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► **To cite this version:**

Raafat Fares, Marion Moreau, Pascal E Sanchez, Béatrice Georges, Colette Moulin, et al.. Beneficial effects of environmental enrichment on structural and genomic brain plasticity are abolished by forced physical exercise. 2009. hal-00145358

HAL Id: hal-00145358

<https://hal.science/hal-00145358>

Preprint submitted on 9 May 2009

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Beneficial effects of environmental enrichment on structural and genomic brain plasticity are abolished by forced physical exercise.

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The aim of the study was to determine whether the effect of forced physical training from weaning to adulthood is the same between rats raised either in impoverished or enriched environments. For environmental enrichment, we have engineered a cage allowing standardization of the procedures of enrichment (under patent examination). This cage allows increased social interactions (12 rats per cage), increased voluntary exercise (increased size of the cage, running wheels), "diverting" activities (ladder, toboggan slide, tunnel), and cognitive stimulations using labyrinths, the configuration of which is changed 3 times a week. The forced physical training consists of a daily swimming program, the time spent in the swimming pool being increased from 5 min the first week to 45 min the fifth week. S rats were housed in groups of 6 from weaning to adulthood.

Four groups are examined: standard housing (S), enriched housing (En), S + forced swimming (SFS) and EN + forced swimming (EnFS).

We found that the effect of FS on structural plasticity is dependent on the initial housing condition:

- 1) FS increases cortical thickness in S rats, as En does; however, the increased cortical thickness measured in En rats is not observed in EnFS rats. [Fig.1]
- 2) En increases neurogenesis in the hippocampus when examined at the end of the protocol (compared to S rats). FS is not a sufficient condition to increase neurogenesis in S rats. However, in rats raised in enriched conditions, FS brings back neurogenesis to the value measured in S rats. [Fig.2]
- 3) In addition, while BDNF, TrkBFL, TrkBT1 and TrkBT2 transcript levels (determined using calibrated RT and real time PCR) are significantly increased in En group compared to S, FS decreased transcript levels in En rats below levels determined in S rats. [Fig.3]
- 4) Levels of mRNA encoding glucocorticoid and mineralocorticoid receptors (GR and MR) are greater in En rats compared to S rats in the hippocampus, but FS decreased GR and MR mRNA levels in En rats below levels determined in S rats. By contrast, GR mRNA levels remained stable in SFS rats compared to S rats, while MR mRNA levels were significantly increased. [Fig.4]
- 5) Surprisingly, basal levels of corticosterone (CORT) were significantly lower in SFS rats and En rats compared to S rats, but also in EnFS rats compared to S rats. [Fig.5]

Our hypothesis is that FS is not interpreted the same way by rats raised in standard (S) or enriched (En) environments. Since CORT plasma levels in SFS rats is below S rats, we suggest that FS decreased stress in rats raised in S conditions. By contrast, FS may be considered as a stressful condition in rats raised in En conditions. Indeed, when the labyrinth is changed, En rats are used to find quickly the issue; in the swimming pool, the same rats try to find an "exit" by diving and exploration of the bottom of the tub in the first sessions, and may rapidly be stressed by the fact that they do not find a solution to escape the swimming pool. In EnFS rats, basal level of CORT are lower than that found in S rats and similar to that measured in En rats. We propose that CORT levels in EnFS rats greatly increase during FS, and return to baseline after a longer time than that measured in En rats that do not experience FS, due to a lower level of GR and MR in the hippocampus.

We are currently measuring the response of plasma CORT to restraint stress, to determine whether basal level is recovered faster in En rats compared to S rats. If that is the case, we will repeat the same kind of experience to compare the responses of En and EnFS rats.

Figure legends:

Fig.1: Effects of forced physical exercise on structural plasticity are dependant on environmental conditions. Forced swimming increases central cortical thickness in standard rats (SFS), but not in enriched rats (EnFS) after 6 weeks of swimming. Results are expressed in percent \pm SEM of standard (S) group. ** $P < 0.01$ in comparison to respective control (S or En). §§§ $P < 0.001$ in comparison to standard group (S).

