ammonis 1 (CA1) hippocampus yielded sufficient hits to estimate general effects; these results and study

Figure 1



Selection process of articles for systematic review.

characteristics are shown in Table 1. Data on all other outcome measures (*e.g.*, paired pulse, current desensitization) and brain areas (*e.g.*, amygdala, prefrontal cortex or hypothalamus) are available in Supplementary Table 1.

ELS-model dependent effects on LTP in the DG

DG basal transmission and LTP were assessed for MS, MD and low LG. None of these ELS models affected basal transmission in the DG, although there was a trend towards increased transmission in low LG animals. LTP was differentially affected by the various ELS models (Figure 2a). Thus, low LG generally decreased LTP induction to around half of the control levels, MD did not affect LTP and MS increased LTP two–threefold. There were no effects of recording age, type of study or time after induction of LTP within any model. However, the duration of maternal separation (MS) appears to impact LTP outcomes in (young) adulthood: LTP was only increased by 1 hour MS, while 6 hours MS or 24 hours MD did not affect LTP induction (Figure 2b). It should be noted that sex differences were difficult to assess since only three studies included females as a separate group. In sum, the effects of ELS on LTP in the DG are most strongly dependent on the exact ELS protocol to which the animals are subjected.

ELS-model dependent effects on LTP in the CA1

Basal transmission and LTP in the CA1 area were assessed for MS, MD, low LG, novelty exposure and limited nesting/bedding. Similar to the DG, basal transmission was not altered by any of these models. Novelty exposure generally increased LTP with one-fifth, while limited nesting/bedding tended to cause a two-thirds decrease (Figure 3). Limited nesting/bedding also showed an effect of age: LTP was not affected at 7–8 weeks, 4 months or 7–8 months, while a decrease was seen in younger (5 weeks) and older (10–12 months) animals. Age-dependent effects were also seen with MS: LTP was not affected until 6 weeks of age, while decreased LTP was seen at older ages up to 70 weeks. In contrast to the DG, the duration of MS did not affect LTP outcomes. Maternal deprivation increased LTP in prepubertal males and adult females, while other age- and sex groups were unaffected. Low LG did not have a clear effect in the dorsal hippocampus, while one study

Table 1

Overview of early life stress effects on basal transmission and long-term potentiation in the dentate gyrus and cornu ammonis 1 area of the rodent hippocampus

Study population and ELS protocol					Outcome parameters					
Refs.	Species and strain (*n* per group)	Breeding method	ELS protocol	Control group	Age	Sex	Type of recording	Effect baseline (ELS vs. control)	Effect LTP (ELS vs. control)	Time after HFS
Dentate gyrus: maternal separation										
[9]	Rat, SD (7–10)	In-house	1 hour indiv. MS at P2–9	Non-separated littermates, shortly handled at P2–9	P28–30	M&F	*In vivo* FP, freely moving	No effect	Increased PS and fEPSP LTP	0–72 hours
[10]	Rat, SD (8–12)	In-house	1 hour indiv. MS at P2–9	Littermates, unhandled or shortly handled	P28–30	M&F	*In vivo* FP, freely moving	No effect	Increased at 1 hour (males), increased at 96 hours (both sexes)	1 hour & 24 hours
[11]	Rat, SD (15–16)	In-house	1 hour indiv. MS at P2–9	Unhandled	P75–95	M&F	*In vivo* FP, freely moving	No effect	Increased PS LTP at 1 hour and 24 hours, no effect on fEPSP LTP	1 hour & 24 hours
[12]	Rat, SD (5–6)	Time-pregnant	30 min MS at P9, 6 hours MS at P10 + saline injections	Unhandled	≥P90	M	*In vitro* PC	GABA transmission: slower current desensitization, no effect on GABA EC50, hill coefficient and current density	Not assessed	–
[13]	Rat, strain n. m. (7–9)	In-house	1 hour indiv. MS at P2–9	Unhandled	±P91–122	M	*In vivo* FP, freely moving	No effect	Increased	0–3 hours & 24 hours
[14]	Rat, W (6–8)	In-house	6 hours MS at P14–16	Unhandled	±P77	M	*In vivo* FP, freely moving	No effect	No effect on PS and fEPSP LTP	0–6 & 24 hours
[15]	Rat, SD (7–10)	In-house	6 hours MS at P2–9 or P14–21	Unhandled	P40	M	*In vivo* FP, anesthetized	Not assessed	Decreased fEPSP LTP in both MS groups, no effect on PS LTP in MS P2–9, decreased PS LTP in MS P14–21	0–60 min
Dentate gyrus: maternal deprivation										
[16]	Rat, LH (12–13)	In-house	24 hours MD at P3	Unhandled	P100	M	*In vivo* FP, anesthetized	No effect	Not assessed	–
[17]	Rat, W (5–6)	In-house	24 hours MD at P4, P9 or P18	Unhandled	±P63	M	*In vivo* FP, freely moving	Increased fEPSP amp at MD P4 vs. ctrl, no effect on PS amp or fEPSP/PS amp ratio	No effect	2 min
[18]	Rat, W (9–12)	In-house	24 hours MD at P3	Unhandled	±P56–91	M	*In vitro* FP	No effect	No effect	0–60 min
[19]	Rat, W (7)	In-house	24 hours MD at P3	Unhandled	±P56–91	F	In vitro FP	No effect	No effect	0–60 min
Dentate gyrus: low licking and grooming										
[20]	Rat, LE (5)	In-house	Low vs. high LG	n/a	±P100	M	*In vivo* FP, freely moving	Decreased PS amp	No effect (trend towards decreased LTP)	0 hour, 1 hour & 24 hours
[21]	Rat, LE (5–7)	In-house	Low vs. high LG	n/a	±P91	M	*In vitro* FP	No effect	Decreased	50–60 min

