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Executive Functions: Inferences from Behavior, Brain and Genetics

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Abstract

Introduction: The term Executive Functions (EFs) are higher-order cognitive processes that control behavior, emotion, and cognition. Neuropsychological evidence suggests that executive processing is intimately connected with the intact function of the frontal cortices. Executive dysfunction has been associated with a range of disorders, and is generally attributed to structural or functional frontal pathology. Besides, genetic influences tend to explain most of the phenotypic correlations between common EFs and other cognitive and clinical constructs throughout the life span.

Method: This systematic review provides an overview of the EFs and associated components of EFs with inferences from brain, behavior and genetics. Electronic databases were searched for this study. A total of 53 articles met the inclusion criteria (published between 2019 and 2021) and were reviewed.

Results: Recent advances in neuroimaging technologies have allowed ever more detailed studies of the human brain. The combination of neuroimaging techniques with genetics may provide a more sensitive measure of the influence of genetic variants on cognitive function than behavioral measures alone.

Conclusion: These studies demonstrate that EFs are associated with a range of pathologies, collection of cognitive abilities and development of behavioral skills, and based on these results, professionals should consider the role of EFs in interventions.

Keywords: Executive Functions, Behavior, Brain, Genetics

Introduction

Executive functions (EFs) include high-order cognitive abilities such as working memory, inhibitory control, cognitive flexibility, planning, reasoning, and problem solving [1]. EFs enable humans to achieve goals, adapt to novel everyday life situations, and manage social interactions and traditionally EFs have been associated with frontal lobe functioning [1]. childhood to adolescence is an important developmental period for these EFs domains [2]. In models of EFs in adults, an executive component is seen as the seat of control of other functions that produces a coherent response through representing rules and rule structures, inhibiting distracting or incorrect information, updating information while completing a task, and finally, providing a correct response or a chain of responses to the situation. These distinct functions are easily dissociated, and the most commonly studied EFs include working memory, inhibitory control, set switching, and planning [3]. It has been shown that greater EF ability is related to general school readiness for children and quality of life [2]. Previous studies show that the pattern of EFs ability differs in children with neurodevelopmental disorders compared with Typically-Developing (TD) children [2]. EFs are a stronger predictor of school achievement than IQ, and have great impacts on adult outcomes, including Socio-Economic Status (SES) and the likelihood of criminal conviction, even after controlling for SES and IQ [4]. Cognitive processes are so important for the development of social skills, and moderating behavioral responses, in particular EFs and these abilities depend on response inhibition, interference control, working memory, and flexibility, which enable regulation of thought and goal-directed behavior. Executive dysfunctions are suggested to be involved in the development of key symptoms and behaviors in many psychiatric disorders such as Autism Spectrum Disorder (ASD) and schizophrenia in which social dysfunctions and abnormal behavior are included [5]. It has been reported to promote the development of adaptive behavior to change environments and predict long-term life outcomes such as health, wealth, and criminal offending [6]. The development of EFs from infancy to an age of cognitive maturity is a thoroughly studied area of great interest to developmental psychologists [7]. Given these important impacts of EFs, scientific interest in the development of EFs have increased dramatically during the past decades [6].

Method

The Preferred Reporting Items for Systematic Reviews-guidelines were adhered to throughout this review. However, the protocol has not been registered. A systematic search of the literature was conducted to search for English language articles on the online databases PubMed, Scopus, ProQuest, PsycINFO, PsycARTICLES and MEDLINE. The last research was conducted on 1September 2021. The search was performed in two stages, first using broad EF-related terms and then using specific EF subcomponents. Restrictions were made, limiting the research to publications in English before 2019. Studies of human populations have been included, with no restrictions on gender and ethnicity. The search strategy used the following keywords: 'Executive Functions', 'Cognitive Flexibility', 'Working Memory', 'Inhibitory Control', 'Brain Organization of Executive Functions', 'Genetic Mechanisms of Executive Functions', and 'Genome-wide Association Study'. Additional studies were identified from a manual search of the reference lists of included articles. The initial search found 1836 articles. After the elimination of duplicates and irrelevant papers, by the title and abstract reading, 128 articles were read. At the end of the revision, 53 articles were included in the review.

Results

Overview of the Concept of EFs

EFs are a complex set of cognitive and mental capacities and abilities related to goal-directed behavior [8] that include Working Memory (WM), Inhibitory Control (IC), Cognitive Flexibility (CF), planning, reasoning, and problem solving [9]. This complex system has different skills; attention, planning, receiving and manipulating information in a proper way allowing individuals to behave in an integrated manner [8]. These skills are necessary to monitor and execute a sequence of goal-directed complex actions [10]. They are responsible for regulatory control over thought and action. EFs have been considered to have multiple subcomponents, including response inhibition, WM, attentional control, and delay of gratification or delay aversion. These subcomponents assume unique responsibilities and are activated in situations that vary in motivational significance [11]. EFs refer to control of mental processes to facilitate current goals [12] also they are considered to be higher-level cognitive processes that often interact with lower-level cognitive processes, and work in a goal-directed way to enable us to adapt to novel situations or circumstances [13]. EFs are a collection of abilities that permit individuals to set and pursue goals [14]. EFs are an umbrella term for a collection of high-order cognitive abilities, which include decision-making and reward sensitivity, broadly referring to a set of processes that enable flexible reasoning and regulation of behaviors and emotions [15] necessary for the top-down control of goal-directed behavior [6]. EFs which are top-down cognitive processes involved in the "orchestration of basic cognitive processes during goal-oriented problem-solving", are involved in the planning and execution of movement and strongly correlate with functional status [16]. WM, IC and CF set shifting are three core components that constitute the suite of cognitive processes commonly referred to as EFs. Besides to being separable to some extent, these components have a common purpose : the allocation of attention and control over behavior, in order to meet an adaptive goal [7].

