МЕЂУНАРОДНА ИСТРАЖИВАЧКА
АКАДЕМИЈА НАУКА И УМЕТНОСТИ - МИАНУ
INTERNATIONAL RESEARCH ACADEMY OF
SCIENCE AND ART – IRASA

# IRASA
# International Scientific Conference
# SCIENCE, EDUCATION, TECHNOLOGY AND INNOVATION
# SETI V 2023

## Book of Proceedings

**Belgrade,**

**October 14, 2023**

*Publisher*
IRASA – International Research Academy of Science and Art

*For the Publisher*
Academician Prof. Vladica Ristić, PhD

*Editors*
Academician Prof. Vladica Ristić, PhD
Academician Prof. Marija Maksin, PhD
Academician Prof. Jelena Bošković, PhD

*Print run*
150

*Printed by*
Instant system

Belgrade, 2023

**ISBN 978-86-81512-11-1**

Publication of the Book of Proceedings has been co-financed by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia.

# GENETIC APPROACH AND EXPLANATION OF INTELLIGENCE

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## Abstract

The brains of some people seem to be more efficient than the brains of others, but what is the neurobiological basis of human intelligence? The former focuses on identifying genes and genetic loci linked to intelligence, while the latter identifies the macroscopic structure and function of the brain to identify the brain regions involved in intelligence. How the characteristics of brain cells relate to intelligence is a mystery. However, the development of transcriptomics and cellular neuroscience of intelligence may offer a third approach and close the gap between genes for intelligence that have been identified and brain structure and function. We also go over the initial research that indicates a connection between particular brain cell populations and intelligence. Finally, we emphasize how particular genes that have been discovered produce cellular characteristics linked to intelligence and may eventually explain the structure and operation of the involved brain regions. By doing this, the way is cleared for a cellular understanding of intelligence, which will offer a conceptual framework for comprehending how the identified gene constellations support the cellular processes that underpin intelligence.

**Key words:** *Intelligence, temporal cortex, frontal cortex, pyramidal cells, dendrites, GWAS of gene expression, action potentials.*

## Introduction

Intuitively, we all know what it means to be intelligent, although definitions of intelligence can vary widely. It is something that helps us plan, reason, solve

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problems, learn quickly, think for ourselves, make decisions and ultimately survive in a modern, rapidly changing world. To capture this elusive trait, cognitive tests have been developed to measure performance in various cognitive areas such as processing speed and language. It quickly became clear that the results of various cognitive testswere highly correlated and created a strong general factor underlying various abilities: general intelligence or Spearman-g (Spearman, 1904). One of the most commonly used tests today to assess Spearman's g is the Wechsler Adult Smart Scale (WAIS).This test combines the results of multiple cognitive tests into a single measure, complete IQ. Tests can measure human intelligence. Does it make sense to express them in a single number: the IQ score? Despite criticism of this reductionist approach to intelligence, the tests have proven to be valid and useful. First, IQ test results are highly correlated with life outcomes, including socioeconomic status and cognitive abilities, even when measured early in life (Foverskov et al., 2017). Increasing complexity and a technology-dependent society place increasing cognitive demands on individuals in almost all aspects of daily life, such as: B. Banking, using maps and timetables, reading and understanding forms and interpreting newspaper articles.Greater intelligence brings many seemingly small benefits, but they add up and impact an individual's overall life chances (Gottfredson, 1997). These include benefits for socioeconomic status, education, social mobility, work performance, and even lifestyle choices and longevity (Lam et al., 2017). Second, intelligence turns out to be a very stable trait from youth to old age in the same person. In a large longitudinal study of English children, the correlation was 0.There were 81 observations between intelligence at age 11 and performance on national academic achievement tests five years later. This contribution of intelligence was evident in all 25 academic disciplines (Dary et al., 2007). Even at much older ages, intelligence remains stable: a single general intelligence test taken at age 11 correlates strongly with performance on a test taken at age 90 (Dary et al., 2013).Finally, one of the most striking findings from twin studies is that the heritability of intelligence is extremely high, ranging from 50 to 80% and in the case of verbal IQ up to 86% (Posthuma et al., 2001). This makes human intelligence one of the most heritable behavioral traits (Plomin and Deary, 2015). Furthermore, assortative mating results in additive genetic variance in the population in each generation, contributing to this high heritability (Plomin and Deary, 2015). Therefore, despite its elusive definition, intelligence is the basis of individual differences between individuals.It can be measured with cognitive tests, and the results of these tests have proven their validity and usefulness: measures of intelligence are stable over time, have high heritability, and predict important life outcomes.

## Biological basis of intelligence: a whole-brain perspective

A question that has puzzled scientists for centuries is that of the origin of human intelligence. What makes some people smarter than others? The search for answers to these questions began in the 1830s in Europe and Russia, where the brains of deceased elite scientists and artists were systematically collected and carefully examined (Vein

and Maat-Schieman, 2008). However, all attempts to explore his unique skills and talents at the time failed to reveal much. The prevailing hypothesis over the last century was that smarter people had bigger brains.With advances in neuroimaging technology, this hypothesis has been tested in numerous studies. In fact, a meta-analysis of 37 studies involving more than 1,500 people on the relationship between in vivo brain volume and intelligence found a moderate but significant positive correlation of 0.33 (McDaniel, 2005). A more recent meta-study with 88 studies involving more than 8,000 people again found a significant, positive and slightly lower correlation coefficient of 0.24.

