

Effect of D-serine on the cognitive reserve in a cognitive flexibility task and functional brain connectivity

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Introduction:

Aging-associated cognitive decline is associated with structural and functional changes in the brain. One of the theories explaining the differences between the trajectories of this decline is the cognitive reserve theory, where differences in the physiology and anatomy allow some individuals to cope better than others. NMDA receptors have a pivotal role in many cognitive functions. Besides the binding of glutamate, it requires the binding of the co-agonists D-serine. During aging, D-serine levels are decreased which has been linked to cognitive deficits. Previous results from our lab have shown that D-serine supplementation to senescent rats restores cognitive flexibility, functional brain connectivity, and spine density that is affected by age. However, it is not clear if the effect of D-serine is comparable to the facilitation of the cognitive flexibility induced by cognitive reserve?

Methods:

To answer this, we did a longitudinal study using 12-month-old rats (early middle-aged) that were trained in a reversal-learning task and the number of perseverations was quantified as an inverse measure of cognitive flexibility. After this, the rats were assigned into two groups, one chronically (two months) supplemented with D-serine (300 mg/kg) in the drinking water, and the control group that received vehicle. The cognitive flexibility was then re-assessed 6 months later (at 18 months, late middle-aged). After every evaluation, we used fMRI to characterize resting-state functional brain connectivity.

Results:

We found that middle-aged rats had more perseverations than young rats (6 months), indicating a decline in cognitive flexibility. Control and D-serine supplemented rats improve their performance when they were tested in the late middle-aged, however, rats with good performance in the cognitive flexibility task in early middle-aged and were supplemented with D-serine, significantly decreased their cognitive flexibility. The analysis of functional brain connectivity show that control rats increase their connectivity between striatum, prefrontal and cingulate cortices. However, rats treated with D-serine did not show changes in their functional connectivity when compare early with late middle age.

Conclusion:

These results shows that D-serine and cognitive reserve have similar effect at a group level. But the effect of D-serine supplementation depends on the cognitive status and that supplementation in high performers is detrimental to cognitive functions. Also the control group and the rat treated with D-serine use different brain mechanisms to improve the cognitive flexibility.