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LaPsyDÉ



Université Paris Cité
Ecole Doctorale 261 - Cognition, Comportements, Conduites Humaines
Laboratoire de Psychologie du Développement et de l'Education de l'Enfant (UMR 8240)

Gene-brain-behavior characterization of executive function development and training: an integrative approach

Présentée par IRIS MENU

Thèse de Doctorat en PSYCHOLOGIE, Mention NEUROSCIENCES COGNITIVES

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ABSTRACT

Several factors, at different scales, support learning: molecular (genetic), cerebral (neural networks), psychological and environmental (education, socioeconomic status, culture...). Psychology and cognitive neuroscience can help to investigate the multi-scale mechanisms underlying learning by providing insights into the capacities and constraints of the learning brain. These approaches require an interdisciplinary approach combining developmental psychology and educational cognitive neuroscience to design the interventions and interpret their findings but also applied mathematics to develop and implement algorithms for the processing and in-depth analysis of the multi-scale (gene-brain-behavior) data.

The aim of this PhD was to investigate the effects of age and cognitive training on the organization of executive functions (EF) changes at different levels: cognitive (Study 1, 2 & 3), cerebral (Study 4 & 5) and genetic (Study 4). These studies were based on the ANR-funded APEX project, a large computerized executive training program carried out in children (9-10 years) and adolescents (16-17 years), with multilevel data (DNA SNP, anatomical/functional/diffusion MRI, cognitive evaluations) measured before and after 5 weeks of training on tactile tablets. In Study 1, we used the network analysis framework to analyze EFs organization at the cognitive level in children and adolescents, before and after cognitive training. In Study 2, we further investigated the developmental changes of EF organization on an independent and larger sample of 1019 participants aged 7.8 to 15.3 years from the Texas Twin Project using three complementary analytical methods: confirmatory factorial analysis, network analysis and latent network analysis. These two studies support that 1) inhibitory control (IC) is initially strongly connected to the two other EFs (working memory updating and cognitive flexibility) and then separates from the other EFs (inter- and intra-EF differentiation); 2) connections of working memory updating strongly increase from 12 years old while a constant decrease in cognitive flexibility can be observed during development. In Study 3, we used structural equation model (SEM) analyses to scrutinize the transfer effects during cognitive training. We found that 1) changes in working memory updating and cognitive flexibility depend on initial levels in each of these EFs but also on initial levels in the other EFs and 2) children and adolescents with lower initial EF abilities progress more than those with higher initial abilities. In Study 4, we investigated the brain regions implicated in EFs performance and in EFs training receptivity. In Study 5, we used Machine Learning algorithms to predict the brain age from structural MRI. Based on the difference between chronological age and predicted brain age before and after the cognitive training, we tested the hypothesis that training could accelerate development. Finally, in Study 6, we used a multilevel SEM model to investigate the cognitive, cerebral, and genetic factors contributing to training gains. We found that IC gains was influenced at different levels, including cognitive (initial IC level), cerebral (pretest and training-related change of the left anterior cingulate cortex volume) and genetic (EF polygenic risk score) factors.

Résumé

Plusieurs facteurs, à différentes échelles, soutiennent l'apprentissage : moléculaire (génétique), cérébral (réseaux cérébraux), psychologique et environnemental (éducation, statut socio-économique, culture...). En apportant un éclairage sur les capacités et les contraintes du cerveau apprenant, la psychologie et les neurosciences cognitives peuvent contribuer à étudier les mécanismes multiniveaux qui sous-tendent les apprentissages. Ces approches nécessitent une approche interdisciplinaire combinant la psychologie du développement et les neurosciences cognitives de l'éducation pour concevoir les interventions et interpréter leurs résultats, mais aussi les mathématiques appliquées pour développer et appliquer des algorithmes pour le traitement et l'analyse approfondie des données multi-niveaux (gène-cerveau-comportement).

L'objectif de cette thèse était d'étudier les effets de l'âge et de l'entraînement cognitif sur l'organisation à différents niveaux des fonctions exécutives (FEs) : cognitif (Etudes 1, 2 & 3), cérébral (Etudes 4 & 5) et génétique (Etude 6). Ces études se sont appuyées sur le projet APEX financé par l'ANR, un programme d'entraînement des FEs mené chez des enfants (9-10 ans) et des adolescents (16-17 ans), avec des données multi-niveaux (ADN, IRM anatomique/fonctionnelle/de diffusion, évaluations cognitives) mesurées avant et après 5 semaines d'entraînement sur tablette tactile. Dans l'Etude 1, nous avons utilisé les méthodes d'analyse en réseau pour analyser l'organisation des FEs au niveau cognitif chez les enfants et les adolescents, avant et après l'entraînement cognitif. Dans l'Etude 2, nous avons étudié plus finement les changements développementaux de l'organisation des FEs sur un échantillon indépendant de 1019 participants âgés de 7,8 à 15,3 ans en utilisant trois méthodes d'analyses complémentaires : l'analyse factorielle confirmatoire, l'analyse en réseau et l'analyse de réseau latent. Ces deux études confirment que 1) le contrôle inhibiteur (CI) est initialement fortement connecté aux deux autres FEs (mise à jour de la mémoire de travail et flexibilité cognitive) puis se sépare des autres FEs (différenciation inter- et intra-FEs) ; 2) les connexions de la mise à jour de la mémoire de travail augmentent fortement à partir de 12 ans tandis qu'une diminution constante de la flexibilité cognitive peut être observée au cours du développement. Dans l'Etude 3, nous avons utilisé des analyses de modèle d'équation structurelle (SEM) pour examiner les effets de transfert après un entraînement cognitif. Nous avons constaté que 1) les changements dans la mise à jour de la mémoire de travail et la flexibilité cognitive dépendent des niveaux initiaux de chacune de ces FEs mais aussi des niveaux initiaux des autres FEs et 2) les enfants et les adolescents dont les capacités initiales aux FEs sont plus faibles progressent davantage que ceux dont les capacités initiales sont plus élevées. Dans l'étude 4, nous avons regardé, à partir d'IRM anatomiques, les régions cérébrales impliquées dans le fonctionnement exécutif et dans l'entraînement cognitif. Dans l'étude 5, nous avons ensuite utilisé des algorithmes de Machine Learning (ML) pour prédire l'âge du cerveau à partir d'IRM anatomiques. Sur la base de la différence entre l'âge chronologique réel et l'âge cérébral prédit avant et après l'entraînement cognitif, nous avons testé l'hypothèse selon laquelle l'entraînement pourrait accélérer le développement. Enfin, dans l'étude 6, nous avons utilisé un modèle SEM multiniveau pour étudier les facteurs cognitifs, cérébraux et génétiques contribuant au progrès cognitif après un entraînement. Nous avons constaté que les progrès en CI étaient influencés par des facteurs à différents niveaux, à la fois cognitifs (niveau initial de CI), cérébraux (volume initial et changement de volume du cortex cingulaire antérieur gauche et du putamen gauche) et génétiques (score de risque polygénique des FEs).

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TABLE OF ACRONYMS

EF(s)	executive function(s)
IC	inhibitory control
WMU	working memory updating
CF	cognitive flexibility
WM	working memory
ANT	attentional network task
SST	stop signal task
SSRT	stop signal reaction time
DDT	delay discounting task
DOT	dot matrix task
TMT	trail making test
WCST	Wisconsin card sorting test
DCCS	dimensional change card sort
D-KEFS	Delis-Kaplan Executive Function Scale
MRI	Magnetic Resonance Imaging
EEG	electroencephalography
fNIRS	functional Near Infra-red Spectroscopy
aMRI	anatomic Magnetic Resonance Imaging
fMRI	functional Magnetic Resonance Imaging
rsfMRI	resting-state functional Magnetic Resonance Imaging
dMRI	diffusion Magnetic Resonance Imaging
FC	functional connectivity
DTI	diffusion tensor imaging
PFC	prefrontal cortex
ACC	anterior cingulate cortex
IFG	inferior frontal gyrus
MFG	middle frontal gyrus

IFJ	inferior frontal junction
SMA	supplementary motor area
CEN	control executive network
DMN	default mode network
SN	salience network
brainAGE	brain age gap estimation
DLPFC	dorsolateral prefrontal cortex
IPS	inferior precentral sulcus
SMC	supplementary motor complex
VLPFC	ventrolateral prefrontal cortex
MTG	middle temporal gyrus
BG	basal ganglia
IPL	inferior parietal lobule
SPL	superior parietal lobule
dACC	dorsal anterior cingulate cortex
FA	fractional anisotropy
RD	radial diffusivity
MD	mean diffusivity
AD	axial diffusivity
SLF	superior longitudinal fasciculus
ILF	inferior longitudinal fasciculus
UF	uncinate fasciculus
FPN	fronto parietal network
CON	cingulo-opercular network
MZ	monozygotic
DZ	dizygotic
SNP(s)	single nucleotide polymorphism(s)
GWAS	genome wide association study

PGS	polygenic score
PRS	polygenic risc score
COMT	catéchol-O-méthyltransférase
DAT	dopamine active transporter
DRD1/D2	dopamine receptor D1/D2
BDNF	brain-derived neurotrophic factor
ADHD	attention deficit hyperactivity disorder
ASD	autism spectrum disorder
MDD	major depressive disorder
SZ	schizophrenic disorder
BP	bipolar disorder
MBP	mindfulness based practice
SES	socio-economic status
RT	reaction time
ANOVA	analyse of variance
SEM	structural equation model
LCS	latent change score
BLCS	bivariate latent change score
NM	network model
LVNM	latent variable network model
PCA	principal component analysis



PART I: BACKGROUND

Factors supporting learning are multiple and at different levels of life: molecular (genetics), cerebral (neural networks), psychological and environmental (educational, socio-economic, cultural).

By providing insights into the capacities and constraints of the learning brain, psychology and cognitive neuroscience can contribute to the investigation of the mechanisms underlying the effectiveness of different types of learning. This requires an interdisciplinary approach combining both developmental psychology and educational cognitive neuroscience, to build and analyze this type of data, and applied mathematics, to develop and apply algorithms for the automatic processing of these databases, in particular the analysis of multi-scale data (gene-brain-behavior) in order to link the different levels of analysis.

A core domain of learning is that of executive functions (EFs), i.e., functions which allow an individual to intentionally regulate his or her thinking and acts in order to achieve goals (Diamond, 2013).

These functions are primarily supported by the prefrontal cortex which develops during childhood and adolescence (Best et al., 2009) and, while under genetic control (Logue and Gould, 2014), are susceptible to improvement through the effect of targeted instructional interventions (Diamond and Lee, 2011; Karbach and Kray, 2021).

In this context, this project aims at analyzing developmental and training multilevel data by developing and applying mathematical methods (multi-scale analysis, supervised and unsupervised prediction).

This project therefore had several objectives:

- 1. Analysis of EF changes associated with development and cognitive training using advanced longitudinal statistical methods**

The first aim of the project was to investigate the change of EF organization at a cognitive level through development and training. The organization of these basic cognitive functions during development is at the heart of several researches (Hartung et al., 2020). Moreover, there is evidence suggesting that cognitive training could speed up development (Jolles and Crone, 2012). The development and improvement of statistical methods such as structural equation modeling (SEM) or network modeling (NM) allows to directly test the EF structure. Thus, the aim of this work was also to investigate EF organization with these new tools under the hypothesis that training is an accelerator of development.

- 2. Testing the hypothesis that training may change the brain age using machine learning models**

Different machine learning algorithms for the classification of massive data (e.g.

imaging or genetics) have been developed recently, proposing parsimonious learning methods taking into account the structure of the data, such as the spatial neighborhood for MRI data (de Pierrefeu et al., 2018b). With this development, age prediction from brain imaging data has become popular (Baecker et al., 2021b). In this context, we aimed at investigating if training changed the brain age and if these changes were related to cognitive progress. The adaptation and application of the algorithms to imaging-behavioral data have been done in collaboration with Edouard Duchesnay & Julie Victor (CEA/Neurospin).

3. **Multilevel analysis of genetic, cerebral and cognitive information**

SEM is a very relevant statistical approach for multilevel analyses because it allows the combination of both causal mechanism modelling and the use of complex constructs with latent variable modelling (Bollen, 2005). Causal modeling thus allows for simultaneous and global testing of the existence of several hypothetical relationships between a set of variables at different levels (gene-brain-behavior) that may be dependent and/or independent. Structural equation modeling is adaptable to longitudinal (McArdle, 2009) and multi-modal (Judd et al., 2020) data. Thus, we aimed at developing a multilevel SEM in order to integrate the different levels of observation (brain, genetics, cognition) and to have a complete picture of EFs through development and training.

4. **The acquisition of a multi-modality and multi-level database to characterize learning**

The creation of the multilevel training database will rely on the APEX-Enfant and APEX-Ado projects (APprentissages EXécutifs et cerveau chez l'enfant d'âge scolaire et chez l'adolescent). These projects aim at testing at different ages the impact of an executive learning targeted on Inhibitory Control (IC) and a more general pure metacognitive learning, mindfulness (PC). Learning will be assessed at the brain level - through anatomical (aMRI), diffusion (dMRI) and functional (fMRI) MRI data - as well as at the genetic (single nucleotide polymorphism, SNP) and behavioral (performance on cognitive tasks) levels. The data for IC learning were already acquired. An objective of this PhD project was to contribute to the acquisition of the data for PC learning (Gabriela Reznde's PhD), including recruitment of participants, acquisition of genetic, MRI, and cognitive data.

This PhD project is at the crossroads of cognitive neuroscience, developmental psychology and applied statistics, funded by a grant for interdisciplinary projects (CNRS PRIME 80). Because of this interdisciplinary funding, this research project has both a theoretical objective - to characterize the organization of EFs through development and training - and a methodological objective - to develop statistical tools in order to analyze longitudinal and multilevel data.

1 Executive functions: definition

The notion of executive functions (EFs) have emerged from studies of frontal lobe functioning and adult clinical neuropsychology. They have given rise to a multitude of overlapping definitions. Current definitions of EFs describe a set of high-level cognitive functions that allow an individual to intentionally regulate his or her thinking and acts in order to achieve goals (Diamond, 2013). These EFs are invoked when automated routines do not work or are not possible (e.g., in novel situations). EFs allow people to both resolve immediate conflict (e.g., ignoring a distractor) and to manage, in the moment, future conflicts/goals (e.g., preparing for tomorrow's class or next year's marathon).

Over the years, studies have shown that these functions are necessary for the development of more complex skills such as reasoning (Richland and Burchinal, 2013), theory of mind (Benson et al., 2013; Marcovitch et al., 2015; Sabbagh et al., 2006), arithmetic (Cragg et al., 2017; Gilmore and Cragg, 2018; Lee et al., 2018; Roell et al., 2019), decision-making (Xu et al., 2020) or creativity (Cassotti et al., 2016; Kleibeuker et al., 2013).

Since EFs are too broad to be modeled computationally or measured by a single variable, they have been either operationalized in a more precise manner or broken down to be studied. Miyake et al., 2000 have laid the foundations in their model of EFs with updating, inhibition and shifting forming three distinct (*diversity of EFs*) but still correlated (*unity of EFs*; Miyake et al., 2000) factors. Each EF would therefore be composed of a common part to all three EFs (*common-EF*) and a specific part to the EF in question (*EF-specific ability*; Miyake and Friedman, 2012; see Figure 1).

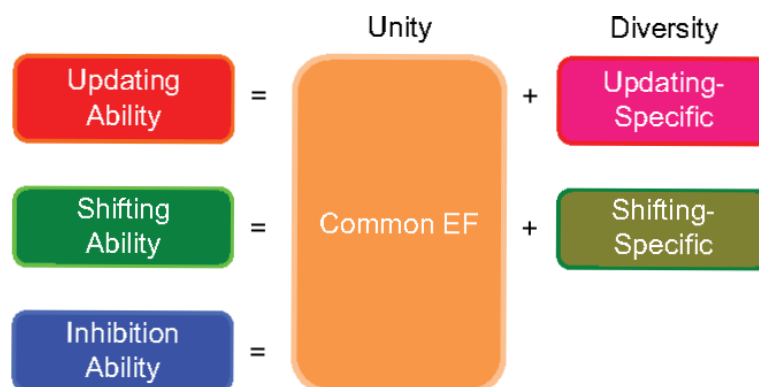


Figure 1: **Unity and Diversity of executive functions.** Figure from Miyake and Friedman, 2012.

1.1 Diversity of EFs

1.1.1 Inhibitory control

Inhibitory control (IC) or inhibition, as we will see, is central to a number of abilities and a source of interest in many disciplines, which has thus led to numerous studies on the subject (see Figure 2). Many conceptual distinctions of IC components exist such as automatic inhibition (Johnson et al., 2003; Pritchard and Neumann, 2009), behavioral inhibition (Harnishfeger, 1995; Nigg, 2000); cognitive inhibition (Harnishfeger, 1995; Nigg, 2000), effortful inhibition (Johnson et al., 2003; Pritchard and Neumann, 2009), inhibition of return (Posner and Cohen, 1984), pre-potent inhibition (Ozonoff et al., 1994), resistance to proactive interference (Friedman and Miyake, 2004), or response inhibition (Verbruggen and Logan, 2008). Consequently, two studies focusing on inhibition may be studying very different processes. It is therefore important to know which specific mechanism is being studied in order to make the most accurate interpretations and inferences possible. For this reason, we will first provide a theoretical overview of IC, notably its components and measures.

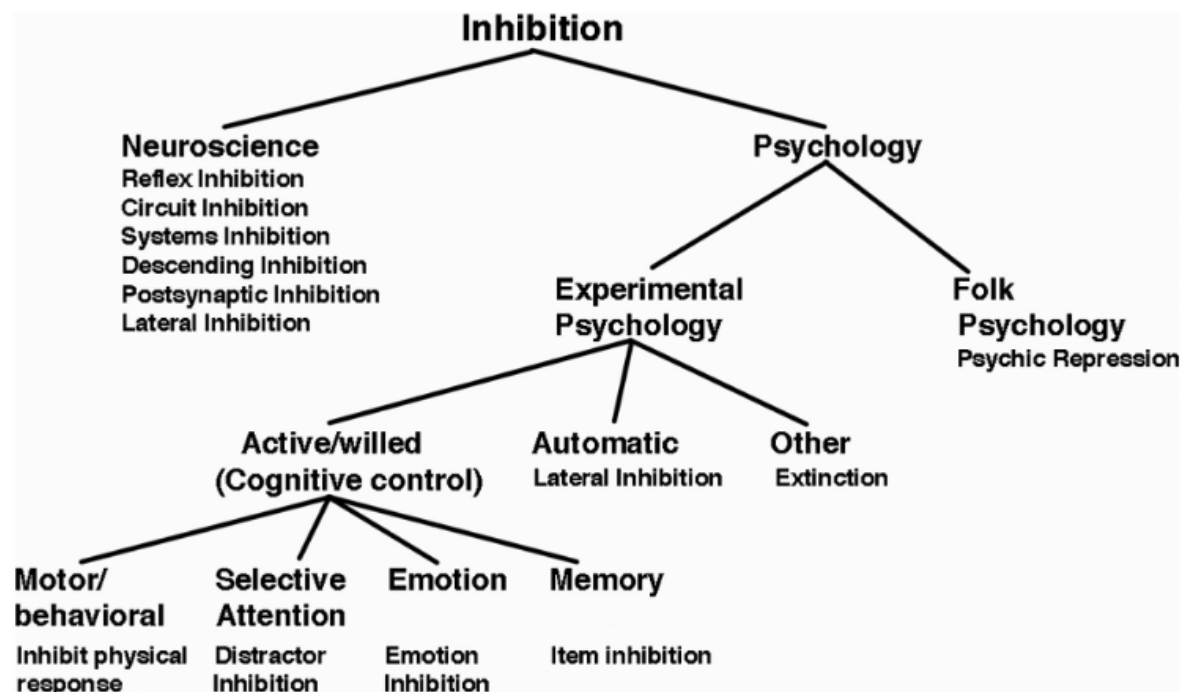


Figure 2: Types of inhibition in neuroscience and psychology. Figure from Aron, 2007.

IC can be defined as the ability to resist automatism and distractions in order to activate the appropriate response in conflict situations (Diamond, 2013). For example, in a cocktail party situation, IC allows one to focus one’s attention on the conversation of interest while ignoring other distracting conversations.

In the literature, most of the IC models consist of one-factor (Cohen et al., 1990; Dempster, 1992; Diamond, 2006; Morton and Munakata, 2002) or two-factor accounts (Andres et al., 2008; Bjorklund and Harnishfeger, 1995; Collette et al., 2009; D’Amico and Passolunghi, 2009; Engelhardt et al., 2008; Johnson et al., 2003; Pritchard and Neumann, 2009).

While one-factor models propose a single inhibitory resource responsible for interrupting task-irrelevant cognitive processes, multi-factor accounts propose that multiple resources contribute to IC, resulting in diverging developmental trajectories and distinct relationships with other cognitive processes.

There is now a consensus about the multi-dimensionality of the IC construct (Diamond, 2013). An early study has shed light on a common inhibition ability which is however not involved in all IC functions (Friedman and Miyake, 2004). Classically, two types of IC are distinguished (Friedman and Miyake, 2004; Gandolfi et al., 2014; Kane et al., 2016; Nigg, 2000; Stahl et al., 2014; Vink et al., 2005; Wiebe et al., 2008):

- *Response inhibition* (or behavioral/motor/prepotent response inhibition):
This sub-function refers to the ability to inhibit a prepotent motor response. It is generally measured by non-selective stopping tasks such as the stop signal, Go/No-go or antisaccade tasks, in which participants have to suppress intermittently a motor response given the presentation of a condition cue (Aron et al., 2014; Chambers, 2009; Verbruggen and Logan, 2008).
- *Interference control* (also referred as attentional inhibition, interference suppression, attention constraint, resistance to distracter/interference):
This sub-function is defined as the ability to resist interference from external environment's stimuli. It is classically measured by visual matching tasks such as Stroop or Flanker tasks, in which participants have to determine whether the target and comparison stimuli are identical or not without taking into account the task-irrelevant stimuli (Friedman and Miyake, 2004; Nigg et al., 2018; Stahl et al., 2014).

A hierarchical model of IC demonstrated that response inhibition and interference control could be modeled as empirically independent constructs, suggesting that they are distinct, and perhaps functionally unrelated cognitive abilities (Tiego et al., 2018).

Another study (Bari and Robbins, 2013) proposed a model of IC integrating impulsivity, with a decomposition of IC in two main sub-functions (see Figure 3): behavioral and cognitive inhibition. Within behavioral inhibition, three sub-functions are defined: response inhibition, deferred gratification and reversal learning. Response inhibition has been defined the same as above. Deferred gratification or impulsivity refers to the urge to obtain an immediate reward. This urge should be inhibited when it enables one to obtain larger rewards after a certain amount of time or effort. Finally, reversal learning is defined as the ability to overcome the strong association between the response and the outcome when the context changes without explicit signals. These response-outcome contexts can either be deterministic or probabilistic. Of note, this definition is really close to that of CF (see section 1.1.3).

Other types of distinction were proposed in the literature such as the distinction between automatic and effortful inhibition (Howard et al., 2014). Overall, the multi-factorial organization of IC points to the importance of using different tasks to measure IC or at least to specify the inhibitory subfunction involved. Furthermore, it also introduces the possibility of separate brain bases and perhaps distinct developmental trajectories between these different subfactors.

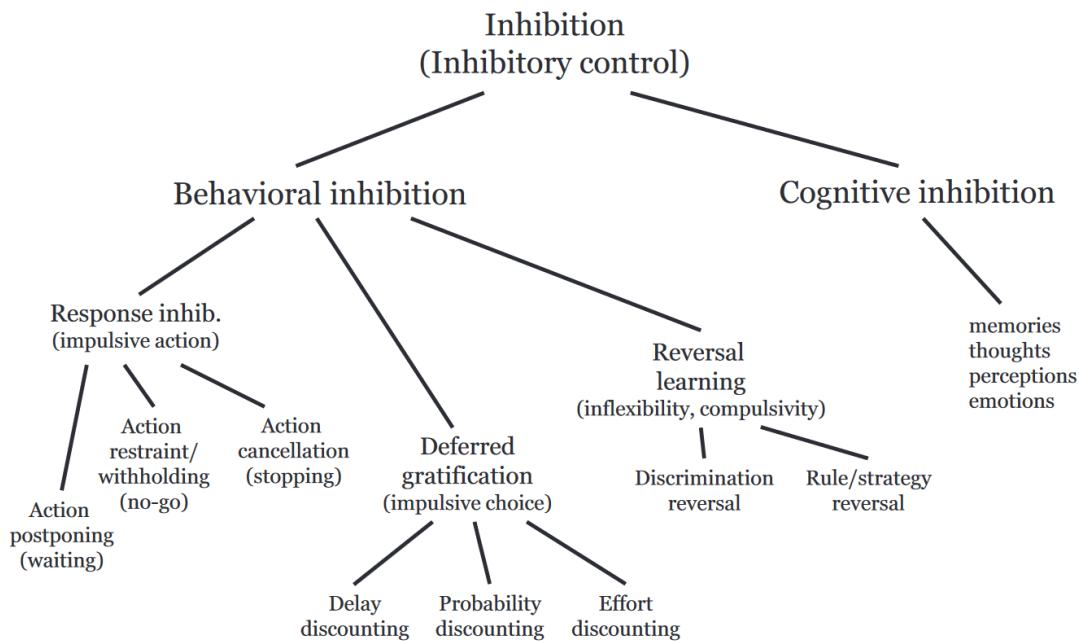


Figure 3: A possible decomposition of IC. Figure from Bari and Robbins, 2013.

1.1.2 Working memory updating

Working memory updating (WMU) is another core component of EFs. This function allows us to keep information in memory and to perform operations on it (Diamond, 2013).

In adult literature, WMU and working memory (WM) are two correlated but distinct constructs whereas, in the developmental literature, WM and WMU are often considered as synonyms (e.g., Garon et al., 2008). Indeed, while the term WM usually refers to the ability to store and process information simultaneously (Engle et al., 1992; Oberauer et al., 2016), WMU refers to the ability to operate on this temporarily stored information in the light of new incoming information and to update the WM regarding the results of this operation (Ecker et al., 2010). There is divergence in the literature in the distinction between these two abilities. Some theories of WM assume a tight link between WM and EFs (Miyake et al., 2001) and thus state that WMU abilities are closely related to that of WM (Schmiedek et al., 2014), WMU being one component of EFs (Miyake et al., 2000). On the other hand, other studies state that WMU and WM may be dissociable processes (Radvansky and Copeland, 2001; Radvansky and Dijkstra, 2007).

Regarding WMU, Ecker et al., 2010 proposed a decomposition of this EF into three components:

- *Retrieval*, which allows the recall of an information maintained in WM in order to operate on it (e.g., "What was the assignment for tomorrow's class? A math exercise")
- *Transformation*, which allows the modification of an information or representation maintained in WM (e.g., "Finally the assignment is no longer a math exercise to do but a poem to learn")

- *Item-removal*, which allows the substitution of a previously relevant information in memory by a new updated one (e.g., removing the information "math exercise to do" from WM)

Classic tasks of WMU are tasks in which participants are asked to remember and operate on a sequence of ongoing stimuli such as reverse digit-span, N-back (Cohen et al., 1994), Dot-Matrix (Miyake et al., 2001) or Memory Updating (Salthouse et al., 1991) tasks.

The three WMU processes are used to different degrees in WMU tasks. For instance, the N-back task involves a retrieval component —because one has to maintain in WM the last n items and retrieve the n^{th} one back at every step— but it does not involve any transformation because the information must be retrieved in a form that is identical to the form in which it was presented (Ecker et al., 2010).

1.1.3 Cognitive flexibility

Cognitive flexibility (CF), also referred to as switching or shifting, is the third EF classically described. It is defined as the function that allows one to switch between different instructions, strategies and thus to move from one cognitive operation to another.

Currently, the two types of tasks commonly used to assess CF are:

- *Task switching* paradigms: the participant has to alternate between tasks (Monsell, 2003; Vandierendonck et al., 2010). Rule-switching tasks such as the trail making test (Reitan and Wolfson, 1992) or the plus-minus (Miyake et al., 2000) are examples of task switching paradigms: participants have to switch their response selection or task to another based on the current rule (Wendelken et al., 2012a).
- *Set-shifting* paradigms: the participant has to shift or switch within a task (Dajani and Uddin, 2015). The Dimensional Change Card Sort (DCCS; Zelazo, 2006) and the Wisconsin Card Sorting Test (WCST; Heaton and Staff, 1993) are set-shifting tasks: participants have to shift their attention from one dimension (like color, shape or number) to another based on external feedbacks (Casey et al., 2004).

Although these two types of tasks differ in terms of switching within versus between tasks, they are both thought to rely on CF. However, these differences may have implications in terms of the neural processes or development underlying the different types of CF.

Task switching and set-shifting performance are usually measured by a “switch cost” representing the difference of performance (reaction times and/or error rate) between task switches and task repetitions (Jersild, 1927; Spector and Biederman, 1976; Vandierendonck et al., 2010). Two different types of switch costs can be identified: the global and the local switch costs. The global switch cost refers to the difference in performance between pure blocks (i.e., blocks including the repetition of one single task; AAAA or BBBB) and mixed blocks (i.e., blocks including the alternation between two tasks; ABABAB). In contrast, local switch costs correspond to the specific difference between task-repetition trials

and task-switch trials in mixed blocks. More specifically, local switch costs are measured by comparing the performance in AA and BB transitions (task-repetition trials) with the performance in BA and AB transitions (task-switch trials) in a mixed block such as AAB-BAABB (e.g., Kiesel et al., 2010; Kray and Lindenberger, 2000; Mayr, 2001; Vandierendonck et al., 2010). To measure CF, local switch costs are currently preferred above global switch costs because the global switch cost is also influenced by a difference in WM load between both blocks (Kiesel et al., 2010; Vandierendonck et al., 2010). Finally, an asymmetrical switch cost is typically observed in task-switching paradigms when the two tasks involve unequal levels of difficulty. That is, the switch cost is larger when switching from a difficult task to an easier task than the opposite, resulting in higher switch costs for the easy task (e.g., Monsell et al., 2000; Wylie and Allport, 2000).

As we have seen, a common explanation of CF is that this process is based on the disengagement from a set of irrelevant tasks to the active engagement in a set of relevant tasks. However, research suggests that this conceptualization of flexibility may be too simplistic (Nigg et al., 2005). Indeed, in everyday life, when a new operation (e.g., subtracting 8) is performed on a set of stimuli (e.g., a list of two-digit numbers), it may be necessary to overcome the induced interference or negative priming due to having previously performed a different operation (e.g., adding 8) on the same type of stimuli. Thus, the differences that can be observed between individuals may not be a simple reflection of the ability to engage and disengage from sets of tasks, but may instead involve the ability to perform a new operation in the face of induced interference or negative priming. Disengaging from this negative priming would then require IC (blocking the negative priming), suggesting that these two EFs are likely to be linked in everyday life. In an experimental situation, however, it is easier to have tasks which measure only *pure* CF, as this negative priming can be controlled.

In addition, CF tasks require the maintenance in WM of two or more rules to then switch between the two (Dajani and Uddin, 2015). CF can thus be decomposed into two processes: the maintenance of rules in WM and the alternation between these rules which, according to some authors, requires IC (Dajani and Uddin, 2015; Nigg et al., 2005). Therefore, due to the complexity of the processes involved in CF and its close relationship with IC and WM(U) (Dajani and Uddin, 2015), this EF is sometimes seen as a common-EF instead of a specific one (Nigg et al., 2005).

1.1.4 High level EFs

From these three core EFs, higher order EFs such as reasoning, problem solving, and planning are built (Collins and Koechlin, 2012; Lunt et al., 2012).

Reasoning is central to the generalization and abstraction processes that enable concept formation and creativity (Cristofori et al., 2019). The bat and ball task (Frederick, 2005; Kahneman and Frederick, 2002) or syllogisms are classic measures of reasoning abilities. For instance, a link between reasoning abilities and adherence to fake news has recently been highlighted by Pennycook and Rand, 2019. The underlying mechanisms however, remain a current issue.

Problem solving requires the examination of the details of a problem to arrive at a solution. It can include mathematical or systematic operations and can also be an indicator of an individual's critical thinking (Cristofori et al., 2019).

Planning includes the executive processes involved in the formulation, evaluation and selection of actions required to achieve a goal (Cristofori et al., 2019). Planning ability has been studied using a variety of tasks, but the most common one is the Tower of London (Shallice, 1982).

These three high-level EFs (with other higher level EFs such as task initiation or self-monitoring) are necessary in everyday life (to organize one's schedule, to adapt to unexpected difficulties, to make decisions, to get to a specific place) but they are also and especially necessary at school for a wide variety of learning tasks (e.g., managing homework, organizing work, mathematical abilities, etc.).

Of note, EFs are sometimes referred to in other terms such as self-control or self-regulation, cognitive control, impulsivity, risk-taking, delayed gratification, amongst others.

Self-regulation is sometimes associated with EFs. However, these two terms are not completely synonymous. Indeed, self-regulation is an adaptive change in our internal state, emotions, thoughts or actions, whereas EFs are a set of cognitive abilities that, when implemented, allow self-regulation to occur. EFs are also available for purposes other than self-regulation. For example, as we have seen, solving a mathematical problem requires good executive functioning but no self-regulating.

Cognitive control is a term often found in the field of EFs. It is defined as the ability to flexibly adjust behavior to achieve a goal in a context where task demands vary dynamically, and thus corresponds to the active maintenance of goals and the means to achieve them. Cognitive control is also divided into different components. The main factors found are WM -considered as central-, executive attention, response inhibition and interference control, which correspond to the low-levels functions of EFs. Thus, despite a close relationship with EFs, cognitive control is more restricted than EFs, with a particular focus on resource allocation, information maintenance (WM) and executive attention, rather than on complex cognition. Cognitive control can thus be seen as the basic top-down operations from which the more complex EFs emerge.

There is also an overlap of EFs with the notion of attentional control, defined as the ability to focus on a task and ignore distractions while constantly scanning the environment for new sources of information (see Figure 4; Bavelier and Green, 2019). Indeed, attentional control involves CF to shift between attentional states, WMU and IC (Bavelier and Green, 2019).

Finally, as we have seen, impulsivity, i.e., the tendency to act without previous thinking nor control, is often associated with EFs (Friedman et al., 2020). It has been described as mediated by top-down EF processes of goal-directed attention and response inhibition in addition to bottom-up reward-related processes (Nigg, 2017). Common brain regions have also been demonstrated between impulsivity and executive dysfunction (Bickel et al., 2012).

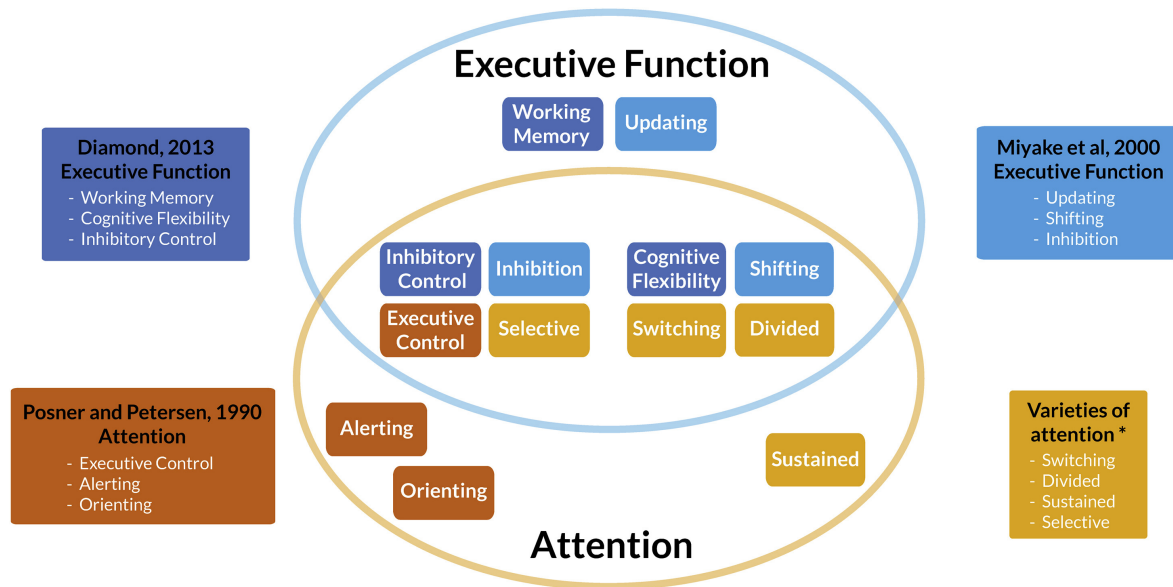


Figure 4: **Overlap with sub-processes from Executive Function and Attention literature.** From Bavelier and Green, 2019.

However, a recent study has suggested that EFs and impulsivity reflect overlapping but phenotypically and genetically distinct constructs (Friedman et al., 2020).

Thus, the literature on EFs can be found under different keywords and in different fields. These multiple names and theories make it necessary to clarify what we are referring to when we speak of *executive functions*.

In the rest of this manuscript, we will only use the terms *inhibitory control*, *working memory updating* and *cognitive flexibility* (or the acronyms IC, WMU and CF respectively). It should be noted that this is my theoretical choice. It is important to look at the tasks used in order to see to which constructs and denominations they refer, in a general way when discussing EFs but also in the particular case of this PhD project as will be pointed out later.

After having seen the specificity of each factor, we will now see how these factors organize themselves to form a whole: the EFs.

1.2 Unity of EFs

Studies of individual differences in EFs indicated that performance on tasks designed to tap into a specific EF domain (e.g., IC) is correlated with, but also separable from performance on tasks tapping into other EF domains (e.g., CF; Miyake et al., 2000). Consequently, several studies have investigated the structure of these functions (e.g., Rey-Mermet et al., 2019; Tiego et al., 2018). We have first seen how each EF was defined, their specificity, we will now see how they form a unity according to different models.