Table 1 (*Continued*)

Study population and ELS protocol					Outcome parameters					
Refs.	Species and strain (*n* per group)	Breeding method	ELS protocol	Control group	Age	Sex	Type of recording	Effect baseline (ELS vs. control)	Effect LTP (ELS vs. control)	Time after HFS
[22]	Rat, LE (6)	In-house	Low vs. high LG	n/a	±P120	M	*In vitro* FP	Increased fEPSP slope, increased NMDAR function, no effect on fiber volley amp/fEPSP slope ratio	Decreased	60 min
[23•]	Rat, LE (15 in total)	In-house	% LG	n/a	±P49–56	M&F	*In vitro* FP	No effect	Positive correlation between %LG and %LTP (males and females pooled)	50–60 min
Dentate gyrus: isolated rearing										
[24]	Guinea pig, B (9)	Time-pregnant	Isolated rearing: individually housed from P6/7 onwards	Social housing: 3–7 P6/7 pups plus 2–3 adult virgin females	P80–100	M&F	*In vivo* FP, anesthetized	Increased PS onset, peak and offset latency, decreased current sink at peak of PS, decreased IO function, no effect on threshold current or latency fEPSP	No effect	50–60 min
CA1: maternal separation										
[25•]	Rat, SD (6–12)	N.m.	1 hour indiv. MS at P1–7	Shortly handled at P1–7	P13–43	N.m.	*In vitro* FP	Not assessed	No effect	0–60 min
[26]	Mouse, C57Bl6 (5–7)	In-house	1 hour MS at P2–15 (room temperature)	Unhandled	P21–28	M&F	*In vitro* FP	No effect	Not assessed	–
[27]	Rat, SD (4–10)	N.m.	1 hour indiv. MS at P1–7	Shortly handled at P1–7	±P14–56	N.m.	*In vitro* FP & PC	Slower decay of EPSC, no effect on EPSC amp, rise time or current-voltage relationship	Not assessed	–
[28]	Rat, FSL & FRL (12)	In-house	3 hour MS at P2–14	Unhandled	P73	M	*In vivo* FP, anesthetized	Reduced excitability in MS FSL vs. ctrl FSL, no effect on fEPSP size	Increased in MS FSL vs. ctrl FSL, no effect in FRL	30 & 60 min
[29]	Mouse, C57/Bl6 (9–18)	N.m.	3 hour indiv. MS at P1–14 (room temperature)	Unhandled	P15 & P70	M&F	*In vitro* PC	P15: no effect. P70: decreased AP amp	P15: no effect, P70: decreased	0–40 min
[30]	Rat, W (4–5)	Time-pregnant	3 hour MS at P2–14	Unhandled (weighed at P2 and P14)	±P490	M	*In vitro* FP	Not assessed	Decreased	50–60 min
[31]	Rat, SD (12–18)	In-house	1 hour indiv. MS and vehicle injection at P 1–9	Littermates, injected with vehicle at P1–9	P42–56	M&F	*In vitro* PC	Increased sIPSC amp, no effect on sIPSC freq or sEPSC amp or freq	Not assessed	–
[32]	Rat, SD (3–4)	N.m.	3 hours MS at P2–14	Unhandled	±P56–70	F	*In vitro* FP	Not assessed	Decreased	60–80 min