## Brain Areas Are Important for Intelligence

Brain functions are distributed across different areas that perform specific functions. Can intelligence be assigned to one or more of these areas? Structural and functional brain imaging studies have focused on the localization of general intelligence in the brain and the relationship between specific types of cognition and specific brain regions (Deary et al., 2010). Early imaging studies linking intelligence to brain structure found that full IQ scores, a measure of general intelligence, showed a broad pattern of correlations with brain structures: IQ scores correlated with intracranial, cerebral, temporal lobe, hippocampus - and cerebellar volumes (Andreasen et al., 1993), which together cover almost all areas of the brain. Voxel-based morphometry (VBM), an imaging analysis technique used to assess focal differences in brain structure, allows us to see whether these areas are clustered or scattered throughout the brain. Application of VBM to brain imaging data revealed that positive correlations between intelligence and cortical thickness are located primarily in multiple association areas of thefrontal and temporal lobes (Hulshoff Pol et al., 2006; Narr et al., 2007; Choi et al. ., 2008; Karama et al., 2009). Based on 37 neuroimaging studies, Jung and Haier (2007) showed that in particular the structure of the Brodmann frontal areas 10, 45 to 47, the parietal areas 39 and 40 and the temporal areas 21 positively influences IQ values (Jung and Haier, 2007) . ). ). This model was expanded in subsequent studies to include the frontal eye field, the orbitofrontal area, as well as a large number of temporal lobe areas: the inferior and middle temporal gyri, the parahippocampal cortex, and the association cortex (Narr et al., 2007; Choi et al. , aluminum.

## Brain structure changes

The structure of the brain is not fixed at a specific point in development and remains unchanged for the rest of our lives. Gray matter volume changes throughout childhood and adulthood (Gogtay et al., 2004) and is influenced by learning, hormonal differences, experience, and age. Changes in gray matter may be due to rearrangements of dendrites and synapses between neurons (Gogtay et al., 2004).When people learn a new skill such as juggling, transient and selective structural changes are observed in brain regions associated with processing and storing complex

visual movements (Draganski et al., 2004). Likewise, gender and age differences are important factors that influence brain structure and may influence areas of the cerebral cortex associated with intelligence.Significant gender differences in the pattern of correlations between intelligence and regional gray and white matter volumes have been reported (Haier et al., 2005; Narr et al., 2007; Yang et al., 2014; Ryman et al., 2016), reports are not entirely consistent regarding which brain regions show gender differences or their relationship to cognitive performance. Haier et al. (2005) reported correlations between IQ and parietal and frontal areas in men, while in women the correlations were found mainly in the frontal lobe (Haier et al., 2005). Similar results were reported by Ryman et al. (2016), frontoparietal gray matter was more strongly associated with general cognitive ability in men. However, in women, results showed an association with intelligence in terms of white matter efficiency and total gray matter volume (Ryman et al., 2016).However, Narr et al. to other conclusions. (2007), where women showed a significant association in gray matter thickness in the prefrontal and temporal association cortices, while men showed this association mainly in the temporo-occipital association cortices (Narr et al., 2007). Finally, a recent study that used surface morphometry (SBM) instead of VBM found significant group differences in brain structure between genders, but cognitive abilities were not associated with within and between genders (Escorial et al., 2015). . .Research agrees that there are significant gender differences in brain structure, but these differences do not always underlie differences in cognitive function. For example, a known difference in brain structure between the sexes is the greater thickness of the cerebral cortex in men compared to women (Lüders et al., 2002), but a connection between the full IQ score and the volume of brain tissue does not exist. do not differ in men and women with greater cerebral cortical thickness than inwomen (Lüders et al., 2002), but the associations between full IQ score and brain tissue volume did not differ between men and women (Narr et al., 2007). ; Escorial et al., Aluminum, 2015).

## Age matters

Furthermore, different areas have their own maturation schedule: the higher-order association cortex matures only after the lower-order somatosensory and visual cortices (Gogtay et al., 2004). Correlations with intelligence follow a similar evolutionary curve. The strongest correlations between gray matter volume and intelligence were observed in children around 10 years of age (Shaw et al., 2006; Jung and Haier, 2007).However, at age 12, when cortical thinning begins, a negative relationship emerges (Brouwer et al., 2014). Furthermore, the overall maturation pattern of the cerebral cortex appears to be different in more intelligent children. Children with higher IQs exhibit a particularly malleable cortex, with an initial period of accelerated and prolonged cortical growth and equally severe cortical thinning during early adolescence (Shaw et al., 2006).

## Brain specialization to different types of intelligence

In addition to connections between cortical structure and intelligence, imaging studies have revealed connections between the functional activation of cortical areas and intelligence. Psychology distinguishes two types of intelligence that together make up Spearman's g: crystallized intelligence and liquid intelligence. Crystallized intelligence builds on prior knowledge and experience and reflects verbal perception, whereas fluid intelligence requires adaptive thinking in new situations (Carroll, 1993;Engle et al., 1999).Numerous studies show that fluid intelligence is based on a more efficient functioning of distributed cortical areas (Duncan et al., 2000; Jung and Haier, 2007; Choi et al., 2008). In particular, the lateral frontal cortex, with its well-known role in thinking, attention, and working memory, appears to support fluid intelligence, but the parietal lobe also plays a role. One of the first studies of fluid intelligence using Raven's advanced progressive matrices by Haier et al. (1988) demonstrated activation of multiple areas of the left hemisphere, particularly the posterior cortex.Cognitive performance has shown a significant negative correlation with cortical metabolic rate, suggesting more efficient neural circuits (Haier et al., 1988). In later research, fluid intelligence has been strongly linked to the function and structure of frontal lobe regions (Choi et al., 2008). When participants performed verbal and nonverbal versions of a difficult working memory task while their brain activity was measured using functional magnetic resonance imaging (fMRI), those with higher fluid intelligence weremore accurate and had increased event-related neural activity in the lateral prefrontal area and parietal regions (Gray et al., 2003). Also in a PET study, participants showed selective recruitment of the lateral frontal cortex during more complex cognitive tasks compared to simpler tasks (Duncan et al., 2000). In a recent report, gray matter volume measurements in two frontal regions—the orbitofrontal cortex (OFC) and the anterior anterior cingulate cortex (rACC)—were complemented by white matter connectivity between these regions. Overall, left gray matter volume and white matter connectivity between the left posterior OFCand the rACC accounted for up to 50% of the variance in general intelligence.Therefore, particularly in the prefrontal cortex, structure, function and connectivity are linked to general intelligence, particularly reasoning and working memory (Ohtani et al., 2014). In contrast, crystallized intelligence, which is largely based on verbal abilities, depends more on the structure of the cortex and its thickness in the lateral regions of the temporal lobes and the temporal pole (Choi et al., 2008; Colom et al., 2009) .Thus, subdividing Spearman's *g* reveals distinct cortical distributions involved in subdomains of intelligence. It is likely that further subdividing fluid and crystallized intelligence, for instance in verbal comprehension, working memory, processing speed, and perceptual organization, may result in a more defined map of cortical regions on left and right hemisphere that relate to these subdomains of intelligence (Jung and Haier, 2007).