1.2.1 A theoretical model: Diamond, 2013

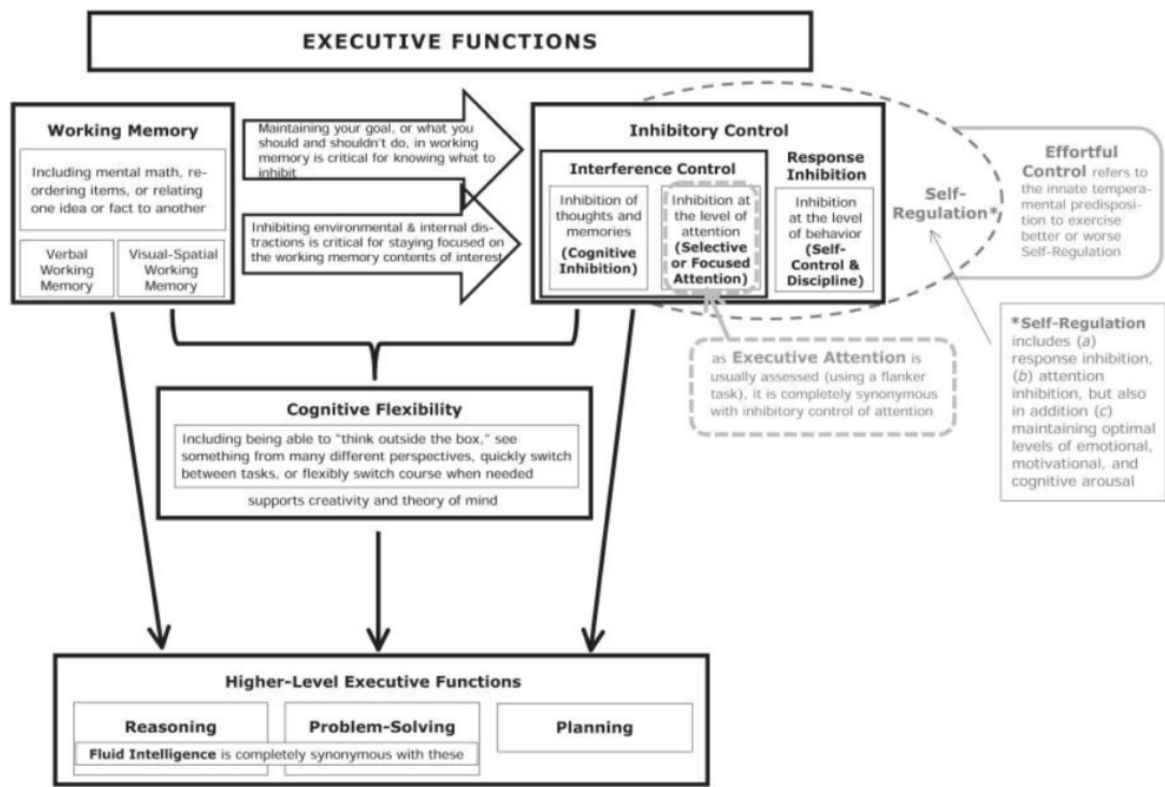


Figure 5: Adele Diamond's model of Executive Functions. From Diamond, 2013.

In her model of 2013, Adele Diamond (Diamond, 2013) gave a detailed definition of each EF and their development along with a description of the organization of these EFs. This model (see Figure 5) proposes an organization of EFs as separated processes, with one serving the other. More precisely, WM and IC serve each other and both of them serve CF. These three core EFs are needed for higher level EFs. This model is therefore a three-stage model with WM and IC at the first stage, CF at the middle stage and finally higher level EFs at the final stage. Finally, this model is based on the theory and knowledge obtained on the different EFs and their organization and development so far, but has not been tested mathematically. Although the current trend is towards operationalization and modeling, theory and knowledge must not be forgotten for both the construction of future models and their interpretation; Adele Diamond's model of EFs is great for that.

1.2.2 An empirical model: Miyake et al., 2000

Using structural equation modeling (SEM), Miyake et al., 2000 have proposed a hierarchical structure of EFs: in their model, each of the three EF domains are represented by a latent factor, i.e. a factor inferred by different manifest variables measuring the same EF (Panel A of Figure 6). In adults, these latent factors are separable (EF diversity), although they share a significant proportion of their variances (EF unity, or common-EF ability; Miyake and Friedman, 2012). Although, similar to Diamond's model (Diamond, 2013), the three

base EFs serve higher level EFs (here Complex Executive Task). In fact, the main difference with Diamond’s model is that, in Miyake’s model, Shifting is placed on the same level as Inhibition and Updating.

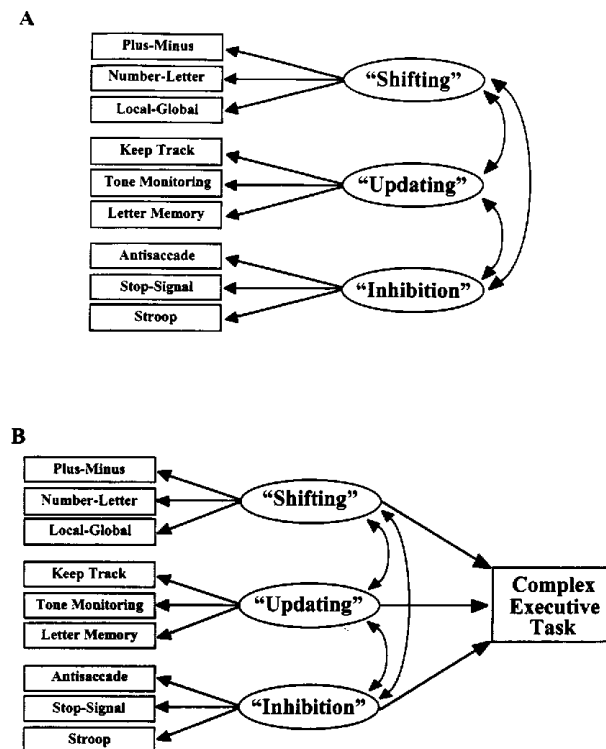


Figure 6: Miyake’s model of Executive Functions. From Miyake et al., 2000.

Specifically, the authors modeled four latent variables (Inhibition, Shifting, Updating and Complex EF Task), each explained by three tasks (Panel B of Figure 6). The complex tasks comprised the Wisconsin Card Sorting Test (WCST), Tower of Hanoi and the Random Number Generation.

Since this model sheds light on the fact that the three core EFs are moderately correlated with one another, but still clearly separable and that they contribute differentially to performance on complex executive tasks, it is therefore important to recognize both the unity and diversity of EFs (see Figure 1). On top of that, this study has shown that latent variable analysis is a useful approach to studying the organization and roles of EFs and has paved the way for many studies using this statistical approach when investigating EFs.

We will see later (see section 1.4.2) that this hierarchical three-factor model has been re-tested several times in developmental studies and that this organization is one of the structures supported by the literature today in adulthood, but not in childhood.

To sum up, this study constitutes the reference in terms of EF organization and has laid the foundations for future research. Unlike the organization proposed by Diamond, 2013, this model has the advantage of being mathematically testable. However, the design of this model is not random, but has instead been inspired by theory. It is by uniting theory and modeling that we will be able to approach a precise definition of EFs and their organization.

1.2.3 Other models

1.2.3.1 Baddeley’s working memory model (2000) Another influential model is Baddeley’s multicomponent model of working memory (Figure 7; Baddeley, 2000, 2010; Baddeley and Hitch, 1974).

This model is composed of a central executive system which regulates other subsystems:

- *The phonological loop*: allows to maintain verbal information
- *The visuospatial sketchpad*: allows to maintain visual and spatial information
- *The episodic buffer*: this subsystem was added in 2000 to the 1974 model. It integrates short- and long-term memory in order to hold and manipulate temporary storage of multimodal information.

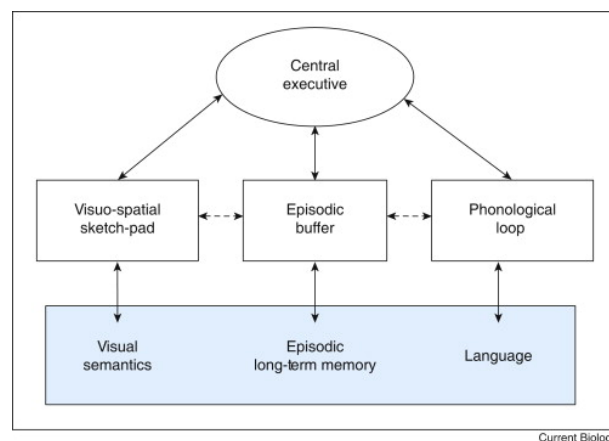


Figure 7: **Baddeley’s model of Working Memory.** From Baddeley, 2010.

Although this model contains an executive center, it focuses on WM and its functioning, but not on WMU or on EFs in general. However, this model is predominant in the field of WM and should be kept in mind because of its overlap with other models of EF organization.

1.2.3.2 Miller and Cohen’s model (2001) Miller and Cohen proposed a neuro-based model of cognitive control (Miller and Cohen, 2001). In this model, cognitive control is the major function of the prefrontal cortex (see Section 2) and results from the active maintenance of activation in the prefrontal cortex which represents goals and the means to achieve them. It provides bias signals to other brain structures whose net effect is to guide the flow of activity along neural pathways which establish the proper mappings between inputs, internal states, and outputs needed to perform a given task.

Therefore, according to this model, the prefrontal cortex could control input (sensory) or output (response) neurons, as well as the structures involved in other functions such as memory, or emotion. Cognitive control might then be mediated by reciprocal prefrontal cortex connectivity with sensory and motor cortices, and with the limbic system. Within

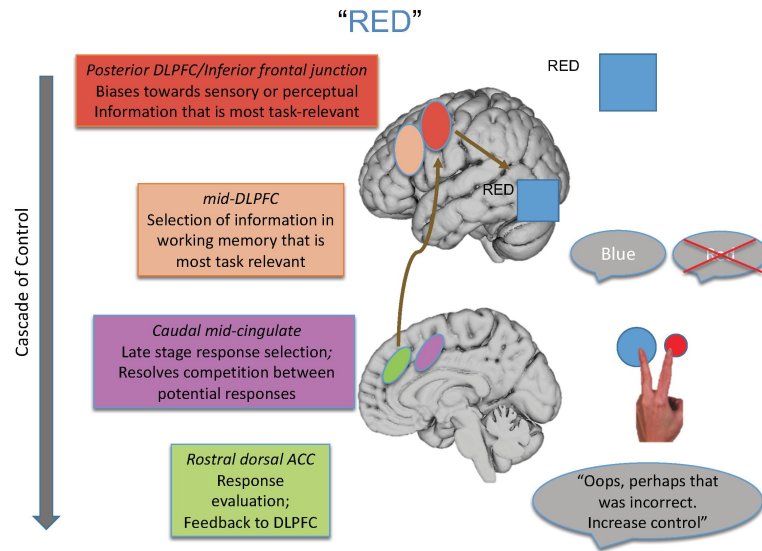


Figure 8: **Banich’s “cascade of control” model.** From Banich, 2019.

this approach, cognitive control refers to a situation where a biasing signal is used to promote task-appropriate response, and thus becomes a core component of different psychological constructs such as selective attention, error monitoring, decision-making, and IC.

1.2.3.3 Banich’s cascade of control model (2009) The “cascade of control” model from Banich, 2009 (Figure 8) has the specificity of involving a sequential cascade of brain regions involved in maintaining attention in order to reach a goal (here, inhibit). In sequence, the model involves four brain areas: the posterior dorsolateral prefrontal cortex (DLPFC), the mid-DLPFC, and the posterior and anterior dorsal anterior cingulate cortex (ACC). This model was developed in a Stroop task situation. For an incongruent trial (**BLUE** written in red), control is implemented via a “cascade”.

1. Posterior DLPFC biases towards task-relevant information relative to task-irrelevant information (depicted in Figure 8 by the larger representation of the color blue than the word RED),
2. Mid-DLPFC allows the relevant information to be maintained in working memory (here maintaining the representation of blue and not red),
3. Posterior ACC favors the correct response when multiple potential responses are competing (here by going toward the response linked to blue and not toward the one linked to red; depicted in Figure 8 by the larger blue circle),
4. Rostral/anterior dorsal areas of ACC are involved in response evaluation and send information to DLPFC to adjust control.

Noteworthy, the degree to which one region is activated in controlling Stroop interference depends on how well control has been implemented at prior points in the cascade.

This model is of great interest because, for a given task, it allows us to highlight the different stages of resolution of the inhibitory interference, based on the contributions of neuroimaging. By linking theory and brain imaging observations, this model allows, in a very original way, to precisely define the processes involved in interference control. However, this model has only been developed for the color-word Stroop, and needs to be validated for other types of IC and EFs.

Other models such as the Supervisory Attentional System (Norman and Shallice, 1980), the Problem-solving model (Zelazo et al., 1997) or Munakata's computational model (Munakata et al., 2011; Munakata et al., 2012) are related to EFs and have influenced the field of research focusing on EF organization.

To conclude, it is important not to forget the theory and the clinical and behavioral observations that allowed the development of the first models. The development of neuroimaging has allowed the development of these models by bringing a complementary level of information. It could be interesting to include other levels of information (genetic, biological, environmental) in order to move toward the most complete model possible. For this, it is essential to keep all these models in mind. Moreover, we must not forget that EFs develop with age and can change with training and these models are therefore not fixed. Here, these models were developed in adult studies. It is therefore important to examine how the organization of EFs is affected by development as we will see in part 1.4.2.

1.3 Importance of EFs

We saw that EFs represent an important field of research in psychology with numerous studies aiming to define EFs, their functioning and organization. If EFs are so extensively studied, it is because they are important for many aspects of our lives, especially for school achievement.

1.3.1 At school

Indeed, EFs are of great importance for school achievement such as reading or mathematics (Diamond, 2013). It was shown that EFs correlate with both early reading and mathematics ability (Blair and Razza, 2007). Even at age 2, EFs are strong predictors of mathematics and literacy outcomes at age five (Mulder et al., 2017). However, the three core EFs are not related in the same way to the different components of mathematics and literacy.

Response inhibition was shown to be related to most mathematics components (Purpura et al., 2017). For example, when learning decimal numbers, a heuristic often observed in children is to think that the decimal number with the greatest value is the one that is composed of the greatest number of digits after the decimal point. (e.g., the child incorrectly thinks that $1.34 > 1.5$; 34 being larger than 5). It has been shown that IC was necessary in order to block the "*the more digits the number has, the larger its value*" automatism and answer correctly (Roell et al., 2019). On the other hand, WMU was related to more advanced

mathematics skills (e.g., when comparing or combining numbers and quantities). Finally, CF was related to more conceptual or abstract mathematics skills (Purpura et al., 2017).

As for early literacy, response inhibition and CF were related to print knowledge, whereas WM was related only to phonological awareness (Purpura et al., 2017). Indeed, the contribution of EFs is primordial for reading acquisition. WM is essential, for example to retain all the phonemes (corresponding to linguistic sounds, like /f/) decoded from a string of graphemes (corresponding to a letter or group of letters, like "ph") in a word, while not forgetting the first decoded sound of the word when reaching the last. IC is also necessary for reading by inhibiting phonological ("dough" and "low") or orthographic ("dough" and "though") neighbors of the word being read. Similarly, the difficulty for kindergartners and first graders to discriminate between mirrored letters is also well known. While it is rather easy to distinguish "a" and "h" as two distinct letters, things get very complicated for the letter pairs "b/d" and "p/q" whose mirror image is another letter (Borst et al., 2015). When children learn to read, the temporo-occipital region of the left hemisphere (i.e., a visual area), also known as the "visual face and word recognition region," becomes specialized for the recognition of written words, making the child capable of quickly processing a string of characters perceived on the retina (Cohen et al., 2000; Dehaene and Cohen, 2011). However, because of neural recycling (our brain, during ontogeny, finds itself obliged to recycle some regions or circuits for new learning such as reading or maths; Dehaene and Cohen, 2007, 2011; Dehaene et al., 2004). Within this circuit, a mirror generalization heuristic was already present, leading to the categorization of two objects in an identical manner, independently of their orientation in space. This heuristic, which works well in the case of object and face recognition, continues to apply in the case of letters (Baylis and Driver, 2001). The child must then unlearn the automatic mirror generalization in order to avoid letter confusion and become a good reader (Dehaene et al., 2010). IC is then necessary to block this mirror generalization, in children and adults (Ahr et al., 2016; Borst et al., 2015). Note that letters mirrored not laterally but vertically (e.g., b/p) are less affected by this phenomenon (Ahr et al., 2017).

An emerging literature focuses on the causality of EF effects. It was shown that a bidirectional relation exists between math and EFs (Clements et al., 2016; Schmitt et al., 2017) but not between EFs and literacy (Schmitt et al., 2017). These new findings suggest that both EFs and academic learning are mutually supportive of each other's development, but it is clear that EFs are necessary for the successful development of academic learning. Indeed, this strong association between EFs and academic achievement is also supported by studies demonstrating the presence of learning disabilities in children with executive deficits (Gathercole et al., 2006; Schuchardt et al., 2008). Moreover, interventional studies proposing to train EFs have the advantage of being able to test this causal effect by looking at the impact of such training on academic performance (see further, section 6).

These relationships between EFs and learning continue in high school and even at University (Duckworth and Seligman, 2005). As adults, we use EFs for a lot of daily activities such as reading, shopping, driving, reasoning, etc., and EFs were shown to be related to work success (Bailey, 2007), marital harmony (Eakin et al., 2004) and parenting (Johnston et al., 2012).

1.3.2 In physical and mental health

It was shown that EFs were related to physical and mental health (for a review, Snyder et al., 2015). First, it was shown that EFs and more specifically WM impairments were found in schizophrenic patients (Barch, 2005; Thomas et al., 2009). Regarding schizophrenia symptomatology, negative symptoms were shown to be predicted by IC (assessed by the color word Stroop task), whereas positive symptoms (in patients with mostly negative symptoms) were predicted by Switching (assessed by the Visual Elevator task; Donohoe et al., 2006). On another hand, auditory hallucinations are related to intentional inhibition deficits, and more generally to an inhibition/excitation imbalance at multiple levels (biological, cognitive, cerebral; Jardri et al., 2016). Moreover, this link between EF impairment and schizophrenia is supported by family studies which have shown that relatives of schizophrenic patients appear to have wide but not severe executive dysfunctions (Szöke et al., 2005).

Such effects were also found in bipolar disorders since bipolar patients showed poorer IC (assessed by the color-word Stroop Task), WM (assessed by letters/numbers sequencing) and high-level EFs (measured by the WCST; Lera-Miguel et al., 2011). CF (measured by TMT) and high-level EFs (assessed by the WCST) also showed familial resemblance among the relatives of bipolar patients (Szöke et al., 2005).

A relationship was also demonstrated between executive dysfunction, autism spectrum disorder (ASD; Craig et al., 2016; Demetriou et al., 2018), attention deficit (hyperactivity) disorder (ADD/ADHD; Brown, 2009; Craig et al., 2016; Diamond, 2005; Nigg et al., 2005), anxiety (Ajilchi and Nejati, 2017), depression (Stordal et al., 2004; Taylor Tavares et al., 2007; Walters and Hines-Martin, 2018), epilepsy (Patrikelis et al., 2009; Riva et al., 2005) and substance consumption (Gustavson et al., 2017).

In addition, EF deficits were found in participants with obesity diagnosis compared to healthy weight controls, with significant deficits in IC and WM, (Favieri et al., 2019; Yang et al., 2018). More generally, negative correlations were shown between BMI (Body Mass Index) and EFs (Ronan et al., 2020), and IC abilities (Mamrot and Hanć, 2019). At the motor level, an interaction between IC and postural control during development has also been demonstrated (Olivier et al., 2007, 2010). The EF brain network would also be involved in the cerebral body schema (Assaiante et al., 2014).

Overall, EFs were shown to predict health related quality of life (Brown and Landgraf, 2010; Davis et al., 2010) and are perhaps the most widely impacted cognitive functions in psychiatric pathologies (see Figure 9).

1.4 Development of EFs

The development of EFs is now widely studied (Hughes, 2002), and the first studies focusing on it are not new. As the frontal lobe is known to have a late maturation (Diamond, 1991; Golden, 1981), its historical link with EFs quickly raised the question of an EF development parallel to that of the frontal lobe (Diamond, 2000; Stuss, 1992). Ten years later, in her paper, Adele Diamond clearly associated the development of the prefrontal cortex with that of the



Figure 9: **Pathologies with executive dysfunction.** From Executive Dysfunction Research & Advocacy.

EFs and had invited neuroimaging studies, which had made major progress in the early part of the century, to provide knowledge on the precise links between neurodevelopment and executive development (Diamond, 2002). Two decades later, neuroimaging and behavioral studies have proliferated and provide much more information on EF development at different levels.

1.4.1 Developmental trajectories of EF components

1.4.1.1 Development of inhibitory control IC is present from childhood (Johnson, 1995) and evolves with age (Bjorklund and Harnishfeger, 1995; Casey et al., 1997; Luna et al., 2004; Marsh et al., 2006; Paulsen et al., 2015; Rubia et al., 2013; Tamm et al., 2002), following a reverse U trajectory with a rapid increase in performance in early childhood, a slower one throughout adolescence, reaching a plateau at adulthood (Bessette et al., 2020) before a decrease in later adulthood (Williams et al., 1999).

More specifically, response inhibition, in its most basic form, is present in the first year of life with the inhibition of neonatal reflexes and the inhibition of predominant behavioral reaching responses (Diamond, 1990). After age 6, IC improves linearly in childhood (Macdonald et al., 2014; McAuley and White, 2011; Williams et al., 1999) and tasks with

greater interference show improvement up to young adolescence (Klenberg et al., 2015). It seems that adolescents have the full capacities for accurate IC but, because of an increased susceptibility to interference demands (such as peer presence), their performance results are irregular and inefficient (Luna et al., 2004; Luna et al., 2013). From adolescence to adulthood, modest improvements continue, with a focus on tasks with greater interference and complexity (Huizinga et al., 2006; McAuley and White, 2011).

Hence, the age at which performance on IC tasks reaches adult levels depends largely upon task complexity and difficulty, with performance on some basic tasks reaching adult levels in early childhood, while performance on other tasks requiring the integration of multiple EFs, continues to improve until adolescence (for a review, see Garon et al., 2008). Therefore, effortful/response inhibition tasks were shown to follow a protracted development across the different ages whereas tasks relying on a more automatic form of inhibition show little to no gain with age (Howard et al., 2014). It is important to point out that studies indicate that the rate of correct inhibitory responses, but not the ability to generate a correct inhibitory response, improves through childhood (Bedard et al., 2002; Luna et al., 2004; Ridderinkhof et al., 1999; van den Wildenberg and van der Molen, 2004; Williams et al., 1999; Wise et al., 1975).

However, in order to observe and measure IC abilities throughout development, it was necessary to adapt the classic tasks. Thus, the color Stroop, requiring the acquisition of reading skills, was modified for younger children. Different versions exist: the Animal Stroop (where the child must name the animal corresponding to the body of a hybrid animal composed of the head of one animal and the body of another), the Day/Night Stroop (where the child must say "day" when shown a picture of the moon and "night" when shown a picture of the sun)... It is important to note that these tasks vary considerably in difficulty (Simpson and Carroll, 2019), raising the question of measure homogeneity during development (Petersen et al., 2016).

Furthermore, it has been shown that the emotional degree of the task interferes with the developmental trajectory. Previous developmental studies have emphasized the importance of differentiating hot (affectively charged contexts: motivationally and emotionally relevant) and cool (affectively neutral contexts) EFs (Prencipe et al., 2011; Schweizer et al., 2020; Welsh and Peterson, 2014; Zelazo and Carlson, 2012; Zelazo and Müller, 2002). For example, hot IC abilities, measured by an emotional Stroop task, in which participants must inhibit the reading of a word referring to an emotion in order to focus on the emotional facial recognition task, follow a quadratic developmental trajectory (with a trough at adolescence), whereas cool IC abilities, measured by a classic color-word Stroop task, develop linearly with age (Aïte et al., 2018). However, some studies have reported a quadratic developmental pattern for response inhibition abilities using an affectively charged Go/No-go task (Hare et al., 2008; Somerville et al., 2011) whereas others reported a linear development using the same task with a protracted development of response inhibition in an affectively charged context (Schel and Crone, 2013; Tottenham et al., 2011). Similarly, based on a stop signal task, studies have reported a linear development of both cool and hot response inhibition abilities from childhood to young adulthood (Salvia et al., 2021; Urben et al., 2012), but with a more protracted development of response inhibition in an affectively charged

context than in an affectively neutral context (Salvia et al., 2021). These last results are in line with another model of the development of EFs in affectively neutral or charged contexts that assumes a later development of EFs and of IC in particular in an affectively charged than in an affectively neutral context (Zelazo and Carlson, 2012). As for adolescents and adults, cool and hot IC were shown to be unrelated (Aïte et al., 2018), suggesting that these two types of IC might rely on different processes (Bouhours et al., 2021).

1.4.1.2 Development of working memory updating Summarizing the development of working memory updating (WMU) is challenging as there is often a confusion between WMU and working memory (WM) in developmental studies (Panesi et al., 2022). This would not be an issue if the two components were interchangeable through development but it has been demonstrated that WMU correlated higher with measures of IC than with WM measures (Panesi and Morra, 2020; Traverso et al., 2015) and that differences between the concepts of WM and WMU already exist in preschoolers (e.g., Morra et al., 2018).

WMU was shown to follow a similar developmental trajectory to that of WM but with slightly lower scores (Garon et al., 2014). A proposition is that WMU depends on WM to develop without coinciding with it while WM develops essentially by maturation and is therefore closely related to age (Panesi et al., 2022). WMU abilities have been demonstrated in 5-months-old (Koechlin, 1997; Wynn, 1992) and 8-months old (Huntley-Fenner et al., 2002; Kaldy and Leslie, 2003) infants. Then, performance increases until mid-adolescence (Gathercole et al., 2004; Huizinga et al., 2006; Klingberg, 2006; Kwon et al., 2002; Pelegrina et al., 2015; Schleepen and Jonkman, 2009; Tamnes et al., 2010; Vuontela et al., 2003), continues to increase over adolescence and into early adulthood (Demetriou et al., 2002; Ferguson et al., 2021; Luna et al., 2004) before declining around the age of 30 (Ferguson et al., 2021) and in later adulthood (Nyberg et al., 2012; Park et al., 2002). Of note, there is a debate regarding the linearity of WMU development in middle childhood, with some studies supporting a linear pattern (Best and Miller, 2010; Carriedo et al., 2016) while others concluding on a nonlinear development (Brocki and Bohlin, 2004; Lensing and Elsner, 2018; Röthlisberger et al., 2013).

Just as IC, WMU performance also depends on the task difficulty (Carriedo et al., 2016; Lee et al., 2013). Complex tasks which require high executive control, showed developmental trajectories which continue up to age 16 and stabilize around 18 to 20 years, but, with lower executive control tasks, development remains stable from ages 11 to 12 (Conklin et al., 2007; Luciana et al., 2005). For example, mature levels in the 1-back task are reached at the end of childhood (10–12 years), whereas at more demanding levels (e.g., 2-back) performance continues to improve well into adolescence (Brahmbhatt et al., 2010; Pelegrina et al., 2015; Schleepen and Jonkman, 2009; Vuontela et al., 2003).

Looking at the 3-component of WMU as defined by Ecker et al., 2010, different developmental trajectories were found according to the different components: retrieval accuracy but not the substitution nor the transformation processes differed with age (Linares et al., 2016).

1.4.1.3 Development of cognitive flexibility Just as the other EFs, cognitive flexibility (CF) evolves with age. CF develops quickly in preschool years, as young children's performance improved on a variety of tasks (Deak, 2000; Espy, 1997; Jacques and Zelazo, 2001; Smidts et al., 2004; Zelazo et al., 1996, for a review see Carlson, 2005). Children as young as 4 years old are able to demonstrate CF and to switch rules on the DCCS task while 3-years-old children persevere in applying the first rule (Doebel and Zelazo, 2015; Frye et al., 1995; Zelazo, 2006; Zelazo et al., 2003). Such persevering errors may be due to failed inhibition of previously relevant information and/or failed activation of previously ignored information (Chevalier and Blaye, 2008; Jacques et al., 1999; Zelazo et al., 2003) and to distraction (Chevalier and Blaye, 2008). Globally, children's CF ability is affected by interference both at the stimulus and the response level but also by the specific tasks which are switched between (Cragg and Nation, 2009). Then, through elementary school age, CF takes a protracted development compared with other EFs (Davidson et al., 2006). CF performance continues to develop with age, as children are able to apply higher-order rules and handle more complex tasks (e.g., Chevalier and Blaye, 2009; Diamond, 2013). For example, while 4.5 year olds perform well on the DCCS, they fail the WCST until the age of 6, performance on this task at an adult level happens only around the age of 10 (Chelune and Baer, 1986; Crone et al., 2004; Dick, 2014; Paniak et al., 1996; Rosselli and Ardila, 1993; Welsh et al., 1991). But, while a rapid development is observed between 3 and 4.5 years of age on the DCCS (i.e., children tend to either pass or fail the task), improvement on the WCST is gradual (Chelune and Baer, 1986; Crone et al., 2004).

It also seems that the two components of CF (i.e., maintenance vs. switching) follow distinct developmental trajectories (Cepeda et al., 2001; Crone et al., 2004; Huizinga and van der Molen, 2007; Karbach and Kray, 2007; Kray et al., 2008; Reimers and Maylor, 2005): task-switching abilities mature earlier (around the age of 11) than task-maintenance and selection abilities (around the age of 15; Huizinga and van der Molen, 2007; Karbach and Kray, 2007). CF skills continue to develop into adolescence and adulthood (Anderson, 2002; Kalkut et al., 2009), peaking between 21 and 30 years (Cepeda et al., 2001).

1.4.1.4 Sum-up To sum up on EF development, infants within their first year of life already exhibit fundamental forms of EFs (Diamond, 1990), but the core components (IC, WMU and CF) rapidly develop during the preschool years (Hughes, 1998), continue developing throughout childhood (e.g., Davidson et al., 2006), adolescence (e.g., Huizinga and van der Molen, 2007) and early adulthood (e.g., Anderson et al., 2001; Ferguson et al., 2021).

The development of EFs requires more than a quantitative increase in the efficiency of executive processes (Chevalier, 2015). Development is also driven by changes in the control strategies available to children, which come with the challenge of adaptively coordinating this expanding control ability. With age, children adjust control engagement (i.e., the amount of control and strategy selection) more effectively as a function of moment-to-moment variations in the demands of tasks. Increasingly optimal coordination of control results in more efficient and more economic cognitive functioning. In other words, the development of EFs reflects, in part, more optimal use of existing control resources with age (Chevalier, 2015; Doebel, 2020).

As we have seen with IC, it is also important to differentiate the developmental tra-

jectory of hot and cool EFs (Prencipe et al., 2011; Welsh and Peterson, 2014; Zelazo and Carlson, 2012). Studies reported that both cool and hot EFs developed linearly but cool EFs developed more rapidly than hot EFs (except for interference in IC which develops quadratically). Moreover, while cool and hot EF capabilities seem correlated in children, they are not related in adolescents suggesting that these two types of EFs become increasingly more specific with age (Aïte et al., 2018; Botdorf et al., 2017; Welsh and Peterson, 2014; Zelazo and Carlson, 2012), also since difficulties in hot EFs can appear without apparent difficulties in cool EFs (Welsh and Peterson, 2014; Zelazo and Carlson, 2012).

1.4.2 Developmental trajectories of EF structure

Since Miyake's model's first publication in 2000 (Miyake et al., 2000), much research has focused on reproducing this model on the same population as they did but also across age and pathologies. The use of latent variable analysis in particular has been the most common approach to evaluating the changing organization of EFs over development.

Published measurement models showed that, with age, EF structure goes from a one-factor structure in early childhood with no clear separation among EF tasks (Shing et al., 2010; Wiebe et al., 2008; Willoughby et al., 2012; Xu et al., 2013) to a two- to four-factors structure at adolescence (Agostino et al., 2010; Friedman et al., 2016; Lee et al., 2013; McAuley and White, 2011; Wu et al., 2011; Xu et al., 2013). Of note, some studies also report an organization with more than one factor in young children (Wu et al., 2011) and less than three factors in older children (Huizinga et al., 2006). Karr et al., 2018 made a systematic review and a re-analysis of the data produced in almost 20 years.

This meta-analysis concluded on a one to two factor model among children and adolescent samples and on a nested factor model among adult samples (Karr et al., 2018). These results suggest greater unity among younger samples and a balance of unity and diversity among adult samples, hence supporting a differentiation of EFs from preschool into adulthood, with the emergence of CF during the school-age to adolescent years (Karr et al., 2018). Moreover, a recent behavioral study on children from 7 to 15 years (Hartung et al., 2020) found that age impacts mostly the common-EF loadings of IC and CF. While in childhood, WMU, CF and IC rely on similar underlying cognitive processes, in adolescence, EFs become more specialized and independent. Another preprint using both latent variable and network analysis approaches showed a stabilization of EF organization around the age of 10 that continues to develop until the age of 14, going from one-factor to three-factor organization (Younger et al., 2021). However, it is important to note that the 7 models examined by Karr et al. showed low acceptance rates (such as convergence problems or poor model fit) and low model selectivity (models did not differ much in fit; Karr et al., 2018). This highlights the need for longitudinal research, with sufficient power, to validate the factorial organization of EFs during development.

This developmental organization of EFs (for a review: Karr et al., 2018; Lee et al., 2013) is also supported by a brain imaging study reporting an increasing segregation of structural brain network modules with age, this segregation mediating the effects of age on EFs (Baum et al., 2017). Indeed, the development of EFs has been widely studied in relation with brain development. Therefore, we will focus now on EF brain network and its development.

2 Neural basis of EFs

We are learning more and more about the functioning and organization of the brain thanks to the development of neuroscience and its brain imaging methods. Brain imaging, such as Magnetic Resonance Imaging (MRI), Electro-Encephalography (EEG) and Magnetoencephalography (MEG), allows to measure in a non-invasive way the functioning of the brain when it is engaged in a cognitive task or in its basal activity (called resting state) but also, using MRI, its anatomy.

Over the last twenty years, neuroimaging research has established two fundamental principles of brain organization: *segregation*, the segregated or modular distribution of anatomical and/or functional specialization within brain regions, and *integration*, the functional and/or effective connectivity between brain regions (Friston, 2009). Details on the history of these two concepts and their measurements in neuroimaging can be found in Appendix A1.

2.1 Segregation: regional brain specialization for EFs

Neuroimaging studies have led to a better understanding of the development and functioning of EFs, which, as we have seen, are essential to the establishment of several functions during development. Because EFs are present in childhood and improve with age, it was suggested that the underlying neural mechanisms are available early in development and develop throughout development (Luna et al., 2010). This developmental trajectory of EFs would thus be linked to the prolonged structural and functional maturation of certain brain regions, notably the prefrontal cortex (PFC; Bunge and Wright, 2007; Casey et al., 2005; Crone and Steinbeis, 2017; Gogtay et al., 2004; Luna et al., 2015; Luna et al., 2010). Indeed, different studies have shown an age-related increase in activity in the prefrontal and parietal cortexes (Kwon et al., 2002; Paus et al., 2008).

Regarding EFs, from a developmental perspective, one hypothesis is that, similar to the organization of EFs at the behavioral level (from a 1-factor organization to a 3-factor organization), EF development is related to the segregation of network modules (Baum et al., 2017, see Figure 10). This will lead to the fact that, in adults, EFs would function in a hierarchical manner: while some regions would play an integrative and more common role, others would be more specialized on a particular EF (Collette et al., 2006; Luna et al., 2015; Niendam et al., 2012; Simmonds et al., 2008; Wager et al., 2004; Wager and Smith, 2003), reflecting on a cerebral level the unity and diversity of EFs. This prefrontal modularity of both unitary (common-EF) and diverse EF (specific-EF) was recently supported using the Delis-Kaplan Executive Function Scale (D-KEFS) (Mace et al., 2019).

2.1.1 Diversity of EFs

Some brain regions are shared by all three EFs and their common part, but others are more specific to each EF. For example, one study was able to identify a prefrontal network, com-

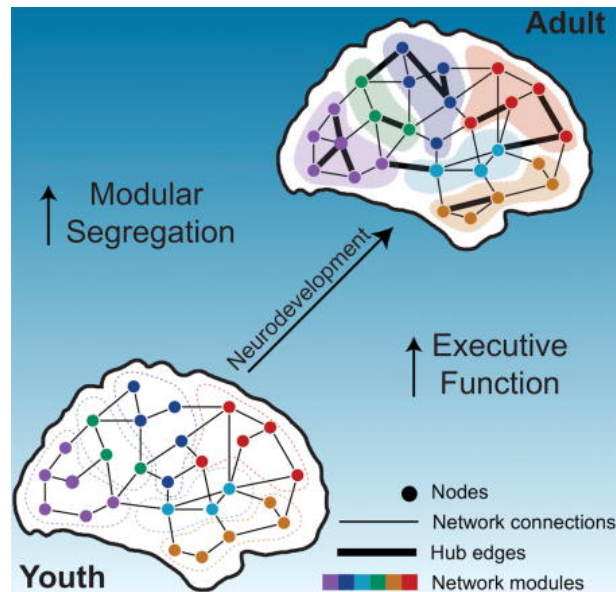


Figure 10: **Modular segregation of structural brain networks supports the development of executive function in youth.** From Baum et al., 2017.

mon to all three EFs, and specific ROIs for each EF (Mace et al., 2019). We will start by describing in detail the brain networks that have been shown to be involved in the different EFs, reflecting their diversity.

2.1.1.1 Neural basis of IC Of the three core EFs, IC is probably the one whose brain bases have been investigated the most, probably because of its overlap with cognitive control, impulsivity... Various studies have shown an age-related increase in activity in the prefrontal and parietal cortex (Kwon et al., 2002; Pas et al., 2021).

2.1.1.1.1 ACC One of the key regions of the IC network is the anterior cingulate cortex (ACC). In its dorsal part, the ACC is connected to the prefrontal and parietal cortex as well as to motor areas. On the ventral side, it is connected to regions such as the hypothalamus, the amygdala and the nucleus accumbens. Thus, because of its position and its connections with these other cerebral areas, it is a place of cerebral control.

At the anatomical level, various studies have highlighted the link between the cortical thickness of this region and IC performance (Elderkin-Thompson et al., 2008; Takeuchi et al., 2012; Westlye et al., 2011). The left-right asymmetry sulcal pattern of the ACC, which can be single or double parallel, has been shown to correlate with Stroop score in 5-year-olds (Cachia et al., 2014), 9-year-olds (Borst et al., 2014), and young adults (Tissier et al., 2018). Specifically, Stroop scores were lower (and thus inhibitory performance better) in subjects with ACC asymmetry (a different sulcal pattern in the two cerebral hemispheres) compared to subjects with symmetric ACC. ACC anatomy, as measured by plastic or fixed markers, is therefore related to IC performance.

Functionally, the activity of this region increases with age and development, as does

IC performance measured by a Stroop task (Adleman et al., 2002). This region has also been shown to be more prominently activated during Simon (Kharitonova et al., 2013) and Go/No-go (Pornpattananangkul et al., 2016) tasks, having a central role in conflict detection and being increasingly activated when errors are committed (Braver et al., 2001). A review has also shown that the anterior part of the ACC is more emotional whereas its posterior part is more cognitive, using an emotional or cognitive Go/No-go (Bush et al., 2000). Thus, ACC represents a key region for attention, motor regulation, and response selection (Carter et al., 1998; Pardo et al., 1990; Paus et al., 1993).

2.1.1.1.2 IFG Similarly, the inferior frontal gyrus (IFG) activity increases with age and inhibitory performance (Bunge et al., 2002). The IFG, which is part of the prefrontal cortex (PFC), is the lowest of the frontal lobe gyrus. It is bounded superiorly by the inferior frontal sulcus (IFS; which separates it from the middle frontal gyrus), inferiorly by the lateral sulcus (which separates it from the superior temporal gyrus) and posteriorly by the inferior precentral sulcus (IPS). Above is located the middle frontal gyrus, behind is located the precentral gyrus.

Functionally, the right IFG is a region which is activated during inhibitory tasks such as the stop signal task (Aron et al., 2003; Obeso et al., 2013), Go/No-go (Pornpattananangkul et al., 2016) and Simon (Kharitonova et al., 2013), and its activation seems to be proportional to the success of the task (negative correlation with stop signal reaction time, SSRT; Aron, 2006; Aron, 2007). Moreover, this activation is proportional to the difficulty of the task (Hughes et al., 2013) and increases with age (Kleerekooper et al., 2016). Unlike other regions involved for IC, the right IFG is activated during preparation for inhibition (anticipation) but also during efficient inhibition (Swann et al., 2012).

