HRVATSKA AKADEMIJA ZNANOSTI I UMJETNOSTI

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# SIMPOZIJ O ISTRAŽIVANJU I BOLESTIMA MOZGA

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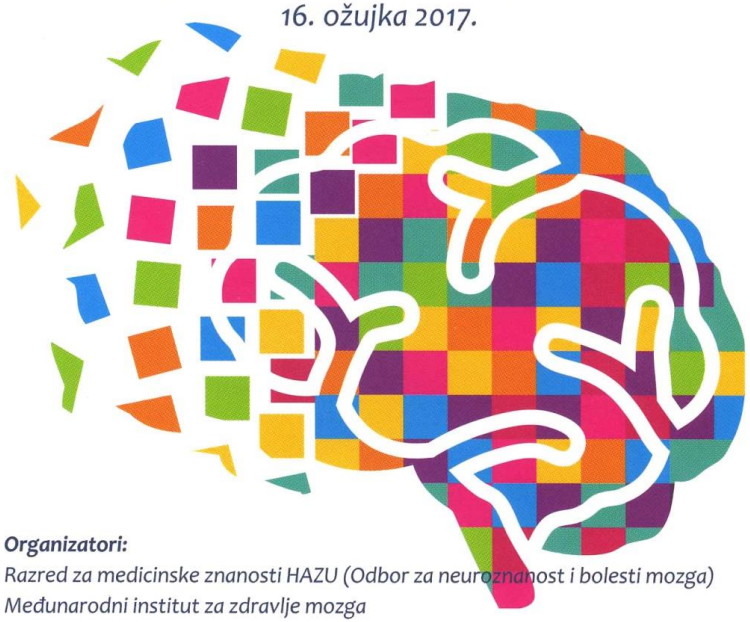

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„hippocampus-dependent" memory processes. One of the specific aspects of ongoing brain maturation and protracted brain development represents the continued postnatal production of new neurons in the dentate gyrus, the subregion of the hippocampal formation. The inability to form stable, persistent memories in early postnatal life coincides with a period of high neurogenesis, whereas the ability to form stable, persistent memories only emerges at later developmental periods as the rate of neurogenesis declines. According to this hypothesis, high rate od neurogenesis levels in the dentate gyrus negatively regulate the ability to shape long-lasting memories. In summary, although infantile amnesia is tightly connected to protracted development of different hippocampal circuits as well as their neurotransmiter systems, its causes are likely to be multifaceted. The understanding of the neurobiological basis for accelerated forgetting during infancy could help us to elucidate the mechanisms involved in memory storage/retrieval across the life span.

## Prvih 30 godina: kad počinje starenje mozga?

Goran Šimić

Kognitivno urušavanje uobičajeno se smatra posljedicom normalnog procesa starenja mozga. Obično počinje već s 30 godina života s usporavanjem brzine obrade osjetnih podražaja, nakon čega slijedi suptilno pogoršavanje sposobnosti prostorne orijentacije, pozornosti, verbalnog pamćenja, računanja i induktivnog zaključivanja. Jedan od rijetkih izuzetaka jest sposobnost govorenja (tečnost), koja često ostaje relativno konstantna kroz odraslu dob, zbog čega mnogi misle da su im kognitivne sposobnosti sačuvane. Nakon 30. godine života, u prosjeku se gubi oko 1% kolagena godišnje, pa se promjene na koži obično javljaju usporedno s kognitivnim urušavanjem.





Opće prihvaćeni stav kako je potrebno 20 godina da bi se razvila demencija vjerojatno nije realistična. Vjerojatnije je da je za razvitak demencije potrebno najmanje oko 40 godina. Naime, cijeli proces počinje predstadijem blagog kognitivnog oštećenja (odnosno malog neurokognitivnog poremećaja) s otprilike 30 godina starosti. Zatim obično napreduje uglavnom asimptomatski, a karakteriziran je usporavanjem brzine obrade informacija sve do prvih subjektivnih simptoma. Blagi spoznajni poremećaj postane i objektivno očit tek 15-20 godina kasnije. Tipično se odlikuje blagim oštećenjima u više kognitivnih domena: snalaženju u prostoru i vremenu, pozornosti i pamćenju. Od toga stadija može potrajati još 10-20 godina do nastanka sindroma demencije (velikog neurokognitivnog poremećaja). U prosjeku je stupanj konverzije blagog kognitivnog oštećenja u demenciju zbog Alzheimerove bolesti oko 7-10% godišnje. Do dobi od 70 godina, većina ljudi ima značajno kognitivno urušavanje, a gotovo polovica svih 85-godišnjaka su klinički dementni (Plassman B. L. i sur., Ann. Intern. Med., 2008;148:427-434).