## White matter and intelligence

Not only gray matter but also white matter volume has been linked to intelligence, which can be explained by common genetic ancestry (Posthuma et al., 2002). White matter consists of myelinated axons that carry information from one area of the brain to another, and the integrity of white matter tracts is essential for normal cognitive function. Therefore, specific patterns of white matter separation are associated with general inherited cognitive and psychopathological factors (Alnæs et al., 2018).Yu et al. (2008) found that patients with intellectual disability experienced significant impairments in the integrity of white matter tracts, as assessed by fractional anisotropy. IQ scores were significantly correlated with the integrity of multiple white matter tracts in healthy controls and patients with intellectual disability (Yu et al., 2008). This connection was particularly clear in the right monofascicle, which connects parts of the temporal lobe with areas of the frontal lobe (Yu et al., 2008). These results support previous findings linking gray matter volume, particularly the temporal lobe and frontal lobe, to intelligence (Hulshoff Pol et al., 2006; Narr et al., 2007; Choi et al., 2008; Karama et al., 2009) and point out that intact connectivity between these areas is important for intelligence.Longitudinal studies tracking white matter changes during development and aging also show that white matter changes are associated with changes in intelligence. During brain maturation in children, white matter structure is linked to intelligence. In a large sample (n = 778) of children aged 6–10 years, white matter microstructure was associated with nonverbal intelligence and visuospatial abilities regardless of age (Muetzel et al., 2015).In another study examining white matter in typically developing children compared to children with learning disabilities, white matter connectome efficiency was strongly associated with intelligence and academic success in both groups (Bathelt et al., 2018).Even in later life, changes in white matter microstructure are associated with changes in intelligence (Ritchie et al., 2015).Significant correlations have been found between the 12 major white matter areas and general intelligence in older adults (Penke et al., 2012). Subsequent analyzes showed that the integrity of the lower part of the white matter has a significant negative impact on general intelligence due to the reduced speed of information processing (Penke et al., 2012). Thus, the brain's structurally intact axonal fibers provide the neuroanatomical infrastructure necessary for rapid information processing in large brain networks and supporting general intelligence (Penke et al., 2012).

## Gross brain distribution of intelligence

Thus, both functional and structural neuroimaging studies show that general intelligence cannot be attributed to one specific region. Rather, intelligence is supported by a distributed network of brain regions in many, if not all, higher-order association cortices, also known as parietal-frontal network (Jung and Haier, 2007). This network includes a large number of regions—the dorsolateral prefrontal cortex,

the parietal lobe, and the anterior cingulate, multiple regions within the temporaland occipital lobes and, finally, major white matter tracts. Some limited division of function can be observed, implicating frontal and parietal areas in fluid intelligence, temporal lobes in crystallized intelligence and white matter integrity in processing speed.Although brain imaging studies have identified anatomical and functional correlates of human intelligence, the actual correlation coefficients have consistently been modest, around 0.15–0,35 (Hulshoff Pol i in., 2006 ; Narr i in., 2007 ; Choi i in., 2008 ; Karama i in., 2009). This most likely has various causes, but the important conclusion is that human intelligence can only be partially explained by the structure of the brain and the functional activation of cortical areas observed on MRI. There are other factors that influence intelligence that need to be taken into account. From an evolutionary perspective, the human brain has unique cognitive abilities compared to other species, which include many human-specific abilities: abstract thinking, language and creativity. However, the anatomy of the human brain is not significantly different from that of other mammalian species and cannot satisfactorily explain the apparent evolutionary leap in intelligence.In terms of both size and number of neurons, the human brain is evolutionarily unremarkable: elephants and whales have larger brains (Manger et al., 2013) and the cerebral cortex of long-finned whales contains more neurons (37 billion) of people (from 19 to 23 billion; Pakkenberg and Gundersen, 1997; Herculano-Houzel, 2012; Mortensen et al., 2014). In particular, the brains of our closest evolutionary neighbors, non-human primates, show striking similarities. In fact, the human brain is, for all intents and purposes, the brain of an anatomically enlarged primate (Herculano-Houzel, 2012), and there appear to be few unique or unusual features to which exceptional cognitive abilities can be attributed.Therefore, the answer to the question of the origin of human intelligence and its differentiation between individuals should probably be sought not only in the general anatomy of the brain, but rather at the level of its components and computational units: neurons, synapses and their genes compose.

## A genetic approach to intelligence

Given that intelligence is one of the most heritable traits, it follows that also its neurobiological correlates should be under strong genetic influence. Indeed, both cortical gray and white matter show a gradient of similarity in subjects with increasing genetic affinity (Thompson et al., 2001; Posthuma et al., 2002). This structural brain similarity is especially strong in frontal and lateral temporal regions, which show most significant heritability (Thompson et al., 2001). Hence, overall brain volume links to intelligence and to a large extent shares a common genetic origin. How and when during the development is genetic influence exerted by individual genes and what are the genes that determine human intelligence?