Finally, the left IFG is not left out. Although less found as a neural center of IC than its right counterpart, several works have shown that this region is also involved for efficient IC (Leite et al., 2018; Menzies et al., 2007; Mirabella et al., 2020; Quidé et al., 2018; Swick et al., 2008; Wiers et al., 2015).

Thus, the PFC, notably the IFG and ACC, seems to be a key zone for IC (Aron et al., 2014). However, other brain regions have also been shown to be involved in this EF.

2.1.1.1.3 pre-SMA The supplementary motor complex (SMC), a region of medial frontal cortex at the interface between the prefrontal and motor systems, is subdivided into two distinct areas: the pre-supplementary motor area (pre-SMA) and the more caudal supplementary motor area (SMA), which are distinguished by different cortical and sub-cortical connectivity (Nachev et al., 2007). Notably, the pre-SMA has extensive prefrontal connectivity (Luppino et al., 1993; Wang et al., 2005).

At the functional level, several studies have shown that inhibitory performance increases with activation of pre-SMA (Duann et al., 2009; Li et al., 2006; Obeso et al., 2013; Schel et al., 2014). Specifically, pre-SMA is thought to be a region involved in the preparation of motor inhibition (in a stop signal task for example, by anticipating a Stop signal: Swann et al., 2012). However, according to some authors, the activation of this region would

not be directly related to IC but rather to cognitive functions solicited in parallel such as attention or WM (Criaud and Boulinguez, 2013).

2.1.1.1.4 Cerebellum The cerebellum is a brain region that has been found to be related to performance in IC measured, for example, by the color-word Stroop (Ravnkilde et al., 2002). Being located behind the brainstem in the posterior fossa, the majority of studies have linked this region to IC through the connections it may have with other brain areas. Thus, the cerebellum would be functionally connected to the fronto-parietal network (Zhang et al., 2015) and to the right IFG (Picazio et al., 2016). Its action on IC would therefore be indirect.

2.1.1.1.5 Striatum The striatum is a subcortical region of the basal ganglia consisting of the caudate nucleus, the putamen, and the ventral striatum (which includes the nucleus accumbens). These striatal regions are areas classically involved in learning (Seger, 2006, 2008; Seger and Cincotta, 2005b). However, regarding IC, Beste et al., 2018 pointed out that the striatum is partially involved in IC due to its structural and functional connections with the PFC.

Thus, activation of the striatum has been shown to be related to reactive response inhibition during a stop signal task (Vink et al., 2005). Further studies have clarified the crucial role of the striatum: it has been shown to be associated with motor response suppression (by deactivating M1 primary motor cortex) and inhibition anticipation (Pas et al., 2021; Zandbelt and Vink, 2010), and this activity would depend on contextual cues such as the proportion of Stop trials in the task (Vink et al., 2015; Zandbelt and Vink, 2010). More specifically, recent studies have shown that a sub-part of the striatum, the putamen, is specifically involved in proactive response inhibition in the stop signal task (anticipation of Stop signals; Pas et al., 2019) but also in the effective stop by suppressing the activation of the response in the motor cortex (Pas et al., 2017).

Finally a meta-analysis on the neural correlates of response inhibition in adults has suggested the activation of a right hemispheric network common to all tasks (IFG, medial cingulate, paracingulate, and superior parietal gyri) but also distinct networks, thus emphasizing that IC is a multi-dimensional construct (Zhang et al., 2018). To conclude, IC would be the result of a particularly complex brain network, including regions that are more or less similar across studies, reviews, and meta-analyses.

2.1.1.1.6 Development of IC neural bases In a neurodevelopmental point of view, adults, who perform better than children, recruit more regions (right VLPFC, thalamus, caudate and cerebellum; Bunge et al., 2002; Rubia et al., 2001) and more strongly other ones (portions of the prefrontal cortex, anterior cingulate cortex, inferior parietal cortex and striatum; Bunge et al., 2002; Bunge and Wright, 2007; Rubia et al., 2006) than children and adolescents. Thus, prefrontal engagement decreases with age (Alahyane et al., 2014; Ordaz et al., 2013) in parallel with performance improvement (Dwyer et al., 2014) whereas increased engagement in performance monitoring in the dACC drives the development of

IC during adolescence, at least to some extent (Adleman et al., 2002; Ferdinand and Kray, 2014; Rubia et al., 2007; Santesso and Segalowitz, 2008; Segalowitz et al., 2010; Velanova et al., 2008). More precisely, there is a shift from global to local activations during IC tasks as the PFC develops and matures (Fiske and Holmboe, 2019). Of note, this general principle of brain development with the shift from a diffuse functional network to a focal network with age is also found in other domains such as body representation in children and adults (Cignetti et al., 2017; Fontan et al., 2017).

2.1.1.2 Neural basis of working memory updating WMU shares many regions with IC as it is thought to be underpinned by a widely distributed bilateral fronto-parietal network involving the ventro and dorsolateral as well as medial PFC, parietal lobes, left frontopolar gyrus, but also the striatum, middle temporal gyrus, and cerebellum (Collette and Van der Linden, 2002; Collette et al., 2005; Rottschy et al., 2012; Sörqvist and Sætrevik, 2010). These regions would be more recruited as cognitive load increases (see Luna et al., 2010 for a review). More precisely, the dorsolateral and medial PFC, in conjunction with the posterior parietal cortex, often referred as the frontoparietal network (FPN), contribute to the maintenance of WM content (D'Esposito and Postle, 2015; Feredoes et al., 2011; Nee et al., 2013; Roth et al., 2006). This FPN was also specifically activated during WMU tasks as N-back (Owen et al., 2005), digit-span (Kharitonova et al., 2013), keeping track (Tamnes et al., 2010), reading-span test (Osaka et al., 2004) or AX-CPT (Lopez-Garcia et al., 2016). These regions have therefore been referred as the core network of WM (Harding et al., 2015; Johnson et al., 2019; Rottschy et al., 2012).

2.1.1.2.1 Basal ganglia The basal ganglia (BG) refer to a network of interconnected subcortical structures, including: the striatum (composed of the caudate nucleus and the putamen), the globus pallidus, or pallidum, the subthalamic nucleus and the substantia nigra. The nucleus accumbens is sometimes added to these structures. All these structures are paired (one for each hemisphere).

Studies have provided support for the involvement of BG in WMU (Chatham and Badre, 2015; Cools et al., 2007; Murty et al., 2011; Nir-Cohen et al., 2020). More precisely, BG activation was shown to precede the selection of relevant information for WM maintenance (McNab and Klingberg, 2008).

2.1.1.2.2 Middle temporal gyrus The middle temporal gyrus (MTG) is a gyrus on the temporal lobe located between the superior temporal gyrus and inferior temporal gyrus.

MTG activation has been shown to be related to both WM, measured by long-term memories task (Axmacher et al., 2008; Ranganath and D'Esposito, 2001), and WMU, measured by the 2-back task (Stern et al., 2001).

2.1.1.2.3 Cerebellum A series of early neuroimaging studies have focused on the role of the cerebellum activation in verbal WM (Chen and Desmond, 2005a, 2005b; Desmond et al., 1997; Kirschen et al., 2005). This studies provide support for the model developed

by Desmond et al., 1997 in which the superior cerebellum participates in the articulatory rehearsal loop (as proposed by Baddeley's model) and the right inferior cerebellum is involved in errors correction by comparing information in the articulatory rehearsal loop with the contents of the phonological store. Cerebellum activation was shown to increase with memory load (Desmond and Fiez, 1998) However, it was shown that the cerebellum was activated across other WM modalities than verbal ones, supporting the fact that the cerebellum, together with prefrontal and parietal areas, is necessary for WM (Hautzel et al., 2009).

The implication of the cerebellum for WM, especially in error corrections, can be important for WMU. At the structural level, a relationship between cerebellum volume and WMU was demonstrated and the shrinkage of this region might be involved in WMU decline with age (Podell et al., 2012). At the functional level, the right cerebellum was activated specifically during WMU trials (Qin and Basak, 2020).

2.1.1.2.4 Midbrain The midbrain or mesencephalon is the uppermost part of the brain stem. It is subdivided in three main components: the cerebral peduncles, the tegmentum - or cap (which contains the substantia nigra) and the tectum. This structure has also been shown to be related with WMU (D'Ardenne et al., 2012; Murty et al., 2011; Podell et al., 2012). More precisely, the midbrain, along with striatal regions, might be associated in the anticipation of updating probability (Yu et al., 2013).

2.1.1.2.5 Development of WMU neural bases From a developmental perspective, fMRI studies consistently indicate that prefrontal systems are engaged in WM and WMU processes as early as 8 years of age but the magnitude of engagement varies with age (Luna, 2009). Most studies found age-related increases in the recruitment of PFC (Ciesielski et al., 2006) due to immaturities in the ability to manipulate information in WM (Crone et al., 2006; Olesen et al., 2007), to generate an accurate response (Klingberg et al., 2002; Scherf et al., 2006), and to suppress distractors (Olesen et al., 2007). Globally, a shift from global to local recruitment of frontal regions from childhood to adolescence and then to adulthood was demonstrated (Fiske and Holmboe, 2019).

2.1.1.3 Neural basis of cognitive flexibility CF tasks activate various brain regions. While it is possible to identify a common brain network underlying this EF (Dajani et al., 2020), brain areas involved in CF are more sensitive to different types of tasks (e.g., Kim et al., 2012; Wager et al., 2004) due to the the fact that these tasks generally include one and/or the other of the alternative components of EFs (Diamond, 2013).

Thus, the brain regions found to be involved in core CF across all tasks include the FPN, the ACC, the IFG, the insula, the inferior frontal junction (IFJ), the pre-SMA, the inferior and superior parietal cortices, inferior temporal cortex, occipital cortex, and subcortical structures such as the caudate and thalamus (Dajani et al., 2020; Dajani and Uddin, 2015; Kim et al., 2012; Niendam et al., 2012).

On the other hand, in contrast to this common "general domain" network of CF, the

activation of regions specific to characteristics of this EF has been highlighted.

2.1.1.3.1 IFJ The inferior frontal junction is located within a transition zone between the premotor and prefrontal cortex, at the junction of the inferior frontal sulcus and the inferior precentral sulcus.

This region is specifically activated during CF tasks (e.g., Armbruster et al., 2012; Armbruster-Genç et al., 2016; Dajani et al., 2020). A meta-analysis of both task-switching and set-shifting tasks have found that IFJ is the most activated region during CF tasks (Derfuss et al., 2005). IFJ seems to play a "domain-general" role (Kim et al., 2011), being involved in task representations by allowing to adjust behavior in advance to a new task environment (Brass and Cramon, 2004; Brass and von Cramon, 2002). Specifically, the left IFJ was shown to be the first region to be activated in response to engagement with CF and leads to engagement with other regions of the prefrontal, parietal and cerebellar regions (Dajani et al., 2020).

2.1.1.3.2 PFC Activations of the PFC were observed during CF tasks (Dove et al., 2000; Sohn et al., 2000). However, in contrast to the IFJ, more "domain-specific" activations were observed across lateral and medial PFC (Kim et al., 2011). Moreover, this PFC activation was shown to follow a gradient depending on the degree of endogenous control processes in the task: the more abstract (i.e., context switches were not triggered by a direct cue-task association) the switching tasks were, the more anterior was the activation of the PFC, and, at the opposite, the more constrained (driven by external cues that directly indicate the upcoming task) was the switching, the more posterior was the activated part of PFC (Kim et al., 2012).

2.1.1.3.3 Dorsal premotor cortex The dorsal premotor cortex is the upper part of the premotor cortex, an area of the motor cortex lying within the frontal lobe of the brain.

This region has been shown to be activated during CF tasks (Kim et al., 2011). More precisely, the dorsal premotor cortex was specifically activated when switching attention between perceptual features of stimuli (e.g., shape and direction) as opposed to switching between response mappings or contextual rules (Kim et al., 2012).

To sum up, CF is not controlled by a single brain network but multiple brain regions appear to be activated for switching, depending upon the type of switch being performed (Kim et al., 2012). These neural results support the hypothesis that CF is not a unitary process and that future studies involving task switching paradigms should consider the type of switch being performed.

2.1.1.3.4 Development of CF neural bases From a developmental point of view, the refinement process that has been demonstrated during tasks of CF follows a protracted developmental trajectory (Fiske and Holmboe, 2019). Like the other EFs, studies hypothe-

sized a functional relation between CF and the PFC development (Bunge and Zelazo, 2006; Crone et al., 2004; Stuss, 1992). With age and the increase of CF performance, larger parts of the brain, including left right inferior PFC, left parietal cortex, anterior cingulate cortex (ACC), and striatum, are recruited (Moriguchi and Hiraki, 2009, 2014; Rubia et al., 2006) and more strongly (Moriguchi and Hiraki, 2011; Morton et al., 2009). Similarly, activation of the FPN and insula increases across development, suggesting that CF abilities increase with the development of these regions (Rubia et al., 2006; Wendelken et al., 2012b). Moreover, this link between CF and brain development depends on the CF component involved: while for switching, an adult-like pattern of activation in the pre-supplementary motor area was observed in adolescence but not in childhood, the activation for maintenance and selection in the ventrolateral PFC differed among children, adolescents, and adults (Crone et al., 2006). In addition, the IFJ activation, specific to CF tasks in adults (Dajani et al., 2020; Kim et al., 2011), was observed only once in children (Morton et al., 2009). The fact that this region is not commonly found as active in CF studies in children supports the fact that switching coordination is under developmental influences. The differential development of the different components of CF mentioned earlier is thus detected at the cerebral level.

To conclude, although we have seen that each EF recruits specific regions, sometimes specific to certain task characteristics, imaging studies have revealed that the three core EFs display extensive overlap in the brain regions recruited, all activating functional networks involving prefrontal and parietal regions arguing for common components to these functions (unity of EFs; Greene et al., 2008).

2.1.2 Unity of EFs

Along with unity of EFs, numerous neuroimaging studies in adult participants have identified a set of brain networks that are consistently activated regardless of the EF engaged. As we have seen, the three basic EFs would jointly involve frontal (e.g., dorsolateral PFC and ACC) and parietal (e.g., superior and inferior parietal lobe and precuneus) activations, reflecting a common-EF (Collette et al., 2006; Niendam et al., 2012; Wager et al., 2004; Wager and Smith, 2003).

At the beginning, lesional studies and early fMRI work provided the first evidence that the PFC was fundamental to WM and IC (Zelazo et al., 2008; for a review, see Collette et al., 2006). Indeed, as early as 1976, Pribram spoke of the importance of the PFC in behavior and "executive programs" (Pribram, 1976).

This area remains the most cited brain region when discussing the neural bases of EFs and especially IC (Aron et al., 2014; Chafee and Heilbronner, 2022). In particular, it was shown that, to accomplish the coordinated operations of multiple neural systems, the PFC must monitor the activities in other cortical and subcortical structures and control and supervise their operations by sending command signals, which is called top-down signaling (Funahashi and Andreau, 2013). The PFC is therefore thought to play a primary role and to manage complex interactions with several cortical and subcortical brain structures (Gruber

et al., 2006; Heyder et al., 2004; Norman and Shallice, 1986; O'Reilly and Frank, 2006).

More recent studies using several tasks measuring different EFs have revealed complex and distributed brain networks of activation. More precisely, it was shown that a largely unified network of prefrontal and parietal regions, along with areas within the basal ganglia, subserve processes of IC and CF and are involved whenever potentially relevant information must be selected from multiple information channels (Hedden and Gabrieli, 2010).

A recent fMRI study in children (Engelhardt et al., 2019) has shown that the cingulo-opercular and fronto-parietal networks that were involved for the three EFs (see Figure 11) are the same networks as in adults, suggesting that the improvement in EFs with age from childhood to adulthood, and perhaps their differentiation, are likely due to changes within these networks rather than in the networks' organization *per se* (Engelhardt et al., 2019).

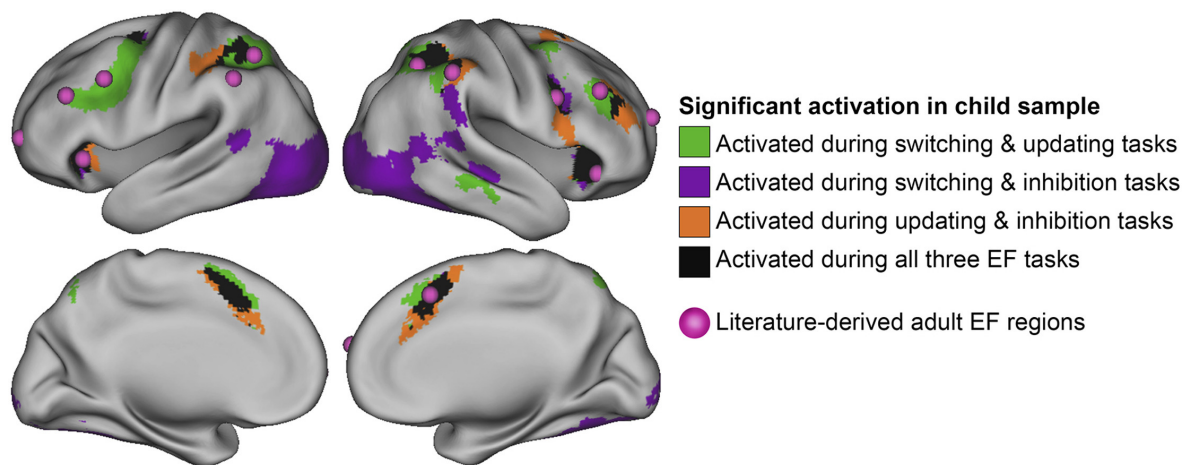


Figure 11: **Overlapping task-positive brain activity across three EF tasks, overlaid with adult ROIs.** From Engelhardt et al., 2019.

However, it was suggested that maturation of EFs is related to the refinement of activity in brain regions directly linked to the EF in question, as well as decreased activity in supplementary brain regions (Durstun et al., 2003; Durstun et al., 2006; Durstun et al., 2002; Fiske and Holmboe, 2019; Lamm et al., 2012).

It was also suggested that some developmental changes can take the form of changes in temporal dynamics rather than qualitative changes in the network of brain regions engaged (Wendelken et al., 2012b).

However, a major limitation in the interpretation of the brain regions involved in the different EF networks is that the results are often analyzed within the framework of the reverse inference hypothesis. The latter consists in inferring the mental processes involved in the task from MRI acquisitions and is based on the hypothesis that the activation of a region is the product of a single process, which is generally not the case (Borst and Cachia, 2018).

2.2 Integration: connectivity of the EF network

As we have seen, although certain brain regions appear to be specific to an EF, there is instead a network of regions that, together, enable proper executive functioning. A great deal of research focuses on these networks under the spectrum of connectivity.

2.2.1 Structural connectivity of the EF network

A recent review (Goddings et al., 2021) summed up the relations between white matter microstructure and the three core EFs over the course of development.

Regarding IC, it was shown that, in childhood and adolescence, IC was positively associated to fractional anisotropy (FA) in frontal regions. In adolescents, this positive association between IC and frontal lobes (Liston et al., 2006) was more precisely found in regions related to IC such as the IFG or pre-SMA (Madsen et al., 2010), the corpus callosum (Fjell et al., 2012) or the anterior corona radiata (Seghete et al., 2013). In children (before 12 years old), IC was related to FA in the forceps major (Fjell et al., 2012). However, these results are still under debate. Indeed, some studies described limited (Jernigan et al., 2016) or no (Ursache et al., 2016) association between DTI metrics and IC performance. A longitudinal study suggested that better IC was associated with earlier white matter microstructural development, specifically with higher FA in the hippocampal portion of the left cingulum in late adolescence/early adulthood but with lower FA in the cingulum in early adolescence, and with higher FA growth during mid-late adolescence (Simmonds et al., 2014).

Regarding WM, there is consensus on an association between developing WM and changes in white matter microstructure during childhood and adolescence, particularly of frontoparietal and occipito-temporal tracts even if some mixed results are still observed (Goddings et al., 2021). Indeed, as young as in infants of 12 month-old, better WM scores were related to higher FA and lower radial diffusion (RD) in white matter tracts that connect brain regions supporting WM in children and adults (Short et al., 2013). In older children and adolescents, better performance in verbal and spatial WM was associated with higher FA and lower RD in the superior longitudinal fasciculus (SLF), independently of age (Vestergaard et al., 2011; Østby et al., 2011) and a longitudinal study even found that FA in frontal tracts predicted later WM capacity (Darki and Klingberg, 2015). However, in another longitudinal study of younger children, scanned between 4 to 11 years-old, there was no significant association between development of either verbal or visuospatial WM capacity and DTI changes in the SLF but with increased FA and decreased MD in the right inferior fronto-occipital fasciculus and the forceps major and a decreased MD in the inferior longitudinal fasciculus (ILF) and uncinate fasciculus (UF) in the right hemisphere (Krogsrud et al., 2018). Finally, in a study with children from 6 to 16 years, for the younger, the executive part of WM (defined by a principal component analysis - PCA on 4 WM tasks) was associated with the corpus callosum and the posterior temporal white matter structure (Bathelt et al., 2018).

Fewer studies have focused on CF and no consensus has yet been reached (Goddings et al., 2021). As CF have been associated with fronto-parietal and striatal regions, studies have

examined whether white matter microstructure of tracts connecting these regions support CF (Badre and Wagner, 2006; Gold et al., 2010). Higher FA and lower RD in anterior portions of the corpus callosum were related to better task-switching, indicating the importance of inter-hemispheric communication for CF, here measured by three tasks: shape-color, spatial- and verbal-switching paradigms (Vallesi et al., 2016). Finally, higher FA in posterior brain regions was associated with better CF (measured by the switching condition in the NEPSY-II Inhibition test) in children from 5 to 16 years (Treit et al., 2014).

2.2.2 Functional connectivity of the EF network

2.2.2.1 Functional networks of common-EF

In an fMRI study, a common pattern of activation was observed in the prefrontal, dorsal anterior cingulate, and parietal cortices across EFs, supporting the idea that EFs are related to a superordinate cognitive control network: the control executive network (CEN; Niendam et al., 2012). Among the CEN, two networks are central to supporting cognitive control and, more broadly, EFs: the fronto parietal network (hereafter referred as FPN) and the cingulo-opercular network (hereafter referred as CON; Alchihabi et al., 2021; Barbey, 2018; Bressler and Menon, 2010; Cocchi et al., 2013; Crone and Steinbeis, 2017; Dosenbach et al., 2007). In adults, a stronger connectivity between the frontal pole and attention network and between crus of the cerebellum and the right FPN were shown to be associated with better efficiency of common-EF (Reineberg et al., 2015). In participants from 8 to 22 years, this FPN segregation was positively related with EF efficiency (Baum et al., 2017).

Based on the differences in their connectivity and activation profiles, it was suggested that FPN et CON support distinct functions: adaptive control (FPN) and stable set-maintenance (CON), supporting a "dual-network" account of task control better than "unitary" models of executive control (Dosenbach et al., 2007). Cooperation between different neural systems, including the FPN, the CON and the default mode network (DMN), would be the key to efficient executive functioning.

2.2.2.2 Functional networks of EF components

On another hand, the specific EFs were associated with other connectivity characteristics. Higher shifting abilities were associated with increased connectivity of the ventral attention network with the angular gyrus (Reineberg et al., 2015) and a decreased connectivity of the ventral attention network with the DMN (Reineberg et al., 2018). Greater posterior cingulate cortex/precuneus (medial-FPN) connectivity with the ventromedial striatopallidum (basal ganglia) was also shown to be correlated with fewer total errors on a set-shifting task (Vatansever et al., 2016). Finally, greater lateral-FPN and medial-FPN connectivity during resting-state was related to poorer cognitive flexibility performance (Douw et al., 2016; Kupis et al., 2021).

WM abilities were related to the anticorrelations between the medial prefrontal cortex (a component of DMN) and between the dorsolateral prefrontal cortex (dLPFC, a component of FPN) (Keller et al., 2015). FC between bilateral dLPFC and the dorsal ACC and between the right dLPFC and the left orbital fronto-insular cortex have also been demonstrated to be related to WM accuracy and could predict individual differences in WM (Fang et al., 2016).

Overall, the level of global connectivity of frontal hubs would predict individual variations in WM performance (Cole et al., 2012).

Regarding IC, stronger intra-FPN connectivity is associated with poorer inhibitory efficiency (Liu et al., 2018). Similarly, stronger connectivity between the FPN and the DMN was associated with decreased SSRT on the Stop signal task (Lee and Hsieh, 2017). White matter damage to the cingulo-opercular network led to less DMN deactivation and poorer inhibitory performance (Bonnelle et al., 2012). Stronger connectivity between the right inferior parietal lobule/lateral occipital cortex and bilateral lingual gyrus, stronger connectivity between the IPS/lateral occipital cortex and right lingual gyrus, weaker connection between the IFG and inferior temporal gyrus, and weaker connection between the left IPS and frontal gyrus opercular part are associated with better inhibitory performance with shorter SSRT (Zhong et al., 2014).

At last, a recent study (Panikratova et al., 2020) focusing on the functional connectivity of the DLPFC concluded that this functional connectivity contributes to distinct EFs: whereas IC efficiency was related to functional connectivity with DMN regions, switching was associated to functional connectivity with visual regions. Also, in children of 6-10 years, WM and response inhibition were related to regional functional connectivity but not topological organization (as local or global efficiency) of functional networks and functional connectivity associated with “bottom-up” processing were more clearly related to children’s performance on WM and response inhibition (Zhong et al., 2014).

Finally, resting-state EEG studies have also focused on EFs. While a first one did not succeed in revealing individual differences in EFs through rsEEG (Gordon et al., 2018) another has shown that some rsEEG features predicted differently IC and planning but none of them could predict WM performance (Cai et al., 2021).

As activity across brain regions becomes more evenly distributed with age, it is possible that as we reach adulthood there is more distributed function across the brain which may decrease the need to recruit prefrontal systems. The hypothesis that integration across the brain is central to cognitive development (Edin et al., 2007; Olesen et al., 2003) is supported by DTI studies (described earlier) showing that age related improvements in WM are related to increased functional connectivity within cortical regions and in corticosubcortical pathways (Luna, 2009).

Neuroimaging techniques continue to develop and with them, new research perspectives. Here we have described mainly MRI or lesion studies: localization studies. Electroencephalography (EEG) or functional Near Infra-red Spectroscopy (fNIRS) studies have also contributed to the knowledge of executive functioning, especially at the temporal level. At the level of psychological research, all of these methods are recent and have not yet been fully exploited. It remains to build bridges between all the knowledge that has already been contributed and that which will be acquired thanks to these new techniques. Only this will allow us to fully understand the complex development and functioning of cognitive functions such as EFs, and only at a neural level. However, it seems important to point out, especially at a time when the prefix *neuro-* is particularly popular, that this research must be done in connection with the theories already developed and the knowledge validated by

experimental research, along with clinicians and with the use of environmental measures. Observing the brain alone, without behavioral correlates, makes little sense. Observing it to test research hypotheses, to validate empirical theories, on the other hand, makes a lot and is now easy and accessible, thanks to the development of all the imaging techniques and the collaborative area that is currently happening.

3 Genetic basis of EFs

As we have seen, different brain characteristics are related to executive abilities. While some represent early markers, such as brain sulcal patterns, others are plastic features that can vary with time, environment, and learning. In the eternal debate between nature and nurture, many studies have thus focused on genetic influences on EFs.

3.1 Non molecular genetics: twin studies

Twin studies, as one of the most popular design in behavioral genetics, have long been used to distinguish between nature and nurture. Indeed, monozygotic twins (MZ, "identical twins") have an identical genome (except for mutations occurring during their individual development) whereas dizygotic twins (DZ, "fraternal twins") share 50% of the genes (in the same way as any pair of brothers/sisters). It is then possible to calculate the correlation between the values observed for a given trait, on the one hand in a cohort of monozygotic twins (with identical genomes), and on the other hand in a group of dizygotic twins (50% identical genes). If the correlation is significantly higher in identical twins, the existence of a genetic factor can be inferred.

Structural equation models (SEM) have provided mathematical modeling for these studies. Individual differences in performance on a measure are modeled due to three types of influences (see Figure 12): additive genetics/heritability (A), shared environment (C), and non-shared environment (E).

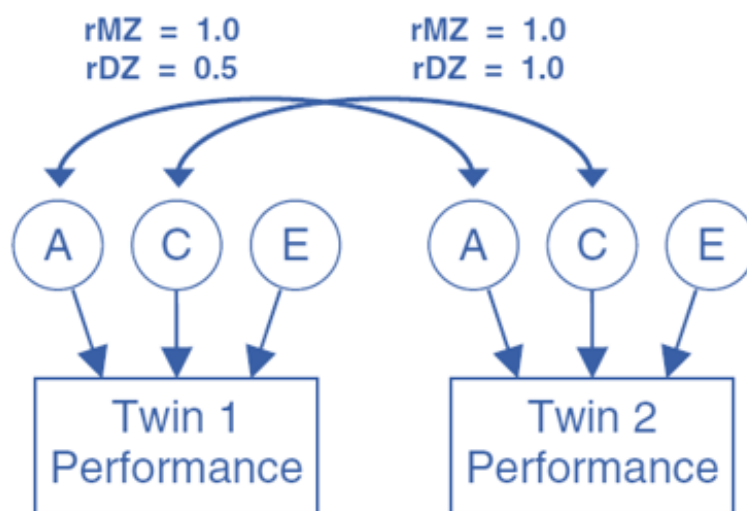


Figure 12: **Structural Equation Modeling for twin studies.** From Friedman et al., 2008.

The correlation A between Twin 1 and Twin 2 is set to 1.0 for MZ twins because they share all of their genes and to 0.5 for DZ twins because they share on average half of their genes per offspring. The C correlation is set to 1.0 for both types of twins because in both cases the two twins are raised together. The E correlation is set to 0 because the non-shared environment is uncorrelated by definition.

Different types of SEM can be modeled, making it a powerful tool for partitioning genetic from environmental factors on a trait (Rijsdijk, 2002). These types of studies and models have been used to investigate EFs and their genetic part. Regarding IC, a study has shown that by using the MZ/DZ twins design that genetic factors accounted for 29% of response inhibition in aging adults, measured by a color-word Stroop task (Lee et al., 2012). In children, a twin study of 9-, 12-, and 18-year-old-twins using a color-word Stroop task has shown that genetic variance ranged from 39 to 51% across age (Polderman et al., 2009). Another study with 6-year-olds tested in a Go/No-go task displayed familial resemblance although model-fitting analyses could not make a distinction between genetic and shared environmental effects (Groot et al., 2004). Interestingly, it was also demonstrated that changes in IC across early childhood (between 2 and 3 years) were explained mostly by genetic influences although there was also an influence of shared and nonshared environmental factors (Gagne and Saudino, 2016).

Regarding WMU, a study (Zhou et al., 2018) found a moderate heritability for spatial WM, of which the genetic factors accounted for 33% of the total variance. For a short-term memory task (digits forward span), the overall heritability was shown to be at .27 (Kremen et al., 2007).

Finally, no significant heritability was found for CF ability, of which the specific environmental factor explained most of the variance (85%; Zhou et al., 2018).

As for more complex EFs, a study using the WCST in a longitudinal sample of adolescent twins tested at ages 12 and 14 showed an increase in heritability in females (19% at age 12 and 49% at age 14) and in shared environmental influences in males (non-significant at age 12 and 34% at age 14; Anokhin et al., 2010). These results suggest increasing influence of familial factors during adolescence, as well as gender differences in the relative role of genetic and environmental factors.

However, the effect of genetics has been shown to vary in strength between the manifest and latent levels. Notably, while the genetic component (influence A) ranged from 15-30% for IC tasks (Stroop, stop signal and antisaccade), it was as high as 99% for the latent IC factor (Friedman et al., 2008). This was replicated with Updating and Shifting where the genetic share was worth 100 and 81% respectively, while it ranged from 0 to 14% for the measured tasks. Moreover, when including the common-EF into the model, this one was shown to be at 99% heritable along with Updating (56%) and Shifting (42%). Taken together, these findings imply that the unity and diversity of EFs are due to genetic influences at the common (for all three EFs) and specific levels (for Updating and Shifting) (Friedman et al., 2008, see Figure 13).

Thus, regarding common-EF, twin studies have established that EF is highly heritable in childhood (Engelhardt et al., 2016; Polderman et al., 2007), early adulthood (Friedman et al., 2008) and middle age (Ando et al., 2001; Gustavson et al., 2017). Indeed, a significant influence of genes was shown with an heritability of about 50% in adults (Ando et al., 2001) but also in children of 5 and 12 years (Polderman et al., 2007). This last study showed that genes contributed significantly to the longitudinal covariances between EF indices at age 5 and age 12. More precisely, it was shown that developmental changes in EFs during preschool period are promoted by genetic and environmental influences, but that EF sta-

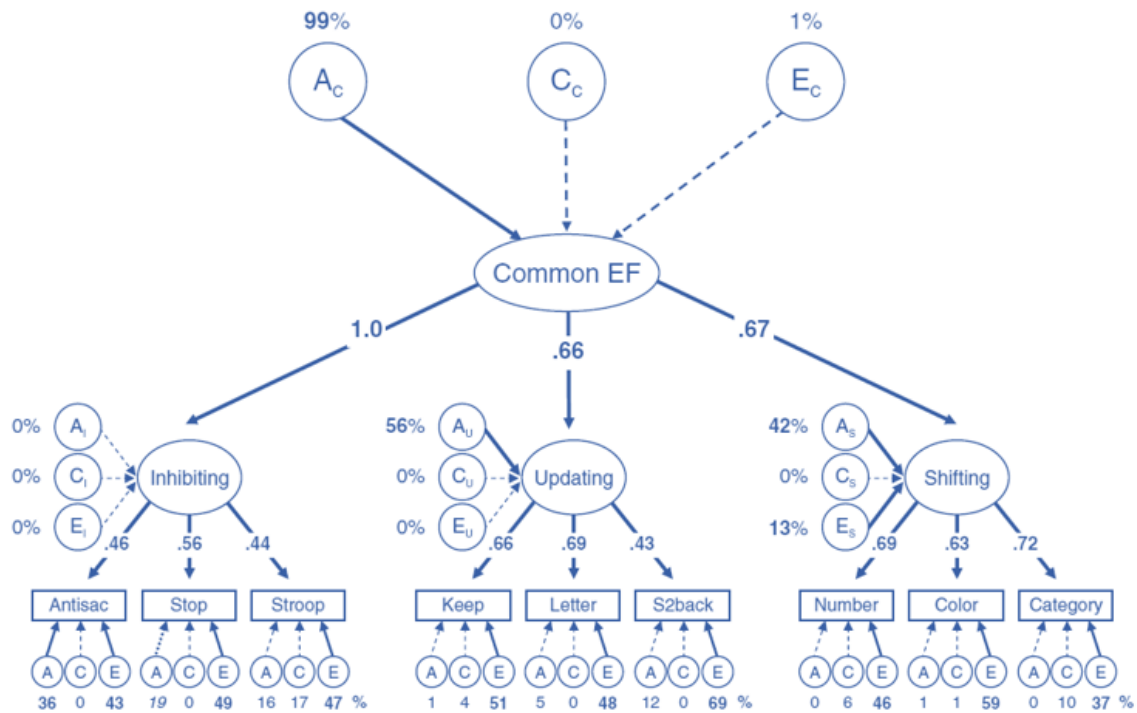


Figure 13: **Hierarchical multivariate executive function ACE model.** From Friedman et al., 2008.

bility during this period is attributed to the experience of shared environments (Fujisawa et al., 2017). At the opposite, during late adolescence, individual differences in EFs seem quite heritable and stable by late adolescence, with this stability due almost entirely to high genetic correlations across time. However, there was still small but significant nonshared environmental influences on change in common-EF (15%; Friedman et al., 2016). Regarding self-reported measures, a study using the BRIEF indicated presence of genetic and non-shared environmental influences for some scales (Initiate, Plan/Organize, Organization of Materials, Shift, and Monitor and Self-Monitor) whereas the Emotional Control scale was only environmental (Little et al., 2017).

Although these studies have highlighted the heritability of EFs, they do not provide information on the genes involved.

3.2 Molecular genetics

After introducing techniques used in molecular genetics, we will describe the dopaminergic system which plays an important role for EFs. Then we will detail the genes involved in this system in relation to their role in EFs (candidate gene approach). We will then conclude with EF genome association studies.

3.2.1 Some genetic bases

3.2.1.1 Genome Each cell of the human body carries our genetic code: the genome (21,000 genes). This genome contains about 3 billion nucleotide bases (Adenine, Thymine, Guanine or Cytosine) which, by three, constitute an amino acid. These chains of amino acids then code for a protein (one protein = a hundred amino acids).

3.2.1.2 Single nucleotide polymorphisms SNPs (Single Nucleotide Polymorphisms) correspond to a minor variation of the genome since it is the substitution of a single nucleotide (Adenine, Thymine, Guanine or Cytosine) by another. A SNP is therefore the variation (polymorphism) of a single base pair of the genome, between individuals of the same species (Figure 14). The terminology SNP is used if the frequency of the substitution is higher than 1% in the population and of mutation otherwise. These variations are mostly silent but can sometimes be at the origin of phenotypic variations (6 million SNPs would characterize the genetic diversity of the world population, Goldberg and Weinberger, 2004) or even pathologies such as sickle cell disease (Higgs and Wood, 2008).

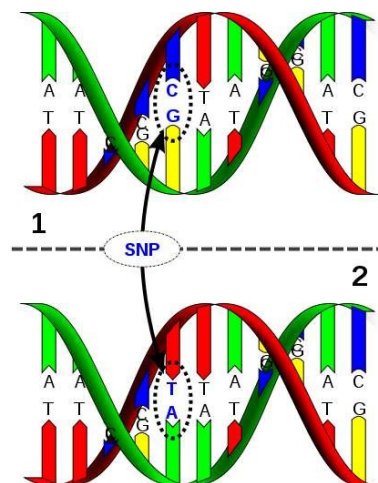


Figure 14: **Single Nucleotid Polymorphism.**

3.2.1.3 Genome wide association studies As we saw, historical candidate genes literature have shown that EFs are supported by the dopaminergic system and its neuro-modulator effect. In addition to candidate gene studies, genome wide association studies (GWAS) have also been able to identify certain SNPs involved in EFs. GWAS is basically a linear regression model with phenotype as the dependant variable and genotype (with or without covariates) as the independant variable. Of note, these analyses require a large sample size to represent all the variability at the genetic and phenotypic levels.

3.2.1.4 Polygenic risk score The use of polygenic risk scores (PRS, also called polygenic scores or PGS) is a powerful approach for gaining insights into the genetic architecture of cognitive phenotypes. PRSs are quantitative scores that index, for each individual

subject in a study sample, their aggregate genetic risk for a phenotype of interest (see Figure 15). Specifically, a PRS is computed as the weighted sum counting all risk alleles for a selected set of SNPs carried by an individual. The weight used for each risk allele is the SNP log odds ratio estimated out of sample in a large GWAS of the given phenotype. PRS have been demonstrated to be powerful and reliable indicators not only for genetic contributions to single traits but also for genetic correlations between phenotypes.