Fig.2: Forced swimming abolishes the effects of environmental enrichment on neurogenesis. (A) Fluorescent detection of BrdU labeled cells in the dentate gyrus of standard (S) and enriched (En) groups. (B). Environmental enrichment increases the number of BrdU-labelled cells in the dentate gyrus of adult rats. This effect is reversed when enriched environment is associated to forced swimming (EnFS). Forced swimming in standard rats (SFS) is not sufficient to induce significant neurogenesis. Results are expressed in percent \pm SEM of standard (S) group. * $P < 0.05$ in comparison to respective control (S or En). §§§ $P < 0.001$ in comparison to standard (S).

Fig.3: Expression profile of trophic factors in different brain regions of adult rats. Enriched environment up-regulates the expression of transcript encoding for BDNF, TrkBFL, TrkBT1 and TrkBT2 in all brain regions. Forced swimming is able to induce the expression of some transcripts in several regions of standard rats (SFS). However, forced swimming reverses completely the effects of enriched in (EnFS) group. Results correspond to the mean \pm SEM of the number of cDNA copies quantified by real time PCR following reverse transcription of mRNAs contained in 500 ng of total RNAs and are expressed in percent of standard (S). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ in comparison to respective control (S or En), § $P < 0.05$, §§ $P < 0.01$, §§§ $P < 0.001$ in comparison to standard (S).

Fig 4: Expression profile of glucocorticoids (GR) and mineralocorticoids (MR) receptors in the hippocampus of adult rats after 6 weeks of housing in either standard or environmental condition associated or not with forced swimming.

Enriched environment increases the expression of transcript encoding for GR and MR. While forced swimming induces the mRNA encoding MR only in standard rats (S), it has a complete opposite effect on MR and GR in enriched rats (EnFS). Results correspond to the mean \pm SEM of the number of cDNA copies quantified by real time PCR following reverse transcription of mRNAs contained in 500 ng of total RNAs and are expressed in percent of standard (S)., ** $p < 0.01$, *** $p < 0.001$ in comparison to control, § $P < 0.05$, in comparison to standard (S).

Fig 5: Basal levels of plasma corticosterone (CORT) after 24 hours of the last swimming session. Forced swimming decreases the basal level of plasma CORT in standard rats (S). Enriched environment also decreases basal level of CORT, but forced swimming has no effect in this condition (EnFS). Results are expressed in percent \pm SEM of standard (S) group. * $p < 0.05$, in comparison to respective control (S or En), §§§ $P < 0.001$ in comparison to standard (S).