## Genes of intelligence

Over the last decade, genome-wide association studies (GWAS) have emerged as a powerful tool for studying genes that drive variation in many human traits and diseases (Bush and Moore, 2012). GWAS studies examine relationships between phenotypes and genetic variants – single nucleotide polymorphisms (SNPs) – in large groups of unrelated people. Although the vast majority of SNPs have minimal effects on biological pathways, some SNPs can also have functional consequences by causing changes in amino acids, leading to the identification of the genetic basis of a disease or trait (Bush and Moore, 2012). .After the first wave of clarification, GWAS studies largely produced non-reproducible results (Butcher et al., 2008; Davies et al., 2011, 2015, 2016; Trampush et al., 2017) it became evident that intelligence is a highly polygenic trait and much larger sample sizes are needed to reliably identify contributing genes (Plomin and von Stumm, 2018). Meta-analysis of the first 31 cohorts (N = 53,949) could only predict 1.2% of the variance in general cognitive function in an independent sample and biological pathway analysis did not produce significant findings (Davies et al., 2015).Using education level as an indicator of intelligence phenotype increased both the sample size and the number of associated genes found. Level of education is the number of years a person has spent in full-time education. Both phenotypically (Dary et al., 2010) and genetically (Trampush et al., 2017) it is strongly related to IQ.Because years of schooling are one of the most common metrics collected on a regular basis, this approach increased the sample size in the recent GWAS study to 400,000 (Okbay et al., 2016). Even larger samples were obtained by combining GWAS cognitive abilities with academic performance (Lam et al., 2017; Trampush et al., 2017) and focusing on GWAS intelligence in multiple cohorts (Savage et al., 2018; Zabaneh et al., 2018).

## Intelligence is a polygenic trait

The most recent and largest genetic association study of intelligence to date identified 206 genomic loci and included 1,041 genes, adding 191 new loci and 963 new genes to those previously associated with cognitive abilities (Savage et al., 2018). These results show that intelligence is a highly polygenic trait, with little or no influence on many different genes, most likely at different stages of development. In fact, the effect sizes reported for each allele are extremely small (generally less than 0.1%, even for the strongest effects), and the combined genome-wide effects explain only a small fraction of the total variance (Lam et al., 2017). For example, the strongest effect of identified alleles on academic performance explains only 0.022% of the phenotypic variance in a replication sample (Okbay et al., 2016), and combined genome-wide effects predict only a small fraction of the total variance in a fixed-sample sample ( Lam et al., 2017).At the same time, the overall heritability of SNPs reported in a recent GWAS study is around 20–21% (Lam et al., 2017; Trampush et al., 2017; Savage et al., 2018; Coleman et al. ., 2019). ). , less than half of the heritability estimates in twin studies

(>50%; Plomin and von Stumm, 2018).However, small genetic effects at critical developmental stages can have significant effects on brain function and development and thus on cognitive abilities. It is therefore important to know which genes are identified, but also when and where they are expressed in nervous tissue.

## Most SNPs found in non-coding regions

Noncoding regions cover the majority of the human genome and contain a significant proportion of risk alleles for neuropsychiatric diseases and behavioral traits. Over the last decade, more than 1,200 GWAS studies have identified nearly 6,500 SNPs that predispose to diseases or traits, but only 7% of these are located in protein-coding regions (Pennisi, 2011). The remaining 93% are located in non-coding regions, suggesting that GWAS-associated SNPs regulate gene transcription levels rather than altering the protein coding sequence or protein structure.A very similar situation arises in the case of GWAS intelligence studies. SNPs significantly associated with intelligence are found primarily in the intron (51.3%) and intergenic regions (33.4%), while only 1.4% are exonic regions (Savage et al., 2018). Similar distributions have also been found in previous association studies (Sniekers et al., 2017; Coleman et al., 2019). However, it is these noncoding gene regulatory regions that make the genome responsive to changes in synaptic activity and are an important driver for the development of human cognitive abilities (Hardingham et al., 2018). Although the function of most intergenic regions of human DNA remains poorly defined, new insights are emerging from studies combining high-resolution mapping of noncoding elements, chromatin accessibility, and gene expression profiling.These studies link regulatory elements to target genes. Therefore, neurogenesis and cortical expansion in humans are thought to be controlled by specific genetic regulatory elements, human-derived enhancers (HGE), which show increased activity in the human lineage (de la Torre-Ubieta et al., 2018). Furthermore, genetic variants associated with academic performance have been shown to be enriched in regulatory elements involved in cortical neurogenesis (de la Torre-Ubieta et al., 2018).Therefore, the effects of genes on cognition are unlikely to function independently of environmental factors, but rather are revealed through signal-regulated and experience-driven transcription. This interplay of epigenetic effects via regulatory elements and genetic structure would also explain the increasing heritability of intelligence with increasing age (Bergen et al., 2007; Davis et al., 2008; Plomin and Deary, 2015). The same regulatory genes require appropriate gene-environment interactions to reveal their role in cognitive abilities.In other words, over development, the same set of genes exerts increasing influence on intelligence as early levels of cognitive ability are enhanced through environmental selection and education consistent with those ability levels (Briley and Tucker-Drob, 2013). . ; Plomina).and by Stumma, 2018).

## Most genes are active during neurodevelopment

Many GWAS results identify genes and biological pathways that are primarily active at different stages of prenatal brain development (Bergen et al., 2007; Okbay et al., 2016; Lam et al., 2017; Sniekers et al., 2017; Trampush et al. Aluminum., 2017). Some of these genes have previously been linked to intellectual disability or developmental delay (Coleman et al., 2019). Notably, some genes with known mutations that have a large impact on mental illness show weaker regulatory effects on cognition, suggesting natural dose-response curves related to gene function (Trumpush et al., 2017; Coleman et al., 2019).Combining SNP data with transcriptome data showed that candidate genes are expressed above baseline in the brain throughout life, but have significantly higher expression levels in the brain during prenatal development (Okbay et al., 2016). When genes are divided into functional groups, many of these groups associated with academic performance are primarily involved in different stages of neuronal development: the proliferation of neuronal progenitor cells and their specialization, the migration of new neurons into different layers of the cortex, the projection of neuron axons toward the signaling target and dendritic sprouting (Okbay et al., 2016).Even in the case of intelligence, gene set analysis identifies neurogenesis, neuronal differentiation and regulation of neurodevelopment as major functions of the identified SNPs (Savage et al., 2018).Some examples from the most recent GWAS study include genes with known functions in cell proliferation and mitosis: the GNL3 gene is involved in stem cell proliferation, NCAPG stabilizes chromosomes during mitosis, and DDX27 alters the secondary structure of RNA and is involved in embryogenesis and involved in growth and department (NCBI Resource Coordinators, 2017; Savage et al., 2018). Finally, the largest and most comprehensive group of genes related to academic performance includesgenes with transcriptional cofactor activity (Okbay et al., 2016), supporting the role of candidate genes in neurological development and regulation of gene expression. In fact, many protein-coding genes identified in the latest GWAS intelligence study produce products that contain domains that interact with DNA and RNA, such as the zinc finger and RING finger domains (ZNF446, MZF1, ZNFX1, ZNF638, RNF123) or known partners that bind RNA. (RBFOX).and CELF4; NCBI Resource Coordinators, 2017; Savage et al., 2018).