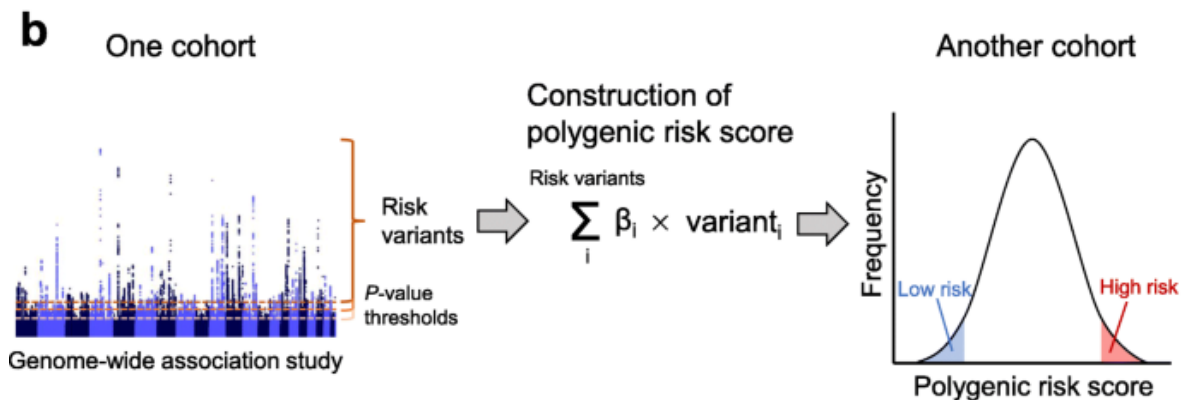


Figure 15: **Polygenic risk score construction.** From Konuma and Okada, 2021

3.2.2 The dopaminergic system

Dopamine is a key neurotransmitter for EFs (e.g., Cropley et al., 2006). Studies have found that increased dopamine levels are linked to better performance on EF tasks (Barnes et al., 2011; Beu et al., 2019; Bowirrat et al., 2012; Eisenberg and Berman, 2010; Luna et al., 2015; Mulligan et al., 2014; Ott and Nieder, 2019) and that a dopaminergic deficit was linked to a deficit in EFs (Hosenbocus and Chahal, 2012). Such deficit is also found in certain pathologies such as ADHD (e.g., Volkow et al., 2009), Alzheimer’s disease (e.g., Pan et al., 2019) or schizophrenia (e.g., Howes et al., 2017). This link can be explained by the fact that the dopaminergic system modulates the activity of brain networks involved in EFs such as the PFC or the striatum (Hosenbocus and Chahal, 2012). Certain genes can therefore vary the level of dopamine by impacting either the number of dopamine receptors at the synaptic cleft, or the reuptake and degradation of dopamine.

There are four main dopaminergic pathways: one cortical, the mesocortical pathway, and three subcortical, the tuberoinfundibular pathway, the nigrostriatal pathway and the mesolimbic pathway. In the mesocortical pathway (in red in Figure 16), dopaminergic neurons project from the ventral tegmental area to the frontal lobes, particularly the prefrontal cortex. In the mesolimbic pathway (in dark blue in Figure 16), dopaminergic neurons project also from the ventral tegmental area but innervate the nucleus accumbens (or ventral striatum). The nigrostriatal pathway (in light blue in Figure 16) consists of dopaminergic neurons that come from the substantia nigra and that terminate in the dorsal striatum. Finally, the tuberoinfundibular pathway (in green in Figure 16) connects the hypothalamus and the pituitary gland.

The dopaminergic system in the PFC, which is, as we have seen, a key region for EFs,

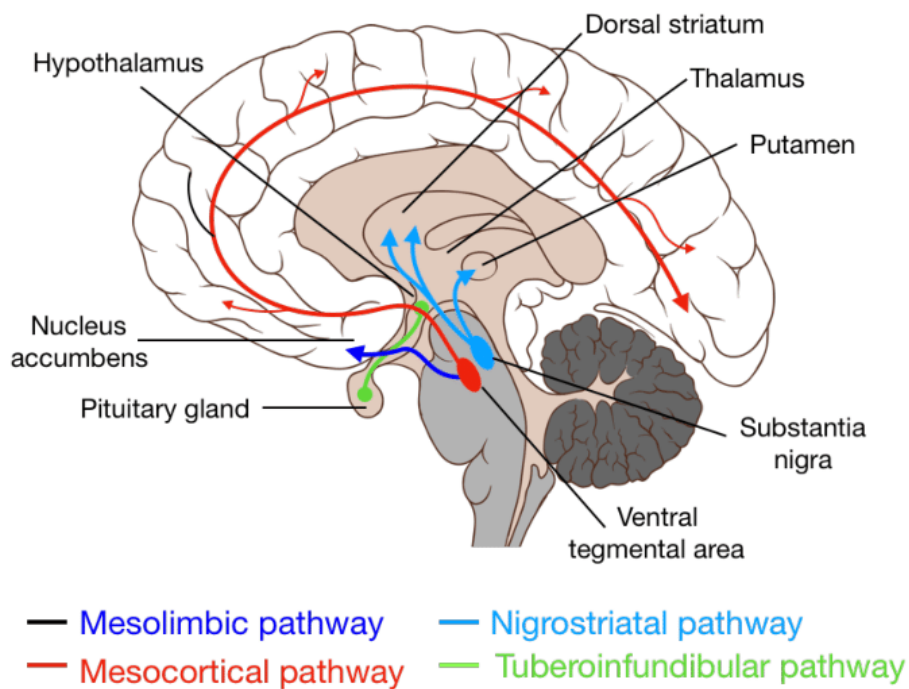


Figure 16: **Dopaminergic pathways in the brain.** Figure from Nummenmaa et al., 2020.

modulates the activation of this region but also of other regions like the striatum. We can see that dopaminoreceptive and dopaminergic regions overlap with the brain areas involved in EFs (Figure 16).

Thus, the study of genes involved in the dopaminergic system (either through knowledge of their mechanisms or through their involvement in pathologies where EFs were impaired) has made possible to highlight a certain number of SNPs linked to executive performance.

A review from 2014 (Logue and Gould, 2014) concluded that EFs, as a collective of multiple complex cognitive processes, are differentially altered by monoamines and cholinergic afferents into the underlying cortical substrates and by polymorphisms associated with these neurotransmitter systems. CF was associated with COMT Val158Met, DRD2/ANKK1, and DRD4 polymorphisms whereas response inhibition was linked to the polymorphism of the 5-HT2A gene. These different polymorphisms impact different aspects of the dopaminergic system (dopamine reuptake, dopamine receptors, etc.).

3.2.3 Candidate genes from the dopaminergic system

3.2.3.1 COMT The COMT gene coding for the protein of the same name is one of these. This gene can vary in polymorphism by changing a single base pair (158-Met, CATG → CGTG) resulting in an amino acid change (Valine → Methionine). The Met allele is associated with methylation and therefore slower degradation of dopamine. Thus, dopamine levels are higher which allows its action to be prolonged (Logue and Gould, 2014).

Various studies have shown that the 158-Met version of the gene was associated with better performance on EF tasks in children and adults (Diamond, 2007; Diamond, 2011; Diamond et al., 2004; Malhotra et al., 2002; Thomason et al., 2009; for a review see Harrison and Weinberger, 2005; Tunbridge et al., 2006) on various measures as the Frontal Assessment Battery (Mitaki et al., 2013), the BRIEF (Zhang et al., 2018), the WCST (Khanthiyong et al., 2019; Nagel, 2008), the Tower of London (Choudhry et al., 2014), the Letter–Number Sequencing (Bruder et al., 2005) and the TMT (Wishart et al., 2011). Two meta-analyses concluded in a effect of Val158Met genotype on EFs (Barnett et al., 2007; Barnett et al., 2008). Regarding IC, results are more debated, with divergent results (Haraldsson et al., 2010; Schneider et al., 2015) or lack of results (Kasparbauer et al., 2015) observed across studies. Regarding WM and WMU, 158-Met individuals were shown to perform better at WM tasks whereas 158-Val individuals performed better in WMU tasks (Bellander et al., 2015; Colzato et al., 2010; Krugel et al., 2009). Moreover, 158-Val carriers presented larger training gains, maybe because WMU operations have a higher level of plasticity than WM maintenance operations (Bellander et al., 2015). At the psychopathological level, the Valine allele is associated with an increased risk of schizophrenia (Egan et al., 2001), bipolarity (Shifman et al., 2004), or ADHD (Diamond, 2007). Furthermore, this polymorphism modulates the impact of schizophrenia (Egan et al., 2001; Ehli et al., 2007) and cannabis use (Verdejo-García et al., 2013) on EFs.

3.2.3.2 DAT1 The DAT1 gene, encoding the selective Dopamine Active Transporter (DAT), acts on the reuptake of dopamine at the synapses of the striatum. One of the allelic versions of this gene is composed of 10 repeats (L-Long) while there are usually 9 (S-Short). The L version leads to a higher expression of the DAT transporter which generates an excess of dopamine reuptake, then decreasing its level (Barnes et al., 2011). This version is linked to poorer performance in IC measured by a stop signal task (Congdon et al., 2008; Cummins et al., 2012; van Rooij et al., 2015), in WM measured by an N-back task (Brown et al., 2011; Stollstorff et al., 2010) and in CF measured by the WCST (Fagundo et al., 2014; Garcia-Garcia et al., 2010) and TMT (Fagundo et al., 2014). Furthermore, this L version is associated with an increased risk of ADHD (Swanson et al., 2000) and modulates the response to Methylphenidate treatment in these patients (Ding et al., 2017).

3.2.3.3 DRD1 and DRD2 The DRD1 and DRD2 genes code for the D1 and D2 dopamine receptors respectively. DRD1 can vary in polymorphism with the substitution of an Adenine by a Guanine. The G (Guanine) allelic version leads to a decrease in the expression of the gene and thus the number of D1 receptors (Huang and Li, 2009), causing dopamine levels to drop. This allelic version is associated with poorer inhibitory performance as measured by a Go - No go task (Beste et al., 2016; Loos et al., 2010) as well as an increased risk of schizophrenia (Zhu et al., 2011), addictions (Batel et al., 2008; Huang et al., 2008; Zhu et al., 2013), entry into the autism spectrum (Hettinger et al., 2008) and ADHD (Bobb et al., 2005). Similarly, DRD2 can vary in polymorphism with the substitution of a Cytosine for a Thymine. The T (Thymine) allelic version results in a decrease in D2 receptor responsiveness to dopamine (Ritchie and Noble, 2003), thus lowering its level. This version is associated with poorer performance on tasks measuring EFs such as ANT or WCST (Nkam et al., 2017; Rodriguez-Jimenez et al., 2006), CF (Stelzel et al., 2010), WM (Klaus

et al., 2017) or IC (delayed gratification task; Eisenberg et al., 2007). However, a recent meta-analysis reported that DRD2 has a limited effect on EFs in healthy adults (Klaus et al., 2019). At the psychopathological level, this version is also associated with an increased risk of schizophrenia (Golimbet et al., 1998), addictions (Ponce et al., 2003), obesity (Noble et al., 1994), ADHD (Comings et al., 1996; Lawford et al., 2000; Noble et al., 1994; Ponce et al., 2003).

3.2.4 Other candidate genes and neurotransmitters systems

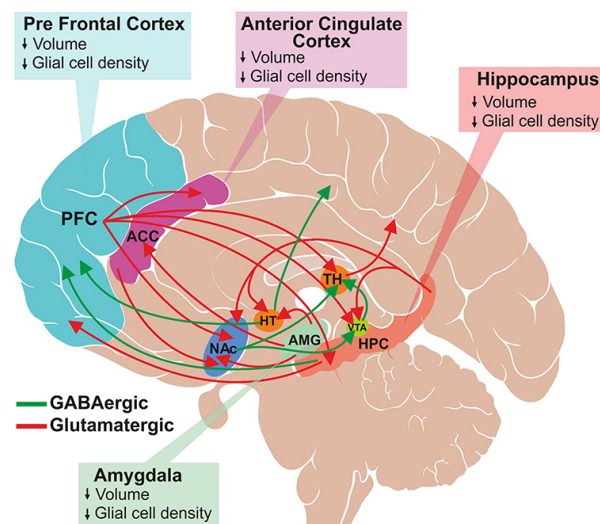


Figure 17: **Schematic of glutamatergic and GABAergic projections.** Major glutamatergic projections (in red) arise from the frontal cortex to the anterior cingulate cortex (ACC), thalamus (TH), ventral tegmental area (VTA), hippocampus (HPC) and nucleus accumbens (NAc). Additionally, glutamatergic neurons originate from hippocampus, and innervate into hypothalamus (HT), VTA, NAc and PFC and from amygdala to HT, ACC and NAc. The GABAergic projections (in green) are widely distributed throughout the brain. In the boxes are described the structural changes observed in the brain regions of depressed subjects. From Sarawagi et al., 2021.

It should be noted that the dopaminergic system, on which many studies have focused, is not the only one to influence EFs. In particular, several studies have shown that the glutamatergic and the GABAergic systems influence executive capacities (see Figure 17; Dauvermann et al., 2017; Logue and Gould, 2014; Thomas et al., 2017). However, these studies are mainly based on psychopathology data and there is a need to study these two systems' mechanisms and their impact on EFs in more detail and in healthy subjects.

Other genes, from the dopaminergic system or not, were identified in the literature as linked with EFs such as RELN (Baune et al., 2010), MAO-A (Söderqvist and Bergman Nutley, 2015), BDNF (Alfimova et al., 2013; Enge et al., 2016) or APOEε4 (Rusted et al., 2013).

3.2.5 EF GWAS

As we have seen, GWAS requires a large sample size and, because of this, few EF GWAS have been performed.

A first study included 1,311 to 32,070 individuals (depending on the task) and analyzed performance on different tasks including EF ones such as trail making or color-word Stroop (Ibrahim-Verbaas et al., 2016). The study highlighted a genome-wide significant association for processing speed but not for the other tasks. Another recent preprint investigated the GWAS of a common-EF factor, based on multiple tasks, using SEM, in a sample of 93,027 to 427,037 adults (depending on the task; Hatoum et al., 2022). They found 299 independent loci with synaptic, potassium channel and GABA pathways associated with common-EF (see Figure 18).

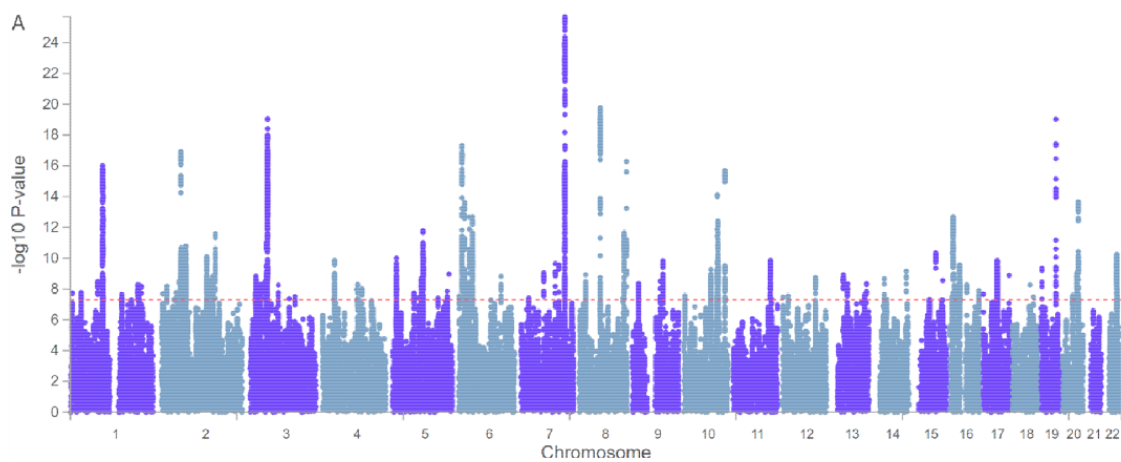


Figure 18: **Manhattan plots for GWAS of Common Executive Functioning.** Each dot is a single nucleotide polymorphism (SNP), chromosomes are organized on the x-axis, and the y-axis represents the negative log₁₀ of the p-value for each SNP. From Hatoum et al., 2022.

Another GWAS study conducted analyses for processing speed, WM (measured by a PCA build on N-back, Digit Vigilance, Counting Span and Dual tasks) and IC (measured by a stop signal task) in 4,611 adolescents. No SNPs were significantly associated with any of the cognitive measures, but two genes were found to be associated with WM as a PCA index (Donati et al., 2019).

Additional studies with large sample size are needed to discover and differentiate the molecular pathways associated with EFs in the general population. Moreover, the inclusion of different age groups is required to investigate the development of genetic basis of EFs.

A novel approach that could lead to a better understanding of EF genetics is genomic SEM (Grotzinger et al., 2019). This multivariate method synthesizes genetic correlations and SNP heritabilities from GWAS summary statistics of individual traits and allows to model multivariate genetic associations among phenotypes. This method is promising as polygenic scores from genomic SEM consistently outperform those from univariate GWASs.

3.2.6 EF PRS

It appears that the genetic architecture of EFs, like other complex cognitive phenotypes, is diffuse across very many variants (polygenic). Few studies have used PRS method to investigate EF phenotypes and their associations with other phenotypes or disorders.

A first one calculated, PRS for multiple psychiatric disorders such as autism spectrum disorder (ASD), major depressive disorder (MDD) and schizophrenia (SZ; Schork et al., 2019). They found that the ASD-PRS score was associated with better performance on the DCCS test, especially in the youngest children, whereas MDD-PRS was associated with poorer performance on the Flanker test. In addition, association between a bipolar disorder (BD) PRS and EFs was shown in children (Mistry et al., 2019). These results were confirmed by a recent study that highlighted, yet again, distinct affects on EF domains for the different psychiatric disorders polygenic risk: whereas ADHD- and MDD-PRSs were associated with IC, BP-PRS was associated with WMU and SZ-PRS with CF (Chang et al., 2020). Interestingly, mediation analyses revealed that ADHD- and MDD- PRSs which were associated with IC, had significant indirect effects on ADHD symptoms through the mediation of IC. Thus, molecular genetic factors contributing to variability in EFs during typical development are at least partially overlapping with those associated with psychiatric disorders.

Finally, a recent study (Rea-Sandin et al., 2021) examined the relationship between a PRS indexing educational attainment (EA) and IC in early and middle childhood through a longitudinal design. Results showed that the EA-PRS predicted middle childhood IC but not early childhood IC. To date and to our knowledge, this study is the first to use a non-psychiatric phenotype to generate PRS and thus, paves the way for a new area of investigation: using non-psychiatric but related to EF outcomes to calculate PRS and emphasize relationships at the genome level.

However, complex gene–gene interaction between SNPs in the genes related to dopamine neurotransmission was shown to influence EFs (Mitaki et al., 2013) and this interaction is not (yet) controlled by PRS techniques.

3.2.7 Genetics perspectives

Since the discovery of the genome is still recent and genetic studies are in full swing, it is likely that discoveries about the genetic basis of EFs will continue to grow in the coming years. But, because it is a recent field of research, new questions arise. For example, especially for the domain of developmental psychology, the effects of the inherited genome, or direct genetic effects, has to be distinguished from the effects of the environment created by the parent or indirect parental genetic effects (Harpak and Edge, 2021). This distinction is important to generalize results as PGS based on GWASs predict less when the GWAS sample is heterogeneous in terms of ancestry or socio-economic background (Harpak and Edge, 2021). This may also raise ethical or political questions (Harden, 2021).

Finally, epigenetics (i.e., the study of factors that impact expression of genes but not to the underlying DNA sequence, like DNA methylation) of EFs are emerging and could lead to the identification of biomarkers for EFs and related pathologies (Ibrahim et al., 2018).

4 Environmental and cultural bases of EFs

Brain and genes have an importance for EF efficiency and development. However, it must not be forgotten that environment and culture also play a fundamental role in EFs (Munakata and Michaelson, 2021).

4.1 Socioeconomic status influence

Socio-economic status (SES) is a classic measure of the wealth (in the financial sense) of the environment in which an individual evolves. This index can be measured in different ways and is used in many fields of research, from psychology to sociology and economics.

Three classical measures for SES in children and adolescents are (Antonoplis, 2022):

- *Parental income*: it might be the most used variable but, in France, it is often the least transmitted information by parents (which results in a lot of missing data for this field)
- *Parental education*: most of the times, either the mother's educational level is measured or the educational level of both parents (calculated with a principle of dominance by attributing to the family the higher educational level of the two parents).
- *Parental occupation*: this indicator is sometimes complicated to track, as parents do not always know which category their occupation falls into, so this measure is more prone to error.

Two common models explaining the relationship between SES and development are the family stress model and the family investment model (Conger and Donnellan, 2007). In the family stress model, the stress due to low SES affects the development by impacting the caregivers' practices' quality, sensitivity, and responsivity. In the family investment model, SES affects development by the time, care and guidance caregivers provide and by the more numerous learning resources and opportunities. Parental care and home environment both impact the development of brain regions involved in EFs as well as overall cognitive and behavioral development, which can support both models (for a review see Hackman et al., 2010).

Indeed, the differences in children's intelligence and behaviors can be seen as early as in the second year of life (Noble et al., 2015). It was demonstrated that income could predict WM performance (measured by memory for sentences) as early as 54 months and, with maternal education, it could also predict planning (measured by the Tower of Hanoi task) by first grade and persisted through middle to late childhood (Hackman et al., 2015). Also, analyses of mediation suggested that early childhood home environment could explain the relationship between SES and EFs (Hackman et al., 2015).

Later, multiple studies have reported SES-related disparities on common-EF in children as young as 2 years old through age 5 (Blair et al., 2011; Noble et al., 2005; Rhoades et al.,

2011; Wiebe et al., 2011). This relationship was also found in specific EFs: indeed, lower-SES children performed worse on tasks of IC, WMU, CF, and higher-level EFs such as planning (Clearfield and Niman, 2012; Lipina et al., 2005; Mezzacappa, 2004; Noble et al., 2007). By middle childhood, this relationship remained for the three core EFs (Ardila et al., 2005; Farah et al., 2006; Sarsour et al., 2011). Overall, a recent meta-analysis has found a small to medium association between SES and EFs with a variability in the samples and measures (Lawson et al., 2018; see Figure 19).

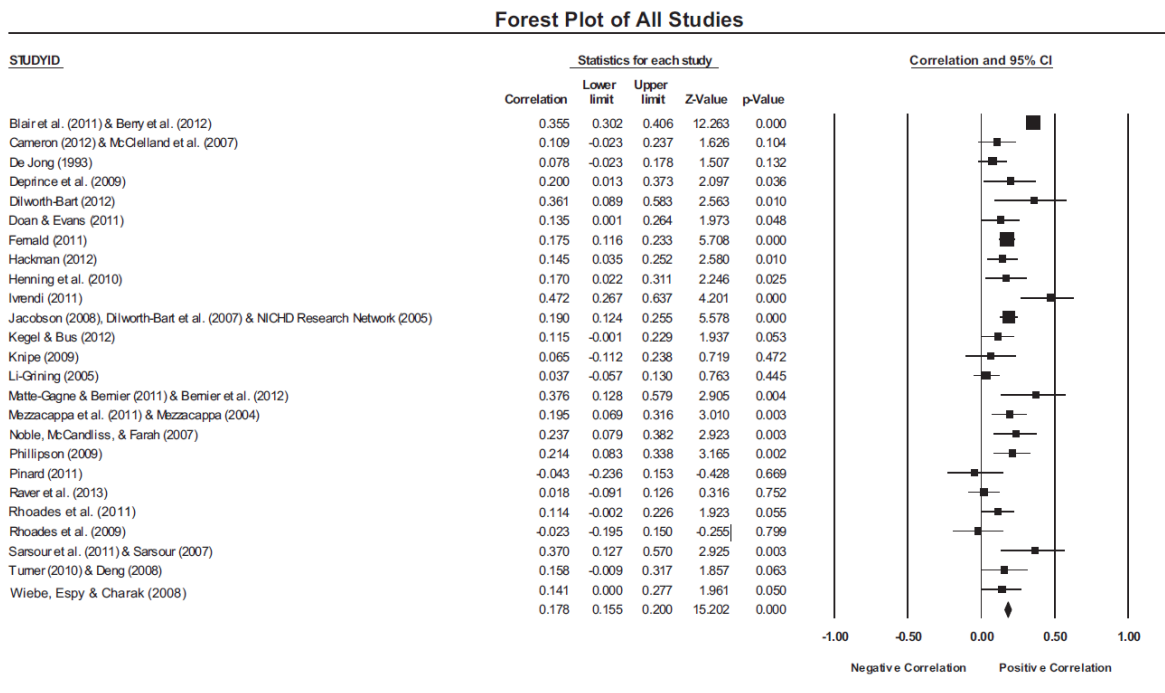


Figure 19: Forest plot of all studies included in the meta-analysis of Lawson et al., 2018. Figure from Lawson et al., 2018.

Interestingly, it has been demonstrated that the duration of poverty through childhood and adolescence was negatively related to WM abilities measured as age 17 (Evans and Schamberg, 2009) and that changes in family income predicted changes in EFs (Hackman et al., 2015). Thus, SES impact does not seem to be fixed even if, as we have seen just before, on another level of observation, a PGS for educational attainment predicted middle but not early childhood IC (Rey-Mermet et al., 2019).

On another hand, the SES-EFs relationship has been shown to be impacted by cortisol reactivity (cortisol being the stress hormone), more precisely, higher SES was associated with a better IC performance in children with high cortisol reactivity but, for WM skills, the SES-WM association was independent from reactivity to cortisol (Wu et al., 2021). The impact of stress on EFs is of major importance as it was demonstrated that the stress a mother experiences during pregnancy can affect the developmental trajectory of their unborn child (O'Donnell and Meaney, 2017).

4.2 Culture and EFs

Culture can be differentially distinguished as an abstract construct characterized by the socialization of shared knowledge, meanings, and understandings of particular groups of people (Shore, 2002).

It has been shown that executive abilities can vary between cultures (for a review: Roos et al., 2017). For example, Chinese children improved more their EFs during preschool compared to US children and that, for every SES (Schmitt et al., 2019). Another example: children of 3-4 years from Eastern culture presented better performance in IC than children from Latin American, themselves performing better than children from Western culture (Tran et al., 2019). Also, U.S. preschoolers, but not South African children, showed an age-related increase in CF assessed by the DCCS task (Legare et al., 2018).

Overall, young children of East Asian cultures present better EF performance and this result was related to the intensive memory-based language demands (Roos et al., 2017).

Maybe more importantly, it was demonstrated that, differing on the culture, EFs predicted differently academic outcomes (Georgiou et al., 2020). WM predicted reading and mathematics performance for Canadian children, while both WM and IC predicted them for Chinese children (Georgiou et al., 2020).

However, it is important to keep in mind that creating material for a culture that is not our own and that we know less well is difficult. Indeed, the experimental material is often developed by researchers belonging to a culture and this culture may already favor people from that culture. This bias has been shown for the Wechsler tests for example (Fernández and Abe, 2018).

4.3 Specific environmental and cultural factors

After having described the effects of general environment and culture, we will now detail the impact on EFs of more specific environmental and cultural factors such as the practice of music, sports or the use of screens which play an important role in children and adolescents.

4.3.1 Sports practice

Among cultural and environmental factors, sports practice was several times studied. Indeed, sports appear to be positively related to EFs in children and adolescents. In particular, this association is thought to be dependent on the type of sports, the purpose of the physical activity (competition vs. enjoyment) and its intensity, and the age of the subjects (e.g., Davis et al., 2011).

Furthermore, sports and exercise do not have an equivalent effect on each EF (for a review: Bidzan-Bluma and Lipowska, 2018). This may be explained, on the one hand, by the diversity of EFs. On the other hand, some sports might have specific demands on IC, shifting, or updating, due to their intrinsic and particular characteristics. For example, karate, in

view of its high demands on self-discipline and respect for rules and others would preferentially solicit WM (Alesi et al., 2014). In contrast, aerobic fitness appears to involve CF and IC more (e.g., Oberer et al., 2018). More specifically, in children, karate practice in childhood is related to better performance in WMU, assessed by both forward and backward digit spans, and planning, as measured by the Tower of London task (Alesi et al., 2014). On the other hand, the practice of tennis was related to a better IC performance assessed by a color-word Stroop task (Ishihara et al., 2017). In adolescents, there is far less research on the effect of sports on EFs than in children. Still, it has been shown that, for example, in adolescents, aerobic fitness is associated with better IC skills, assessed by a Go/No-go or Flanker task (Chuang et al., 2015; Hogan et al., 2013; Westfall et al., 2018). Thus, the executive common core appears to be amenable to improvement through certain types of physical activities. Several studies show an effect of sports or physical activity on EFs in general, while others show an effect specific to one or two EFs (Bidzan-Bluma and Lipowska, 2018). However, these results should be taken with caution. Several studies also show a lack of association, particularly for IC (Chuang et al., 2015; de Greeff et al., 2016; Kvalø et al., 2017; Stroth et al., 2009).

Still, because of these observed links between sports practice and executive skills, many sports-based interventions have been proposed with the aim of improving EFs. For example, an intervention on 7- to 9-year-old children based on 2 hours of daily fitness training led to increased skills in WM assessed by an adapted Sternberg task (Kamijo et al., 2011). On another hand, a 6-months soccer practice in children had a general influence on EFs and notably increased skills in planning and IC required by the Tower of London task in comparison to a control group of sedentary subjects (Alesi et al., 2016). Furthermore, in a meta-analysis, the authors report a small but significant effect size of regular exercise interventions on EFs in general and IC in particular for a child and adolescent population (Xue et al., 2019).

Taken together, these results should be viewed with caution. First, they generally have few participants and no cultural or socioeconomic level balance. In addition, there is poor information on participants' initial skills (Bidzan-Bluma and Lipowska, 2018). Finally, when regular physical activity is associated with improved cognitive functioning in youth, these associations are often small (Biddle and Asare, 2011).

4.3.2 Music

As for sports practice, musical practice has also been investigated multiple times. Indeed, learning to play an instrument has been shown to increase an individual's abilities in a wide range of cognitive domains (Suárez et al., 2016), such as attention (Patston et al., 2007), reading-spelling (McPherson, 1995), as well as auditory (Kraus and Chandrasekaran, 2010), motor (Amunts et al., 1997), verbal (Chan et al., 1998), and visuospatial (Brochard et al., 2004) abilities.

At the level of EFs, a recent study concluded that musically trained children had an advantage in attention inhibition (assessed by a color-word Stroop task), response inhibition (assessed by a Go/No-go task), and WM (assessed by the Continuous Performance task), but not in CF (assessed by the Switching task) and that the level of musical training

was positively correlated with response inhibition and working memory abilities (Chen et al., 2022). On top of that, early-trained musicians performed better on Stroop, Go/No-go and Continuous Performance suggesting that the proposed musical training was associated with enhanced EF abilities and that early childhood is a sensitive period when musical training has a more powerful effect on the development of EFs (Chen et al., 2022). In particular, much research was conducted on music and working memory skills and suggested that musicians perform better in WMU compared to non-musicians (D'Souza et al., 2018). Similarly, musical training leads to better performance in WMU (George and Coch, 2011; Suárez et al., 2016) but these effects differ across components (Suárez et al., 2016). Notably, 7-8 year olds have been shown to perform better on tasks testing WM at the executive center level after 18 months of music training compared to control training in natural science (Roden et al., 2014).

Just like with sports, some studies proposed musical training in order to boost EF performances. First, a 45 minutes twice a week for 6 weeks preschool music program in children aged 4 and 5 years led to better performance compared to a control group in Matching Familiar Figures Test, a task requiring IC and visual discrimination, but not in the Day/Night Stroop Task (requiring IC of a dominant verbal response; Bugos and DeMarie, 2017). In another study, 5-year-old children who followed a short-term program of computer-based musical training improved on IC (measured by a Go/No-go) after 20 days of training, while no significant changes were observed in children who followed a painting training (Moreno et al., 2011). Another interventional study showed that 3-4 years old children who received 8 music classes (once a week) showed greater improvement on planning, measured by the Tower of London task, and on IC, measured by peg tapping, than their peers who remained in regular nursery playtime but these small differences in performance were not maintained when an active control condition was introduced even if there was a trend for greater improvement in the music intervention groups on IC (Bowmer et al., 2018). Finally, a last study indicated that children following music lessons performed better on tasks designed to measure planning (the Tower of London task) and IC (here, a Go/No-go task) but not in Working Memory (measured here by the Dot Matrix task) in comparison with a "no-art" control group (Jaschke et al., 2018).

Just like sports, we know that musical practice is not accessible to all socio-economical backgrounds. Cultural accessibility is a main point of inequality between the richest and the poorest. Thus, some programs started to emerge in order to minimize this gap. One of them is the Demos project at Paris's Philharmonie (<https://demos.philharmoniedeparis.fr/>) which offers to children from difficult minorities a weekly musical practice in group.

4.3.3 Other cultural and environmental influences

Some other practices could also impact EF performance and development. Among them, the trendy Mindfulness or Yoga practices along with relaxation exercises (see Diamond, 2016). A recent meta-analysis on 56 studies which proposed a Mindfulness Based Practice (MBP) concluded that this type of training conferred a significant benefit on EFs ($g = 0.15$; [0.02, 0.27]) but, among EF subdomains, on WMU only ($g = 0.23$; [0.11, 0.36]; Whitfield et al., 2021).

Another emerging field in research concerns screen-use: a growing number of studies are focusing on the effects of early exposure to screens on cognitive and emotional development (e.g., Sauce et al., 2022). The scientific literature used to make a distinction between two types of screens: passive and active screens (Kim et al., 2020; Sweetser et al., 2012). This distinction has been made based on the type of use and content they offer. Active screens are defined as screens that allow for physical, social, or cognitive engagement and include video games, virtual chats, or Internet searches. Passive screens involve the passive reception of information via a screen and therefore include watching a movie, a program or a video. Earlier studies made this distinction, but now the focus is more on the specific content, which plays an important role (Sauce et al., 2022). Effects can vary depending on the type of content viewed. In particular, fantasy and action programs induce a significant decrease in IC and involve more attentional difficulties (Rhodes et al., 2020). Violent programs also induce poorer executive functioning with lower scores on the Stroop tasks in adolescents (Lillard and Peterson, 2011). The duration of the programs also modulates these effects. Short programs, lasting between ten and fifteen minutes, induce poorer IC and greater impulsivity on the DDT in four-year-olds (Lillard and Peterson, 2011). The results regarding active screens are much more mixed and contradictory. Some authors find no correlation between play time, type of play, and IC performance (McCarthy et al., 2016; Nordby et al., 2019). Other studies find negative results: playing video games daily is positively correlated with increased temporal impulsivity (Crone and Konijn, 2018). Playing time is also positively correlated with players' impulsivity scores (Buono et al., 2017; Gentile et al., 2012). However, many studies find positive outcomes of video game use. Indeed, playing video games moderately increases performance in attention, IC, CF, and visual-spatial WM (Green and Bavelier, 2012; Yeh, 2015). With respect to active screens and especially video games, results may vary depending on the type of video game. For example, action video games (e.g., GTA) have been shown to be related to visual-spatial WM abilities (e.g., Colzato et al., 2013) while this is not the case for life simulation video games (e.g., The Sims; Blacker et al., 2014).

However, like other out-of-school factors, screen use is closely related to SES and gender, which may represent confounding factors.

Other cultural factors as maternal scaffolding or disorganized/unpredictable family life (Hughes and Ensor, 2009), sleep quality (Morales-Muñoz et al., 2021) or sleep deprivation (Pesoli et al., 2021), paternal mind-mindedness (Regueiro et al., 2022) or physical abuse and neglect (Spann et al., 2012) have been showed to be related to executive functioning.

However, the neural, genetic, environmental and cultural basis are not totally independent from one another. With the development of both neuroimaging techniques and statistical modelings, multi-level studies of EFs have started to emerge.

5 Multi-scale analysis of EFs

The type of studies which includes different levels of analysis (such as genetic, cerebral, behavioral, environmental, cultural...) are called multi-scale studies. These studies aim to better represent the complexity of reality. On top of that, we already know that these different levels interact with each other. Indeed, many studies have highlighted the influence of genetics on various brain modalities for example.

Most studies have focused on the relationships between two different levels. Thus, as we have seen, there is a rich literature regarding the brain, genetic and environmental bases of EFs, but fewer studies have investigated the relationship that may exist between all these levels.

5.1 Genes, brain and EFs

Among these levels, based on the dopaminergic system, multiple studies have investigated the relationship between brain, genes and EFs and, in particular, the mediating role that could have the brain between genes and EFs. The influence of genes, by twin studies or genetic psychophysiology, on the human brain structure have been studied for a long time (for reviews: Peper et al., 2007; Toga and Thompson, 2005). Indeed, in 1997, the utility of genetic psychophysiology has already been demonstrated for the investigation of the gene-brain-behavior relationships (Boomsma et al., 1997). Recently, it was demonstrated that changes in subcortical volumes follow a genetic organization that remains stable throughout the lifespan (Fjell et al., 2021).

Regarding EFs, it was demonstrated that brain activation of regions involved in EFs could mediate the relationship between COMT polymorphism and IC performance (Green et al., 2013) and on the relationship between genes and EFs in general (for a review: Greene et al., 2008). In a twin study, the genetic influenced the activation of frontal brain in EEG regarding IC, measured by a Go/No-go task (Anokhin et al., 2004). It was also shown that genetic factors could influence the relationship between WM performance and, on one hand, gray and white matter volumes (Posthuma et al., 2002) and, on the other hand, brain activation (Blokland et al., 2008). Recently, it was shown that the thickness of important dopaminergic regions (here PFC, parietal and posterior cingulate cortices) mediated the effect of COMT polymorphism on common-EF and this mediation was independent of age (Miranda-Dominguez et al. 2019).

5.2 Brain, environment and EFs

The cultural neuroscience is a growing field of research investigating the relationships between the environment and the brain (Han et al., 2013). As a matter of fact, it was demonstrated that cultural background could influence neural activity underlying high- as well as low-level cognitive functions (e.g., Han and Northoff, 2008). Because of repeated cultural impact, related brain pathways might experience rewiring and thus a neuroplasticity

induced by culture (Kitayama and Uskul, 2011).

SES could also impact the brain. Indeed, higher SES in childhood was associated with a protracted structural brain development and a prolonged functional connectivity segregation, resulting in more efficient cortical networks in adulthood (Tooley et al., 2021). However, SES relationship with brain and cognition was shown to be greater in North American than in European subjects, reflecting a moderating role of culture (Walhovd et al., 2022).

On another note, the relationship between environment and brain measures related to EFs have also been studied. For example, SES differences in PFC activation and cortical structure have been reported (D'Angiulli et al., 2008; Jednoróg et al., 2012; Noble et al., 2012; Sheridan et al., 2012). Children and infants in low SES households were also shown to have smaller brain growth, smaller surface area, and smaller lobes of the brain that support EFs (Johnson et al., 2016). Early caregiving environments were also shown to be related to the developmental plasticity of brain regions underlying EFs (McDermott et al., 2012). Culture can also impact brain activation: Chinese-Canadian children presented an ERP pattern of hemispheric differentiation during a Go/No-go task that was more pronounced than that of European-Canadian children (Lahat et al., 2010). Similarly, US-american children presented more important activations of PFC regions than Japanese children during a shifting task (Senzaki et al., 2021). Also, as structural and functional changes and reorganization in EF neural bases and in the social brain occur at adolescence, changes in the social environment that could happen during this period could interact with EFs (Blakemore and Mills, 2014).