Fig. 1

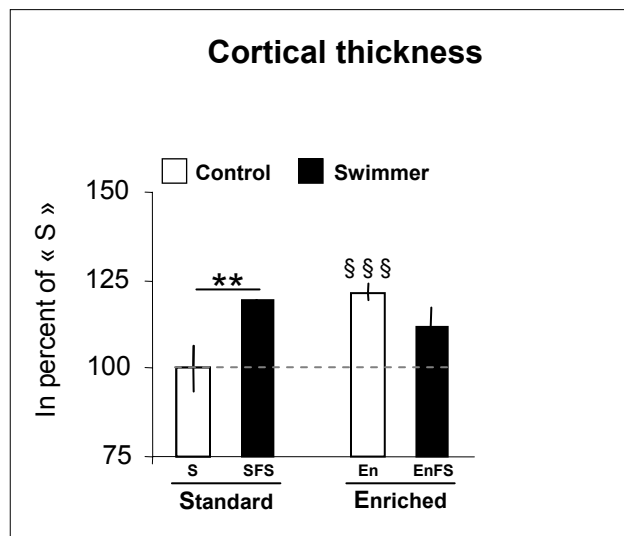


Fig. 2

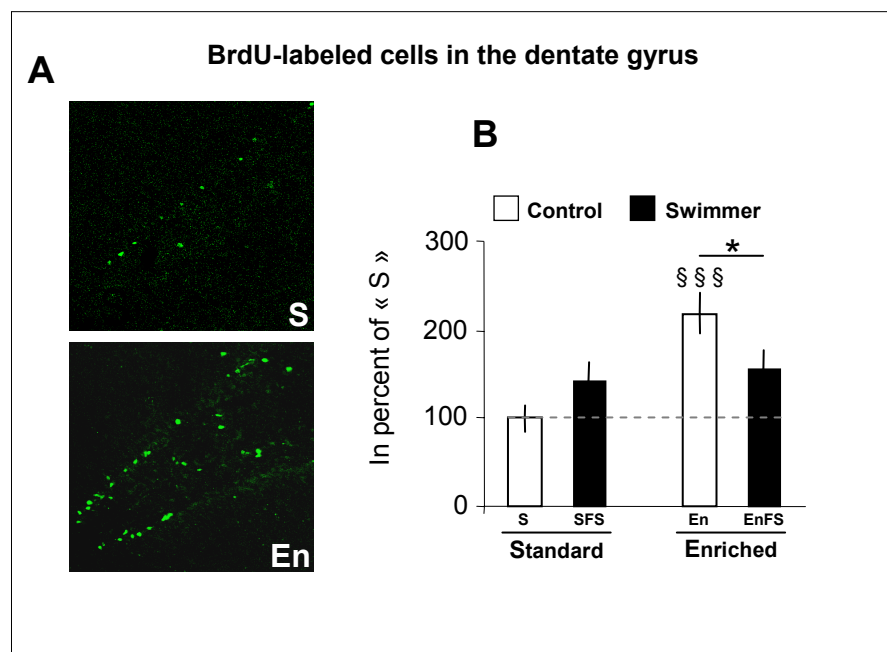