## Genes involved in cell-cell interactions

Many identified genes that play a role in nervous system development can influence synaptic function and plasticity. Brain function relies on highly dynamic, activity-dependent processes that turn genes on and off. These can lead to profound structural and functional changes and include the formation of new synapses and the elimination of unused synapses, as well as changes in the cytoskeleton, receptor mobility and energy metabolism. Cognitive abilities may depend on how effectively neurons can regulate theseprocesses. Cellular interactions with the environment play

a fundamental role in neurological development and synaptic function.Many of the key protein-coding genes associated with cognitive ability are membrane-anchored proteins responsible for cell-cell and cell-matrix communication. For example, the ITIH3 gene, which encodes a protein that stabilizes the extracellular matrix. Another example is the LAMB2 gene, which encodes laminin, an extracellular matrix glycoprotein, an important component of basement membranes. In addition, several cadherin genes, from PCDHA1 to PCDHA7, CDHR4, which are involved in cell adhesion, are associated withcognitive abilities (NCBI Resource Coordinators, 2017; Savage et al., 2018).Furthermore, in the extremely high IQ cohort, the most enriched gene in terms of association is ADAM12, a membrane-anchored protein involved in cell-cell and cell-matrix interactions (Zabaneh et al., 2018). Finally, some candidate genes encoding cell adhesion molecules (DCC and SEMA3F; Savage et al., 2018) are particularly involved in axon guidance during neuronal development.Some candidate genes are involved in the regulation of various signaling pathways via surface receptors.These examples include DMXL2, which regulates the Notch signaling pathway; The signal peptide peptidase SPPL2C as 2C, the ring finger 43 protein RNF43, which negatively regulates Wnt signaling pathways (Savage et al., 2018), and the WNT4 gene, which encodes secreted signaling proteins (Sniekers et al., 2017; Coleman et al., 2019). These signaling pathways play a fundamental role in embryogenesis, cell proliferation, migration, but also in synaptic communication during development.Interestingly, recent large-scale genetic profiling based on cellular resolution has identified species-specific differences in exactly the same functional categories of genes involved in intercellular communication (Zeng et al., 2012). Comparing mouse and human gene expression profiles in the neocortex revealed differences between species in gene expression, including genes for secreted protein (48%), extracellular matrix (50%), cell adhesion (36%) and the peptide ligands (31%). These results may highlight the importance of cell-environment interactions not only for human intelligence but also for human evolution in general.

## Genes of synaptic function and plasticity

Some GWAS results on intelligence point directly to genes with known functions in synaptic communication, plasticity, and neuronal excitability. Some identified genes are mainly involved in presynaptic organization and vesicle release. One of these is TSNARE1, which encodes a t-SNARE domain containing 1 (Savage et al., 2018). The main role of SNARE proteins is to ensure the docking of synaptic vesicles to the presynaptic membrane in neurons and vesicle fusion (NCBI Resource Coordinators, 2017). In addition, at least two other identified genes are involved in vesicle transport: GBF1 mediates vesicle transport into the Golgi apparatus and ARHGAP27 plays a role in clathrin-mediated endocytosis. Finally, the BSN gene encodes a scaffolding protein involved in the organization of the presynaptic cytoskeleton.One of the transcriptional activators associated with intelligence is the cAMP-responsive element binding 3L4 (CREB3L4). This gene encodes CREB, a nuclear protein that modulates gene transcription. It is an important component of intracellular signaling events and has

extensive biological functions.However, the best documented and most studied role of neurons is the regulation of synaptic plasticity, learning and memory formation (Silva et al., 1998).The use of drug target databases and associated gene annotations can shed new light on the association of drug gene sets with phenotype (Gaspar and Breen, 2017). This drug pathway analysis, combined with GWAS intelligence results, revealed that the target genes of two drugs involved in synaptic regulation and neuronal excitability were significantly enriched: a T-type calcium channel blocker and an inhibitor of potassium channels (Lam et al., 2017). ). . .In a related drug class analysis, significant enrichment for voltage-gated calcium channel subunits was also observed (Lam et al., 2017). In another study, genes involved in regulating the voltage-gated calcium channel complex were also significantly associated with academic performance in a previous study (Okbay et al., 2016). Both types of ion channels play a key role in synaptic communication and action potential activation.T-type calcium channels are involved in firing action potentials and switching between different firing modes (Cain and Snutch, 2010). Potassium channels are crucial for rapid repolarization during AP generation and for maintaining resting membrane potential (Hodgkin and Huxley, 1952).

## Genes with supporting functions

The human brain uses at least 20% of the energy used by the entire body. The majority of this energy requirement is spent on the generation of postsynaptic potentials (Attwell and Laughlin, 2001; Magistretti and Allaman, 2015). Notably, the emergence of higher cognitive functions in humans during evolution is also associated with increased expression of energy metabolism genes (Magistretti and Allaman, 2015). Genes involved in energy supply and metabolism may therefore influence the maintenance of high-frequencyemissions during cognitive tasks. In fact, cognitive ability is associated with genetic variation in several genes encoding regulators of mitochondrial function – GPD2, NDUFS3, MTCH2 (NCBI Resource Coordinators, 2017; Savage et al.Microtubules are an essential part of the cytoskeleton and are involved in maintaining cell structure during development. At the same time, microtubules represent important intracellular transport routes and thus influence the recycling of synaptic receptors and the release of neurotransmitters in neurons (Hernández and Ávila, 2017). Several studies have linked the MAPT gene, which encodes a microtubule-associated protein, to intelligence (Sniekers et al., 2017; Trampush et al., 2017; Savage et al., 2018; Coleman et al., 2019). MAPT is also impaired in many brain diseases: Alzheimer's disease, Parkinson's disease and Huntington's disease (Hernández and Ávila, 2017). In addition to MAPT, other genes encoding microtubule-related proteins have been shown to be significantly associated with intelligence: microtubule-associated serine/threonine kinase 3 (MAST3), ALMS1 functions in microtubule organization, and SAXO2 (FAM154B), a microtubule stabilizer protein. (NCBI Resources Coordinators, 2017; Savage et al., 2018).