Finally, stress hormones were shown to be related to EF development through their regulatory role in the PFC (Mizoguchi et al., 2008). Physiological effects of stress (increased cortisol levels) might cause structural and functional changes in the brain, maybe underlying modifications in neurocognitive functioning (Müller et al., 2013).

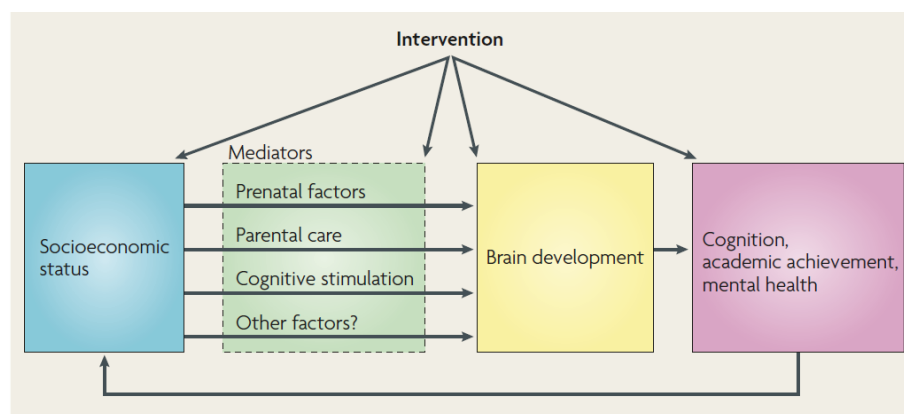


Figure 20: **Relationship between socioeconomic status, brain development and cognition.** Figure from Hackman et al., 2010.

Altogether, these results might be indicative of possible SES differences in the neural substrates underlying EFs. Notably, Hackman et al., 2010 proposed that SES has an effect on brain development which has an effect on cognition (see Figure 20).

5.3 Genes, environment and EFs

The environment effect on genes can be studied through epigenetics investigations for example. Indeed, developmental outcomes can be characterized by “a probabilistic epigenesis in the sense that there are bidirectional influences within and between different levels of analysis” (Müller et al., 2013).

Also, a recent study on COMT showed that Val-allele Japanese children carriers presented better shifting abilities than Met-allele Japanese children carriers while no difference between Val- and Met-alleles carriers was found in a sample of US-american children, demonstrating that culture could moderate the effect of COMT polymorphism on shifting (Senzaki et al., 2021). Another study found an interaction of parental warmth on updating by 4 genetic variants and also on the common-EF by another variant (Chen et al., 2020a).

These studies highlight an interaction between different levels but also between different modalities within the same level. As we have seen, EFs are a complex and important area for the development of other capabilities. It is therefore important to know the mechanisms underlying these functions in order to understand how they function and to think about solutions and remediation if a deficit is observed in these functions. Classical regression analyses allow us to highlight the effect of one or more IVs on a DV or correlations between different variables. However, as soon as we have several modalities and/or several levels, these analyses do not allow us to answer all the questions we might have and to create all the bridges needed. It is then necessary to use more complex statistical analyses for multilevel modeling (Hoffman and Walters, 2022).

All this leads us to different ways to improve functioning that requires EFs. For example, we can find ways to reduce the demands on EFs by reducing the number of distractors, the amount of information presented... Another way could be to work on the environment by reducing factors that impair EFs such as stress, low SES, etc. Finally, another solution to improve EFs and related functions might be to propose cognitive training during development.

6 Cognitive training to improve EF abilities

A cognitive training can be defined as a means to increase cognitive functioning through practice and/or instruction (Jolles and Crone, 2012). First, we will see the different characteristics of cognitive training in general, then we will focus on EF training.

6.1 What makes a good training?

6.1.1 An adjusted content

The literature shows that training is effective when the difficulty level of the task is adapted to participants' individual performance throughout the training (Diamond, 2016; Diamond and Lee, 2011; Green and Bavelier, 2008; Jolles and Crone, 2012). In particular, this adaptive difficulty prevents premature automation of processes or strategy development during practice (Green and Bavelier, 2008; Klingberg, 2010). Indeed, in the case where automation occurs, the cognitive function of interest cannot be trained efficiently due to the obvious mismatch between the participant's cognitive abilities and the demands of the task (Enriquez-Geppert et al., 2013). In order to observe an improvement in EFs, therefore, the limits of the EFs must be continually pushed so that the participant moves out of his or her "comfort zone" and so that that he or she exceeds his or her current skill level (see Diamond, 2011; Diamond and Ling, 2016).

From a cerebral point of view, changes also occur when there is a mismatch between the environmental demands and environmental requirements and the possibilities of the current structural system. In other words, training with an "adaptive" difficulty is necessary, although not sufficient to induce long-term brain changes (Lövdén et al., 2010). For example, plastic changes in the FPN were observed if the practice of a WM task requires them to mentally hold more objects than they can (Klingberg, 2010). However, some modifications remain impossible, such as WM capacity, which cannot be infinitely increased (Jolles and Crone, 2012).

A high degree of variability in stimuli, response modalities, and tasks (both within and across cognitive domains) must be considered during training to avoid any priming effect or alternatively the development of strategies by participants to complete the task (Green and Bavelier, 2008; Jolles and Crone, 2012). Variability in stimuli thus keeps the participant motivated and prevents automaticity (Green and Bavelier, 2008). Similarly, the use of multiple tasks during training of a specific cognitive function also prevents strategy development while increasing the likelihood of effective training of the targeted process (Enriquez-Geppert et al., 2013). Finally, the complexity of the trained task, i.e., the fact that it is specific to a function or that it recruits different processes at the same time, is likely to influence the benefits of training (Jolles and Crone, 2012). Indeed, a study which aims to develop effective cognitive training in practice may benefit more from a complex and variable task paradigm, as the latter may generate increased generalization in real-world situations (Buschkuhl et al., 2012; Green and Bavelier, 2008).

6.1.2 The right duration

Second, the benefits of EF training depend on the duration of training (Diamond, 2016; Jolles and Crone, 2012). Studies show that the longer EF training (i.e., several weeks), the better the results are, when the duration (i.e., length of a session) and frequency (i.e., number of sessions per week) of sessions are held constant (see Diamond, 2016). Similarly, in order to see specific brain changes, the duration of a training session should be long enough (Lövdén et al., 2010).

6.1.3 The good timing: sensitive periods

Training receptivity can also evolve with age. If we learn to walk around 1 year old or read around 6 years old, it is because these periods are more opportune (i.e., sensitive) to acquire these new skills. Thus, sensitivity periods can be defined as developmental periods during which certain capacities are easily modulated by experience (Knudsen, 2004). It is important to take these sensitive periods into account when implementing interventions in order to get the most out of them because, once these time windows have passed, acquisition becomes much more difficult (see, for example, the acquisition of a foreign language: White et al., 2013). These periods correspond to periods of high neuronal abundance, axonal projections and synaptic connections (Greenough et al., 1987; Huttenlocher, 2002; Uylings, 2006).

The strong changes in neural organization during childhood (Gogtay and Thompson, 2010) indicate that this period would be ideal for cognitive interventions (Kray and Ferdinand, 2013). For example, young children admit a greater degree of plasticity than young adults, making them more receptive to learning (Kray and Ferdinand, 2013). The brain would then be sensitive to executive interventions during childhood, as it is more capable of quantitatively and qualitatively restructuring neural networks (Galván, 2010).

6.2 Training EFs

Given the importance of EFs for cognitive and socio-emotional development as well as for academic and professional success (Best et al., 2011; Diamond, 2013), various studies have been conducted on intervention programs to stimulate various aspects of EFs (Diamond, 2013; Hu et al., 2017; Jaeggi et al., 2011; Klingberg, 2010; Liu et al., 2015; Maraver et al., 2016; Xu et al., 2020; Zhao et al., 2015).

6.2.1 How? Different types of EF training

Many training materials have been tested to train EFs. As we have previously seen, sports practice and EFs are related. As a result, many programs aiming to improve EFs have used sports as a training. For example, aerobic activity improved CF of 8-12 years old children, although aerobic effectiveness is still under debate (for a quick review: Diamond and Lee,

2011). On another hand, martial arts, which emphasize self-control, discipline, and character development (Diamond and Lee, 2011) also appear to improve EF abilities. For example, Lakes and Hoyt, 2004 have compared the effects of taekwondo training to regular physical education practice in children aged 5-11 years. Greater improvements on tasks of cognitive inhibition, discipline, and emotional regulation were found in the taekwondo group, indicating a generalization of training to multiple cognitive and behavioral measures. The practice of yoga also showed increase in planning and executive tasks such as the Tower of London in girls of 10 to 13 years (Manjunath and Telles, 2001).

In addition, meditation based practice has been demonstrated to improve performance in executive components, assessed by the BRIEF, in children aged 7 to 9 years with lower initial EF levels (Flook et al., 2010). Intense mindfulness training has also been shown to increase the resting-state functional connectivity between brain regions associated with EFs in adults with high level of psychological distress (Taren et al., 2017).

Furthermore, curriculum-based approaches, such as Montessori and Tools of the Mind, appear to improve EFs (Diamond, 2007; Lillard and Else-Quest, 2006). Indeed, children who studied according to the Montessori method performed better in reading, mathematics, but also in executive control at the end of kindergarten (Lillard and Else-Quest, 2006). Similarly, in the "Tools of the Mind" program (which is based on social simulation play) implemented in an urban school setting with a low school setting (Diamond, 2007), children aged 4 to 5 years performed better on EF tasks (e.g., Dot matrix and Flanker tasks) than those who had attended another educational program and the variance in EFs was better explained by participation in this program than either age or gender of the children.

On the other hand, studies have focused on training EFs by targeting them directly, often using computerized cognitive training.

A lot of studies have focused on training WM (e.g., Holmes et al., 2009; Klingberg et al., 2005; for a review, see Klingberg, 2010) or WMU (e.g., Dahlin et al., 2008; Jaeggi et al., 2011; Jaeggi et al., 2008). For example, following training on *CogMed*®, participants generally improved their performance on both trained and untrained WM tasks (Bergman Nutley et al., 2011; Holmes et al., 2010; Klingberg et al., 2005; Thorell et al., 2009). Other studies have focused on executive attention (e.g., Rueda et al., 2005b), mental flexibility (e.g., Karbach and Kray, 2009; Zinke et al., 2012) or IC, although the latter has shown limited success (e.g., Thorell et al., 2009).

6.2.1.1 IC training Because of the importance of IC for many aspects of life (Benson et al., 2013; Borst et al., 2015; Cassotti et al., 2016; Gilmore et al., 2013), some studies have focused on training IC.

In adults, a stop signal training led to a better IC performance (Manuel et al., 2013), a training coupling IC and WM decreased impulsivity (Peckham and Johnson, 2018). Similarly, an IC training, proposed for 20 minutes, 3 times a week, for 2 weeks (i.e., 6 hours of training as a result) and composed of 3 activities: a color Stroop task, a conflict resolution task and a Go/No-go, increased the performance of adults in the color Stroop task but also on the stop signal task (Maraver et al., 2016).

Thorell et al., 2009 trained children aged 4-5 years 15 minutes per day, five days per week, for five weeks, via a program that targeted WM or IC. Children in the IC group (who practiced on Go/No-go, stop signal and Flanker tasks) showed increased performance on the stop signal and Flanker tasks but not on the Go/No-go, whose training did not appear to be effective at this age.

At the same time, studies have also investigated the effect of IC training on different brain characteristics (Jolles and Crone, 2012; Owen et al., 2010) including the degree of activity in areas previously defined as IC related such as the prefrontal cortex including IFG and ACC (e.g., Aron et al., 2014; Houdé et al., 2010; see section 2). In adults, studies have shown that short term training (i.e., 1 hour) and middle term training (i.e., 5 to 10 hours over several weeks) using the stop signal task (SST) or the Go/No Go task lead to functional changes in the regions of the inhibition brain network, especially the cortices prefrontals (Berkman et al., 2014; Chavan et al., 2015; Manuel et al., 2013; Spierer et al., 2013) and parietals (Manuel et al., 2010). Delalande et al., 2020 put in evidence an evolution of neuroplastic characteristics, cortical thickness, and cortical surface area, in the same regions, after IC training. Moreover, this type of executive training not only increases activity in specific areas, but also improves functional connectivity between the IC network and other networks (Hu et al., 2017).

6.2.2 When? Childhood and adolescence: sensitive periods for an executive training

Many authors advocate the practice of a training program in childhood, from an early age (for a review, see Park and Mackey, 2022). However, it was demonstrated that EF training is more beneficial in 8-12 year olds than in 4-5 year olds (Diamond and Lee, 2011).

On the other hand, adolescence, due to the maturation of the PFC, is a sensitive period of brain development. The brain system is more receptive to interventions related to executive functions during this period (Blakemore and Choudhury, 2006). Therefore, analogous to the sensitive periods of brain development that are evident in the early sensory system in the first years of life, the brain would be more sensitive to EF interventions in adolescence than in the early years of life (Blakemore and Choudhury, 2006). Training could thus lead to both cognitive and cerebral changes. For example, cortical thickness or grey matter volume are plastic features that, in addition to changing over time, may change with environment and training (Bengtsson et al., 2005; Maguire et al., 2006).

6.3 Evaluate the effectiveness of a training

Ideally, training should have both a long-term and a generalizable effect. While many studies are reduced to an assessment of cognitive skills under laboratory conditions, the ultimate goal of training in children and adolescents is on the one hand to optimize performance in the trained domain and on the other to enable application in everyday life, especially in school learning (Karbach and Unger, 2014; Titz and Karbach, 2014).

6.3.1 Near and far transfer

Indeed, when studying an experimental training, the questions of training receptivity and transfer are often debated. While there is no doubt that specific training improves performance directly linked to the trained skill (referred to as near transfer), it remains unclear whether training in a given task can improve other skills that are not directly related to the training activities (referred to as far transfer) (Bigand and Tillmann, 2021). Most cognitive stimulation programs claim to provide far transfer effects, but there are almost as many studies confirming this claim than those denying it (Sala et al., 2019; Sala and Gobet, 2019). These differences could be explained by the fact that transfer effects can vary with training time (Jaeggi et al., 2008) but also with individual differences that play a major role in training performance (Jaeggi et al., 2011; Jaeggi et al., 2014).

Regarding EFs, a recent meta-analysis suggests that training a single EF have non-systematic effects on the improvement of untrained EFs (i.e., Kassai et al., 2019). For instance, studies in which one EF is trained have reported no effect of the training (Enge et al., 2014; Talanow and Ettinger, 2018; Thorell et al., 2009), only near transfer, i.e., improvement on the same EF (Bergman Nutley et al., 2011; Dunning et al., 2013; Zhao et al., 2015) or far transfer, i.e., abilities that are not targeted by the intervention (Aydmune et al., 2019; Beauchamp et al., 2016; Jaeggi et al., 2011; Liu et al., 2015; Maraver et al., 2016; Söderqvist and Bergman Nutley, 2015). Interestingly, studies in which all the EFs were trained reported far transfer effects on school abilities (Blakey and Carroll, 2015; Traverso et al., 2019) as well as near transfer to specific EF, including WMU (Blakey and Carroll, 2015) and IC (Dowsett and Livesey, 2000). Given the particular organization of EFs in united but specific functions, one can imagine that the variations affecting one of the functions (e.g., IC) are not totally independent of the other two EFs (e.g., WMU and CF). Thus, receptivity to learning (the progress of a function after having trained it) could be seen as not independent of the other related functions, as well as transfer effects.

6.3.2 Training and development

A training during childhood or adolescence may influence developmental trajectories in different ways (Jolles and Crone, 2012).

Development and training can be regarded as two ends of the same continuum (Galván, 2010) as development is driven by an interaction between pre-specified biological maturation and experience (Stiles, 2011). Indeed, training may simply “speed-up” development, such that the cognition of an individual is more similar after training than before training to the cognition of older individuals (Jolles and Crone, 2012). Patterns of change observed during development are sometimes similar to those involved in skill acquisition in adults (Casey et al., 2005; Johnson, 2001, 2011).

However, a potential difference between developmental and training-related mechanisms concerns the fact that training could influence cognitive processing and brain structure in a way that deviates from typical developmental trajectory (Denney, 1984; Fong et al., 2012; Hertzog et al., 2008; Jolles and Crone, 2012). The specialization of a particular

brain region could be the consequence of its interaction and competition with other brain regions over the course of development (Changeux and Danchin, 1976; Greenough et al., 1987; Huttenlocher, 2002; Uylings, 2006). It has been argued that (early) development relies to a large extent on experience-expectant neural mechanisms, while training is more influenced by experience-dependent processes (Galván, 2010). Therefore, age differences could be magnified rather than reduced after training (Baltes and Kliegl, 1992; Nyberg et al., 2003).

6.3.3 Inter-individual differences in training receptivity

Regarding training, the impact of the baseline level is often studied since it is important to know who benefits the most from the training proposed. Two hypotheses have been developed in literature.

First, the "magnification account" hypothesis suggests that cognitive training will benefit most individuals who are already performing well. According to this hypothesis, these individuals already possess sufficiently efficient cognitive resources to acquire and implement new strategies and abilities (Karbach and Kray, 2021; Karbach and Unger, 2014; Lövdén et al., 2012b; Titz and Karbach, 2014). Training could result in an amplification of age-related and individual differences according to the hypothesis of training being an accelerator of development.

The second hypothesis, the "compensation account" hypothesis suggests that individuals who are already high performers will benefit the least from cognitive training because they are already functioning at an optimal level. This then leaves them less room to improve, in contrast to individuals who show more fragile baseline performance (Karbach and Kray, 2021; Karbach and Unger, 2014; Lövdén et al., 2012a; Titz and Karbach, 2014). Indeed, several studies of EF training have found greater benefits for children and older adults than for young adults (see Karbach and Unger, 2014, for a review see Lövdén et al., 2012a).

For example, children with low WM and children with ADHD improved more their performance following EF training (Diamond and Lee, 2011). However, EF training did not appear to be useful in cases where the study population showed an IQ too low or severe cognitive decline (Colcombe and Kramer, 2003; Söderqvist et al., 2012). Nonetheless, it is possible that the exercise was too demanding for them and thus a simpler EF training might be more suitable for their conditions (Diamond, 2016).

In conclusion, the magnification mechanism would generally be involved during strategy-based training (e.g., memory training), whereas the compensation mechanism would be more likely associated with process-based training such as EF training (see Karbach and Unger, 2014). However, this conclusion is still under debate as Foster et al., 2017 pointed out that WM training predominantly benefited participants showing high baseline level compared to participants with lower level.

Other variables could explain inter-individual differences.

At the brain level, direct links (controlling for baseline) between cerebral organization

and training receptivity have also been demonstrated: brain network organization predicted cognitive gains after training in children (Chaddock-Heyman et al., 2020), and young adults (Baniqued et al., 2019) and older adults (Baniqued et al., 2018; Gallen et al., 2016).

At the genetic level, a first indirect link between genetic polymorphism and training receptivity was proposed by Rueda et al., 2005b. Children with poorer initial performance on attentional conflict were more likely to show training effects than others (compensation account hypothesis). Moreover, DAT1, a gene implicated in the dopamine system, polymorphism explained attentional conflict scores at pre-test. The link between DAT1 polymorphism and training receptivity was thus really indirect. One study established a direct link between genetic factor and training receptivity while controlling for baseline and showed that BDNF polymorphism mediated the effect of a physical training intervention on executive functions in older adults (Leckie et al., 2014). Other levels of information are thus important factors to consider when investigating the effects of an EF training.

7 Aim of the project

The aim of this PhD project is to contribute to the characterization of EF organization change through development and training using a multi-level approach, including cognitive, neural and genetic levels. Obviously, a PhD thesis cannot meet such a wide goal, but it can try, at its own level, to bring some stones to the edifice, both at the methodological and applied levels.

8 Thesis organization

This thesis is based on an interventional, developmental and multilevel research project, APEX, described in the following section, which allows to address some of the issues raised in the General introduction. These issues, although not new, will be approached with recent methodological frameworks.

Study 1 uses network modeling to evaluate EF organization changes with development and cognitive training. Study 2 uses both network and structural equation models to evaluate the EF organization changes with development on a large independent cohort. Study 3 uses SEM to investigate the transfer of cognitive training during development. Study 4 investigates the relations between brain and EFs through development and training. Study 5 uses deep and machine learning to investigate the acceleration of brain development related to cognitive training. Study 6 uses SEM to evaluate the contribution of genetic, behavioral and brain factors to cognitive training during development.

PART II: EXPERIMENTAL PART

1 The APEX project

APEX - "APprentissages EXécutifs" , in english, executive learning - is a basic research project (PIs: O. Houdé, G. Borst, A. Cachia) funded by the Agence Nationale de la Recherche (ANR) to investigate the IC training at cognitive, neural and and genetic levels.

This project's acquisitions were spread out from January 2016 to December 2020 and 6 PhD students and one post-doctoral student have worked (full time) on it until now.

The aim of the APEX project is to investigate in 4th and 5th grades children (9-10 years) and 11th and 12th grades adolescents (16-17 years) the respective effects of one executive training of a key process of the prefrontal cortex – Inhibitory Control – and of a more general pure metacognitive learning - mindfulness - using the most adapted brain imaging techniques to date (Magnetic Resonance Imaging). The APEX project aims at first devising computerized training tasks on tactile tablets, a device that can be used in ecological settings both at school and at home. Then, a goal is to investigate the effects of these two training conditions at a cerebral level, both anatomically (anatomical MRI and diffusion MRI) and functionally (functional MRI), in relation with the polymorphism of certain genes and a set of cognitive and academic performance. The data collected will ultimately allow us to propose pedagogical interventions validated experimentally.

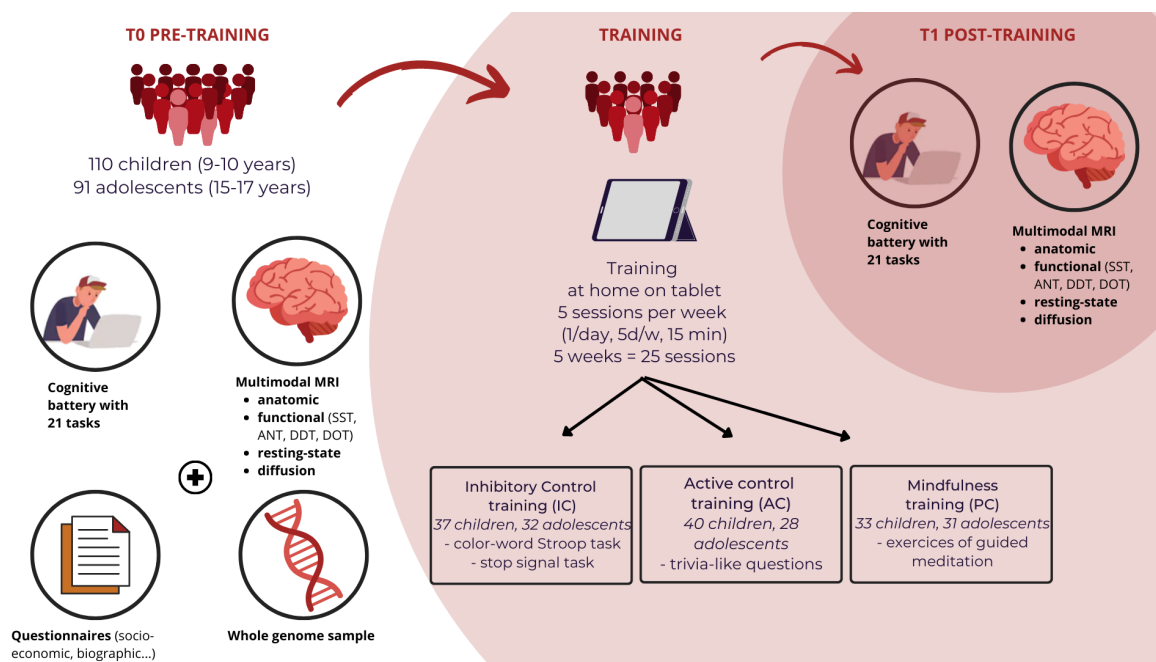


Figure 21: APEX protocol.

To do this, children and adolescents completed a 5-week touch tablet training at home. Prior to this, a pre-test provided a baseline with cognitive, brain and genetic measures and a

post-test, including the same cognitive and brain measures, highlighted the training effects (see Figure 21).

2 Participants

For the APEX project, 201 healthy participants from public schools were recruited: 110 children (33 males, $M \pm SD = 9.84 \pm 0.53$ years, range = 9–10 years) and 91 adolescents (20 males, $M = 16.71 \pm 0.53$ years, range = 15–17 years, see Table 1). Of note, 3 children also took part in a work memory training but this axis of the project was interrupted due to practical constraints.

	Children	Adolescents
N	110	91
Age	9.84 (0.53)	16.71 (0.53)
Sex		
F	61 (55.5%)	55 (60.4%)
M	49 (44.5%)	36 (39.6%)
Training group		
Active Control (AC)	40 (36.4%)	28 (30.8%)
Inhibitory Control (IC)	37 (33.6%)	32 (35.2%)
Mindfulness (PC)	33 (30.0%)	31 (34.1%)

Table 1: **Description of the APEX sample.** Age is given in years with a mean (SD) estimation. For Sex and Training group, the proportion in percentage is represented.

All participants were right-handed as determined by the Edinburgh Handedness Inventory Oldfield, 1971, were born full-term, had normal or corrected-to-normal vision, had no history of neurological disease and had no cerebral abnormalities. Parents or legal guardians gave written consent for the children and the adolescents, and all children and adolescents agreed to participate. All participants were tested in accordance with the national and international norms that govern the use of human research participants. Two ethics committees approved our study (IRB 2015-A00383-46 and IRB 2015-A00811-48).

3 Training sessions

The training was carried out on a tablet, at the child’s or adolescent’s home, for a period of 5 weeks. It was made clear to the participant that he/she had to do this training daily in order to reach 5 sessions per week and that he/she should not do several sessions during the same day, even if he/she had forgotten to do one the day before. Each training session lasted about 15 minutes. Number of sessions followed are depicted in Figure 22. Note that assiduity for the Mindfulness training are not represented as the information was missing for this group, however, we ensure that a minimum of 15 sessions were followed.

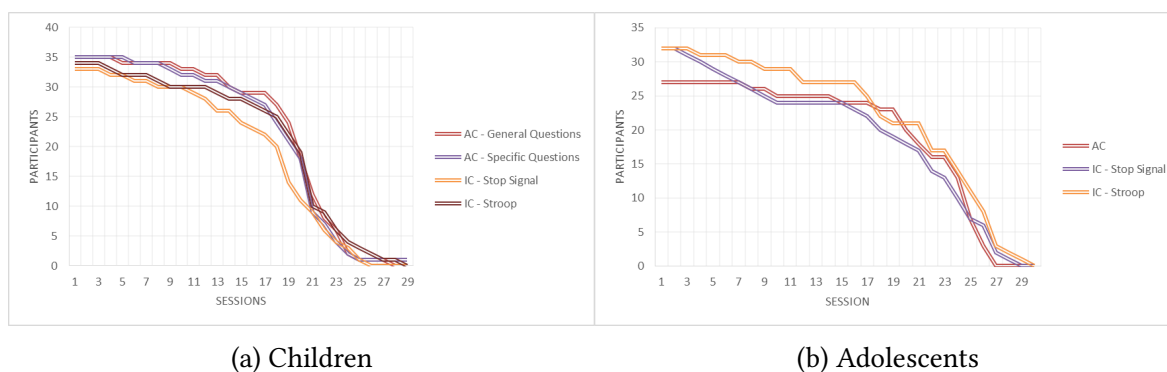


Figure 22: **Training assiduity in children (a) and adolescents (b).** The number of participants per session is represented. The different colors correspond to the different training exercises. This data is extracted from the tactile tablets.

At the end of each session, the participant (or his/her parents) was asked to send the data file generated by E-prime 2.0 to the experimenter (Marine Moyon for the children's cohort, Cloélia Tissier for the adolescents) and was asked to fill in his/her logbook, evaluating in particular his/her motivation and commitment during the session.

3.1 The Active Control training



Figure 23: **Active control training task.** Image: Marine Moyon.

For participants who were assigned to the control group (active control or AC group), the training, adapted from Jaeggi et al., 2011, consisted of general knowledge tasks or "General Questions Game" (e.g., What type of skiing is done on water? Alpine skiing/cross-country skiing/water skiing/freestyle skiing) and academic skills "Specific Questions Game" (e.g., What is the number of grams in $\frac{1}{2}$ kg?), again of increasing difficulty. Each question required the participant to answer within 30 seconds by touching one of the 4 answers provided on the touch pad. The questions were inspired by the collection Les Incollables®. An

online pre-test carried out with more than 1600 children and adolescents allowed the selection of the questions and their organization in levels of difficulty. As with the inhibitory control training, the control tasks were organized into 8 levels of difficulty, each consisting of 10 questions. If the rate of correct answers was higher than 90%, the level was validated and the participant moved on to the next level. If the number of correct answers was less than 70%, the participant returned to the lower level. Finally, if the rate of correct answers was between 70 and 90%, the level remained the same. Levels reached at each session are represented in Figures 26 & 27.

3.2 The Inhibitory Control training

For participants who were assigned to the experimental group (cognitive inhibitory control training or IC group), the training consisted of two tasks. Since inhibitory control is a multidimensional construct (Diamond, 2013), the first (color-word Stroop, Stroop, 1935) involved interference control while the second (stop signal task, Logan, 1994) involved inhibitory response.

3.2.1 The trained Stroop

During a Stroop or "Word and Color Game" session, participants had to press the button whose color corresponded to the ink color of the word presented among the four (red, blue, yellow, green) proposed on the tablet. The task was composed of congruent items where the ink color corresponded to the word (e.g. red written in red) and incongruent items where the ink color differed from the word presented (e.g. blue written in red). Control items where the word was presented written in black (e.g. RED) were also proposed. Subjects were then instructed to press the colored button corresponding to the color designated by the word. All stimuli were presented in the center of the tablet screen in Arial font, bold, size 24. Each training session consisted of 13 control, 13 congruent, and 13 incongruent items.

As the training sessions progressed, the difficulty of the task increased by decreasing the SOA (Stimulus Onset Asynchrony), i.e. the delay between the presentation of the word (written in light grey) and its colouring in one of the four colors. The SOA of the first level was 450 ms and decreased by 50 ms per level until it reached 100 ms at level 8. If the number of correct answers per block was greater than 90%, the level was validated and the participant moved on to the next level. If the number of correct answers was less than 70%, the participant went back to the lower level. Finally, if the number of correct answers was between 70 and 90%, the level remained the same. Levels reached at each session are represented in Figures 26 & 27.



Figure 24: **Color-word color task.** Here an incongruent trial is represented. Image: Marine Moyon.

3.2.2 The trained stop signal

During a stop signal session, participants had to press one of the two response buttons (the left or the right one) on the touchpad to indicate in which direction the arrow on the screen was pointing, except when a beep sounded, in which case they had to hold back their response. Each training session began with 16 Go items and was followed by 30 Go items and 10 randomly assigned Stop items.

The difficulty increased with an increase in the SOA, the time between the presentation of the arrow and the Stop tone. The SOA in the first level was 100 ms and increased by 50 ms per level until it reached 450 ms in level 8. If the success rate of the Stop trials was greater than 80% and the success rate of the Go trials was greater than 90%, the level was validated and the participant moved on to the next level. If the success rate was less than 60% for the Stop trials and/or less than 80% for the Go trials, the participant returned to the lower level. Finally, for intermediate scores, the level remained the same. Levels reached at each session are represented in Figures 26 & 27.

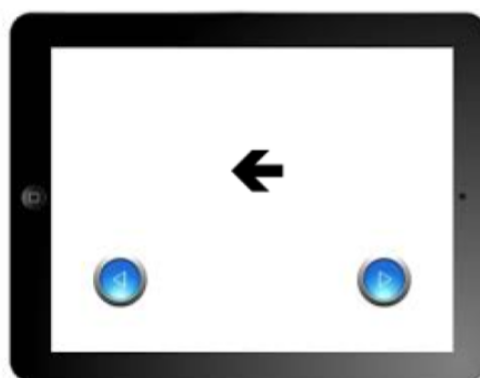


Figure 25: **Stop signal task.** Image: Marine Moyon.

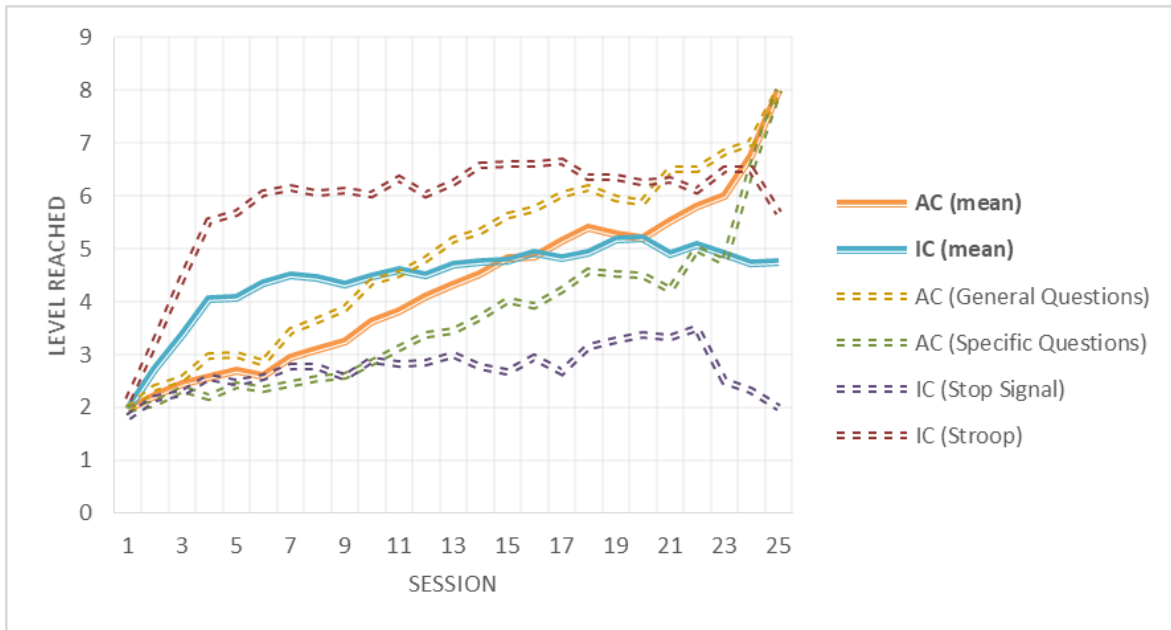


Figure 26: **Learning curves in children for each training block.** Levels go from 1 (minimum) to 8 (maximum). Mean lines represent the weighted mean by the number of participants.

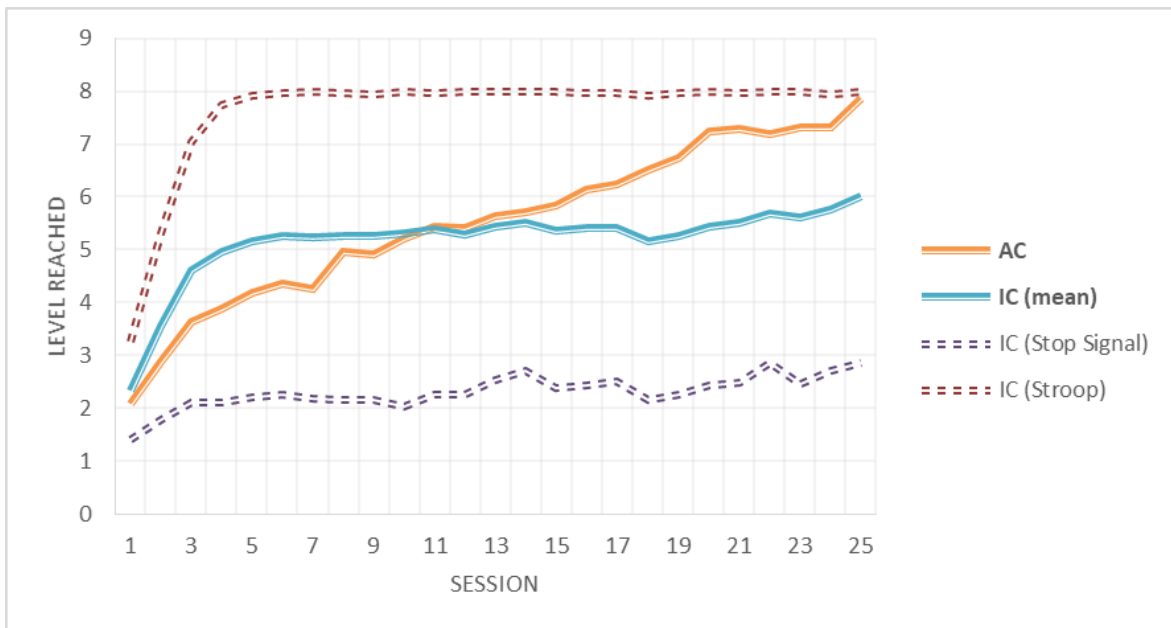


Figure 27: **Learning curves in adolescents for each training block.** Levels go from 1 (minimum) to 8 (maximum). Mean lines represent the weighted mean by the number of participants.

3.3 The Mindfulness based training

This mindfulness training was composed of different exercises of guided meditation. These exercises were inspired by the book *Calme et attentif comme une grenouille*. Each session of 15 minutes was composed of two different exercises. On the contrary of the two other types of training, there were no progression in this training as no score was collected after the sessions.

3.4 The logbook

To ensure follow-up and motivational support, a logbook was provided to participants at the beginning of the training. After each session, they were asked to indicate the day and time of the practice as well as their state of mind and remarks. These information, crossed with those of the tablet, made it possible to check the good respect of the protocol by the participants.

4 Pre- and post-training sessions

4.1 Medical appointment

For the inclusion interview, the presence of at least one of the legal guardians was essential. The interview with the investigating physician had a supervisory role, on a double level, ethical and medical. The health professional first made sure that the child or adolescent understood the reason for his/ her visit, the scientific issues and objectives that his/her participation would attempt to address, as well as the expectations that the team had of him/her and the practicalities of the research study. Participant consent was then collected.

4.2 Genetic sampling

The genetic sample was only taken as a pre-test. The participant had to fill a plastic tube with his/her saliva.

DNA was extracted from saliva recovered with the Oragene saliva collection kit (DNA Genotek, Inc., Canada) and the pangenome analysis pangenome analysis by nucleotide polymorphism (SNP) genotyping was performed by the IntegraGen SA (Genopole, Evry).

4.3 MRI acquisition

4.3.1 Protocol

The participants came for an MRI before and after their training. They came to the Cyceron platform in Caen for the children or to the CIREN (Centre d'Imagerie et de Recherche En Neurosciences) at the GHU Sainte-Anne in Paris for the adolescents.

The appointment started with a training on computers for the four tasks presented in the MRI: attention network task (ANT), stop signal task (SST), delayed discounting task (DDT) and DOT-matrix task (DOT). This training allowed the participant to properly integrate the instructions and to practice the response modalities (right or left button). Once this training was completed, a blood glucose measurement was performed. Finally, the participant (or a parent) completed an MRI safety questionnaire.