Table 1 (*Continued*)

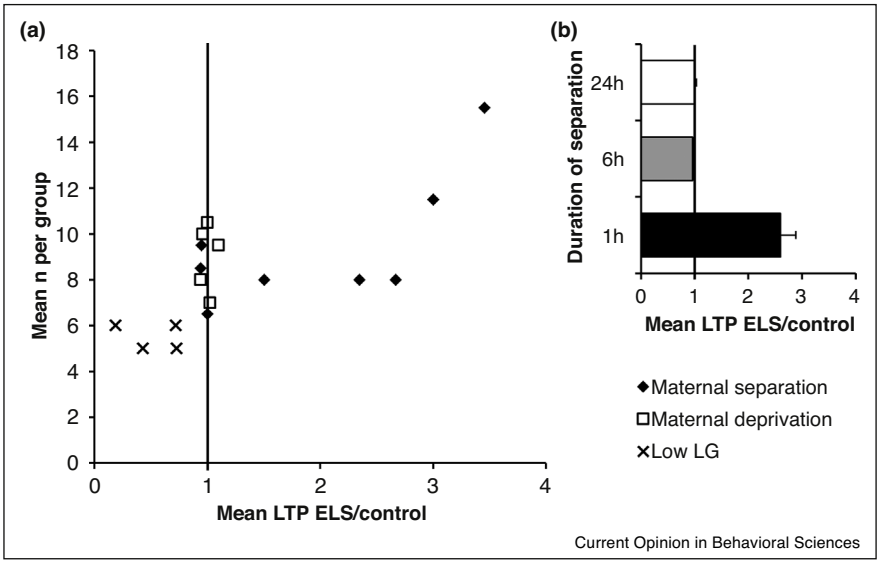
Study population and ELS protocol					Outcome parameters					
Refs.	Species and strain (*n* per group)	Breeding method	ELS protocol	Control group	Age	Sex	Type of recording	Effect baseline (ELS vs. control)	Effect LTP (ELS vs. control)	Time after HFS
[33•]	Mouse, C57Bl/6JRj (6)	In-house	3 hours MS at P1–14 at	unpredictable times, dams additionally stressed	Unhandled	Adult (age not	specified)	M&F	*In vitro* FP	No effect
		Decreased	40–60 min							
[34]	Mouse, C57Bl/6 (7–10)	Time-pregnant	4 hours MS at P2–20	Shortly handled at P2–20	P35–55	M	*In vitro* FP	No effect	No effect	58–60 min
[35]	Rat, SD (4–5)	Time-pregnant	2 hours or 6 hours MS at P2–15	Non-separated littermates	P42–49	N.m.	*In vitro* PC	Increased mIPSC freq, no effect on mIPSC amp	Not assessed	–
CA1: 24 hours Maternal deprivation										
[36]	Rat, W (14–17 cells)	In-house	24 hours MD at P3	Non-deprived littermates	±P91	M	*In vitro* PC	More depolarized RMP, no effect on input resistance, inward rectification, membrane time constant, spike freq accommodation or AHP	Not assessed	–
[37]	Rat, W (4–15)	In-house	24 hours MD at P3	Unhandled	P8–9, 22–24 & 85–95	M&F	*In vitro* FP	No effect	Increased in P22–24 males and P85–95 females, no effect in other groups	50–60 min
CA1: Low licking and grooming										
[38••]	Rat, LE (10–11)	In-house	Low vs. high LG	n/a	±P61–91	M	*In vitro* FP	Decreased fEPSP amp, no effect on stimulation intensity	Decreased	0–60 min
[39]	Rat, LE (10–14)	In-house	%LG	n/a	±P49–56	M&F	*In vitro* FP	Not assessed	No effect in males or females (non-significant positive correlation between %LG and %LTP in males)	0–60 min
[40•]	Rat, LE (4–6)	In-house	Low vs. high LG	n/a	±P120	M	*In vitro* FP & PC	Dorsal part: no effect. Ventral part: increased E-S coupling, RMP hyperpolarization, AP amp and rise time, decreased AP threshold, no effect on mEPSC freq or amp	Decreased in dorsal hippocampus, increased in ventral hippocampus	55–60 min
CA1: novelty exposure										
[41]	Rat, SD (10–25)	Time-pregnant	3 min novelty exposure at P1–21	Littermates, daily 3 min MS at P2–21	±P213–243 & 395–426	N.m.	*In vitro* FP	No effect on PS amp or fEPSP amp	P213–243: increased PS PTP & LTP and fEPSP PTP & LTP. P395–426: increased PS PTP & LTP	0–30 min

