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Enriched environment and physical activity reverse astrogliodegeneration in the hippocampus of AD transgenic mice

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Dear Editor,

Astrocytes, being the principal cellular component of homoeostatic system of the central nervous system, are involved in numerous physiological functions, including maintenance of synaptic connectivity, plasticity and survival, and facilitating synaptogenesis. In many neurodegenerative diseases, including Alzheimer's disease (AD), astrocytes undergo complex morphological and functional modifications, manifested by both degenerative and reactive changes.[1,2]

In several brain regions, formation of β-amyloid plaques triggers reactive astrogliosis characterised by a substantial increase in expression of GFAP, increase in astroglial cytoskeleton, and overall hypertrophy of astrocytes. Our previous studies demonstrated that early (i.e., pre-plaque) stages of AD-type pathology in transgenic animals are characterised by atrophic alterations of the astrocytes in areas of the brain affected by the disease such as the entorhinal cortex, hippocampal formation, and the prefrontal cortex. After formation of senile plaques, reactive astrocytes preferentially accumulate around plaques, whereas astrocytes distant from the plaques retain atrophic morphology.[3–5]

These findings taken together led us to hypothesise that astroglial dysfunction in AD could represent a critical pathological step, where they by failing to provide adequate support for neuronal networks define early synaptic deficiency, weaken synaptic connectivity thus contributing to cognitive abnormalities.

Here we exposed 3xTg-AD mice (an established model of AD) to a long-lasting physical or cognitive stimulation represented by voluntary running (RUN) or enriched environment (ENR), and studied morphology of astrocytes in the dentate gyrus (DG) of the 3xTg-AD mouse model exposed to long term (for Materials and methods see Supplementary materials). We found (Figure 1) that both RUN and ENR led to a significant increase in the surface and volume of GFAP-positive profiles (which was more prominent in cell processes) in both non-transgenic and 3xTg-AD animals. Importantly, we could not detect any differences neither in the surface area nor in the volume of the GFAP-labelled astrocytes in the 3xTg-AD mice housed both in RUN and ENR when we compared them with the non-Tg mice exposed to the same housing conditions (Figure 1C).

Thus, we demonstrated that cognitive and physical stimulations affect morphology of astrocytes in DG area of hippocampus and completely reverse atrophic changes observed in the context of AD-like pathology. Restoration of the astrocytic morphology induced by the different housing conditions might convert into increased astrocytic support of synaptic connectivity by recovering the AD-induced reduction of astrocytic coverage of the neuronal structures and, as consequence, restoring synaptic connectivity altered by the AD pathology.

Paradoxically, hypertrophic astrocytes, detected after exposure to ENR and RUN, somewhat resemble reactive astrocytes that surround amyloid plaques. However, recent studies have demonstrated that reactive astrocytic cells, as sources of inflammatory agents, had significantly affected signalling pathways in addition to the altered antigen expression, when rodents were exposed to the ENR. Williamson *et al.*[6] have reported a selective reduction of pro-inflammatory chemokines and cytokines within the hippocampi of rodents exposed to ENR after general LPS administration. Although the mitigating effect of the RUN and ENR on the inflammatory responses of the reactive astrocytes in AD is yet to be determined, these studies indicated that cognitive stimuli, as well as continuous physical activity, might counteract astrogliodegeneration associated with altered astrocytic morphology and function induced by the AD pathology. Whether environmental stimulation-induced recovery of astroglial atrophy is one of the crucial mechanisms that initiates and/or supports recovery of AD-associated synaptic degeneration thus rescuing cognitive function is a question for future studies.