The participant was then taken to an individual room to change comfortably, remove any jewelry and metal objects from their pockets. For adolescent participants only, a series of questions were asked about their recent behaviors (alcohol consumption the day before, last tobacco and cannabis consumption, tea or coffee consumption during the day, and last sweet meal or drink). Finally, the participant was reminded of the protocol once they were installed in the MRI and the questions from the MRI safety questionnaire were repeated.

The participant was then accompanied into the MRI. The participant was provided with earplugs, a headset and a cap before lying down and positioning themselves in the machine. A call button (in case the participant was not feeling well or if a problem occurred during one of the tasks) was presented and taped to the participant's chest. Similarly, a response box was presented and then installed after positioning the fingers (index finger on the left button, middle finger on the right button). The participant's head was then wedged with foam pads after which the antenna was placed. The participant could then adjust the mirror attached to the antenna so that he/she could see the screen behind the MRI on which the stimuli would be presented during the tasks during the functional sequences. Finally, after checking that the participant was well positioned but above all comfortable, the table was moved forward and the experimenters (and possibly the parents) left the room.

The MRI run consisted of 11 sequences: a calibration, a first anatomical sequence (3DT1), a resting MRI sequence (rsfMRI), four functional sequences (ANT, DDT, DOT and SST), a second anatomical sequence (AxT2) and a diffusion sequence (DTI). We only detail the anatomical sequence, as the imaging data from the other sequences are not exploited in this thesis work.

4.3.2 Anatomical MRI Acquisition

The high-resolution (1 x 1 x 1 mm) isotropic 3T sagittal MRI data were acquired in children and adolescents. MRI data in children were acquired on Cyceron's biomedical imaging platform in Caen (Archieva, Philips Medical System, Netherlands). Prior to the MRI session, the children had become familiar with the noise of MRI and had practiced not moving

during acquisition in a mock MRI (or mockscanner). In order to reduce waiting time and to provide a more positive experience for the participants and thus to reduce movement during acquisition, children watched passively a cartoon on an MRI-compatible screen (Lemaire et al., 2009). MRI data in adolescents were acquired on the biomedical imaging platform of the Imaging Center for Research and Teaching in Neurosciences (CIREN, Paris; General Electric). The parameters of the sequences have been optimized in each site to obtain an acquisition similar to Cyceron (TE = 3.3ms; TR = 7.2ms; flip angle = 9°; matrix size = 256 x 240mm; field of view = 256mm) and at CIREN (TE = 3.2ms; TR = 8.2ms ; flip angle = 11°; matrix size = 256 x 256mm; fields of view = 256mm).

4.4 Questionnaires

Several questionnaires were filled by the participants and/or their parents before training.

The first questionnaire filled by the parents was the socio-economic questionnaire. This questionnaire was composed of questions to assess for the education level, the actual work title and work time of each parent as well as the parental income. This questionnaire also included questions about the family, more broadly, as the parental relation (married, divorced, widowed, etc.), the presence of step parents, the number of siblings. Finally, this questionnaire had a section about important events that happened in the participant's life and over the last year.

The second questionnaire was filled by the participants with help of the parents for the children and concerned the participant's habits. It included questions about

- extra-scholar activities (which ones? for how many years? at which frequency?),
- reading habits (number of hours dedicated to reading per week, presence of books, library cards, magazine subscriptions, etc.),
- screen habits (number of hours per day or per week watching TV, on the phone, playing video-games on phone/tablet/computer/play-station, playing education games, etc.),
- cultural habits (number of exhibitions, movies, concerts, visited per year,

4.5 Cognitive tasks

The cognitive battery took place during the week of the MRI (either pre- or post-test) but necessarily after it. It took place in the same premises as the MRI. The participant was then received by the experimenter and, after a blood sugar measurement, the cognitive battery could be started.

This consisted of 24 tasks for children and 21 tasks for children. Optional tasks had been considered but the battery was already very complete and long (about 2h15), so they were not performed. The order of these tasks was the same for all subjects and for both sessions

In children, this battery was split in two, in order to keep the children focused during all tasks. No break was mandated to participants but they were free to ask one whenever they needed to.

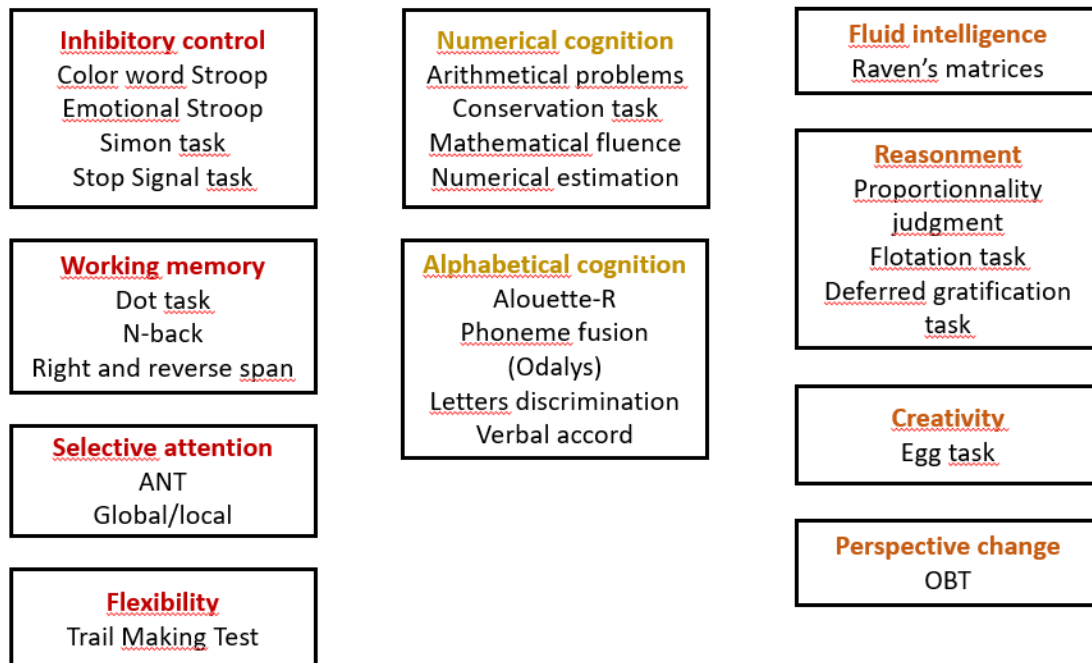


Figure 28: APEX cognitive tasks.

The tasks were the same for children and adolescents except for few ones:

- Raven’s matrices differed: children answered with paper/pencil medium whereas adolescents performed the tasks directly on the computer. Matrices adapted for children included 36 items vs 12 items for adolescents.
- Alphabetical cognition tasks (Alouette-R, Phoneme fusion, Letters discrimination, Verbal accord) were passed only by children. Adolescents did not performed these tasks.
- In the same way, the Right and reverse span and the Mathematical fluence tasks were performed by children only.

The Table 28 below summarizes the task design, the instructions given to the participants and the computed scores for the six tasks considered during this PhD project. Detailed descriptions of the tasks and the theories associated are described below.

4.5.1 Color-word Stroop task

4.5.1.1 Stroop theory The Stroop task (Stroop, 1935) is perhaps one of the most classic measures of inhibitory control, at least one of the best known. It has even been integrated

Task	Reference	Protocol	DV
Color-word Stroop	Stroop, 1935	Indicate the ink color of the word presented on the screen. Incongruent trials are trials where the color indicated by the words does not match the color in which the words are printed (for example, the word GREEN is written in blue).	Interference score calculated as RT for incongruent trials - RT for congruent trials (for correct answers only).
Stop signal	Verbruggen and Logan, 2008	Indicate which way an arrow points, but do not respond if a tone (stop signal) sounds after the arrow is presented.	SSRT measured by subtracting the stop signal delay from the median value of the subject's Go RT distribution (when there is no Stop signal).
Simon	Lu and Proctor, 1995	Indicate whether the stimulus presented on the screen is a butterfly or a frog. On congruent trials, the response key for a stimulus was on the same side as that stimulus; on incongruent trials, the response key was on the opposite side.	Interference score calculated as RT for incongruent trials - RT for congruent trials (for correct answers only).
ANT	Fan et al., 2002	Look at the five fish on the screen and indicate which way the middle fish is swimming. It is surrounded on both sides by fish swimming in the same direction (congruent condition), in the opposite direction (incongruent condition).	Interference score calculated as RT for incongruent trials - RT for congruent trials (for correct answers only).
Trail Making Test	Reitan and Wolfson, 1992	In part A, connect circles containing numbers in numerical sequence. In part B, only numbers are presented. In part C, both numbers and letters are presented and the circles should be connected in an alternating sequence (numbers-letters: 1-A-2-B, etc.)	Shifting score calculated as the time needed to fill the part B - time needed to fill the part A.
Nback	Cohen et al., 1994	View a sequence of squares popping at different places of the screen and indicate when the current square emplacement matches the emplacement from n trials prior. Blocks consist of 1-, 2- and 3-back targets.	Score is the RT for successful trials in the 3-back condition minus the RT for successful trials in the 1-back condition.

Table 2: Descriptions of the tasks.

in very popular "brain training" programs proposed on game consoles in the 2000s.

This task consists in presenting the subject with a board of color names written with different colored inks. Two control conditions exist. The first one is the color-control condition: the subject must then name the color of pellets of different colors. There is no interference between reading and naming since reading is absent. The second one is the reading-control condition: the subject must then read different color names written in black on a white board. Here again, there is no interference between reading and naming since naming is absent. In the test conditions, the stimuli can be congruent, in which case the color of the ink corresponds to the word itself (BLUE written in blue) or incongruent, where

the color of the ink differs from the word (BLUE written in red). The subject must then name the color of the ink and, to do so, he must inhibit the reading of the word. The difference in reading time (but also in correctly read words) between congruent and incongruent items is called the Stroop effect or semantic interference. Logan, 1997 explains failure on this task as due to reading automatism.

Indeed, according to Logan, 1997, the automatism of a process has an influence on performance in terms of speed, motivation, cognitive resources required and the level of awareness of the subject during the task. For him, reading is an automatic process, at least at the word-to-word level, including decoding the word and accessing its lexicon. Thus, in a Stroop task, naming the color of the ink would require more motivation, time and cognitive resources than simply reading the word. Since the reading of the word is automatic, it is also compulsory, leading to a strong interference during the conflicting Stroop task.

Also, good reading skills would allow for automation of this reading, resulting in failure on the Stroop task. Therefore, this type of task is not effective to measure IC in young children who didn't finish their reading acquisition. Indeed, it was demonstrated that the interference increased with the learning of reading (Ehri and Wilce, 1979). Similarly, in an experimental study, when reading was blocked, a negative linear relationship between age and Stroop interference was observed (Leon-Carrion et al., 2004).

Of note, other models were proposed to explain Stroop effects like the tectonic (Melara and Algom, 2003), the parallel race (Eidels, 2012) or the three component (Demetriou et al., 2002) models.

Then, Stroop effect evolution through development is studied for a long time. It was shown that there were a greatest interference in young children (6-7 years) that declined from around 10 years into adulthood (around 17 years of age) before increasing again in elderly (Comalli et al., 1962; Leon-Carrion et al., 2004). Of note, interference was shown to be minimal in grade 1, before the acquisition of lecture (Schiller, 1966).

4.5.1.2 Task design As for the SST, the color-word Stroop task presented in the cognitive battery featured two training blocks followed by an experimental block.

The first practice block included 12 trials was proposed to allow an associative learning between the colors and the answer buttons. Monochrome dots (yellow, blue, green or red) appeared successively on the computer screen. Their order of presentation was randomized (three trials per color). The participant was instructed to press the associated key as quickly as possible and without making a mistake. In order to facilitate the memorization of the keys, stickers with the corresponding colors were previously glued to the computer keyboard. Blue and yellow stickers were stuck on the "s" key, lateralized to the left. Green and red stickers were stuck on the "l" key, lateralized to the right. Thus, participants had to press the key "s" in the case of a yellow or blue dot and the key "l" in the case of a green or red dot. During the whole exercise, the participant were asked to keep their left index finger above the "s" key and their right index finger above the "l" key. The visual stimulus (colored dot) always appeared after a 500 ms fixation cross. In order to guarantee a good motor learning, the colored dot remained displayed until the participant pressed the right response button.

The second practice block was proposed to really practice the task. It was composed of 8 trials (2 per color) of which seven were incongruent and only one was congruent. Apart from the first two stimuli which were presented without fixation cross or feedback, the other 6 were presented after a fixation cross of 500 ms, during 7000ms maximum and a feedback on the performance during 1500ms. As soon as the participant pressed the answer button, the computer told him/her if his/her answer was successful ("Good answer!!!") or not ("Bad answer"). If the participant did not answered within the time limit of 7000ms, the message "Answer faster" was displayed.

After these two practice blocks, the experimental block started. This color-word Stroop task was composed of 32 pairs of stimuli, for a total of 64 trials. A fixation cross of 1500ms separated the pairs of stimuli. Within each pair, a faster fixation cross of 500ms separated the presentation of the two trials. These trials were presented in the center of the screen, in Courier New font, bold, size 24, on a gray background. Participants responded by pressing a key on the keyboard, 's' for yellow and blue, 'l' for red and green. Each trial was presented for a duration of 3000ms, and in order for their response to be taken into account, participants were required to respond during this stimulus presentation period. Thus, the response times were reduced compared to the training condition. There were three types of trials:

- congruent trials
- incongruent trials for which a reading error would lead to pressing the same answer button (e.g. the word **RED** written in green; the "l" button allowing to answer both "red" and "green"), noted CP for Perceptual Conflict
- incongruent trials for which a reading error would lead to pressing the wrong answer button (e.g. the word **BLUE** written in red; answer button "l" to answer "red" if correct denomination versus answer button "s" to answer "blue" if expression of the reading automatism), noted CPCM for Perceptual and Motor Conflict

The combination of these three types of trials resulted in eight types of trial pairs, each represented four times in this task:

- IC-CPCM pair composed of an incongruent CPCM item and a congruent item
- CI-CPCM pair composed of a congruent item then an incongruent CPCM item
- II-CPCM pair composed of two incongruent items CPCM
- IC-CP pair composed of one incongruent item CP and one congruent item
- CC-CPCM pair composed of a congruent item for which the "s" answer key must be pressed and then a congruent item for which the "l" answer key must be pressed
- CC-CP pair composed of a congruent item for which the "s" answer key must be pressed and then a congruent item for which the "l" answer key must be pressed
- CI-CP pair composed of a congruent item then an incongruent item CP

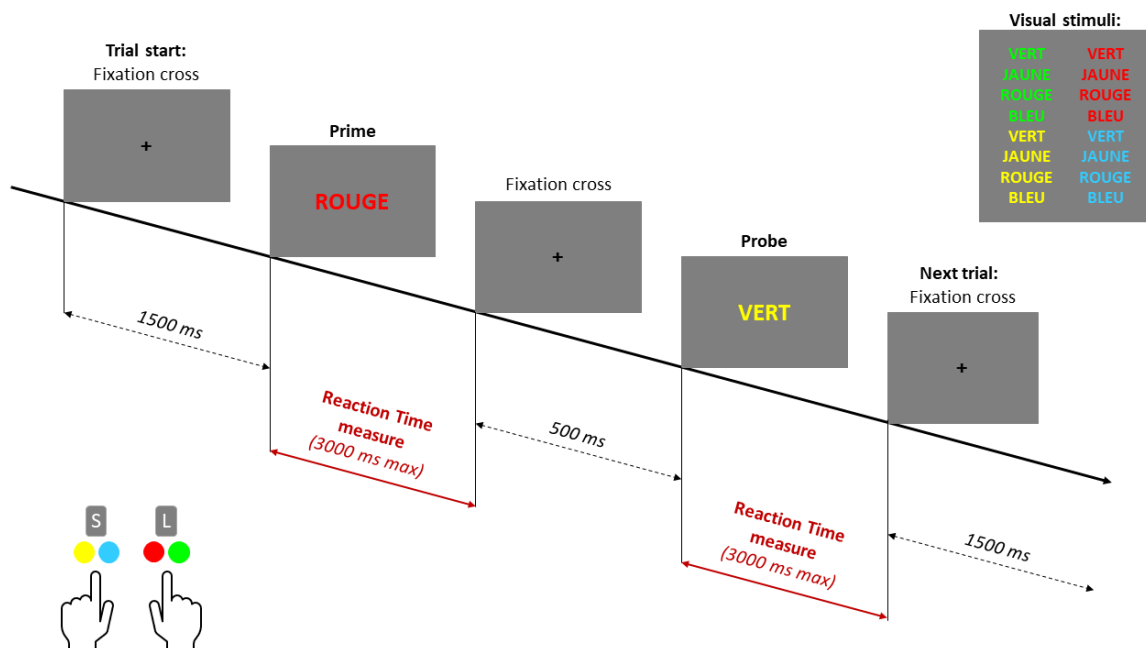


Figure 29: **Negative-priming color-word Stroop design.** Here, the prime is congruent (RED written in red) and the probe is incongruent (GREEN written in yellow) with a Perceptual and Motor Conflict constituting a CI-CPCM trial pair.

- II-CP pair composed of two incongruent items CP

This paired design was made to investigate negative priming effects. First trials of the pairs were therefore the primes and second trials the probes. In our case, we were not interested in negative priming effects. Thus, we only looked at the primes.

4.5.1.3 Stroop interference score

Based on the theory from Logan, 1997, an interference score could be calculated from the color-word Stroop task.

As we were not interested in negative priming effects, we only considered the primes. The Stroop interference score was then computed for each subject as follow:

$$\text{Interference} = \text{mean}(\text{RTs for CPCM successful trials}) - \text{mean}(\text{RTs for congruent successful trials})$$

CP trials were not included as it was not possible to discriminate correct to incorrect responses within this task design.

Intra-subject corrections were applied to exclude premature or too slow responses. Two types of corrections were applied:

- a SD (Standard Deviation) correction: a RT was considered outlier if it was below or above the RTs mean + or - 2.5 SD.

- a MAD (Median Absolute Deviation) correction: for a trial i , a RT was considered outlier if it was below or above the RTs median + or - $2.5 * 1.4826 * median(Dist_i)$ where $Dist_i = |median(RTs) - RT_i|$

We thus obtained three scores: an interference Stroop score without any intra-subject correction, a score with a SD correction and a score with a MAD correction.

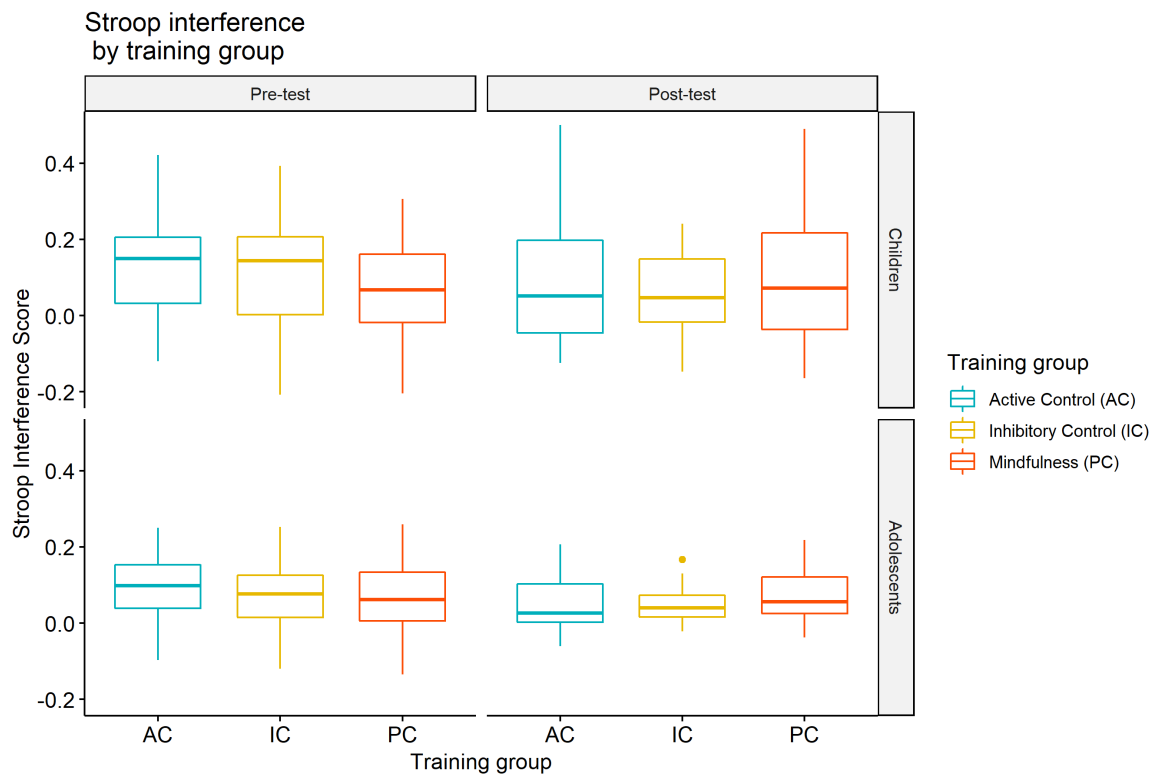


Figure 30: **Stroop interference distribution before and after training.** The top panel corresponds to the children, the bottom one to the adolescents. The left panel corresponds to pre-training distribution, right panel to post-training. Training groups are represented in color (blue for Active Control, yellow for Inhibitory Control and red for Mindfulness).

4.5.1.4 Descriptive results Behavioral data for the color-word Stroop task in the APEX project can be found in Table 3. Distribution plots are disposed in Figure 30. Of note, this task has been further investigated in the following experimental studies.

4.5.2 Stop signal task

4.5.2.1 Horse-race model The stop-signal paradigm (Logan, 1994) provides tools for examining this relatively simple type of control (i.e., its success, duration, and variability).

The stop-signal paradigm consists of a reaction time (RT) task in which the occasional presentation of a stop signal indicates that the pending response should be cancelled. The

probability of stopping can be manipulated by the timing of the stop signal regarding the reaction signal.

Response inhibition in the stop-signal task can be conceptualized as an independent race between a 'go runner', triggered by the presentation of a go stimulus, and a 'stop runner', triggered by the presentation of a stop signal (Logan and Cowan, 1984). When the 'stop runner' finishes before the 'go runner', response inhibition is successful and no response is emitted (successful stop trial); but when the 'go runner' finishes before the 'stop runner', response inhibition is unsuccessful and the response is emitted (unsuccessful stop trial).

The independent race model mathematically relates (a) the latencies (RT) of responses on unsuccessful stop trials; (b) RTs on go trials; and (c) the probability of responding on stop-signal trials [$p(\text{respond}|\text{stop signal})$] as a function of stop-signal delay (yielding 'inhibition functions').

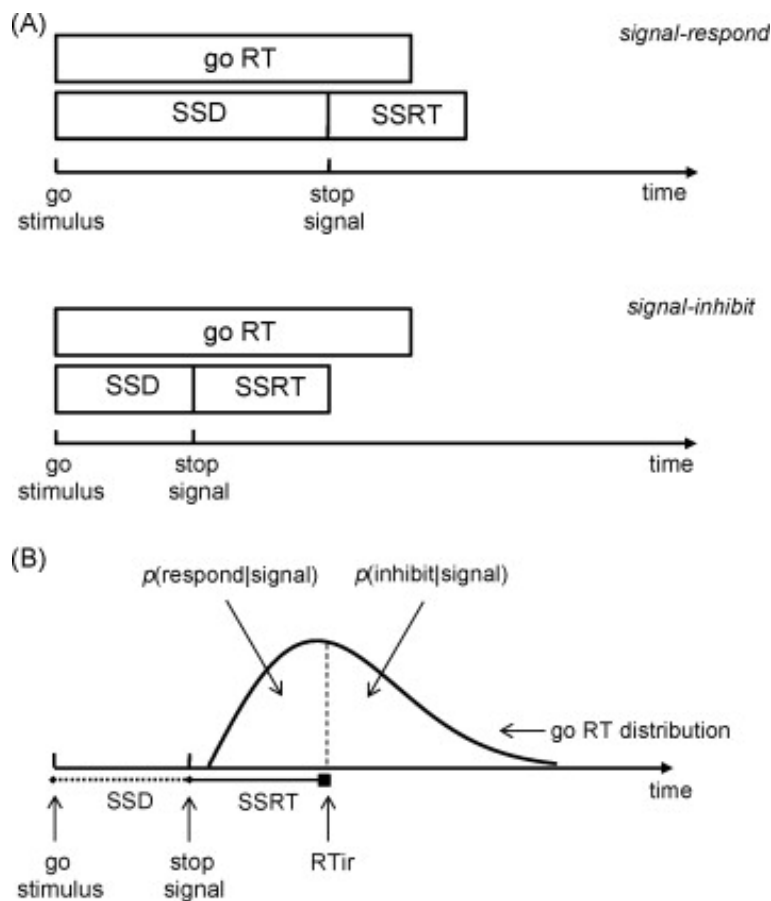


Figure 31: (A) **Graphic representation of the horse-race idea.** The length of the bars represents the duration of the process (SSD = stop-signal delay; SSRT = stop-signal reaction time). (B) **Graphic representation of the assumptions of the independent horse-race model of Logan and Cowan, 1984,** indicating how the probability of responding [$p(\text{respond}|\text{signal})$] and the probability of inhibiting [$p(\text{inhibit}|\text{signal})$] depend on the distribution of go reaction times, stop-signal delay (SSD) and stop-signal reaction time (SSRT). From Verbruggen and Logan, 2008.

Because this task is very popular in the literature and because different designs and

methods for indices calculation exist, an extensive consultation round was organized to reach an agreement. The resulting paper (Verbruggen et al., 2019) lists twelve recommendations to improve the overall quality of future stop-signal research. These recommendations were based on previous methodological studies or, where further empirical support was required, on novel simulations.

4.5.2.2 Task design The task presented in the cognitive battery featured two training blocks followed by an experimental block.

Each trial began with the presentation of a circle for 250 ms and then an arrow appeared in the circle. Participants were then instructed to click the left mouse button as quickly as possible if the arrow pointed left, and the right mouse button if the arrow pointed right. Specifically, participants were asked not to wait for a stop signal, that the task was difficult because it was designed so that they would fail 50% of the time. If a tone (the Stop signal, 750 Hz, 75 ms) sounded after a variable delay (the stop signal delay, SSD) following the presentation of the arrow, then subjects were instructed to inhibit their response, by not clicking any buttons. Regarding the Stop trials, the task was adaptive in difficulty. The SSD was initially set at 350 ms and increased by 50 ms after each successful Stop trial, to a maximum of 1150 ms, and decreased by 50 ms after each failed Stop trial, to a minimum of 50 ms. This tracking procedure, recommended by the literature, allowed to approach a probability of 0.50 in order to fit the horse race model theory. Each trial lasted 2000 ms during which participants could respond (see Figure 32).

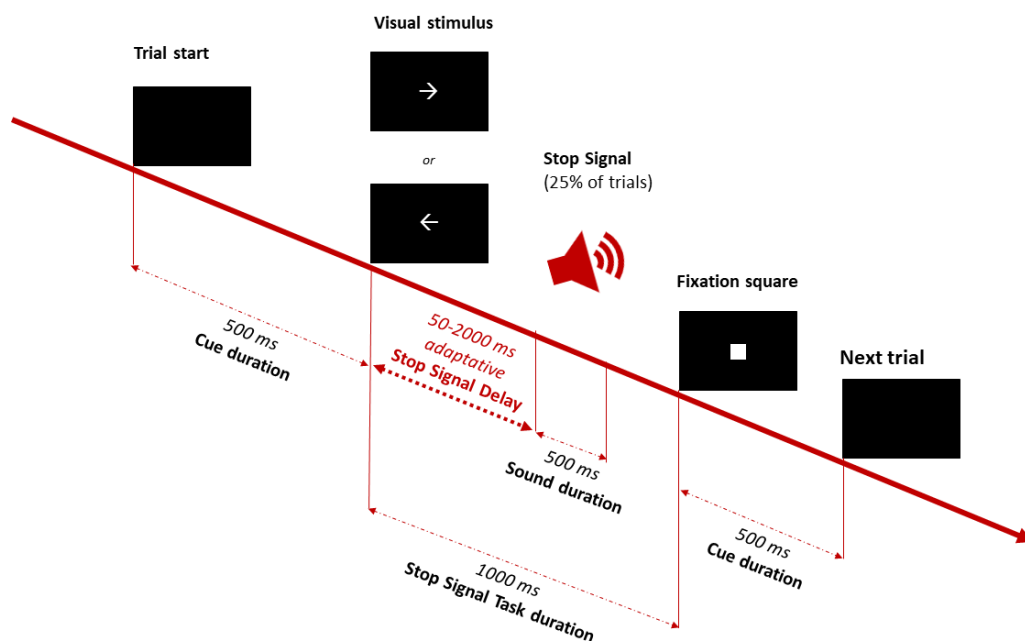


Figure 32: Stop signal task design.

The first training block included only Go trials to train participants in the response modalities (if the arrow points to the left, left click; if the arrow points to the right, right click).

A second training block was then proposed. This block allowed participants to actually practice the task and to become familiar with the stop signals. This block of 16 trials in total consisted of 4 Stop trials and 12 Go trials.

Finally, once these two training blocks were completed, the task could begin. It consisted of 64 trials, including 16 Stop trials and 48 Go trials.

Every block was counterbalanced in terms of stimulus orientation (as many arrows pointing to the left as to the right).

The recommendations from the consensus paper Verbruggen et al., 2019) regarding the task design are the following:

1. Use an appropriate go task, a standard two-choice reaction time task is recommended → this was the case in our study as described above
2. Use a salient stop signal, indeed, the stop signals should be salients and easily detectable → the Stop signals were salient in our study, it was a sound signal, so in another modality (auditory) than the stimuli (visual)
3. Present stop signals on a minority of trials, a ratio of 25% Stop trials/75% Go trials is recommended → the ratio was respected for our study as 16 Stop trials represented 25% of the total of 64 trials
4. Use the tracking procedure to obtain a broad range of stop-signal delays, with 50 ms steps → this recommendation was also followed
5. Instruct participants not to wait and include block-based feedback and for certain populations as young children, include a practice block without stop signals in addition to a practice block with go and stop trials → the instruction "*not to wait for the stop signal*" was given orally to the participants but also written on the screen before the beginning of the task. The task, as described above, included the two types of practice blocks.
6. Include sufficient trials, that is about 50 stop trials → this was not the case in our study. As the SST was one of more than 20 tasks and the participants were aged between 9 and 17 years old, the task had to be short in time and could not include more items if we didn't want to lose our participants' engagement in the protocol.

4.5.2.3 Stop signal reaction time Given a small set of assumptions, it is possible to calculate the time required for stopping the response; that is, the stop-signal reaction time (SSRT).

The recommendations from Verbruggen et al., 2019 regarding the SSRT estimation are the following:

1. Do not estimate the SSRT when the assumptions of the race model are violated, the mean RT on unsuccessful stop trials should not be numerically longer than the mean

RT on go trials (all trials with a response, even with choice errors or premature response, should be included)

2. If using a non-parametric approach, SSRT should be estimated by the integration method with replacement of go omissions
3. SSRT should not be estimated if the probability of responding on stop-signal trials deviates substantially from 0.50 or when the probability of omissions on go trials is high. More precisely, individual SSRTs should not be estimated when $p(\text{respond}|\text{signal})$ is lower than 0.25 or higher than 0.75 (Congdon et al., 2012).

Finally, two ways to calculate SSRT have been chosen.

The first one is the **mean and median method** described in Aron, 2006. For each subject, we estimated the mean RT of all go trials (correct as uncorrect or premature) and the median of the SSD for all stop trials (successful ones and unsuccessful ones). The SSRT was calculated as the equation below:

$$SSRTa = \text{median}(RT \text{ of go trials}) - \text{mean}(SSD)$$

Then, before making any analysis, the SSRTs were deleted for subjects with a $p(\text{respond}|\text{signal})$ lower than 0.25 or higher than 0.75 and for subjects with a mean RT on unsuccessful stop trials numerically longer than the mean RT on go trials.

Then, a second method recommended by Verbruggen et al., 2019 was used to estimate SSRT: the **integration method with replacement of go omissions**. This method is described as the authors as the most reliable and least biased SSRT estimates.

To do so, for each subject, we:

1. ranked the RT of all go trials with a response in ascending order,
2. assigned the maximum RT to the omitted Go trials (i.e., those where the participants would not have responded at all)
3. determined the n th RT with $n =$ the number of RT in the RT distribution of the go trials multiplied by $p(\text{respond}|\text{signal})$. In our case we have 48 Go trials, we should then, for each subject calculate $n = 48 * p$.
4. calculated the SSRT as in the equation

$$SSRTb = \text{nth fastest RT} - \text{mean}(SSD)$$

In the ideal case where $p = 0.5$, $n = 48 * 0.5 = 24$ so the n th fastest RT equals $\text{median}(RTs \text{ of go trials})$ and we should therefore obtain the same score as with the first calculation method ($SSRTa = SSRTb$).

As with the previous calculation method, SSRTs were deleted for subjects with a $p(\text{respond}|\text{signal})$ lower than 0.25 or higher than 0.75 and for subjects with a mean RT on unsuccessful stop trials numerically longer than the mean RT on go trials.

Previous studies have found SSRT of young adults close to 200 ms when they try to interrupt continuous actions such as typing (Logan, 1982), overlearned responses, such as speaking (Ladefoged et al., 1973). The similarity of stop results has been interpreted as support for a model with one stopping mechanism that can be used to stop a variety of actions (see Logan, 1994).

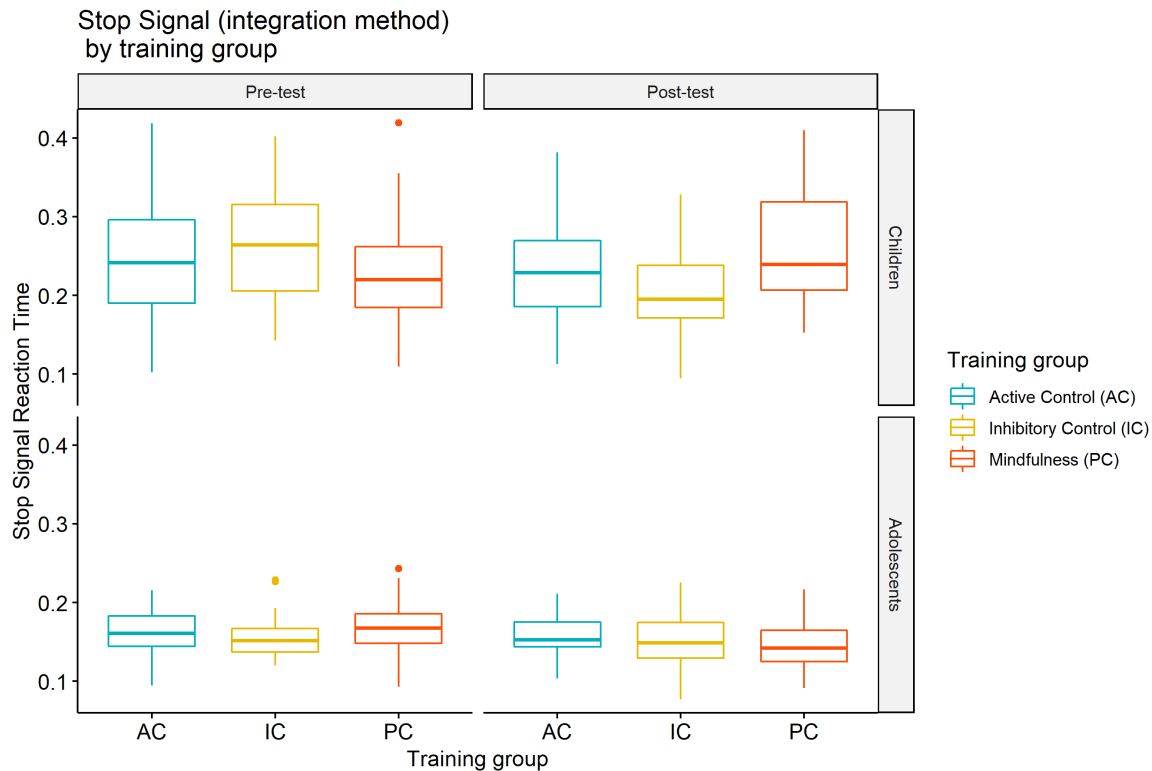


Figure 33: **Stop signal distribution before and after training.** The top panel corresponds to the children, the bottom one to the adolescents. The left panel corresponds to pre-training distribution, right panel to post-training. Training groups are represented in color (blue for Active Control, yellow for Inhibitory Control and red for Mindfulness).

4.5.2.4 Descriptive results The behavioral data for the stop signal task in the APEX project can be found in Table 3. Distribution plots are disposed in Figure 33. Of note, this task has been further investigated in the following experimental studies.

4.5.3 Simon task

4.5.3.1 Simon effect The Simon task (Simon and WOLF, 1963) is based on stimulus-response compatibility and assesses the extent to which prepotent association with irrelevant spatial information affects participants' response to task-relevant non-spatial information. The so-called Simon effect (Simon and Berbaum, 1990) refers to the fact that spatially arranged responses (e.g., with left or right hands) to nonspatial stimulus features (e.g., stimulus shapes) are faster when the task-irrelevant stimulus location and the response location are compatible than when they are incompatible.

Simon and Berbaum, 1990 considered the eponymous effect to be rooted in a processing competition occurring during response selection. He claimed that the location of a stimulus elicits an unlearned tendency to respond in its direction. When the required response is directionally opposite this natural tendency, the observer must overcome the latter in selecting the correct response, an effort that yields the Simon effect. Although many theorists do not subscribe to Simon's idea of reflexive orienting (e.g., Dutta and Proctor, 1992), there is widespread agreement (see Lu and Proctor, 1995) that the Simon effect emerges primarily from competition at a response-selection stage (Melara et al., 2008).

A common approach for characterizing response competition is embodied in dual-route models of the Simon effect (Hommel, 1993; Ridderinkhof, 2002). In these models, Simon effect arises because the spatial position of the stimulus directly activates or primes a response position (direct route), which, for incongruent trials, differs from the response position defined by the instructed stimulus–response assignment (conditional route; Schacht et al., 2010). Response selection is facilitated on the congruent trials of a Simon task – those in which the location of the correct response coincides with the actual stimulus location – because fast automatic activation primes the code for the correct response. However, response selection is hindered on the incongruent trials – those in which the location of the correct response mismatches the stimulus location. Indeed, the intentional route must inhibit the automatically primed response code before selecting the correct one, a competitive process that yields response interference (Melara et al., 2008; Schacht et al., 2010).

Electrophysiological studies have provided strong evidence in favor of response conflicts in the Simon tasks by demonstrating early and transient incorrect response activation in the case of incompatible trials followed by activation of the correct response (e.g., Stürmer et al., 2002i).

To be noted, there are other accounts of the Simon effect as well (Melara et al., 2008).

Developmental investigations of the Simon task have revealed substantial age-related gains in cognitive control between childhood and adulthood as evidenced by reductions in the size of the Simon effect (e.g., Davidson et al., 2006).

4.5.3.2 Task design As for the other tasks, the Simon task presented in the cognitive battery featured two training blocks followed by an experimental block.