Fig. 3

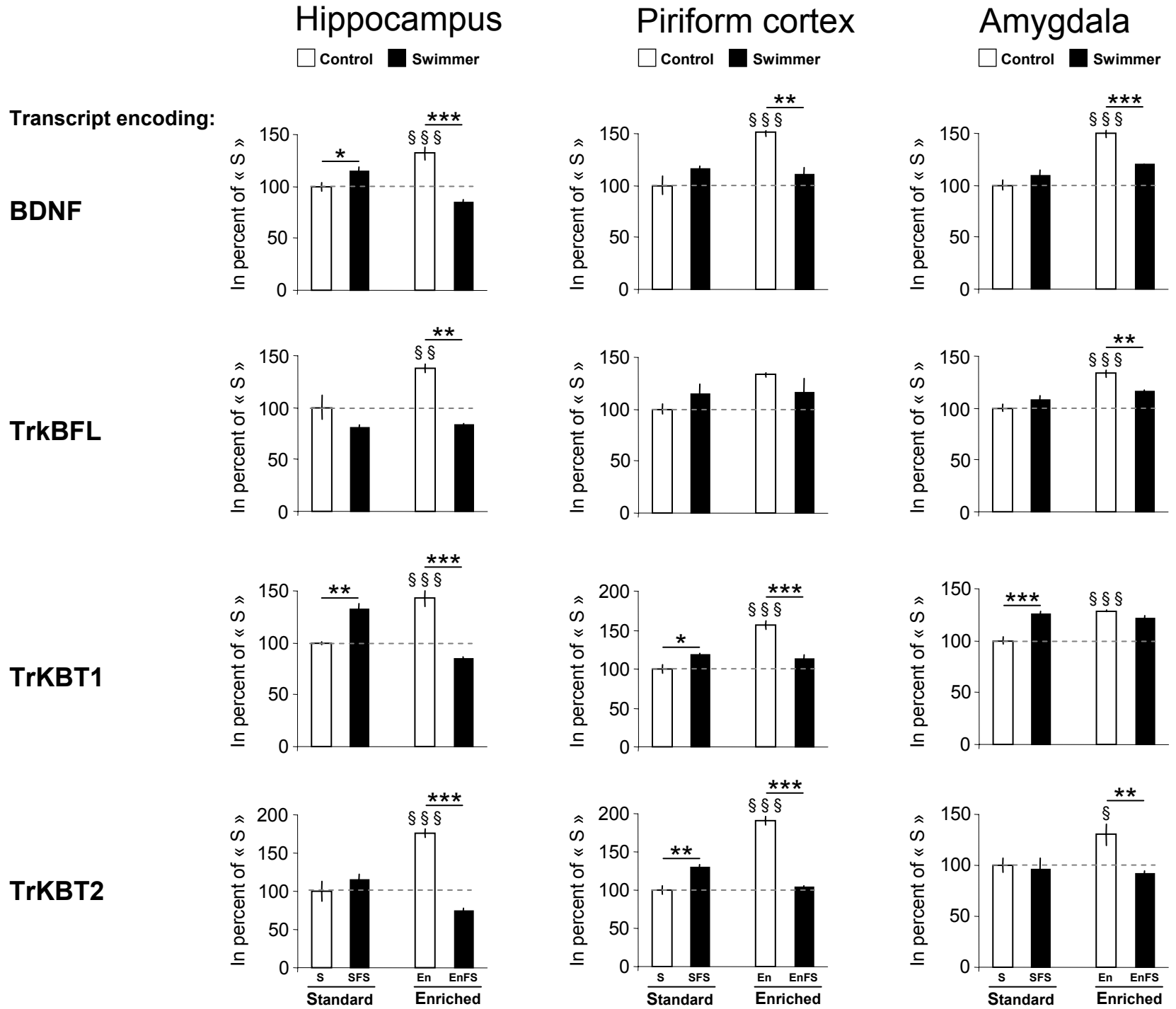


Fig. 4

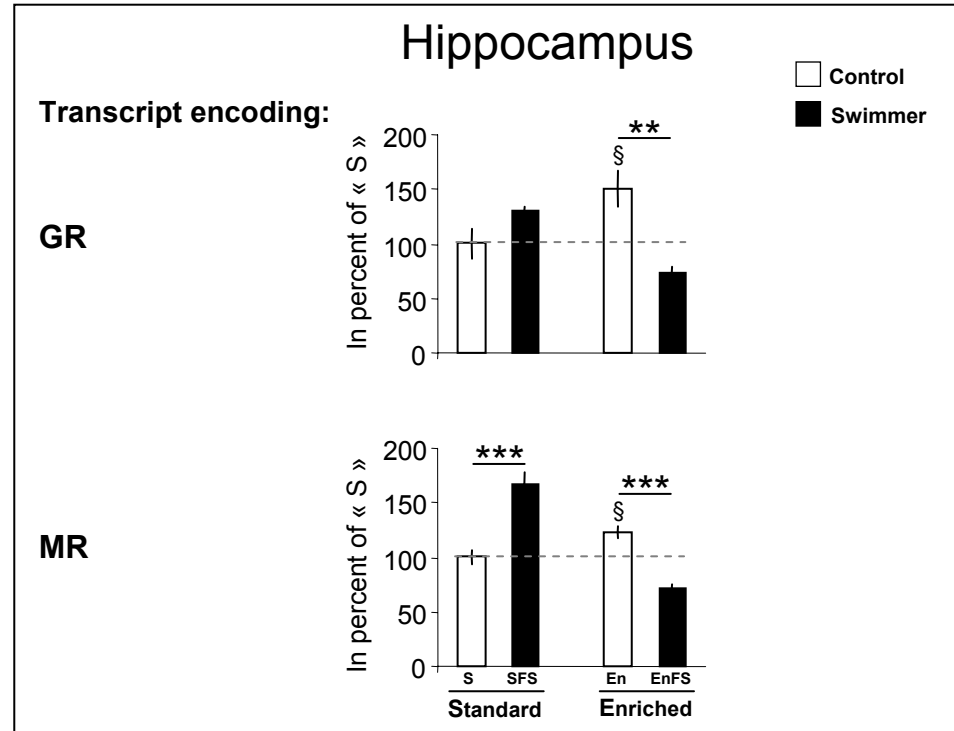


Fig. 5