Table 1 (*Continued*)

Study population and ELS protocol					Outcome parameters					
Refs.	Species and strain (*n* per group)	Breeding method	ELS protocol	Control group	Age	Sex	Type of recording	Effect baseline (ELS vs. control)	Effect LTP (ELS vs. control)	Time after HFS
[42]	Rat, LE (4–5)	Time-pregnant	25 min MS at P1, 3 min novelty exposure at P2–21	Littermates, 25 min MS in novel environment at P1, daily 3 min MS at P 2–21	±P137–243	N.m.	*In vitro* FP	No effect on fEPSP slope	No effect on PTP, increased LTP	0-3 & 20–30 min
[43]	Rat, SD (4)	Time-pregnant	3 min novelty exposure at P1–21	Littermates, daily 3 min MS at P2–21	±P213–243	M	*In vitro* FP	Increased right/left ratio of fEPSP amp: larger fEPSPs in right hemisphere of novelty-exposed rats, no difference in control	No effect on PTP, increased STP and LTP in right hemisphere	2, 10 & 30 min
CA1: limited nesting/bedding										
[44•]	Rat, SD (5–12)	In-house	LN/B at P2–9	Animal facility rearing	±P122 & 365	M	*In vitro* PC	P122: not assessed. P365: no effect	P122: no effect. P365: decreased	20 min
[45]	Rat, strain n. m. (5–6)	N.m.	LN/B at P2–21	Animal facility rearing	P53–57	M	*In vitro* FP	Not assessed	Decreased	55–60 min
[46]	Rat, SD (4–6)	Time-pregnant	LN/B at P2–9	Animal facility rearing	±P304–365	M	*In vitro* FP	No effect	Decreased	30–40 min
[47]	Mouse, 129S2/Sv x C57Bl/6J (4–6)	In-house	LN/B at P2–9	Animal facility rearing	±213–243	M	*In vitro* FP	Not assessed	No effect	70–80 min
[48]	Mouse, C57Bl/6 (6–8)	N.m.	LN/B at P2–9	Animal facility rearing	P35	M	*In vitro* FP	Not assessed	Decreased	50–60 min
CA1: isolated rearing										
[24]	Guinea pig, B (9)	Time-pregnant	Isolated rearing: individually housed from P6/7 onwards	Social housing: 3–7 P6/7 pups plus 2–3 adult virgin Fs	P80–100	M&F	*In vivo* FP, anesthetized	Increased PS and fEPSP latency, decreased IO function, decreased fEPSP/granule cell PS ratio	Not assessed	–
CA1: foot shocks										
[49]	Rat, W (3–6)	In-house	Daily footshocks at P14–18 or P21–25	Daily exposed to shockbox, never shocked	P70–84	M	*In vivo* FP, anesthetized	No effect	No effect	0–60 min