Cognitive flexibility/ CF set shifting

Since CF is one of the most essential EFs in everyday communication, we assume that this function should be prioritized [17]. As a core aspect of executive functioning, CF has been defined as the ability to freely shift cognitive sets to perceive or respond to external environment in a variety of ways, including by thinking out multiple solutions to the problem, switching freely between different categories of knowledge, and inhibiting the interferential prepotent responses in order to achieve a specific goal [18]. CF enables individuals to quickly switch to alternative thoughts in the face of problems and not to be obstructed by them and not to experience a kind of despair [19]. Set-shifting, a core component of executive functioning is typically investigated in task-switching procedures [20]. It is the ability to shift focus between mental sets in response to changing demands, and is a measure of CF [21]. Set shifting, also refers to the ability to shift between tasks or mental sets; and updating, referring to the process of updating and monitoring the contents of WM [22]. The year 2020 will be remembered as a time marked by an unprecedented need for flexibility. In response to the global COVID-19 pandemic, governments, institutions, businesses and individuals made necessary and creative adaptations to cope with an uncertain, rapidly evolving situation. This public health and economic crisis necessitated a great degree of cognitive and behavioral flexibility on the part of individuals adapting to the novel situation with which they were confronted. Responses to the pandemic, ranging from denial and maintenance of the status quo to swift and decisive action to curtail the spread of the causative virus, provided a real-world example of why an optimal level of flexibility is adaptive [23].

Working Memory (WM)

WM refers to a set of processes that makes task-relevant information accessible to higher-level cognitive processes such as learning, decision making, reasoning, and reading comprehension. WM is extremely capacity limited, with current research suggesting that between one and four items can be maintained in an activated state in WM at a time [24]. WM is a core cognitive process essential for EFs such as planning and problem-solving [25]. It is a temporary short-term memory storage system distinguished by its capacity to maintain, as well as manipulate, a limited amount of temporally ordered information. It is produced by interactions between functionally specialized brain regions, which subserve various cognitive subprocesses integrated within a large scale frontoparietal network [26]. One of the most dominant theoretical accounts in the literature concerning EFs and reading comprehension is the WM model of Baddeley and Hitch. It proposes that WM is a mechanism that facilitates the ability to store information while simultaneously carrying out processing operations. Therefore, it is considered to be drawn upon when integrating stored representations with incoming information [27]. WM facilitates the process of temporary storage and manipulation of the information necessary for most higher-level cognitive tasks, such as learning, reasoning, and comprehension. Although WM plays an indispensable role for humans in aspects of daily life, academic performance and work, its capacity displays limitation. Moreover, deficits in WM are usually associated with several neuropsychiatric disorders, for instance, cognitive impairment, Parkinson's Disease (PD), Attention-Deficit Hyperactivity Disorder (ADHD), Alzheimer's Disease (AD) and schizophrenia. Encouragingly, increasing evidence on brain plasticity demonstrate that memory performance improvement can be achieved via memory training. The two major memory training approaches are: process-based memory training and strategy-based memory training [28].

Inhibitory Control (IC)

IC represents a central component of EFs. Although various terms and taxonomies exist, a common working definition is that IC focuses on the ability to actively inhibit or delay a dominant response to achieve a goal. Importantly, research has shown that IC represents a core ability that is associated with various types of EFs, e.g., WM updating and shifting. Not surprisingly, the construct is widely used in numerous research domains and has been proposed as an underlying mechanism implicated in different skills and cognitive achievements. For example attention, WM span and reading comprehension, problem solving, general cognitive ability as well as emotion regulation [29]. Among these cognitive functions, IC particularly may play a vital role. IC comprises the ability to withhold automatic or context-inappropriate responses in order to maintain goal-directed behavior [30]. Inhibition refers to mental processes responsible for intentional and voluntary control or the ability to prevent interference of non-pertinent information in the face of responses or patterns of responses underway and to suppress previously relevant information which is not currently useful [31]. Therefore, IC is a key lower-order EFs and is defined as the ability to withhold behavior, thoughts, and/or emotion during distraction [32]. Based on Barkley's model, impairments in inhibitory behavior include delays or disorders in the development of four neurocognitive functions: 1) nonverbal memory, 2) verbal WM, 3) emotional self-regulation, and 4) reconstruction. The most important constituent of this model is inhibitory behavior that provides a foundation for neurocognitive skills. Another constituent is motor control that is directly linked to the previous constituent and intermediates the four aforementioned EFs, which control behavior [33]. Deficient inhibition-related processes have been postulated in several forms of psychopathology and mental disorders, for example rumination and depression, externalizing behavior, ADHD, substance use disorders, schizophrenia, autism and OCD [29].