## Conclusions from genetic studies

Taken together, twin studies show that individual differences in human intelligence can largely (50-80%) be explained by genetic influences, making intelligence one of the most heritable traits. However, current GWAS studies can capture less than half of this heritability (21–22%; Lam et al., 2017; Trampush et al., 2017; Savage et al., 2018; Coleman et al., 2019). Furthermore, genetic influences are attributed to small influences from a large number of genes. 95 percent of these genetic variants occur in intronic and intergenic regions and could have gene regulatory functions. Only a very small proportion of the associated SNPs (1.4%) are found in DNA fragments translated into proteins.Most of the associated genes are involved in early, probably prenatal, development, and some genes are essential for synaptic function and plasticity throughout life. The fact that traits such as height/birth weight and longevity have strong polygenic correlations with cognitive outcomes (Lam et al., 2017; Trampush et al., 2017) suggests that overall healthy development is a prerequisite for optimal cognitive function .GWAS tests possible relationships between genes and phenotype.However, the availability of cell type- and tissue-specific transcriptome data from postmortem human brains (Ardlie et al., 2015) has opened a new horizon for GWAS research. By linking GWAS data with cell type- and tissue-specific transcriptome profiles (GTEx), it is possible to indicate in which brain region or even in which cell type intelligence genes are potentially expressed. This approach has obvious caveats because intelligence-related genes do not need to be expressed simultaneously during development and because the brain locations responsible for intelligence are widely distributed, not all genes need to be expressed in the same brain. Area or cell type. However, using this approach, genes associated with academic performance and intelligence were found to be preferentially co-expressed in neural tissue (Okbay et al., 2016; I'm in, 2017; Trampush in., 2017; Wild Inside., 2018; Coleman, 2019).In particular, the hippocampus, midbrain, and global and frontal cortical areas show the greatest enrichment in the expression of these genes (Savage et al., 2018; Coleman et al., 2019). With the exception of the midbrain, these are areas of the brain that have already been linked to intelligence in brain imaging studies.gene expression profiles of cell type-specific intelligence illustrate the role of neuronal cell types.Although glial cells are the most abundant cell type in the human brain (Vasile et al., 2017), no evidence of enrichment of candidate genes in oligodendrocytes or astrocytes has been found (Lam et al., 2017; Trampush et al., 2017). . . Neurons remain the main carriers of genetic variation. Further analysis of neuron types revealed significant enrichment of associated genes in pyramidal neurons in area CA1 of the hippocampus and in somatosensory areas of the cortex.In addition, significant associations were found in the main cell type of the striatum, medium spiny neurons (Savage et al., 2018; Coleman et al., 2019).

## Cells of intelligence

Since Ramón y Cajal postulated his neural doctrine of information processing and called neurons “butterflies of the soul” (Cajal, 1893), neuroscience has agreed that the basis of human intelligence must lie in neurons or neural networks. However, neuroscientific research into the biological basis of intelligence has so far focused almost exclusively on the macroscopic level of the brain and the genetics of intelligence, leaving a large gap in knowledge at the cellular level.We consider that our mind functions thanks to the activity of 86 billion neurons (Herculano-Houzel, 2012) and their connections, which represent the main components of encoding, processing and storing information in the brain and ultimately They lead to cognitive processes ( Salinas and Sejnowski, 2001). Given the astronomical number of neuronal connections (Drachman, 2005), even small changes in the efficiency of information processing by neurons can lead to large differences in cognitive abilities.In fact, one of the most robust and reproducible relationships in behavioral psychology is the relationship between intelligence and mental processing speed, as measured by the reaction time of the subjects studied (Vernon, 1983; Barrett et al., 1986). However, there has been little research into the question of whether the activity and structure of individual human neurons support human intelligence and how the properties of our brain cells can accelerate mental processing.This lack of knowledge is not surprising: access to neurons in the living human brain is very limited and most knowledge about neuronal function comes from studies of laboratory animals. In recent decades, the use of brain tissue harvested during neurosurgical treatment of epilepsy or cancer has opened up new opportunities for studying the human brain at the cellular level (Molnár et al., 2008; Testa-Silva et al., 2010, 2014; Verhoog et al., 2013, 2016). To gain access to affected deep brain structures, neurosurgeons dissect the overlying non-pathological neocortex, which can be transported to the laboratory for further examination. Combined with preoperative cognitive testing, this approach provides an excellent opportunity to study neural function related to human intelligence. This use of live human brain tissue from neurosurgery cannot be replaced by other techniques: post-mortem tissue is generally not suitable for physiological studies (but see Kramvis et al., 2018), while brain imaging studies lack the necessary cellular precision.