S obzirom na dramatičan porast udjela starijeg stanovništva, od velike je važnosti razumjeti genetske i molekularne mehanizme zdravog starenja i dugovječnosti. Jedno od najznačajnijih nedavnih otkrića je Horvathov epigenetički sat, koji se temelji na analizi 353 mjesta metilacije DNA. Iako je snažan utjecaj dobi na razinu metilacije DNA bio poznat još od kasnih 1960-tih, algoritmi temeljeni na epigenetičkim promjenama bili su u slaboj korelaciji s kronološkom dobi (u rasponu od 60-70%). Uporabom 8000 uzoraka iz 82 potpuna DNA metiloma, 2013. godine je na 51 vrsti zdravih tkiva i stanica Horvath razvio algoritam za procjenu starosti, kojemu je i od drugih laboratorija potvrđena korelacija između dobi predviđene algoritmom i stvarne dobi od 96-99,7%, sa srednjom pogreškom što se mjeri u mjesecima (Horvath S. Genome Biol., 2013;14:R115). Glavna prednost Horvathovog epigenetičkog sata leži u njegovoj širokoj primjenjivosti: bez ikakvih prilagodbi ili korekcija rabi se isti skup odabranih 353 CpG dinukleotida i isti algoritam predviđanja bez obzira odakle je iz organizma izuzet uzorak tkiva ili stanica za analizu. To svojstvo nam omogućuje usporediti starost različitih dijelova ljudskog tijela pomoću

istoga biološkog sata iako još uvijek nije poznato što se zapravo mjeri metilacijskom dobi DNA odnosno kako radi sustav nadzora epigenetičkih promjena. Ipak, s obzirom na činjenicu da je dob određena epigenetičkim satom iz stanica krvi snažan predskazatelj dobi u kojoj će nastupiti smrt zbog bilo kojeg mogućeg uzroka u kasnijem životu, najvjerojatnije se sustav nadzora navedenih epigenetičkih promjena odnosi na procese koji uzrokuju starenje (Chen B.H. i sur., Aging, 2016;8:1844-1865).

Primjena Horvathovog sata je već polučila značajne uvide. Na primjer, dok tkiva zloćudnih tumora pokazuju učinke i ubrzavanja i usporavanja epigenetičkog starenja, Downov sindrom povećava dob krvnih stanica i moždanog tkiva u prosjeku za 6,6 godina (Horvath S. i sur. Aging Cell, 2015;14:491-495), a mali mozak normalnih ljudi stari sporije nego drugi dijelovi mozga, te je u stogodišnjaka oko 15 godina mlađi od prosjeka (Horvath S. i sur., Aging, 2015;7:294-305). Također je pokazano da djeca super-stogodišnjaka koji su doživjeli 105-109 godina imaju nižu epigenetičku dob od kontrolnih ispitanika iste starosti s prosjekom od 5,1 godine epigenetičke razlike, dok je epigenetička dob stogodišnjaka u prosjeku 8,6 godina manja od kronološke. Nasuprot tome, utrđeno je kako je povećana epigenetička dob stanica prefrontalne moždane kore povezana s padom svekupnog kognitivnog funkcioniranja u osoba s Alzheimerovom bolešću (Levine M.E. i sur., Aging, 2015;7:1198-1211). Iako je preostalo još puno posla kako bi se razumjeli mehanizmi odgovorni za epigenetički sat, s obzirom na činjenicu da je metilacija reverzibilna, nadamo se kako će jednoga dana biti moguće usporiti njegovo otkucavanje.





## First 30 years: when brain aging begins?

Goran Šimić

Cognitive decline is commonly considered to be a consequence of the normal process of brain aging. It usually begins as early as 30, starting with a slowing of perceptual processing speed, followed by a day-to-day insidious worsening of spatial orientation, attention, verbal memory, numeric ability, and inductive reasoning. One of the rare exceptions is verbal ability (fluency), which often remains relatively constant throughout adulthood and leads many individuals into thinking that their cognitive abilities are preserved. After age 30, on average 1% of collagen a year is lost, so skin changes usually occur in parallel with cognitive deterioration.