Development of EFs

EFs govern processes needed on a daily basis when making, planning, and executing goals. To achieve daily goals, individuals must engage WM, response inhibition and CF to respectively, maintain goals, ignore distracting information and invoke flexibility when circumstances or plans change. The period from childhood to adolescence is the important developmental period for these EFs domains [2]. In models of EFs in adults, an executive component is seen as the seat of control of other functions that produces a coherent response through representing rules and rule structures, inhibiting distracting or incorrect information, updating information while completing a task, and finally, providing a correct response or a chain of responses to the situation. These distinct functions are easily dissociated, and the most commonly studied EFs include WM, IC, set switching, and planning. The picture of EFs in children is less clear. In some models, EFs are considered to consist of three distinct functions in children generally comprising WM, IC, and set shifting, whereas other models have still found EFs to be a single factor in young children. Developmentally, EFs are seen as distinguishable both in terms of behavioral function and cortical activation [3]. EFs develop from early childhood into adulthood, and are related to the theory of mind (understanding that others may have a differing viewpoint from one's own) and math and reading abilities. EFs develop over a long time-span, with research starting as early as two years of age and extending well into adulthood. These functions are very important for daily life in adulthood [3]. It has been shown that greater EFs ability is related to general school readiness for children and quality of life [2]. Previous studies show that the pattern of EFs ability differ in children with neurodevelopmental disorders compared with Typically-Developing (TD) children [2]. Goal-directed regulation of thoughts, actions, and emotions is impaired in multiple developmental disorders. Regulatory processes collectively termed EFs permit for managing oneself and our resources flexibly in the pursuit of goals. EFs are a stronger predictor of school achievement than IQ, and has great impacts on adult outcomes, including SES and likelihood of criminal conviction, even after controlling SES and IQ. Processes comprising EFs reflect a spectrum, manifested as dispositional traits at the normative end and psychopathology at the maladaptive end [4]. Current symptom nosology for identifying EFs impairment are limited in capturing heterogeneity observed within and across disorders [4]. Cognitive processes are extremely important for the development of social skills, and in moderating behavioral responses, in particular EFs. These abilities depend on response inhibition, interference control, WM, and flexibility, which enable regulation of thought and goal-directed behavior. Executive dysfunctions are suggested to be involved in the development of key symptoms and behaviors in many psychiatric disorders such as ASD and schizophrenia in which social dysfunctions and abnormal behavior are included [5]. It has been reported to support the management of a wide range of cognitive tasks and promote the development of adaptive behavior to change environments and predict long-term life outcomes such as health, wealth, and criminal offending. Given these important impacts of EFs, scientific interest in the development of EFs have increased dramatically during the past decades [6]. The development of EFs from infancy to an age of cognitive maturity is a thoroughly studied area of great interest to developmental psychologists [7]. Understanding the functional specialization of cortical areas based on their patterns of connectivity has been central to understanding the hierarchies of brain organization [34]. One of the first inclusive reviews of the development of EFs from infancy to early adulthood was published by Adele Diamond in 2002. Diamond’s chapter discussed the normal maturation of the Prefrontal Cortex (PFC) by integrating evidence of developments in cognitive functioning, anatomy and biochemistry. However, Diamond’s chapter closed with a wealth of unanswered questions that were ripe for future investigations at the time: “what are the developmental changes in the PFC that support the improvement in cognitive functions? ”, “ what role do regions beyond the dorsolateral PFC play in subserving cognitive functions?”, and “when do functional connections between frontal regions develop? [7]. EFs refer to the directing, managerial, and guiding function of the brain. It is the “brain of the brain”. In reality, the guiding or managerial function of the brain is a series of directing functions that include a variety of programming and implementing cerebral activities. For E. Goldberg, one of the disciples of the great teacher of neuropsychology, Alexander R. Luria, EFs are intimately connected to the integrity of the frontal lobes, to which he refers to as the “lobes of human civilization” [35]. The definition of EFs have been approached from brain-based research and behavior-based research. The central role of the frontal cortex in EFs has been emphasized in brain-based research for several decades, but recent works have expanded to studying EFs as subserved by networks, that frontal areas are included in all of them, but also incorporate areas such as the amygdala, hippocampus, and cerebellum depending on the EFs of interest. Behavior based research has often defined EFs as control of goal-directed behaviors or regulatory processes that control automatic responses [3]. EFs including the ability to generate actions that are planned and goal directed, necessitate integration of function across circuitries supporting core processes of cognitive function. Developmentally, core EFs function such as WM and cognitive control are present in infancy and show important growth through childhood, and refinement toward reliable engagement in their ability to support higher-order cognition in adolescence [36]. At the level of the brain, even chronic stress can cause structural and functional changes in areas underlying EFs like the PFC and the hippocampus [37]. Traumatic Brain Injury (TBI) causes lifelong cognitive problems , particularly impairments of EFs [38]. Neurocognitive EFs, or the ability to control and influence one's thoughts and actions to achieve goal-orientated behaviors, varies continuously across the general population. EFs are correlated with, but distinguishable from, a general intelligence factor at the phenotypic and genetic levels, and predicts behavior over and above intelligence. Furthermore, EFs are important construct in clinical neuroscience, and EFs impairments are connected with multiple neurological and behavioral disorders, including AD, vascular dementia, lateral sclerosis, and almost all psychiatric disorders, including schizophrenia, depression, ADHD, antisocial personality disorder, sleeping dysfunction, and suicidal ideation. Because of these broad associations, it has been argued that EFs deficits are a common risk factor across all psychiatric symptoms [39].