## The key role of pyramidal neurons

Genetic studies indicate that expression of intelligence-related genes accumulates in cortical pyramidal neurons (Savage et al., 2018; Coleman et al., 2019). Comparisons of the key cellular properties of pyramidal neurons from different species could shed light on the functional significance of these differences for human cognition. In fact, the human tissues used in research always come from higher order association areas, usually the temporal cortex, in order to spare the patient's basic sensory and linguistic functions.These are precisely the areas in which brain imaging influences human

intelligence. What characteristics distinguish pyramidal neurons in the temporal cortex from other types? First, the structure of pyramidal cells is different (Elston and Fujita, 2014): compared to rodents and macaques, human layer 2/3 pyramidal cells have three times larger and more complex dendrites (Mohan et al., 2015). Furthermore, these large dendrites also receive twice as many synapses as rodent pyramidal neurons (DeFelipe et al., 2010; Verhoog et al., 2013). These species differences may indicate evolutionary pressures on dendritic structure and neuronal function in the temporal lobe and indicate human pyramidal cell-specific adaptations in the cognitive functions of these brain regions. Recently, these differences in the function and structure of human pyramidal neurons have been linked to intelligence scores and the anatomical structure of the temporal lobes of the same individuals (Goriounova et al., 2018; Fig. 3).The results showed that high IQ scores are associated with greater temporal cortex thickness in patients undergoing neurosurgery, as well as in healthy individuals (Choi et al., 2008). In addition, the thicker temporal cortex is connected to the larger and more complex dendrites of human pyramidal neurons. Incorporating these realistic dendritic morphologies into the computational model showed that neurons in the larger model were able to process synaptic signals with greater temporal precision.Finally, as predicted by the model, experimental recordings of action potential spiking in human pyramidal neurons demonstrated that individuals with higher IQ scores were able to sustain fast action potentials during neuronal activity. These findings provide the first evidence that human intelligence is associated with larger and more complex neurons and faster action potentials and more efficient synaptic information transfer (Goriounova et al., 2018).

## Connecting levels: genes, cells, networks and brain areas

Pyramidal cells, especially in superficial layers of multimodal integration areas such as temporal or frontal cortex, are main integrators and accumulators of synaptic information. Larger dendrites can physically contain more synaptic contacts and process more information. Indeed, dendrites of human pyramidal neuron receive twice as many synapses than those in rodents (DeFelipe et al., 2002). The increasing information integration capacity of these brain areas is also reflected in a gradient in complexity of pyramidal cells across cortical areas—cells have increasingly larger dendrites in regions involved in higher-order cortical processing (Elston et al., 2001; Jacobs et al., 2001; Elston, 2003; Elston and Fujita, 2014; van denHeuvel et al., 2015). Both in humans and other primates, cortico- cortical whole-brain connectivity positively correlates with the size of pyramidal cell dendrites (Scholtens et al., 2014; van denHeuvel et al., 2015).

Overall, larger dendritic length in human neurons compared to other species, and in particular elongation of their basal dendritic terminals (Deitcher et al., 2017) would enable these cells to use branches of their dendritic tree as independent computational compartments. Recently, Eyal et al. (2016, 2018) have provided new insights into signal processing and computational capabilities of the human pyramidal cells by testing their detailed models including excitatory synapses, dendritic spines, dendritic

NMDA- and somatic spikes (Eyalet al., 2018). The results show that particularly large number of basal dendrites in human pyramidal cells and elongation of their terminals compared to other species result in electrical decoupling of the basal terminals from each other. Similar observations were also recently made by dendritic recordings from human layer 5 pyramidal neurons (Beaulieu-Larocheet al., 2018). In this way, human dendrites can function as multiple, semi-independent subunits and generate more dendritic NMDA- spikes independently and simultaneously, compared to rat temporal cortex (Eyal et al., 2014). Dendritic spikes through NMDA receptors are an essential component of behaviorally relevant computations in neurons. In mice, manipulation of these spikes lead to decreased orientation selectivity of visual cortical neurons linking the function of dendrites to visual information processing by neurons (Smithet al., 2013). Furthermore, larger dendrites have an impact on excitability of cells (Vetter et al., 2001; Bekkers and Häusser, 2007) and determine the shape and rapidity of action potentials (Eyal et al., 2014). Increasing the size of dendritic compartments *in silico* lead to acceleration of action potential onset and increased encoding capability of neurons (Eyal et al., 2014; Goriounova et al., 2018). In addition, compared to mouse, human pyramidal neurons in superficial layers show more hyperpolarization activated currents that facilitate excitability of these cells (Kalmbach et al., 2018).

Thus, larger dendrites equip cells with many computational advantages necessary for rapid and efficient integration of large amounts of information. The fact that the larger and faster human neurons in temporal cortex link to intelligence (Goriounova et al., 2018) provides evidence that there is a continuum of these cellular properties across the human population. At the high end of the IQ score distribution, pyramidal cells of individuals with high IQ receive more synaptic inputs and are able to achieve higher resolution of synaptic integration by processing these multiple synaptic inputs separately and simultaneously. As cells are constantly bombarded by a large load of incoming signals during cognitive activity, the neuron has to relay these multiple inputs into output. Human neurons of individuals with higher IQ are able to translate these inputs into action potentials—output signal of the cell—much more efficiently, transfer more information and sustain fast action potential firing compared to lower IQ subjects. These findings harmonize well with genetic and imaging studies identifying metabolic rate as an important correlate of intelligence (Haier et al., 1988; Savage et al., 2018).

Finally, genetic studies of intelligence also implicate genes supporting dendritic structure in human cognitive ability. Clustering of candidate genes from GWAS of educational attainment in gene sets with known biological function identified gene sets involved in cerebral cortex morphology and specifically in dendrites and dendritic spine organization (Okbay et al., 2016). Furthermore, the strongest emerging genetic association with intelligence established by Sniekers et al. (2017) and later replicated in a much larger sample (Coleman et al., 2019) is in an intronic region of the FOXO3 gene and its promoter. The FOXO3 gene is part of the insulin/insulin-like growth factor 1 (IGF-1) signaling pathway (Costales and Kolevzon, 2016). Notably, IGF-I was shown to increase branching and dendritic size in rat primary

somatosensory cortex, specifically in pyramidal cells in superficial cortical layers (Niblock et al., 2000). Low IGF-1 levels have also been associated with poor cognitive function during aging (Aleman et al., 1999; Tumatiet al., 2016) and a less integrated functional network of connected brain areas (Sorrentino et al., 2017). Thus, individual differences in dendritic elaboration in pyramidal cells are subject to genetic control, go accompanied by functional adaptations in these cells and underlie human variability in intelligence.