In the implementation of this task, stimuli (a butterfly and a frog) are presented on the left or right side of the screen. Participants must press the e key when they see the butterfly (located on the left side of the keyboard) and the p key (on the right side of the keyboard) when they see the frog. On congruent trials, the correct response for a stimulus was on the same side as that stimulus; on non-congruent trials, the correct response was on the opposite side. Irrelevant location information leads to longer reaction times (RTs) for incongruent items. The extra time required to respond to incongruent items is the Simon effect. The Simon effect refers to the fact that responses are faster when the location of the stimulus matches the location of the assigned response. A key-press response to a word (located, for example, on the left) is faster when the word appears in a congruent position (here, left side) than when it appears in an incongruent position (right side).

The first practice block included 6 trials was proposed to allow an associative learning between the stimuli (a drawing of a frog and another of a butterfly) and the answer buttons. Stimuli appeared successively on the center of the computer screen. Their order of presentation was randomized (3 trials per stimulus). The participant was instructed to press the associated key as quickly as possible and without making a mistake. In order to facilitate the memorization of the keys, stickers with the corresponding drawing were previously glued to the computer keyboard. A butterfly sticker was stuck on the "e" key, lateralized to the left. A frog sticker was stuck on the "p" key, lateralized to the right. Thus, participants had to press the key "e" in the case of a butterfly stimulus and the key "p" in the case of a frog stimulus. During the whole exercise, the participant were asked to keep their left index finger above the "e" key and their right index finger above the "p" key. The visual stimulus always appeared after a 500 ms fixation cross.

The second practice block was proposed to really practice the task. It was composed of 8 trials (4 per stimulus) of which half were incongruent. This time the stimuli were no longer presented in the center of the screen but in a rectangular frame. This frame had a central fixation cross and the stimuli were presented in the frame, either to the left or to the right of the cross. The distance between the central cross and the stimulus could vary, as the stimulus could be close, far or very far from this cross (see Figure 34).

On congruent trials, the correct response for a stimulus was on the same side as that stimulus (a butterfly on the left side of the screen or a frog on the right side); on incongruent trials, the correct response was on the opposite side (a butterfly on the right side of the screen or a frog on the left side). As soon as the participant pressed the answer button, the computer told him/her if his/her answer was successful ("Good answer!!!") or not ("Bad answer"). If the participant did not answered within the time limit of 7000ms, the message "Answer faster" was displayed.

After these two practice blocks, the experimental block started. The proposed Simon task was composed of 48 trials, half of which were incongruent trials. As in the practice blocks, participants responded by pressing a key on the keyboard, 'e' for butterfly, 'p' for frog. Each trial was presented for a duration of 3000ms, and in order for their response to be taken into account, participants were required to respond during this stimulus presentation period.

4.5.3.3 Simon effect Two Simon scores were calculated as below.

RT Simon effect = mean(RTs for incongruent successful trials) - mean(RTs for congruent successful trials)

Accuracy Simon effect = mean(accuracy for incongruent trials) - mean(accuracy)

Intra-subject correction was applied to exclude premature or too slow responses. As for the other tasks, the MAD correction was applied.

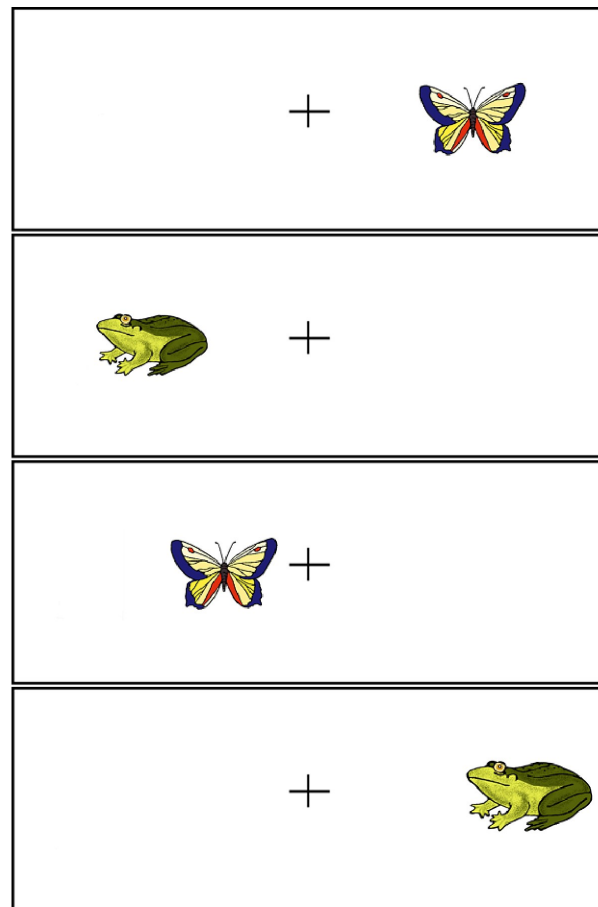


Figure 34: **Simon task's stimuli.** The top two trials are incongruent trials, the bottom stimulus trials are congruent trials. For the top two trials, the distance between the central cross and the stimulus is medium, for the 3rd trial the stimulus is close to the cross and for the last one, the stimulus is very far from the cross.

4.5.3.4 Descriptive results Behavioral data for the Simon task of the APEX project can be found in Table 3. Distribution plot is disposed in Figure 35.

4.5.4 Attention network task

4.5.4.1 ANT theory The Attention network task or test (ANT) assesses vigilance (alertness), spatial orientation and attentional control and can easily be performed by children, patients or monkeys (Fan et al., 2002).

The ANT combines a cued reaction time task (Posner, 1980) and a flanker task (Eriksen and Eriksen, 1974). In the classic ANT, rows of arrows are presented on the screen, pointing to the left or right. The target is an arrow pointing left or right in the center of the screen. It can be surrounded on either side by arrows pointing in the same direction (congruent condition), in the opposite direction (incongruent condition), or by lines without arrows (neutral condition). Participants must identify the direction of the target (middle arrow) by pressing the left mouse button when the middle arrow points to the left and right when it

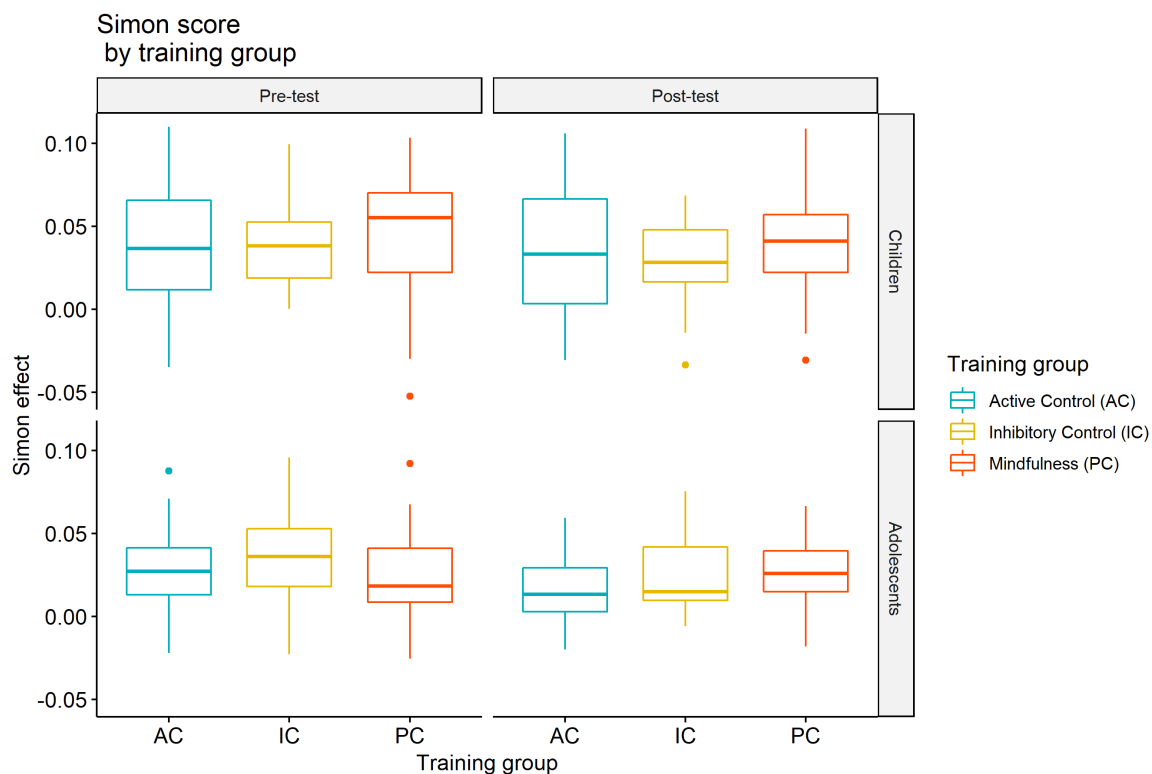


Figure 35: **Simon effect distribution before and after training.** The top panel corresponds to the children, the bottom one to the adolescents. The left panel corresponds to pre-training distribution, right panel to post-training. Training groups are represented in color (blue for Active Control, yellow for Inhibitory Control and red for Mindfulness).

points to the right.

This task was developed to assess the operation of the attention system across three kinds of attention processing: alerting, orienting, and executive control (Posner and Petersen, 1989).

The alerting condition of the ANT reflects the extent to which there is a benefit of temporal cueing to maintain cognitive vigilance. To assess orienting, a spatial cue is used before onset of the primary stimulus which reveals the efficiency with which subsequent targets can be located in space. Executive function is assessed by using peripheral or flanking arrows incongruent with a central target arrow that requires quick decision making, response coordination, and execution (Togo et al., 2015).

Studies in adults observed that these three networks are uncorrelated but that there are some interactions in which alerting and orienting can modulate the degree of interference from flankers (Fan et al., 2002). This executive control network is also under the influence of working memory as individual differences in WMC reflect variation in the ability to control attention (Redick and Engle, 2006).

Development of each of these networks is debated in the literature.

A first study used an adapted ANT in children from 6 to 9 years-old and showed that re-

action time and accuracy improved at each age interval (Rueda et al., 2004). More precisely, regarding each network, alertness showed evidence of change up to and beyond age 10, while conflict scores appeared stable after age seven and orienting scores did not change in the age range studied. Moreover, children, as adults, showed independence between these three networks (Rueda et al., 2004).

On the other hand, results from more recent studies (Pozuelos et al., 2014) revealed separate developmental trajectories for each attention network in children from 6 to 12 years old. Developmental changes in orienting were mostly observed on response accuracy between middle and late childhood, whereas executive attention showed increases in efficiency between 7 years and older ages, and further improvements in late childhood. Significant interactions between alerting and orienting, as well as between each of these and the executive attention network, were observed. Indeed, both alerting and orienting cues modulated the magnitude of the flanker interference effect.

Another developmental study in children from 6.5 to 12.5 years old found evidence for developmental changes to alerting and executive control but stable orienting (Mullane et al., 2016). More precisely, there was evidence for continued development of the alerting network in this cohort and it seemed that alerting had not yet achieved the adult form at 12.5 years-old. Regarding networks interaction, orienting interacts with alerting and with executive control in a manner similar to what has been observed in adults whereas interaction between alerting and executive control was at the opposite to the pattern that is common in adults.

Finally, another study in EEG on children from 4 to 13 years and on adults revealed protracted developmental curves for orienting and executive attention scores, while no differences were observed on the alerting score (Abundis-Gutiérrez et al., 2014). Both alerting and orienting interacted with conflict processing by the executive attention network but the Orienting and Executive networks interactions was only observed after about age 7.

4.5.4.2 Task design In APEX, the child version of the ANT from Rueda et al., 2004 was proposed with arrows being replaced by drawing of fishes to engage participants more easily. Participants received the instruction to feed the middle fish by pressing the mouse button corresponding to its swimming direction. This fish was surrounded by 2 other fishes on each side that could swim in the same direction or not.

Each trial began with a central fixation cross. The target array was a yellow colored line drawing of either a single yellow fish or a horizontal row of five yellow fish, presented above or below fixation, over a blue-green background. The participant was to respond based on whether the central fish was pointing to the left or right by pressing the corresponding left or right key on the mouse (see Figure 36). On congruent trials the flanking fish were pointing in the same direction, on incongruent trials the flankers point in the opposite direction from the central fish, and on neutral trials the central fish appeared alone (Fan et al., 2002). Each target was preceded by one of four warning cue conditions: a center cue, a double cue, a spatial cue, or no cue. In the center cue condition, an asterisk is presented at the location of the fixation cross. In the double cue condition, an asterisk appears at the locations of the target above and below the fixation cross. Spatial cues involve a single

asterisk presented in the position of the upcoming target

A session of the ANT consisted of a total of 8 practice trials and two experimental blocks of 48 trials in each. Each trial represented one of 12 conditions in equal proportions: three target types (congruent, incongruent and neutral) × four cues (no cue, central cue, double cue and spatial cue). Participants indicate their responses via a right or left button-press on a mouse. Accuracy and reaction time are recorded. Each trial began with a fixation period of a random variable duration of between 400 and 1600 ms. Subsequently, on some trials a warning cue was presented for 150 ms. A brief fixation period of 450 ms appeared after the disappearance of the cue, followed by either the simultaneous appearance of the target and flanker, or by the appearance of the target alone. This display remained on the screen until a response was detected, to a maximum of 1700 ms. After responding, the participant received auditory and visual feedback from the computer. For correct responses a simple animation sequence showed the target fish blowing bubbles and the participant was presented with a recording of child exclaiming “Woohoo!”. Incorrect responses were followed by a single tone and no animation of the fish

Participants were told that a hungry fish would appear on the screen and they were instructed to feed the fish by pressing the button on the mouse that matched the way the fish was pointing. They were first shown index cards of the single rightward and leftward fish stimuli (corresponding to the neutral condition) and were asked to demonstrate which button on the mouse would successfully feed the fish. They were then told that sometimes the hungry fish would be alone, the way they had just seen, and sometimes the fish would be swimming with some other fish as well. They were instructed that in this case they should pay attention to the fish in the middle and feed that fish using the mouse. The experimenters then showed the participants cue cards showing the stimuli in a congruent configuration and an incongruent configuration and asked them to demonstrate which button they should press to feed the fish in the middle. Finally, participants were instructed to maintain fixation on the cross in the center of the screen throughout the task and to respond as quickly and accurately as possible

4.5.4.3 Interference score Three scores can be extracted from the ANT, each corresponding to an attentional network (see above):

- *Alerting score = mean(RTs for No Cue successful trials) - mean(RTs for Double Cue successful trials)*
- *Orienting score = mean(RTs for Central Cue successful trials) - mean(RTs for Spatial Cue successful trials)*
- *Conflict score = mean(RTs for Incongruent successful trials) - mean(RTs for Congruent successful trials)*

In the APEX project, as the main interest is inhibitory control, only the conflict score was analyzed. Intra-subject correction was applied to exclude premature or too slow responses. As for the other tasks, the MAD correction was applied.

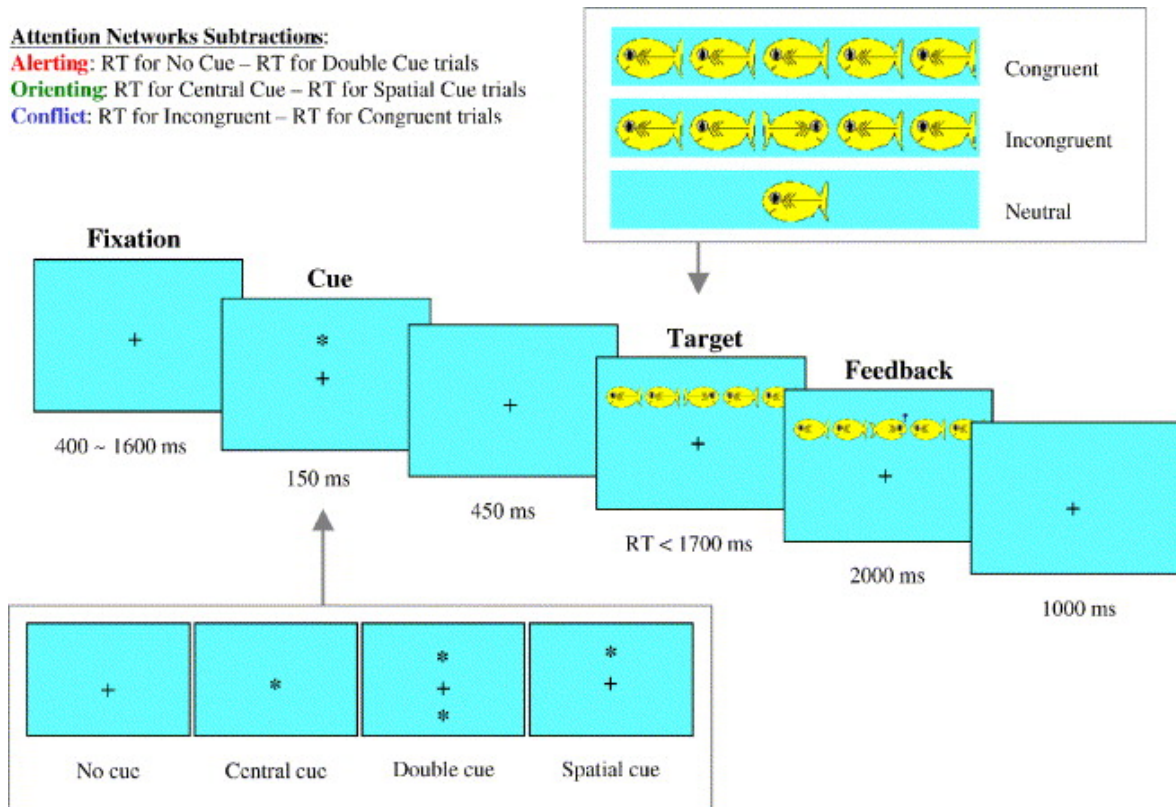


Figure 36: ANT design. The child version of the task is from Rueda et al., 2004.

4.5.4.4 Descriptive results Behavioral data for the ANT in the APEX project can be found in Table 3. Distribution plot is disposed in Figure 37.

4.5.5 Trail Making Test

4.5.5.1 Behind the task The Trail Making Test (TMT) is a neuropsychological instrument used as an indicator of cognitive processing speed and executive functioning (Reitan and Wolfson, 1992).

This timed test consists of two parts. In Part A, numbers from 1 to 25 are spread across the page and participants are asked to draw lines connecting the numbers in ascending order, starting with 1, without lifting the pencil from the page. Part B contains numbers from 1 to 12 and letters from A to L. The participant must then connect the symbols by alternating numbers and letters, i.e. 1-A-2-B-3-C... 12-L. The direct score is the time in seconds required to complete each A and B part. Other derived scores can also be computed: the difference score (B-A), the ratio score (B : A) and the logarithmic transformation of B : A (Log B : A), which aims at reducing the potential impact of scatter in the scores.

In particular, this task requires inhibitory (ignoring irrelevant symbols) and flexibility (switching between symbols by switching from numbers to letters, depending on the current rule) abilities. In addition, the presence of conflict creates conditions in which the demands of the executive are greater (Part B) or lesser (Part A).

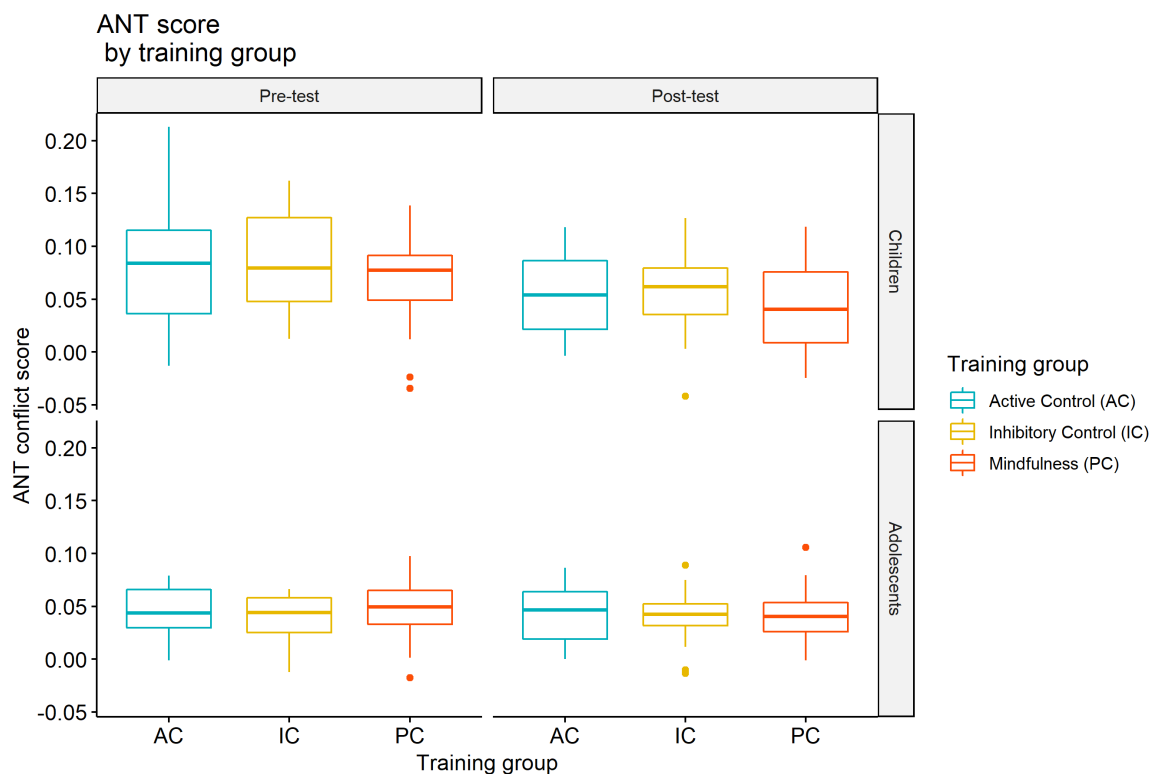


Figure 37: **ANT conflict scores distribution before and after training.** The top panel corresponds to the children, the bottom one to the adolescents. The left panel corresponds to pre-training distribution, right panel to post-training. Training groups are represented in color (blue for Active Control, yellow for Inhibitory Control and red for Mindfulness).

4.5.5.2 Task design The TMT of APEX was one of the few paper and pencil tasks. It was adapted for children and adolescents in number of stimuli to connect.

Instead of 25 numbers in Part A, only 15 numbers were present on the page. Similarly, Part B contained numbers from 1 to 8 and letters from A to G (see Figure 38).

Before each Part, a training was proposed to be certain that the participant understood the instruction. The training of Part A contained numbers from 1 to 8. This training was not just a sample from the experimental part as the numbers were not disposed at the same emplacements in both parts. The training of Part B contained numbers from 1 to 4 and letters from A to D. In the same way, stimuli were not disposed at the same place on the training sheet and on the experimental sheet.

The participants were timed during the experimental part only and, if they made a mistake (connected the wrong stimuli or omitted one stimulus), the time didn't stop before they corrected their mistake.

4.5.5.3 Flexibility score The TMT score, of flexibility score, was calculated based on the difference score.

$$\text{Flexibility score} = \text{Time to complete Part B} - \text{Time to complete Part A}$$

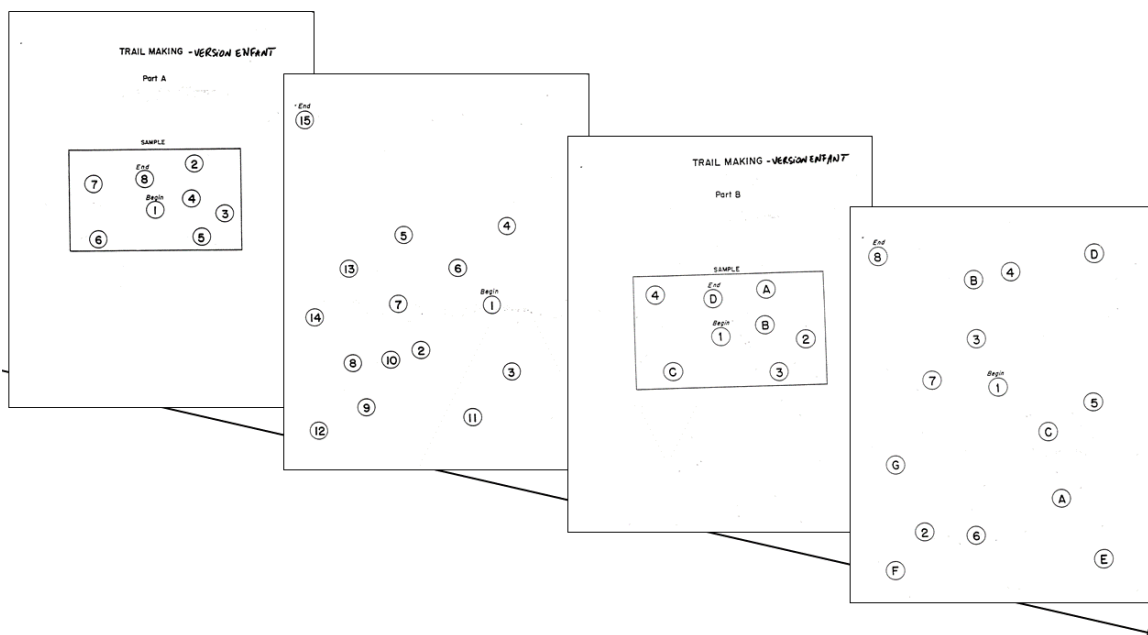


Figure 38: **Trail Making Test design.** This version of TMT is adapted for children.

No intra-subject correction was applied as they were only two trials, part A and part B.

4.5.5.4 Descriptive results Behavioral data for the Trail Making Test of the APEX project can be found in Table 3. Distribution plot is disposed in Figure 39.

4.5.6 N-back

4.5.6.1 Behind the task The N-back task (e.g., Cohen et al., 1997; Gevins and Cutillo, 1993) is a continuous performance measure in working memory. It is a popular paradigm for studying working memory in neuroimaging research. The subject must press the left mouse button when the square on the screen is at the same position as the square that appeared n trials before, and otherwise click the right button. The more n increases, the greater the cognitive load and the more the working memory is solicited. Thus, in its higher cognitive load conditions (at 2-back and 3-back), this task reinforces the demands on working memory.

4.5.6.2 Task design The N-back was divided in three levels.

At each level, a black square was presented on a grey font screen. Participants were instructed to press the left mouse button when the square on the screen is at the same position as the square that appeared n trials before, and otherwise click the right button.

The participants first received a general instruction about the task and then, before each level, they received a more precise instruction. Therefore, when the task started with the

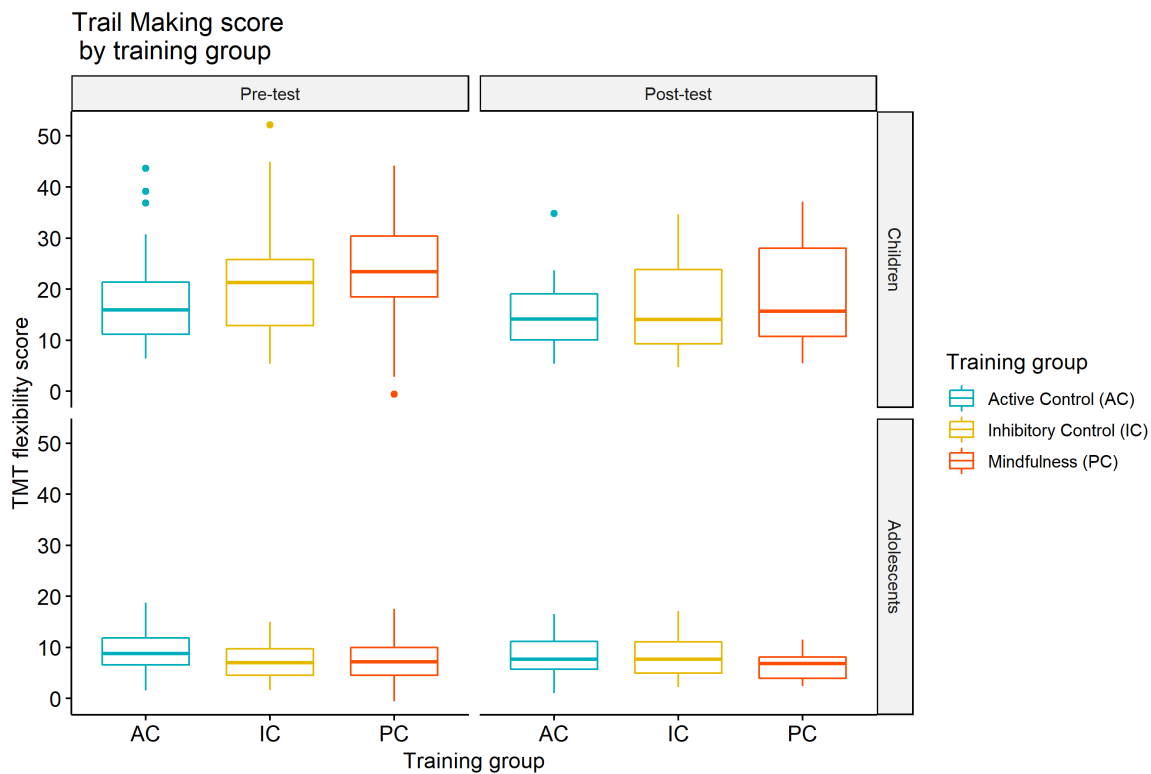


Figure 39: **Trail Making scores distribution before and after training.** The top panel corresponds to the children, the bottom one to the adolescents. The left panel corresponds to pre-training distribution, right panel to post-training. Training groups are represented in color (blue for Active Control, yellow for Inhibitory Control and red for Mindfulness).

first level where $n = 1$, they were asked to press the left mouse button when the square on the screen is at the same position as the square that appeared one trial before, and otherwise click the right button (see Figure 40).

For this first level, right after the instruction, participants had a practice block to be sure the instruction was properly understood. This practice block contained 5 trials. After this practice block, an experimental block of 21 trials started.

At the end of the first level, the task continued to the level $n = 2$. As before, participants were showed the personalized instruction and then they could practice this time for 6 trials. After this practice block, the experimental block of 22 trials started.

The task ended with the level $n = 3$. As before, participants were showed the personalized instruction and then they could practice for this level for 5 trials. After this practice block, the experimental block of 23 trials started.

For the n first trials, as there were no stimulus to compare the position before, participants were instructed to answer false so to click on the right button. Therefore, all experimental blocks contained really 20 experimental trials with a stimulus to compare the target to.

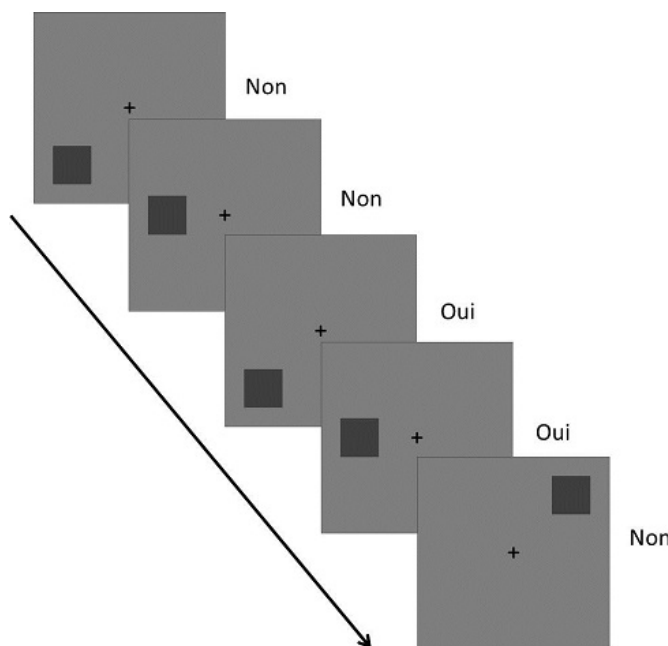


Figure 40: **N-back design for $n = 2$** . This figure was presented to the participants during the instruction to be sure they had understand the task correctly.

4.5.6.3 Updating score Three Updating score were calculated based on RT for successful trials:

$Nback31 = \text{mean}(\text{RTs for successful trials at level 3}) - \text{mean}(\text{RTs for successful trials at level 1})$

$Nback21 = \text{mean}(\text{RTs for successful trials at level 2}) - \text{mean}(\text{RTs for successful trials at level 1})$

$Nback32 = \text{mean}(\text{RTs for successful trials at level 3}) - \text{mean}(\text{RTs for successful trials at level 2})$

Intra-subject corrections were applied to exclude premature or too slow responses. As for the previous tasks, the SD and the MAD corrections were applied. We thus obtained nine scores: a score without any intra-subject correction, a score with a SD correction and a score with a MAD correction, each per difference of levels. For the rest of the analysis, we focused on the Nback21 with a MAD correction.

4.5.6.4 Descriptive results Behavioral data for the N-back task in the APEX project can be found in Table 3. Distribution plot is disposed in Figure 41.

4.5.7 Univariate statistical analyses

Note: For inferential analyses and in the rest of the manuscript, we will focus on the AC and IC training groups.

Training-related changes in task efficiency were evaluated with classical univariate statistical analyses (Analyses Of Variances, ANOVAs). ANOVAs were conducted separately

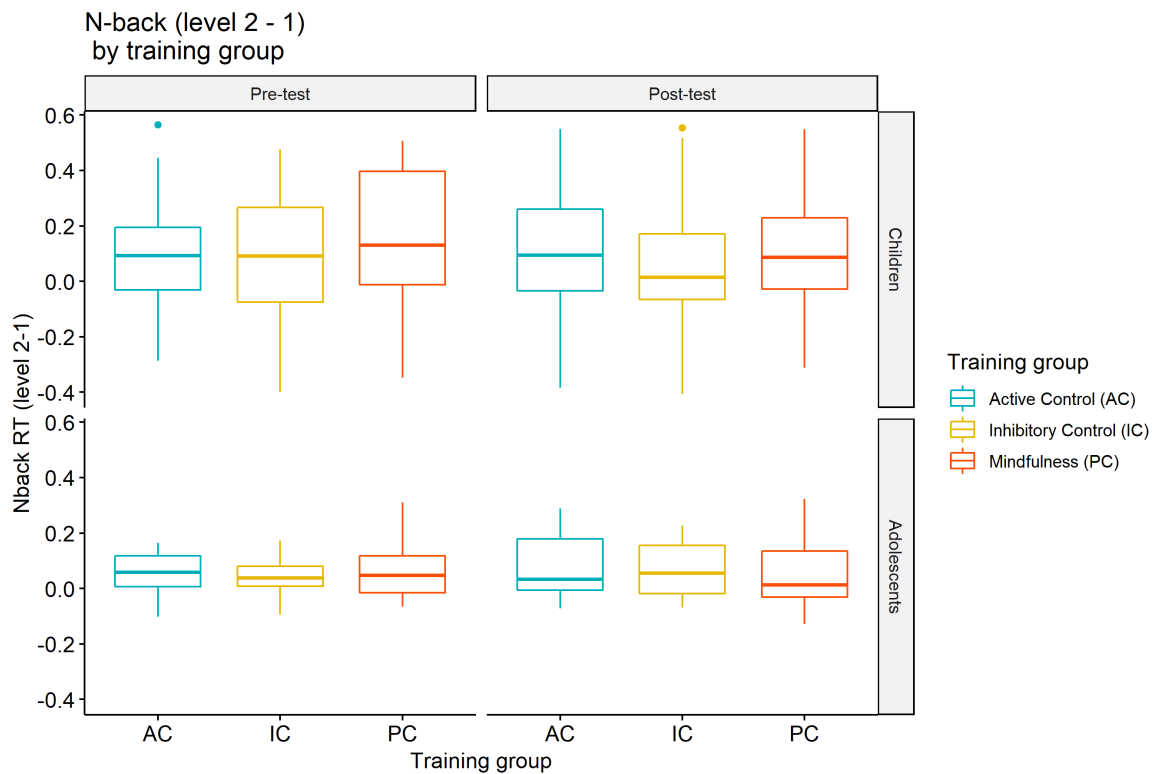


Figure 41: **N-back (level 2-1) distribution before and after training.** The top panel corresponds to the children, the bottom one to the adolescents. The left panel corresponds to pre-training distribution, right panel to post-training. Training groups are represented in color (blue for Active Control, yellow for Inhibitory Control and red for Mindfulness).

for each of the six EF tasks for the two age groups and the two training groups (AC and IC). In order to assess possible group-specific effects, complementary ANOVAs were run for each task, including age group (children vs adolescents) and training group (IC vs AC) in the models. The repeated-measures ANOVAs were estimated using mixed-effects linear models. We used the package *lme4* (Bates et al., 2012). with the Time (pre- or post-training) as fixed effects and intercepts for subjects as random effects. P-values were obtained by using likelihood ratio tests of the full model, including the tested effect against the model without the tested effect.

	Children				Adolescents			
	Pre IC-training	Pre AC-training	Post IC-training	Post AC-training	Pre IC-training	Pre AC-training	Post IC-training	Post AC-training
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
SST	0.26 ± 0.08	0.25 ± 0.08	0.21 ± 0.06*	0.23 ± 0.08	0.16 ± 0.03	0.16 ± 0.03	0.15 ± 0.04	0.16 ± 0.03
Stroop	0.11 ± 0.16	0.13 ± 0.15	0.06 ± 0.10*	0.08 ± 0.16	0.07 ± 0.09	0.09 ± 0.08	0.04 ± 0.05	0.06 ± 0.07*
Simon	0.04 ± 0.03	0.04 ± 0.03	0.03 ± 0.03	0.03 ± 0.04	0.08 ± 0.05	0.08 ± 0.06	0.02 ± 0.02 ^o	0.02 ± 0.02
ANT	0.04 ± 0.03	0.03 ± 0.03	0.06 ± 0.04**	0.05 ± 0.04**	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.02	0.04 ± 0.03
TMT	22.14 ± 12.01	18.18 ± 10.04	16.40 ± 9.07 ^o	15.03 ± 6.66	6.87 ± 3.63	9.62 ± 4.73	7.83 ± 4.33	8.71 ± 4.15
N-back	0.09 ± 0.23	0.10 ± 0.20	0.06 ± 0.23	0.12 ± 0.24	0.04 ± 0.07	0.06 ± 0.08	0.07 ± 0.11	0.09 ± 0.11

Table 3: **Efficiency of EFs in children and adolescents before and after an active control (AC) or an inhibitory control (IC) training.** For all tasks, scores were derived from RTs (in s). Training-related changes in task efficiency were evaluated with repeated measures ANOVAs. Significance levels: ^o < .10; * < .05; ** < .01; *** < .001. SST = stop signal task; TMT = trail making test.

Complementary analyses, including age and training groups as factors in order to investigate possible age- and training-specific effects, only revealed significant main effects of the age group for SST ($p = 1.3 \times 10^{-5}$), for TMT ($p = 0.01$) and for Simon ($p = 0.04$) but no interactions effect involving the age nor the training group (all $ps > 0.27$; see details of the analyses in Table S1). Post-hoc analyses, with Tukey correction for multiple testing, revealed significant pre-post changes in children in IC group for SST ($p = 0.009$) and TMT ($p = 0.03$).