Brain Organization of EFs

EFs are higher-order cognitive processes that control behavior, emotion, and cognition and are supported by the frontal lobes [3]. For decades, EFs have been associated with the frontal lobes. This association originated in the famous case of Phineas Gage, who was working on a railroad construction site when in 1848 a large iron rod passed through his left frontal lobe. Phineas Gage survived this accident but his behavior and personality were dramatically changed, providing the first documented evidence for the complexity of EFs and their neural basis [9].

In conventional and contemporary conceptualizations of EFs, there is an agreement that the frontal lobe and especially the PFC have a critical role. The PFC has broad associations with almost all sensory systems, cortical regions, and subcortical structures involved in action, motor response, memory, emotion, and affect. The most essential anatomical division within the PFC defines three cortical areas: the lateral PFC, the medial PFC, and the orbital PFC. The lateral PFC lies anterior to the premotor areas and the frontal eye fields and is situated close to the surface of the skull. It includes the dorsolateral prefrontal cortex (DLPFC) (Brodmann's areas 46 and 9) and the ventrolateral prefrontal cortex (VLPFC) (Brodmann's areas 44, 45, and 47). The medial PFC lies between the two hemispheres and anterior to the corpus callosum and the anterior cingulate cortex (ACC) (Brodmann's area 24 and adjacent regions). The orbitofrontal cortex (OFC) lies above the orbits of the eyes and the nasal cavity (Brodmann's areas 11, 12, 13, and 14). It is of note that the OFC is functionally and anatomically identified with the ventral part of the medial PFC and is sometimes referred to as the ventromedial prefrontal cortex (VMPFC) (Brodmann's area 10, 14, 25, and 32 and parts of 11, 12, and 13), however these areas are not identical at finer anatomical divisions [40]. Figure 1 shows the general connections and flow of information in the neural substrates that support EFs. Gradients in the frontal cortex have led to some consistent conclusions regarding the role of the frontal cortex in EFs, such as the role of the DLPFC in WM and the VMPFC and orbitofrontal prefrontal cortex (OPFC) in the IC. It is important to note that these frontal areas (and the functions they subserve) have a protracted development period. The prefrontal cortex is the last area of the brain to mature, and performance on EFs tasks continues to improve well into adulthood. So, the functional connectivity and segregation of function mentioned briefly earlier, develops slowly. Two main changes characterize the development of a mature frontal cortex and related EFs: a change from diffuse to focal activity and increased segregation and integration of brain areas (3). As noted earlier, the PFC is the brain region most commonly associated with EFs. The PFC comprises more than 30% of the entire complement of cortical cells and is the last evolved brain region. It is also the part of the cortex that is more highly developed in humans than in other primates. There are three broad PFC subdivisions: the medial part, the dorsolateral part, and the orbitofrontal region (Figure 2) [9]. Luria (1966) also characterized the hierarchical nature of brain function. In his model, the PFC was at the highest level in the hierarchy, exerting top-down control over other brain regions, but was also influenced by other regions in a reciprocal, bidirectional way. Subsequent research has supported Luria's hierarchical conceptualization and expanded it to include a characterization of hierarchical structure within the PFC [41].