Refs. indicates reference number; ELS, early life stress; SD, Sprague-Dawley; W, Wistar; LH, Lister Hooded; FSL, Flinders sensitive line; FRL, Flinders resistant line; LE, Long–Evans; B, Brescia; N.m., not mentioned; MS, maternal separation; Indiv. MS, individual maternal separation; MD, maternal deprivation; LG, licking and grooming; LN/B, limited nesting/bedding; n/a, not applicable; P, postnatal day; M, male; F, female; FP, field potentials; PC, (whole-cell) patch clamp; GABA, γ-aminobutyric acid; EC50, half-maximal effective concentration; fEPSP, field excitatory post-synaptic potential; amp, amplitude; PS, pop spike; NMDAR, *N*-methyl-D-aspartate receptor; IO, input–output; EPSC, excitatory post-synaptic current; AP, action potential; sIPSC, spontaneous inhibitory post-synaptic current; sEPSC, spontaneous excitatory post-synaptic current; freq, frequency; mIPSC, miniature inhibitory post-synaptic current; RMP, resting membrane potential; AHP, after-hyperpolarization; E–S coupling, excitatory postsynaptic potential-to-spike coupling; mEPSC, miniature excitatory post-synaptic current; LTP, long term potentiation; PTP, post tetanic potentiation; STP, short term potentiation; HFS, high frequency stimulation; CA1, cornu ammonis 1.

Figure 2



ELS model-dependent effects on long-term potentiation in the dentate gyrus. **(a)** Low licking and grooming impaired LTP, whereas maternal deprivation had no effect. Maternal separation increased LTP. A ratio equal to one indicates no effect. **(b)** Enhancement of LTP was only seen after 1 hour separations; longer durations did not affect LTP.

observed a strong increase of LTP in the ventral part. All in all, similar to the DG, ELS effects on LTP in the CA1 differed per ELS model. The expression of these effects can be age-dependent, an effect that was not observed in the DG.

Discussion

We performed a systematic review on the effects of rodent ELS models on electrophysiological properties of the brain. Here, we specifically focused on basal transmission and LTP in the DG and CA1 hippocampus. We found that basal transmission is unaltered, while LTP was differentially affected depending on the specific ELS model and hippocampal subregion.

Region-specific effects of ELS in the hippocampus

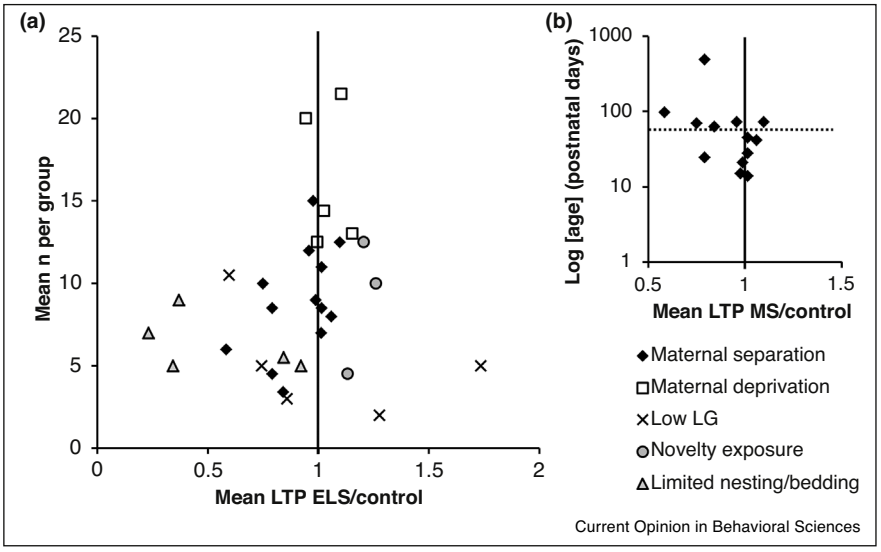
ELS affected LTP in both the DG and CA1. Interestingly, most investigated ELS models affected only one of these areas, indicating that the sensitivity to each model is region-specific. However, no clear patterns were found in common factors within ELS models that could explain this region-specificity. Comparisons of the magnitude of effect on LTP indicate that, in general, the DG is more strongly affected by ELS than the CA1, especially in case of MS. These larger effects on the DG could be explained by the developmental timing: while the CA1 is mostly formed *in utero*, the DG is still strongly developing during the first two postnatal weeks [1]. Therefore, exposure to stress during this period can probably shape DG development more strongly than that of the further developed CA1 area. Although data on other brain areas than the hippocampus have been included in this systematic review, more studies on these areas are needed before conclusions can be drawn.