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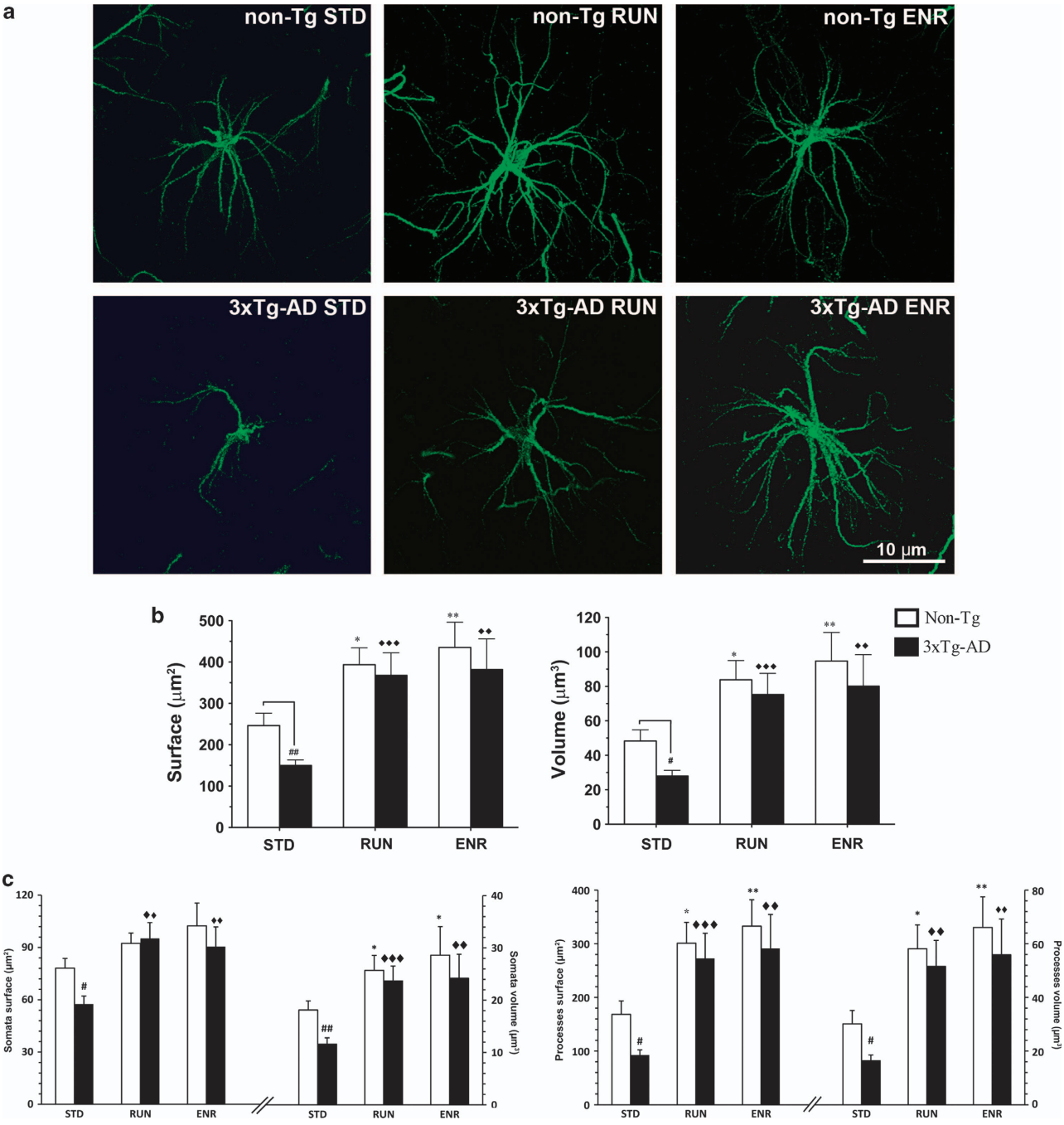

Figure 1 GFAP-immunorectivity of astrocytes in the DG of non-Tg and 3xTg-AD animals housed in different conditions. (**a**) High magnification of representative confocal micrographs showing the astrocytic morphology in mice housed in standard conditions (STD;), RUN, and ENR. Scale bars, 10 μm. Note the morphological changes of the astrocytes from both genotypes induced by the different living conditions. (**b**) Histograms showing difference of surface area and volume of GFAP-positive astrocytes in the DG of non-Tg and 3xTg-AD mice housed under different housing conditions. (**c**) Histograms showing differences in surface area and volume of GFAP-IR astrocytic cell bodies and processes detected between non-Tg and 3xTg-AD mice housed under different housing conditions. Bars represent means ± S.E.M., $^{\#}P<0.05$, $^{\#\#}P<0.01$ compared with non-Tg animals in same housing environment; $^{*}P<0.05$, $^{**}P<0.01$ compared with non-Tg mice housed under STD; $^{\blacklozenge\blacklozenge}P<0.01$ and $^{\blacklozenge\blacklozenge\blacklozenge}P<0.001$ compared with 3xTg-AD mice housed under STD

Conflict of Interest

The authors declare no conflict of interest.

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Supplementary Information accompanies this paper on Cell Death and Disease website (http://www.nature.com/cddis)