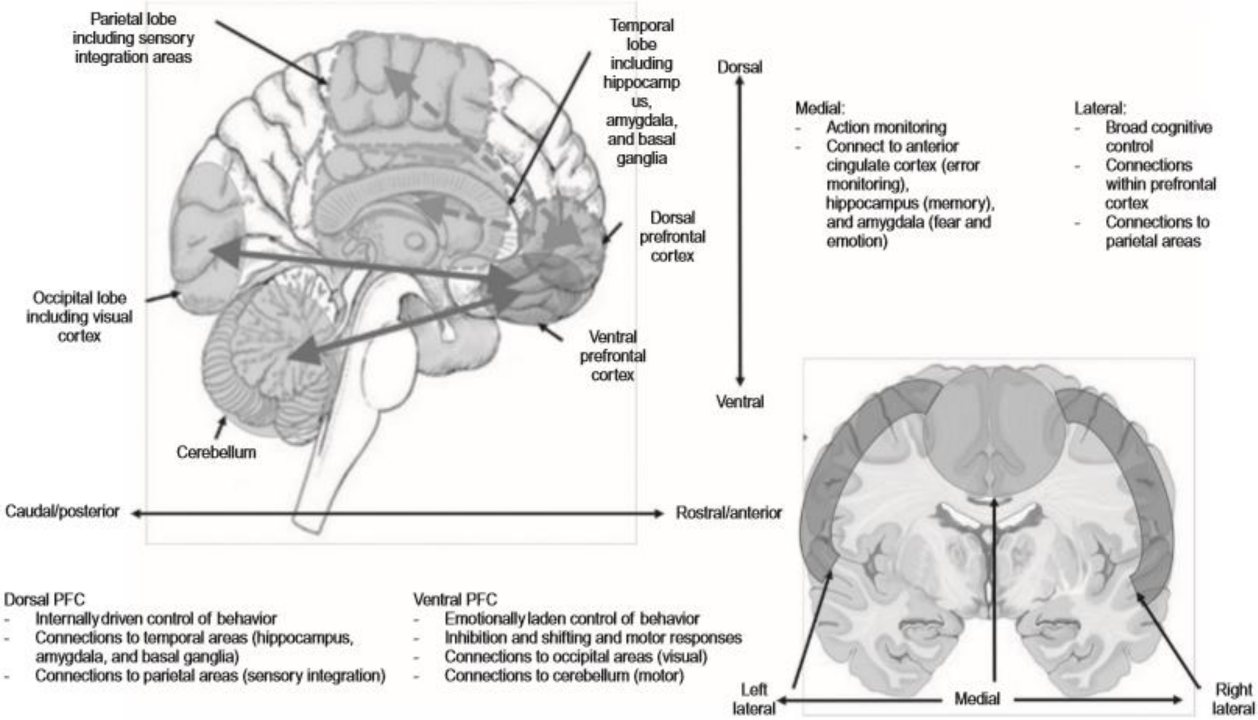

Figure 1. Diagram of information flow in the brain for executive functions. Sagittal view of brain from Clipart Library 2016 [3].

However, non-frontal brain areas are also found to be connected with EFs. For example, it has been recognized that EFs rely on several other brain areas that are closely linked with the PFC and form larger executive neural networks. The PFC is strongly linked with the limbic region of the medial temporal lobe (including the hippocampus and amygdala). The PFC and the hippocampus are both connected to the nucleus accumbens, which plays a crucial role in integrating cortical and limbic information into goal-directed behavior while PFC is usually the focus of neuroimaging investigations of EFs, but EFs are actually subserved by additional functional cortical networks that incorporate areas outside the frontal cortex. There are different networks related to different elements of EFs (Figure 3) [9]. Historically, the construct of EFs were derived from neuropsychological observations of the results of damage to the PFC [41]. It has long been known that the PFC plays a very important role in EFs across the lifespan, finding evidence of its active involvement during the performance of EFs tasks [7]. Today, EF skills are known to depend on increasingly well-understood neural circuits involving brain regions in the PFC and other areas [41]. The prefrontal cortex is primarily responsible for top-down control over cognitive processes and is the brain area that has the closest connection with EFs [42]. Patients with damage to the PFC often don't show any basic damage in cognitive skills (e.g., memory, language) together with difficulty regulating those basic skills in a goal-directed, contextually appropriate way. For example, the neurologist L Hermitte (1983) noted that patients with lesions to the PFC may become stimulus bound and respond automatically to objects in a stereotypical fashion—they exhibit utilization behavior [41].

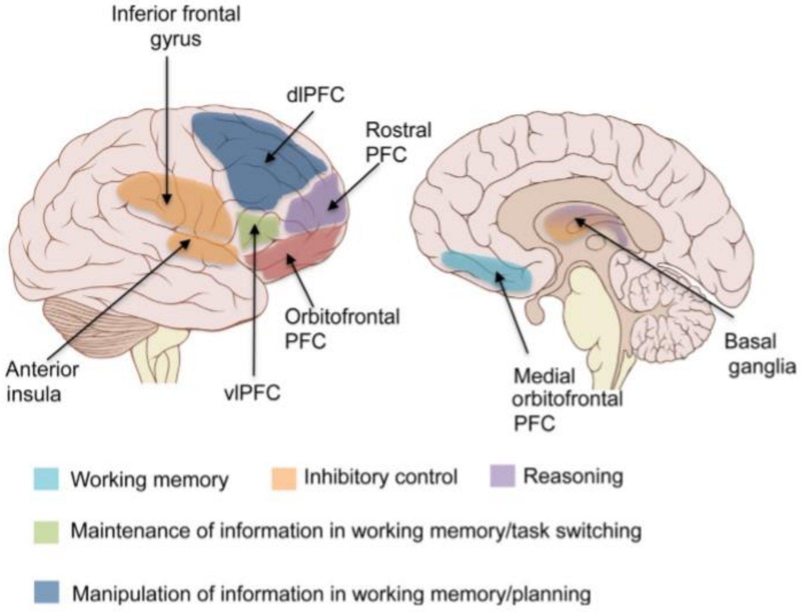

Figure 2. Brain areas associated with different EFs based on lesion and/or neuroimaging studies. These brain images are adapted from a work by PatrickJ. Lynch, medicalillustrator ;C. Carl Jaffe, MD, cardiologist Creative Commons Attribution 2.5 License 2006 [9].