Opposing effects of mild vs. severe models for ELS on LTP

Both enhancement and impairment of LTP was seen in the hippocampus; the direction of the effect depended on the applied ELS model. In general, enhancements in either the DG or CA1 were caused by mild models with short durations of separation (1 hour MS, novelty exposure), while severe models with more chronic ELS or severe stressing of the dam impaired LTP (low LG, limited nesting/bedding). Interestingly, MS durations >1 hour or 24 hours MD did not consistently impair LTP, although these models can be regarded as severe, though not chronic. Of note, in most studies the group exposed to adverse conditions (>1 hour MS, MD, limited nesting/bedding) was compared to non-handled controls. In some studies though, handled controls were used for comparison. Behavioral studies generally show opposite effects of handling vs. >1 hour MS [3••]. The limited amount of neurophysiological data on this comparison, however, does not confirm these opposing effects. This issue clearly needs more investigation.

The observation that model severity or duration determines the direction of ELS effects on synaptic plasticity has been made in 2012 by Joëls *et al.* [50]. In fact, the stimulating effect of mild ELS in the form of 15 min neonatal handling, although not included in our review, has been shown already in 1956 by Levine *et al.* [51•]. Standard animal facility rearing, a minimal-intervention

Figure 3



ELS model-dependent effects on long-term potentiation in the cornu ammonis 1 area of the hippocampus. **(a)** Increased LTP was seen after novelty exposure; maternal deprivation caused a slight increase and limited nesting/bedding as well as maternal separation decreased LTP. Low licking and grooming had mixed effects. A ratio equal to one indicates no effect. **(b)** Plotting the maternal separation data against the animal's age of recording revealed a turning point in LTP effects around 8 weeks: LTP is not affected before 8 weeks (dashed line), whereas it is impaired in older animals.

condition which served as a control for most reviewed studies, might therefore not be regarded as an optimal rearing environment. However, it should be noted that neonatal handling also induces negative effects including deficits in social behavior and impaired renal and reproductive function [52], indicating that enhanced plasticity comes at a price.

Additional factors contributing to LTP outcome

Besides severity and duration of the ELS model, there are many additional factors that are likely to interfere with its impact on neuronal transmission and plasticity. Starvation in 24 hours MD can lastingly modify metabolism and thereby affect neuronal energy supply [53], while hypothermia due to MS at room temperature could alter brain metabolism and thereby interact with separation stress. In addition, the predictability of stress episodes strongly affects how the stressful intervention is perceived by the pups and dam [54]. The effects of sex, age or time of day may also be important but since these factors were seldom systematically studied in the published reports we cannot comment on their influence.

Stressor-specific outcomes are also found in humans. Early physical and sexual abuse mainly increased the risk of mood and anxiety disorders, while childhood emotional abuse often resulted in personality disorders and schizophrenia [2]. However, since many types of ELS occur simultaneously in children, it remains difficult to disentangle the separate effects of single early stressors. Animal models are therefore essential to pinpoint the contributions of each type of stressor to alterations of brain functioning and behavior.

Possible mechanisms underlying ELS effects on synaptic plasticity

We observed opposite effects of brief or mild ELS models vs. more chronic and severe models on LTP. These two types of models differently affect the HPA axis: brief and mild manipulations cause small and short increases of corticosterone (CORT) levels in the pups, while more chronic and severe models cause much stronger and/or more frequent rises in CORT that may perturb corticosterone levels more severely.

The level of HPA axis activation during exposure to the ELS model is likely to drive distinct molecular mechanisms that either enhance or diminish synaptic plasticity. First, ELS can alter the basal level of HPA axis activity in adulthood, depending on the ELS model used. For instance, basal CORT levels were found to be increased in adult offspring from dams exposed to limited nesting material conditions [44•,55]; this might decrease the ability to induce LTP under basal conditions, as a rise in corticosterone generally suppresses the degree to which LTP can be induced (reviewed in Ref. [50]). Second, the molecular machinery of the glutamatergic system, which is crucial for LTP induction, might be impaired by prolonged ELS, again in a manner that depends on the model used. Thus, hippocampal