How do these findings on cellular and genetic level translate to macroscale findings in brain imaging? One of the most robust finding in brain imaging is that cortical thickness and volume associate with intelligence (Haier et al., 2004; Colomet al., 2006, 2009; Narr et al., 2007; Choi et al., 2008; Karamaet al., 2009). Reconstruction of cortical column at nanoscale resolution shows that cortical volume consists largely of dendritic and axonal processes with 7-fold greater number of axons over dendrites (Kasthuri et al., 2015), only a small proportion of this volume is occupied by cell bodies. The dendrites and axons are structures that mediate synaptic plasticity, store information and continue to grow and change during lifetime. Indeed, during normal postnatal development cortical areas follow a similar pattern: dendrites show continuous growth that is accompanied by increased cortical volume and decreased neuronal densities (Huttenlocher, 1990). In addition, frontal cortical areas that are more shaped by age and experience show a slower time course of these changes compared to primary visual areas that have an earlier critical period (Huttenlocher, 1990). In line with this prolonged development, dendritic trees in human temporal lobe continue to grow throughout maturity and into the old age. In 80-year-olds dendritic trees are more extensive than at the age of 50, with most of the difference resulting from increases in the number and average length of terminal segments of the dendritic tree. The link between dendritic size and cognition is emphasized by the fact that in senile dementia, dendritic trees are less extensive, largely because their terminal segments are fewer and shorter (Buell and Coleman, 1979).

Also, within human cortex, a gradient of dendritic complexity exists across cortical areas. Higher order association areas that store and process more complex information contain neurons with larger and more complex dendrites compared to primary sensory areas. At the same time neuronal cell body density is lower in cortical association areas compared to primary sensory areas (Buell and Coleman, 1979; DeFelipe et al., 2002; Elston, 2003).

A recent study by Genç et al. (2018) used multi-shell diffusion tensor imaging to estimate parieto-frontal cortical dendritic density in relation to human cognition. This study found that higher scores in cognitive tests correlated with lower values of neurite density (Genç et al., 2018). As neurite density decreases go together with the increases of dendrite length (Huttenlocher, 1990), the results obtained by Genç et al. (2018) may indicate that parieto-frontal cortical areas in individuals with higher intelligence have less densely packed neurons, and imply that these neurons have larger dendrites. Taking the results of Gençet al. (2018) and Goriounova et al. (2018) together suggests that the neuronal circuitry associated with higher intelligence is

organized in a sparse and efficient manner. Larger and more complex pyramidal neurons are more dispersed in cortical space and occupy larger cortical volume.

## Future perspectives

Brain imaging has become the cornerstone of research on the neurobiology of intelligence, identifying key functional and structural anatomical regions associated with intelligence: total gray matter volume and thickness, white matter integrity, and function of the temporal, frontal, and parietal cortex. However, it is clear that neuroimaging in its current form cannot provide sufficient temporal and spatial resolution to study the brain'scomputational building blocks: neurons and synaptic contacts. On the other hand, GWAS studies have focused on the other end of the spectrum: intelligence genes. Great progress has been made by increasing the sample size and combining multiple cohorts. The results show that 98% of the associated genetic variants are not encoded in a functional protein and likely have a regulatory function at different stages of neuronal development.However, a small percentage of genes that produce functional proteins are involved in various neuronal functions, including synaptic function and plasticity, cellular interactions, and energy metabolism. Importantly, a growing database of gene expression profiles indicates the expression of related genes in major neurons of the cortex and midbrain: pyramidal neurons and median spiny neurons. The cellular neuroscience of resected human brain tissue may provide a new perspective. Interesting preliminary results have already linked the function and structure of pyramidal cells to human intelligence, revealing positive correlations between dendrite size, action potential velocity and IQ. However, many questions still remain unanswered.What types of neurons are responsible for human intelligence? Recent advances in neuronal genetic profiling at single-cell resolution suggest that approximately 50 transcriptomic cell types in the form of pyramidal cells exist in mice and that several brain regions also contain novel sets of transcriptomic types (Tasic et al., 2018). Information in transcriptomes links types with region-specific long-range target specificity. The same is true for thespiny neurons of the striatum, where a detailed connectivity projection map of the entire cerebral cortex identified 29 distinct functional domains (Hintiryan et al., 2016). Therefore, pyramidal neurons and medium-sized spiny neurons form very heterogeneous populations in which different cell types have different functions and specific connection patterns with the rest of the brain. How do these mouse cell types correspond to human cell types? How do different cell types support the general intelligence and specific cognitive abilities of the human brain? Finding answers will require extensive efforts, analyzing not only large numbers of human cohorts, but alsocells and cell types.This could be possible thanks to recent large-scale collaborative initiatives around the world (Brose, 2016).

**Acknowledgements**

The organizer gratefully acknowledges the work done by Scientific Committee of the SETI V 2023 International Scientific Conference for efforts done for the success of this event.

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CIP - Каталогизација у публикацији Народна библиотека Србије, Београд

0/9(082)(0.034.2)

IRASA. International Scientific Conference Science, Education, Technology and Innovation (5 ; 2023 ; Beograd)
Book of Proceedings [Електронски извор] / [IRASA] International Scientific Conference Science, Education, Technology and Innovation SETI V, Belgrade, October 14, 2023 ; [editors Vladica Ristić, Marija Maksin, Jelena Bošković]. - Belgrade : IRASA - International Research Academy of Science and Art, 2023 (Belgrade : Instant System). - 1 elektronski optički disk (CD-ROM) ; 12 cm

Sistemski zahtevi: Nisu navedeni. - Nasl. sa naslovne strane dokumenta. - Tiraž 150. - Napomene i bibliografske reference uz radove. - Bibliografija uz svaki rad. - Abstracts.

ISBN 978-86-81512-11-1

a) Наука -- Зборници b) Технологија -- Зборници v) Образовање -- Зборници g) Животна средина -- Зборници d) Одрживи развој -- Зборници đ) Национална безбедност -- Зборници

COBISS.SR-ID 128307465