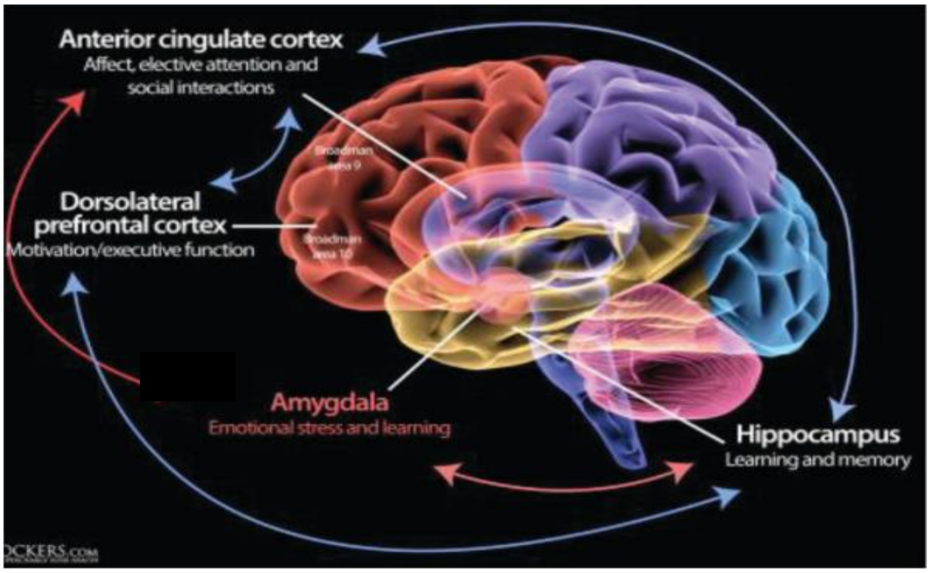

Figure 3. ACC with limbic system [43].

It is important to mention two additional brain areas functionally connected to the frontal cortex that are important for EFs. The hippocampus (HPC), a brain area in the temporal lobe linked to spatial processing and memory, is physically connected to frontal areas through the dentate gyrus and fornix. Functionally, the hippocampus has been found to be involved in WM and inhibition tasks through its connections to areas involved in the medial-lateral and dorsal-ventral gradients. It holds a seat of importance that has not been fully made clear, but the hippocampus is involved in mature use of EFs [3]. HPC has been increasingly seen to be involved in EFs tasks through its connectivity with PFC and there is growing evidence for delayed maturation of HPC-PFC circuits through adolescence. While PFC has long been associated with cognitive control tasks, accumulating research suggests that there is a role for the HPC in supporting both WM and EFs during delayed match-to-sample, including those encompassing memory-guided saccades, as well as spatial span (SSP) tasks, although at least some of these functions remain intact following hippocampal damage. HPC, and in particular its connectivity with medial PFC, has also been linked to EFs related to future planning and problem solving , suggesting that it may play a more general role across different EFs [36]. The PFC receives input projections from other neocortical areas, such as parietal and temporal regions. The PFC also receives information from the HPC, the cingulate cortex, the substantia nigra, and the thalamus, primarily from the medial dorsal nuclei. The PFC sends back projections to the medial dorsal nuclei as well as to the amygdala, the septal nuclei, the basal ganglia, and the hypothalamus, and therefore is greatly interconnected with other cortical and subcortical structures [9]. In addition, the cerebellum, the brain area responsible for executing motor movements, is functionally connected to the frontal cortex and thus, is implicated in EFs. In both laboratory EFs tasks and daily life, EFs often require motor movements, such as responding according to task rules (e.g., pressing a button) or executing a planned action (e.g., walking through a store picking up groceries). Evolutionarily newer areas of the cerebellum have also been connected to complex motor sequences that require coordination by an executive. The cerebellum and prefrontal cortex develop along similar trajectories (physical and temporal) and become increasingly connected as we age. The cerebellum also connects to the frontal cortex across the medial-lateral and dorsal-ventral gradients, implying its high level of importance to all EFs [3]. Linked to the movement from diffuse to focal activity across development is increased in segregation and integration of function. As EFs develop, specific brain areas are used for specific functions, as in examples offered earlier. However, there is also increased integration among brain areas, such that the frontal cortex connects to more areas in the brain (e.g., the cerebellum), and as a result of the formation of more complex networks, more complex functions are supported. This segregation and integration mirrors the overall developmental trajectory in the brain, which includes pruning of gray matter (segregation, more efficient use of specific brain areas for specific tasks) and increases in white matter tracts (integration, myelinated axons used for long-distance communication between brain areas). Increased segregation and integration are generally the result of improved behavioral performance on EFs tasks. Researchers also find that EFs task performance clusters on a single factor in early childhood, but can be dissociated into three or more factors from later childhood onward (Figure 4) [3].