expression of AMPA receptor subunits GluR1 and GluR2 was decreased by 6 hours daily MS [56]. In addition, NMDA receptor subunits NR2A and NR2B expression was also decreased by 6 hours MS and by 24 hours MD [56,57].These changes in expression pattern may depend on the type of ELS conditions to which pups were exposed, but this was not systematically investigated so far. In agreement, the expression of NR2B was increased by 15 min handling [58], thereby facilitating LTP induction. Since the presence of available AMPA and NMDA receptors is essential for the induction of LTP, the reduced receptor pool observed under the conditions mentioned directly impairs LTP. Third, ELS is known to affect dendritic complexity which will also affect the degree of synaptic plasticity. For example, pups raised under conditions of limited nesting were reported to have impaired dendritic complexity in the CA1 region [46], which limits neuronal connectivity and can thereby hamper total LTP induction.

Although we consider the duration and severity of the ELS model as the main determining factor for the direction of LTP effects, there are many other factors in which the ELS models differ. These factors could also contribute to LTP impairment or enhancement. An example of such additional effects concerns the metabolic state caused by ELS, which is expected to occur with low LG, MD and MS, either due to the lack of anogenital stimulation necessary for defecation or due to dehydration (in the case of MS or MD). Absence of the dam from the nest in the limited nesting model and MS at room temperature cause hypothermia in the pups, which impairs memory function, possibly via attenuating COX-II expression [59]. While all of these factors cause additional stress and thereby increase the overall adversity of the used model, their direct effects should not be overlooked.

Exactly how these potential mediators of ELS effects on synaptic plasticity exert their effect is still unresolved. Epigenetic changes – as were demonstrated in the pathway initiated by maternal licking-grooming of the pups [60] – are likely to be involved, but generally have not been investigated.

Interplay between ELS and later stressful conditions

We reviewed effects of ELS on LTP under basal, non-stress conditions. Stressful contexts are known to largely impact memory function: both LTP induction as well as memory formation are thought to be increased during a mildly stressful event, and impaired during the hours afterwards [50]. ELS can determine how an animal responds to later-life stressful situations by changing the responsivity of the stress system and the way in which neuronal functioning is affected by elevated CORT levels. The impairment of LTP seen after an acute stressor or CORT exposure in control animals is often even reversed into LTP enhancement in animals with an ELS history [16,18,38••] (however: [19,37]). We would need to combine the results of the current review with an overview of ELS effects under stressful conditions to get a complete insight in the overall effects of ELS on plasticity.

Behavioral effects of ELS are consistent with neurophysiology

How do the ELS effects on neurophysiology translate to behavior? Since LTP is an essential underlying process of memory formation, we expect that ELS models causing LTP impairments would also hamper the performance on learning and memory tasks, while improving performance in models showing LTP enhancement. Comparing our LTP findings to behavioral effects of ELS shows that under low-stress conditions, LTP and memory function are indeed positively correlated. For example, object recognition is enhanced by handling but impaired by 3 hours MS and limited nesting/bedding [3••]. Likewise, novelty exposure improved social memory whereas this was impaired by 3 hours MS. Although possibly stressful, performance on the Morris water maze was also improved by handling and novelty exposure and impaired by MS, MD and limited nesting/bedding [3••]. Interestingly, 1 hours MS impaired memory performance in the Morris water maze and object recognition, while LTP induction was improved. We hypothesize that in this particular case, either the transmission or plasticity of adjacent hippocampal areas could be impaired, or the level of plasticity is above an optimal value. In sum, effects on neurophysiology are indeed reflected on the behavioral level, although ELS effects on other forms of plasticity or areas outside the hippocampus should not be overlooked.

Summary/conclusion

Postnatal mild and brief ELS generally enhances LTP in the DG or CA1 hippocampus, while LTP is impaired by more severe and chronic paradigms. These effects are largely reflected at the behavioral level, as determined in non-stressful hippocampal memory tasks. The observations that both in rodents and humans different types of ELS cause different outcomes (regarding plasticity, memory or mental functioning) and that humans are often subjected to mixed forms of ELS advocate for the importance of research in ELS animal models. By comparing the effects of different rodent ELS models, we can gain a better understanding of the different contributors to the neurophysiological and behavioral effects in individuals.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cobeha.2017.03.005.

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