The general consensus that dementia takes 20 years to develop is probably not realistic - it is more likely that dementia takes at least about 40 years to develop. The process begins with the development of pre-mild cognitive impairment (MCI, also known as minor neurocognitive disorder) at around 30 years of age. Then it usually progresses mostly asymptomatically and is marked by a slowing of processing speed until the first subjective symptoms. MCI become objectively apparent only about 15-20 years later. It is typically characterized by slight impairment in multiple cognitive domains: orientation in space and time, attention span, and memory. It may then take another 10-20 years for MCI to become dementia (major neurocognitive disorder). On average, about 7-10% of MCI cases convert to Alzheimer's disease annually. By the age of 70, most people are cognitively impaired, and almost half of all 85-year-olds are clinically demented (Plassman B.L. et al., Ann. Intern. Med., 2008;148:427-434).

Given the dramatic increase in aging populations, it is of great importance to understand the genetic and molecular mechanisms underlying healthy aging and longevity. One of the most important recent discoveries has been Horvath's epigenetic clock, which is based on analysis of 353 DNA

methylation sites. Although the strong effect of age on DNA methylation levels has been known since the late 1960s, algorithms based on epigenetic changes had weak correlations with chronological age (in a range from 0.6-0.7). Using 8,000 samples from 82 complete DNA methylation array datasets, in 2013 Horvath developed the age estimator encompassing 51 healthy tissues and cell types, whose correlation between predicted and actual ages has been confirmed to be 96-99.7%, with a median error measured in months (Horvath S. Genome Biol., 2013;14:R115). The major advantage of Horvath's epigenetic clock lies in its wide applicability: the same set of 353 CpG dinucleotides and the same prediction algorithm is used irrespective of the DNA source within the organism meaning that it does not require any adjustments or offsets. This property allows one to compare the ages of different parts of the human body using the same aging clock. It is not known what is actually measured by DNA methylation age or how the epigenetic maintenance system works. However, based on the fact that DNA methylation age of blood is a strong predictor of all-cause mortality in later life, it likely relates to processes that cause aging (Chen B.H. et al., Aging, 2016;8:1844-1865).

The application of the Horvath's clock has already revealed important insights. For example, while tissues of malignant tumors show both positive and negative age acceleration effects, Down syndrome increases the age of blood and brain tissue on average by 6.6 years (Horvath S. et al., Aging Cell, 2015;14:491-495), while the cerebellum of normal people ages more slowly than other parts of the brain: it is about 15 years younger than expected in a centenarian (Horvath S. et al., Aging, 2015;7:294-305). It has also been shown that the offspring of super-centenarians who reached an age of 105-109 years have a lower epigenetic age than age-matched controls with a 5.1 age difference, whereas centenarians themselves are on average 8.6 years younger than expected based on their chronological age. Conversely, epigenetic age acceleration of the human prefrontal cortex has been found to be associated with a decline in global cognitive functioning among individuals with Alzheimer's disease (Levine M.E. et al., Aging, 2015;7:1198-1211). Although much work





is needed to understand mechanisms behind the epigenetic clock, due to the fact that methylation is reversible, it might be possible to retard its permanent progress.

## New developments in fetal MRI

Christian Mitter

Fetal MRI has established itself as an important adjunct to ultrasound in the prenatal assessment of both normal human brain development as well as central nervous system pathologies. In addition to structural brain imaging, recent advancements in MRI technology have allowed the inclusion of advanced sequences like diffusion tensor imaging (DTI) and functional resting-state MRI (fMRI) in prenatal imaging protocols, providing information beyond morphology. In utero resting-state fMRI can be used to identify developing cortical networks of synchronized activity in the human fetal brain, and pathological connectomes may be of use as potential markers of disrupted development and plasticity. In utero DTI offers the unique possibility to investigate the three-dimensional anatomy of developing white matter fiber tracts in vivo, and has successfully been used to visualize the corpus callosum, the internal capsule, and even association fibers in the second and third trimester human fetal brain. It can also be used to non-invasively assess abnormal connectivity in brain malformations like the Probst bundles in cases of agenesis of the corpus callosum. Although typically performed on 1.5T MR scanners, recently a growing interest in 3T fetal MR examinations has emerged, as the higher image resolution and SNR with 3T may allow the identification of finer structures and lesions. As exciting as these new developments in fetal MRI may be, they also underline the growing need for cross validation of in utero imaging results with postnatal imaging and, in the case of fetal death, postmortem MRI and histology.