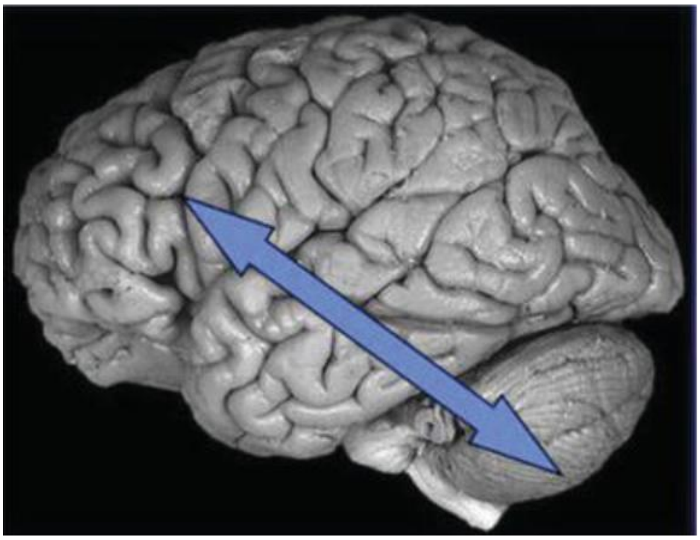

Figure 4. Prefrontal cortex and Cerebellum [43].

Genetic Mechanisms of EFs

Increasing evidence suggests that many of the gene variants connected with mental health disorders such as schizophrenia, bipolar disorder and depression are also linked to underlying cognitive processes fundamental to enabling effective reasoning and problem-solving, decision-making, and future planning. WM, response inhibition and CF are components of these processes and are often grouped under the umbrella term of EFs. Understanding the genetic basis of individual endophenotypes known to confer risk is key in enabling the polygenic basis of the disorder to be better understood in terms of its component parts [44]. Past twin and family studies have shown that EFs are highly heritable in childhood, early adulthood and middle age, and the genetic variance underlying EFs reflect the same genes across multiple time points. Furthermore, twin studies have shown that EFs genetically relate to several different psychiatric disorders and behavioral dimensions of health, such as sleep. However, little is known about the molecular underpinnings of EFs in humans. Most historical perspectives from the candidate gene and animal literature have argued that neurocognitive function is supported by metabotropic processes, in particular the slow neuromodulator effects of the dopaminergic systems [39]. EFs may be influenced by genetic polymorphisms. Twin studies have shown that genetic influences may account for a significant amount of variation in EFs especially for inhibition, shifting, and monitoring/WM ranging from 43% to 77%. One candidate gene associated with EFs is serotonin (5-HT). The role of 5-HT in the development of EFs is related to the expression of 5-HT in the PFC. Serotonergic receptors are expressed in the PFC, which control the 5-HT activity. Variations in extracellular 5-HT in the PFC have been linked to performance in response inhibition, reversal learning tasks, and other EFs in humans and nonhuman primates. Given the prevalence of 5-HT regulation and EFs performance in general, the functional polymorphism in the promoter region of the 5-HT transporter gene (5-HTTLPR) is a plausible candidate for EFs functioning [9]. Fast inhibitory GABAergic processes have also been studied in linked to EFs [39]. Importantly, genetic influences are the reason for a large portion of variance in common EF and the specific factors. Heritability estimates of common EFs range from 46% to 81% in young and middle adulthood and are essentially 100% in adolescence [45]. Besides, genetic influences tend to explain most of the phenotypic correlations between common EFs and other cognitive and clinical constructs throughout the life span [45]. The human genome changes very slowly, and so, humans today have the same or at least, a genome very identical to their Paleolithic ancestors [3]. Over the past decade, findings from multiple twin study data bases have established that EFs are among the most heritable psychological traits [46]. Previous findings have shown that the EF domains are: 1) correlated, due to a common factor considered to be (almost) entirely inherited (i.e.,99–100%); and 2) distinct, due to specific genetic influences linked to unique EFs, such as inhibition, WM, and shifting attention/CF [46].

Genome-Wide Association Study (GWAS)

Genome-Wide Association Study (GWAS) is a screening method used to assess the genetic architecture of complex traits. Since its inception in 2002, GWASs have led to the discovery of thousands of trait-associated loci. The number of samples analyzed by GWASs recently exceeded one million and continues to increase dramatically. Recent advances in genetic analysis shed light on the polygenic architecture of complex traits, revealing a fundamental view of the polygenic architecture underlying complex traits. Importantly, genetic markers identified by GWAS have explained limited proportions of heritability. Although the amount of phenotypic variance explained by genetic markers is generally increasing, more than half of all genetic components remain undetermined [47]. In particular, EF deficits are associated with almost all psychiatric disorders, leading some to suggest that EF deficits are a risk factor for general psychopathology (i.e., the p factor). Recent work using Single Nucleotide Polymorphism (SNP) effects from large GWAS to estimate genetic correlations suggests that cognition–psychopathology associations may be partially genetic in origin [48]. Based on GWAS summary statistics for a supposed complex disorder, it is possible to derive measures of the cumulative genetic loads for the disorders inherent to an individual's genotype. Such measures are often called Polygenic Scores (PGS). Individuals with high PGS for a particular disorder might also be at increased risk for known comorbid traits and disorders. Thus, "extreme" PGS analysis can be a promising tool to investigate the genetic contribution to symptom severity and disease characteristics in Neurodevelopmental Disorders (NDs). Still, there are several unclear aspects related to cross diagnostic features of NDs, and their relation to cognitive dysfunctions which are behaviorally defined. Building on the recent progress in GWAS of different traits and disorders, the PGS has emerged as a tool that enables investigation of the polygenic components of different disorders and explores the association between genes, symptoms, and functioning. Besides, genetic underpinnings of the general cognitive ability (intelligence) can be used to identify differences in cognitive factors between NDs, including EFs. This could provide a novel understanding of the underlying disease mechanisms, as outlined in the Research Domain Criteria initiative. Approaches to dissect social and cognitive traits are also of clinical importance in the ASD field since children and adolescents are admitted to specialist health care due to functional deficits, mainly related to social and/or behavioral deficit [5]. Twin studies suggested that inter-individual variation in cognitive function has a genetic component. Several GWAS have been conducted and have identified common variants associated with various measures of cognitive function, which aside from the apolipoprotein E (APOE) region have yielded a limited number of replicable loci. However, these have been conducted primarily in European populations [49]. The heritability of cognitive functioning has been reported to be considerable, in the range of 50–80% as estimated in twin studies. GWAS of general cognitive functioning have so far identified more than 300 associated genetic variants, however, despite this success, large parts of the heritability of cognitive functioning are still unaccounted for [50].

Conclusion

EFs serve as an umbrella term to encompass the set of higher-order cognitive abilities that are necessary to peruse and attain a goal. These functions are what enable us to understand complex or abstract concepts, solve problems we never came across before, plan our next vacation, and manage our relationships. However, despite its importance, the executive system has been traditionally quite difficult to define. While it is intuitive to think how a patient with a short term memory problem might manifest in the clinic, it is harder to predict the specific manifestation of an executive-impaired patient since there is no single behavior that can be directly tied to EFs [9]. EFs are a broad term referring to "high-level" cognitive processes that enable individuals to regulate their thoughts and actions during goal-directed behavior. There is no agreement on the exact definition of the term, but various cognitive processes such as set-shifting (switching from one task to another), inhibition (avoiding a dominant or prepotent response), and updating (continuously updating the contents of WM) have been proposed as key components of EFs [38]. EFs abilities are critical for academic, social, and professional achievements and have been attached to positive life outcomes [2]. EF skills are a collection of neurocognitive skills that support the conscious, top-down control of thought, action, and emotion; which are necessary for deliberate reasoning, intentional action, emotion regulation, and complex social functioning and allow self-regulated learning and adaptation to changing circumstances [41]. The PFC is known to mature slowly, with some parts continuing to develop through adolescence and into adulthood. Similarly, EFs gradually develop and are among the last mental functions to reach maturity. This development of the EFs is believed to account for many of the differences perceived between the stages of cognitive development across the life span. On average, children and older adults both show poorer EF performance in comparison to young adults [9]. Executive dysfunction have been reported in a wide range of conditions with childhood or youth onset, including learning difficulties and learning disorders, externalizing disorders or disruptive behavior problems such as ADHD and CD/Oppositional Defiant Disorder (ODD), internalizing disorders such as anxiety and depression and Obsessive Compulsive Disorder (OCD) and thought disorders such as ASD and schizophrenia [51]. Its neural and genetic bases have been studied extensively. For example, a recent review has shown that the medial prefrontal and orbital frontal cortices are involved in different aspects of EFs and that genes related to neurotransmitters (i.e., dopamine, serotonin, norepinephrine, and acetylcholine) modulate functions of these brain regions and therefore contribute to EFs [52]. Cognitive impairments differ in patients, depending on injury severity and location, but most deficits are in the domains of attention, memory, communication, and EFs [38]. It is generally known that the prefrontal cortex is important for behavioral planning and WM, the two key components of EFs [53]. EFs are mediated by complex neural circuits or feedback loops that connect detached regions in the prefrontal lobes with other cortical regions in the brain and sub-cortical structures [8]. Besides, genetic influences tend to explain most of the phenotypic correlations between common EFs and other cognitive and clinical constructs throughout the life span [45]. Future studies should investigate in more depth the possible relationships among the EFs components and how these may change in the presence of diseases and disabilities. In addition, future studies should investigate the impact of associated EFs components on everyday life among individuals with executive dysfunction and healthy people. The future plan of our team is to study and investigate the interaction of sex and gender with EFs and their causal mechanisms and specifically examine how EFs are differently impacted in different genders by specific genotypes and other related factors.

Although these results are promising, they arise from a limited number of studies and might therefore need to be followed up with additional well-powered studies. Furthermore, more knowledge is needed about the relationship between EFs and behavior and genetics.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethical Approval

Not applicable.

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