	Main effects			Interaction effects			
	Time	Training	Age	Time*Training	Time*Age	Age*Training	Time*Training*Age
	χ^2, p	χ^2, p	χ^2, p	χ^2, p	χ^2, p	χ^2, p	χ^2, p
SST	0.01, 0.91	0.06, 0.81	18.96, 1.34e-05	0.07, 0.79	0.38, 0.54	0.72, 0.40	1.05, 0.31
Stroop	1.24, 0.27	0.08, 0.78	0.60, 0.44	0.08, 0.77	0.07, 0.80	0.05, 0.82	0.10, 0.75
Simon	1.88, 0.17	0.40, 0.53	4.16, 0.04	0.00, 0.98	0.23, 0.63	0.76, 0.38	0.04, 0.84
ANT	0.14, 0.71	0.00, 0.98	1.74, 0.19	0.41, 0.52	2.52, 0.11	0.04, 0.83	0.24, 0.62
TMT	0.16, 0.69	0.19, 0.66	7.78, 0.01	0.31, 0.58	1.07, 0.30	0.70, 0.40	1.05, 0.31
N-back	0.19, 0.66	0.08, 0.78	0.63, 0.43	0.00, 0.96	0.15, 0.70	0.54, 0.46	0.88, 0.35

Table 4: **Main and interaction effects of a repeated measures ANOVAs** with Time (pre- vs post-training), Training (IC vs AC) and Age (children vs adolescents) as fixed effects and with intercepts for subjects as random effects.

Of note, Welch Two Sample t-tests revealed no significant differences between the two training groups at pretest except for TMT in adolescents ($t(39.39) = -2.16, p < .05$) where adolescents affected to the IC training showed lower score (6.87 ± 3.63) than those who were affected to the AC training (9.62 ± 4.73). All other $ps > .17$. See details of raw pretraining and posttraining scores for the three EF tasks in Table 1 and in the radar-plots representing the relative changes after the two types of training in Figures 48 & 49.

To conduct these analysis, only participants who followed at least 15 IC or AC training sessions were included. Thereafter, for all analyses focusing on training effects (and thus post-test scores), only subjects who completed at least 15 training sessions will be included. This reduced sample was composed of 57 children (24 males, $M \pm SD = 9.79 \pm 0.55$ years, range = 9–10 years) and 46 adolescents (13 males, $M \pm SD = 16.56 \pm 0.50$ years, range = 15–17 years). For other studies concerned only with pre-training executive abilities (e.g., Study 4), all subjects who completed the pre-test will be included.

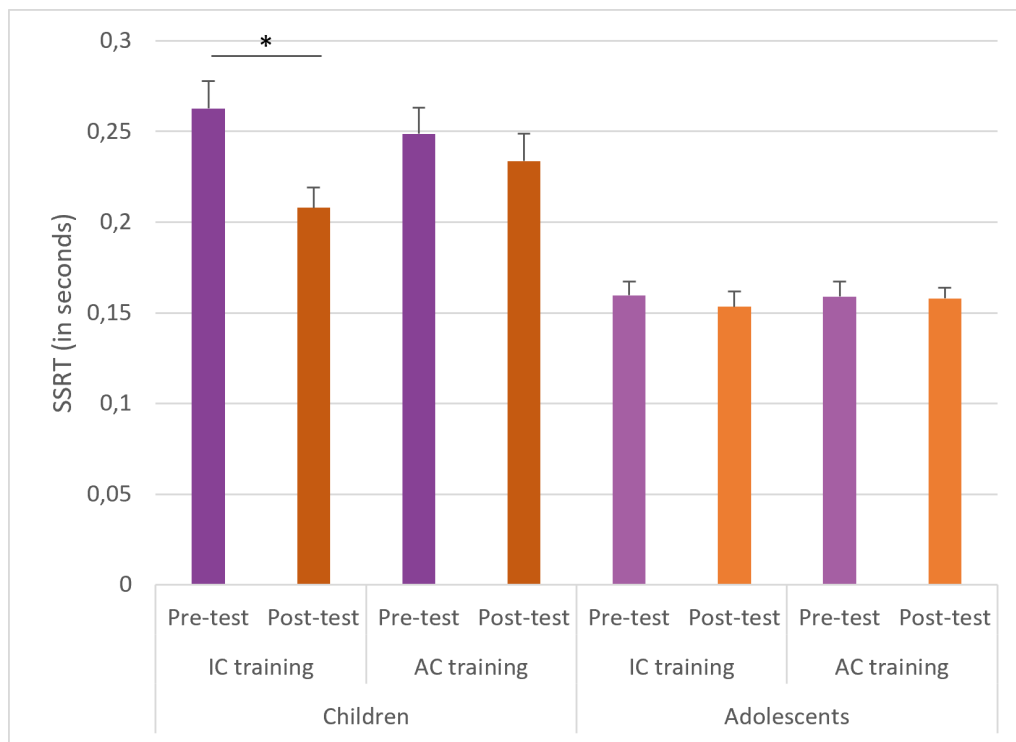


Figure 42: **Stop signal scores before and after IC- and AC-training, in children and adolescents.** Significance levels: $\circ < .10$; * $< .05$; ** $< .01$; *** $< .001$.

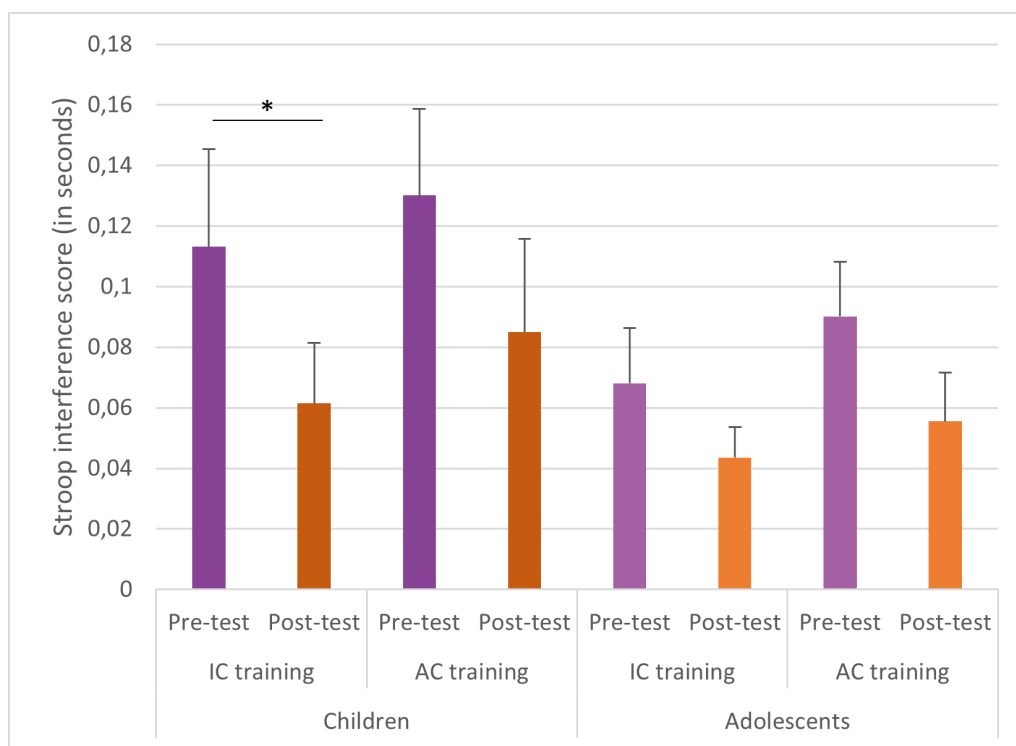


Figure 43: **Color-word Stroop scores before and after IC- and AC-training, in children and adolescents.** Significance levels: $\circ < .10$; * $< .05$; ** $< .01$; *** $< .001$.

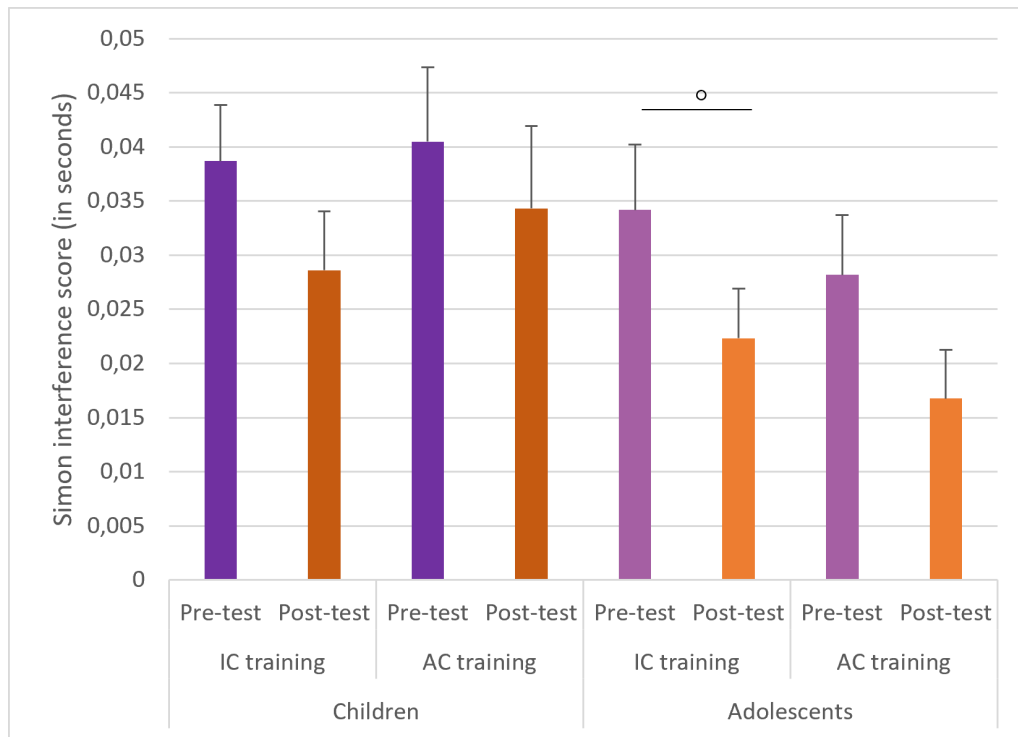


Figure 44: **Simon scores before and after IC- and AC-training, in children and adolescents.** Significance levels: $\circ < .10$; * $< .05$; ** $< .01$; *** $< .001$.

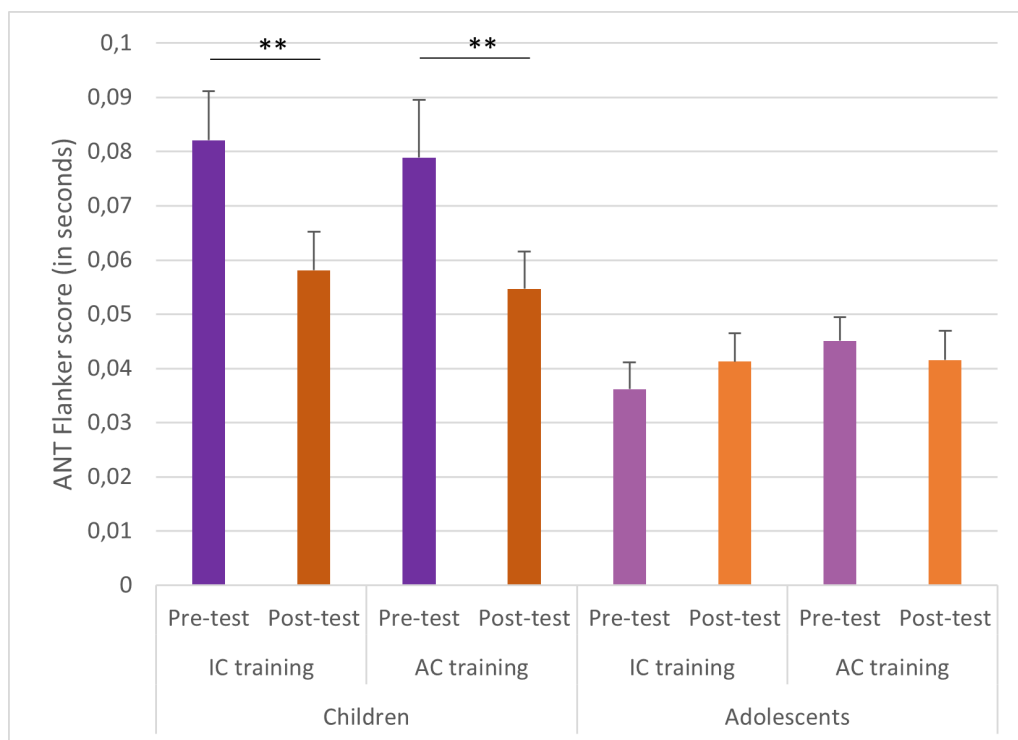


Figure 45: **ANT scores before and after IC- and AC-training, in children and adolescents.** Significance levels: $\circ < .10$; * $< .05$; ** $< .01$; *** $< .001$.

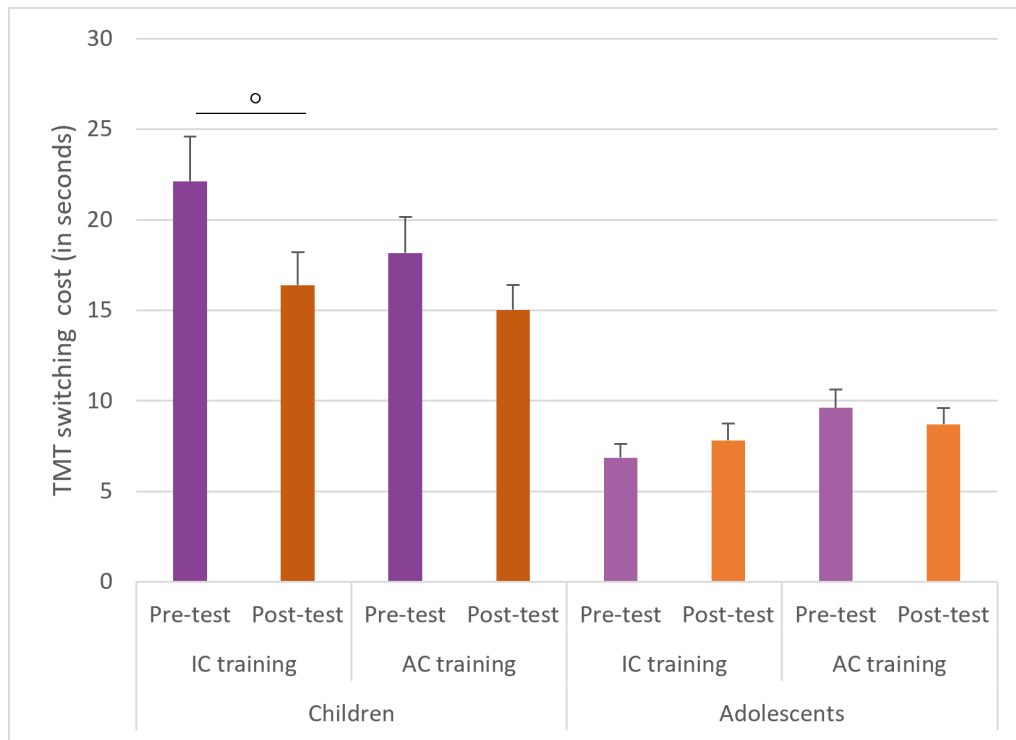


Figure 46:]

TMT scores before and after IC- and AC-training, in children and adolescents.

Significance levels: o < .10; * < .05; ** < .01; *** < .001.

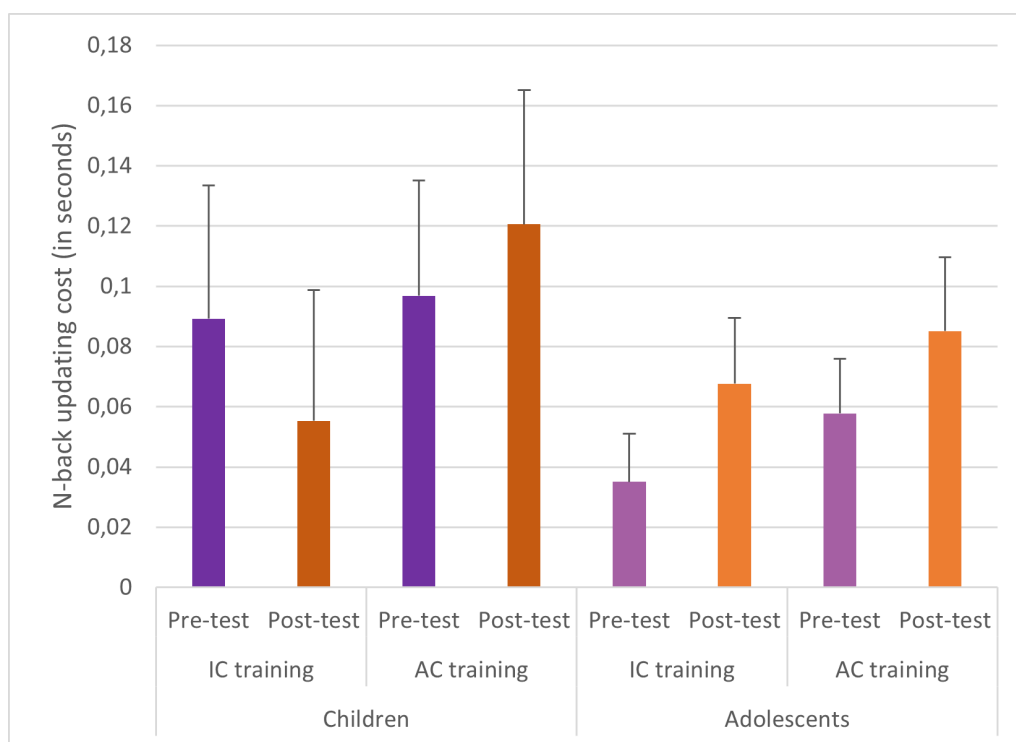


Figure 47: N-back scores before and after IC- and AC-training, in children and adolescents. Significance levels: o < .10; * < .05; ** < .01; *** < .001.

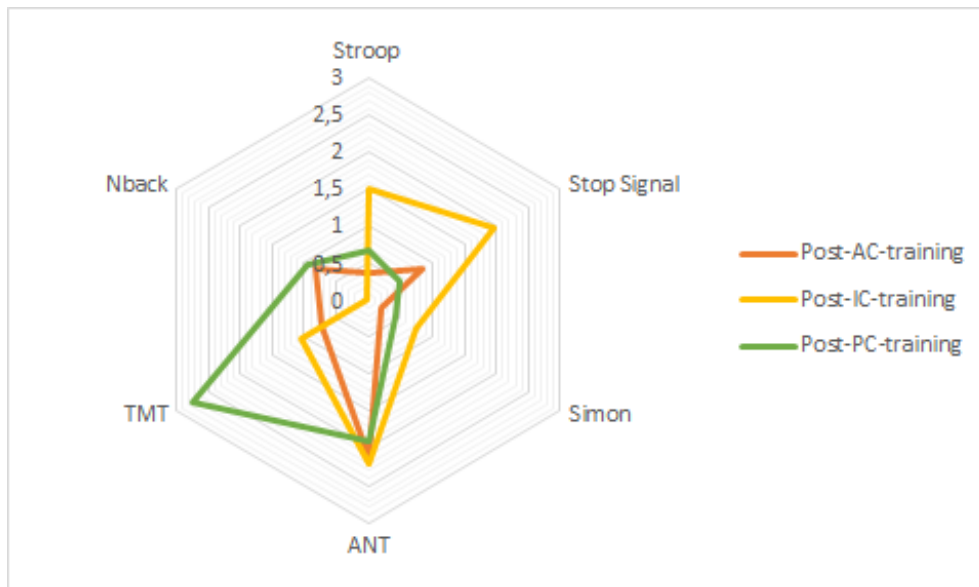


Figure 48: **Relative changes in EF tasks after cognitive training in children.** The radar graphs represent relative changes after Active Control (AC, in orange), Inhibitory Control (IC, in yellow) and Mindfulness (in green) trainings. Values corresponds to $-\log(p)$ with p being the main effect of training in the repeated ANOVA presented in Table 3.

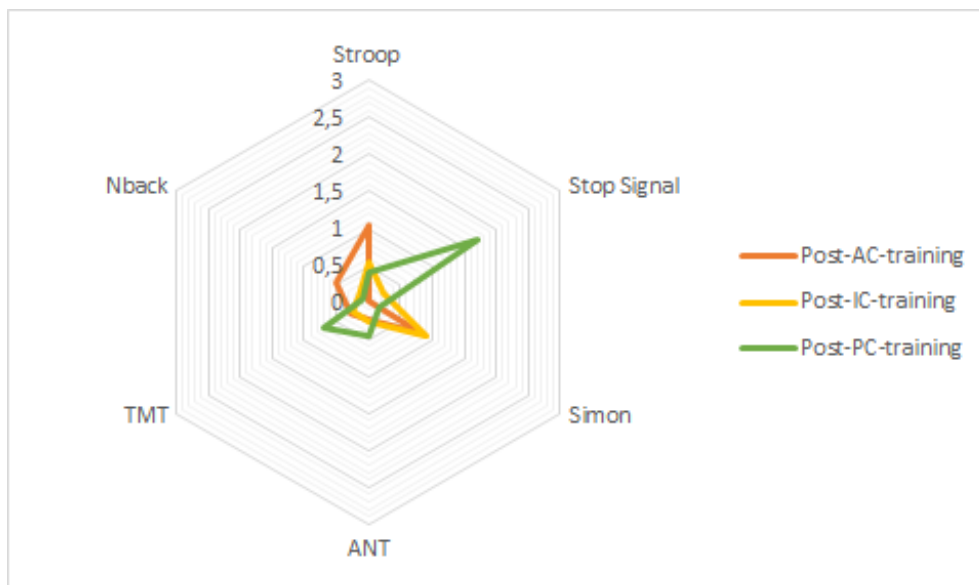


Figure 49: **Relative changes in EF tasks after cognitive training in adolescents.** The radar graphs represent relative changes after Active Control (AC, in orange), Inhibitory Control (IC, in yellow) and Mindfulness (in green) trainings. Values corresponds to $-\log(p)$ with p being the main effect of training in the repeated ANOVA presented in Table 3.

STUDY 1: NETWORK ANALYSIS OF EF CHANGES WITH AGE AND TRAINING

This study led to a manuscript: **Menu, I., Rezende, G., Le Stanc, L., Borst, G.* & Cachia, A.*** (accepted). A network analysis of executive functions before and after computerized cognitive training in children and adolescents. *Scientific reports*.

In this first study, we investigated the impact of an inhibitory control training and development on the organization of EFs, with the hypothesis that training could accelerate development, using network models.

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1 Introduction

As we have seen in the section 1.4.2 of the General Introduction, studies have investigated the structure of EFs to determine the extent to which (a) they reflect distinct or common abilities and (b) these abilities become more specific with age. Using structural equation modeling (SEM), Miyake et al., 2000 proposed a hierarchical structure of EFs, with three latent factors representing each EF domain. In adults, these latent factors are separable (EF diversity), although they share a significant proportion of variances (EF unity, or common-EF ability) (Friedman et al., 2011). The EF organization evolves from a one-factor structure in early childhood with no clear separation among EF tasks (Shing et al., 2010; Wiebe et al., 2008; Willoughby et al., 2012; Xu et al., 2013) to a two- to four-factor structure in adolescence (Agostino et al., 2010; Friedman et al., 2016; Lee et al., 2013; McAuley and White, 2011; Wu et al., 2011; Xu et al., 2013). Of note, some studies also reported an organization with more than one factor in young children (Wu et al., 2011) and fewer than three factors in older children (Huizinga et al., 2006). A recent meta-analysis (Karr et al., 2018) tested seven models of EF structure and found some evidence for greater unidimensionality of EFs among child/adolescent samples and both unity and diversity among adult samples. The developmental organization of EFs (Lee et al., 2013) is also supported by a brain imaging study reporting an increasing segregation of structural brain network modules with age, and this segregation mediates the effects of age on EFs (Baum et al., 2017). In addition, a recent behavioral study on children from 7 to 15 years (Hartung et al., 2020) found that age mostly impacts the common-EF loadings of IC and CF. Hence, while in childhood, WMU, CF and IC likely rely on similar underlying cognitive processes, in adolescence, EFs become more specialized and independent.

Because EFs are implicated in learning, academic achievement, psychiatric health, and everyday functioning (see section 1.3 of the General Introduction; Best et al., 2011; Diamond, 2013), several intervention programs have tested the possibility of stimulating various aspects of EFs, including IC (see section 6.2 of the General Introduction; Diamond, 2013; Hu et al., 2017; Jaeggi et al., 2011; Liu et al., 2015; Xu et al., 2020; Zhao et al., 2015). But, to date no EF training studies have assessed the extent to which EF training changes the structure of EFs.

Another way to understand EF organization and how it changes with age is to use network modeling (NM), a graph theory based-approach allowing us to describe the structure of complex systems (Newman, 2018). The underlying principle of NM is that systems can be represented as nodes that are interconnected with edges (the thicker the edges are, the stronger the interconnection). The complete graph (nodes and edges) summarizes the pattern of relations among the elements (Barabási, 2012). While in SEM, shared variance of observed variables (e.g., scores on cognitive tasks) is assumed to reflect a latent construct (e.g., IC or WMU), in NM, shared variance is assumed to reflect a causal network (van Bork et al., 2019).

NM applied to EFs allows us to identify which nodes (here, a specific EF task) play a pivotal role within the whole network (here, different EF tasks). In addition, NM has the potential to test theoretical models on how EF structures transform with age and more specifically which components can become more central to general executive processing

and, therefore, have a greater influence on other EF processes with age. Using NM on a twin cohort aged 7 to 15 years of age, Hartung et al., 2020 found that the interconnections between EF tasks remained stable with age except for the inhibition tasks, whose shared variance with the other tasks was reduced with age. These findings provided convergent evidence that IC is particularly important for allowing young children to employ other EFs in pursuit of goals but plays a smaller role in regulating other EFs later in development (Best et al., 2011; Huizinga et al., 2006; Isquith et al., 2004). NM can also provide interesting insights into the effects of training on the structure of cognitive functions. To date, only one study has used NM to treat such effects in young adults (Roca et al., 2019). The study showed that the interconnections between 25 variables related to mindfulness, compassion, psychological well-being, psychological distress and emotional-cognitive control changed after a mindfulness-based stress reduction (MBSR) program.

In the present study, we investigated how the structure of EFs was affected by training IC in children and in adolescents using NM. By using such an approach, we aimed to determine whether training speeds up the development of EFs or qualitatively changes the development of EFs by deviating from the developmental trajectory typically observed from childhood to adolescence (Jolles and Crone, 2012). We reasoned that if training IC speeds up the development of IC, then training-related changes should mimic developmental-related changes, namely, the structure of EFs in children after IC training but not after control training should be more similar to the structure of EFs in adolescents than before training. On the other hand, if training IC changes the developmental trajectories of IC, then the structure of EFs in children after IC training should differ from that before training (but not after control training) and from the structure of EFs in adolescents. This study, which is preliminary given the sample size, will allow testing these hypotheses before replication on an independent sample.

2 Material and Methods

2.1 Participants

Of the APEX cohort, 124 participants of the IC and AC training groups, 67 children (29 males, $M \pm SD = 9.8 \pm 0.54$ years, range = 9–10 years) and 57 adolescents (20 males, $M = 16.7 \pm 0.56$ years, range = 15–17 years) were included for the pre-test network analysis. Of these, 103 participants completed a minimum of 15 training sessions and were included for the post-test network analyses (pre-hoc inclusion criteria): 57 children (24 males, $M \pm SD = 9.79 \pm 0.55$ years, range = 9–10 years) and 46 adolescents (13 males, $M \pm SD = 16.56 \pm 0.50$ years, range = 15–17 years).

2.2 Evaluation of EFs

As we have seen in the General Method section, participants performed a cognitive battery measuring different facets of EFs in the pre- and post-training sessions. Six tasks were administered to measure the three EFs: cognitive flexibility (in this study referred to as

switching), working memory updating (in this study referred to as updating), and IC. The task used to identify the switching factor was the trail making test (TMT) (Reitan and Wolfson, 1992) and for the updating factor, the N-back task (Kirchner, 1958) was used. Four tasks were used to identify the IC factor: the Color-Word Stroop (Stroop, 1935), the Stop-Signal task (Logan, 1994), the Simon task (Simon and WOLF, 1963) and the ANT (Attention Network Task) (Fan et al., 2002); each of these tasks taps on different aspects of IC: Stroop on interference control, stop signal and Simon on response inhibition and ANT on attentional inhibition (Diamond, 2013; Tiego et al., 2018). To limit potential differences in familiarity with the Stroop and Stop-Signal tasks used in the pre- and post-training sessions between participants of the IC and AC groups, we introduced a number of differences between these tasks and those used in the IC training sessions: (a) we used no control trials, and we did not vary the difficulty of the task in the Color-Word Stroop task; (b) the Stop-Signal delay was adapted on a trial-by-trial basis and not on a block-of-trial basis in the SST.

For each task, scores were screened and cleaned for possible aberrant values using a nonparametric approach: outliers were defined as values lower than median -2.5 MAD or greater than median $+2.5$ MAD (MAD: median absolute deviation) and considered missing values in the analyses.

2.3 Construction and analysis of cognitive networks

NM were completed with classical univariate statistical analyses (Analyses Of Variances, ANOVAs) as seen in section 4.5.7 of the General Method. Like for NM, ANOVAs were conducted separately for each of the six EF tasks for the two age groups and the two training groups. In order to assess possible group-specific effects, complementary ANOVAs were run for each task, including age group (children vs adolescents) and training group (IC vs AC) in the models.

The repeated-measures ANOVAs were estimated using mixed-effects linear models. We used the package *lme4* (Bates et al., 2012) with the Time (pre- or post-training) as fixed effects and intercepts for subjects as random effects. P-values were obtained by using likelihood ratio tests of the full model, including the tested effect against the model without the tested effect.

Then, separate networks, based on the correlation matrix of the EF task scores, were built for children and adolescents before training (pretest) and after training (inhibitory control training: posttest IC; active control training: posttest AC). Six networks (3 per age range) were estimated. These networks included 6 nodes corresponding to the scores of the 6 cognitive tasks, which we grouped into three EFs:

- **Inhibitory control:** Color-Word Stroop, stop signal, Simon, and ANT scores (for stop signal, we calculated the stop signal reaction time - SSRT as recommended (Verbruggen et al., 2019), and, for the other tasks, we calculated the difference in reaction time (RT) between incongruent and congruent trials)
- **Switching:** TMT flexibility score (RT difference between TMT-B and TMT-A)

- **Updating:** N-back score (RT difference between the 2-back and the 1-back trials)

The inclusion of trained (Stroop and Stop-Signal) and untrained (Simon and ANT) IC tasks allowed us to observe the direct effects of IC targeted training on the trained tasks but also on other IC tasks (intra-EF) and thus, to assess near transfer effects within the same EF. The inclusion of TMT and N-back allowed us to assess the effects of IC training on other EF tasks (inter-EFs) and thus to evaluate the effects of a more distant transfer while keeping the number of nodes limited to 6 (Mansueto et al., 2020).

In addition to the 6-node networks, balanced 3-node networks, with only one node per EF (stop signal for IC, TMT for switching and N-back for updating), were built. Such balanced networks overcome the issues for the interpretation of the 6-node network related to the partial network models that remove shared variance associated with all other EFs tests in the model (i.e., the relationship between each IC task with switching and updating involved controlling for other tests IC inhibition).

NM was used to analyze 1) the multiple relations (edges) between the different EF tasks (nodes) simultaneously and 2) how these relations change during development (children vs adolescents) and after cognitive training (before vs after training). We used the successive steps procedure proposed for network analysis in psychology (Fried et al., 2018): 1) network estimation; 2) network inference (topological characterization); and 3) node community analysis. The interrelation between the different variables was modeled with a Gaussian graphical model (GGM; Lauritzen and Wermuth, 1989), a regularized partial correlation network (RPCN). The edge between two nodes/tasks corresponded to the partial correlation between the two corresponding variables, controlling for the effects of the remaining variables. We used Spearman correlations, as recommended (Epskamp et al., 2018).

Statistical analyses were performed using R-statistical software, version 3.6.1 (R Development Core Team, 2014). The networks were constructed and visualized using the package *qgraph* version 1.6.4 (Epskamp et al., 2012). As previously recommended (Borsboom et al., 2018), we investigated the robustness and replicability of the analyses (accuracy check) using the *bootnet* package version 1.4 (Epskamp et al., 2018). Figures of edge-weight accuracy can be found in the Appendix A2.

2.4 Characterization of the networks

The networks were characterized using both quantitative and qualitative measures. Five classical centrality measures were used to quantitatively characterize the network at node levels (Opsahl et al., 2010): strength (the sum of the weights of the direct relations of a node to all other nodes), closeness centrality (the inverse of the total length of all the shortest paths between the selected node and all other nodes in the network), betweenness centrality (the shortest path length connecting any two variables), expected influence (the sum of both positive and negative weights between a node and all the other nodes in the network), and degree (number of connections for each node in the network), thus defining hubs (nodes with the highest degree). The community analysis was based on the Spinglass algorithm

(Reichardt and Bornholdt, 2006) with standard parameters ($\gamma = 1$, start temperature = 1, stop temperature = 0.01, cooling factor = 0.99, spins = 25). The correlation between edge weights across networks was also estimated.

3 Results

3.1 Developmental analysis: children vs adolescents at baseline (before training)

We first studied the EF structure in children and adolescents from the analysis of the EF networks at pretest before training (see Figure 1.1 and Figure 1.2). Visual inspections indicated that networks in adolescents present more and stronger connections than in children.

This visual inspection was followed by a quantitative analysis of the network topology using classical graph indices (see Figure 1.1 and Figure 1.2). The different indices were similar in children and adolescents. Three common centrality measures were used to quantitatively characterize the network at node levels (Opsahl et al., 2010): strength (a measure of how strongly a node is directly connected with the network), betweenness centrality (a measure of how a node is central in connecting other variables) and closeness centrality (a measure of how strongly a node is connected indirectly with the network). Higher closeness centrality indicates that a node (task) is more related, even indirectly, to other nodes (tasks). Higher strength indicates that a node (task) is more strongly connected to other nodes (tasks). Because these indices are calculated based on the absolute values of edge-weights and may therefore miss information on the network structure if negative relationships between nodes are present (Robinaugh et al., 2016), two other centrality measures were also used: expected influence (EI), which is the sum of both positive and negative weights between a node and all the other nodes in the network, and degree, which is the number of connections for each node in the network, thus defining hubs (nodes with highest degree). In both children and adolescents, the variables with the highest betweenness were also the variables with the highest strength, closeness and EI. However, such central variables varied with age: in children, the most central nodes included the Stroop, stop signal and TMT while in adolescents, they included the ANT and TMT. In children, a high number of relations (i.e., high degree) was generally accompanied by low weights (i.e., low EI and strength).

In adolescents, analysis of hubs revealed homogeneous results, with similar weights over the four indices. Overall, these indices were slightly lower in children than in adolescents, reflecting a less connected network in 9-10-year-old children than in 16-17-year-old children.

We then analyzed the communities. A community corresponds to a set of nodes that cluster more strongly among each other than with other nodes in the network; such communities reflect high mutual influences among nodes in a given cluster. The community analysis detected two clusters in each age group's network (Figures 1.1 and 1.2, left panel). In children, the two clusters were as follows: 1) Cluster A (in orange), which included 3

Study 1: Network analysis of EF changes with age and training

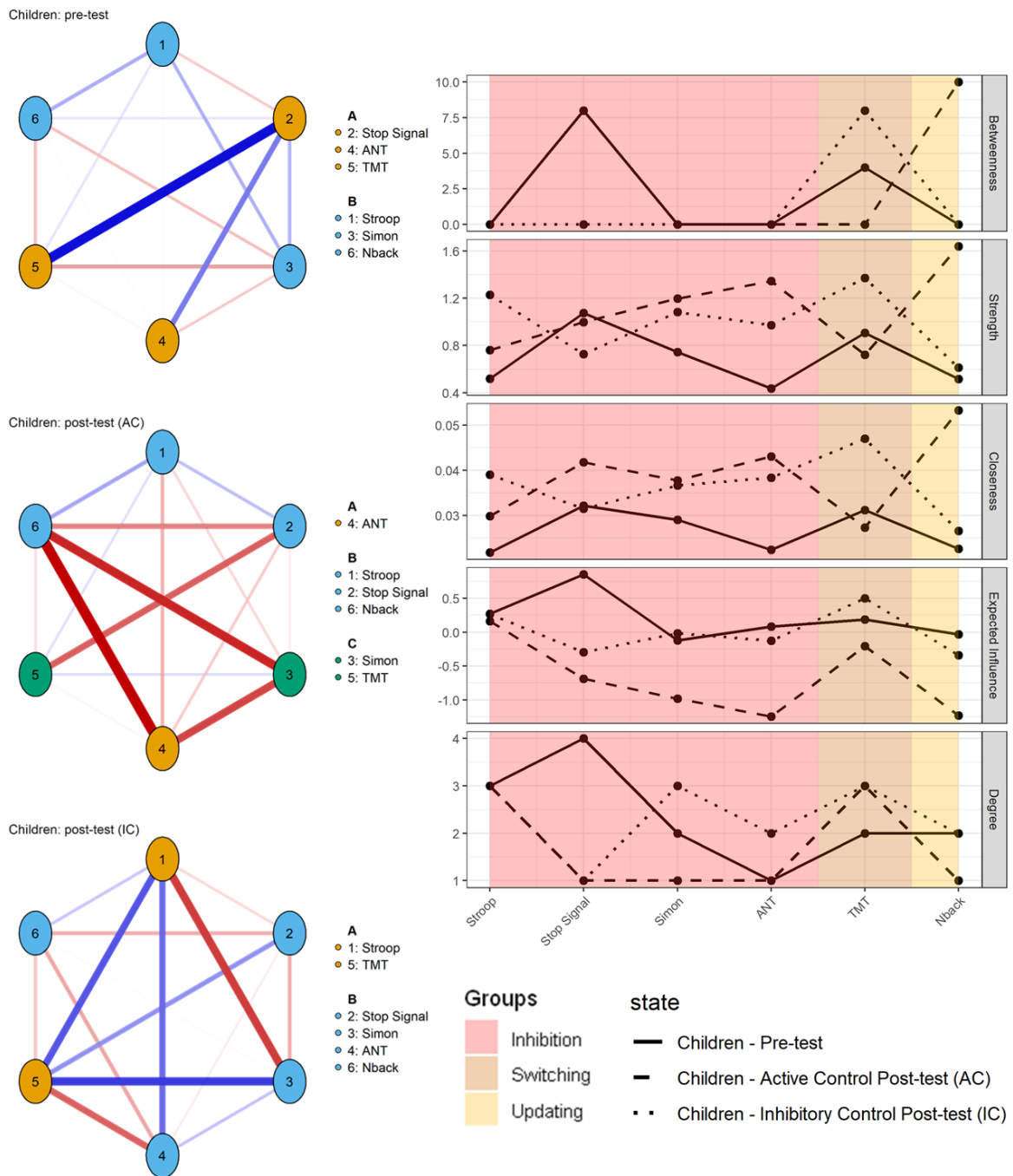


Figure 1.1: Networks for children, before, after an active control training (AC) and after an inhibitory control (IC) training (left panel) with the corresponding centrality indices (right panel). Color of nodes correspond to the communities. Each number in the networks corresponds to an EF task (see details in the legend).

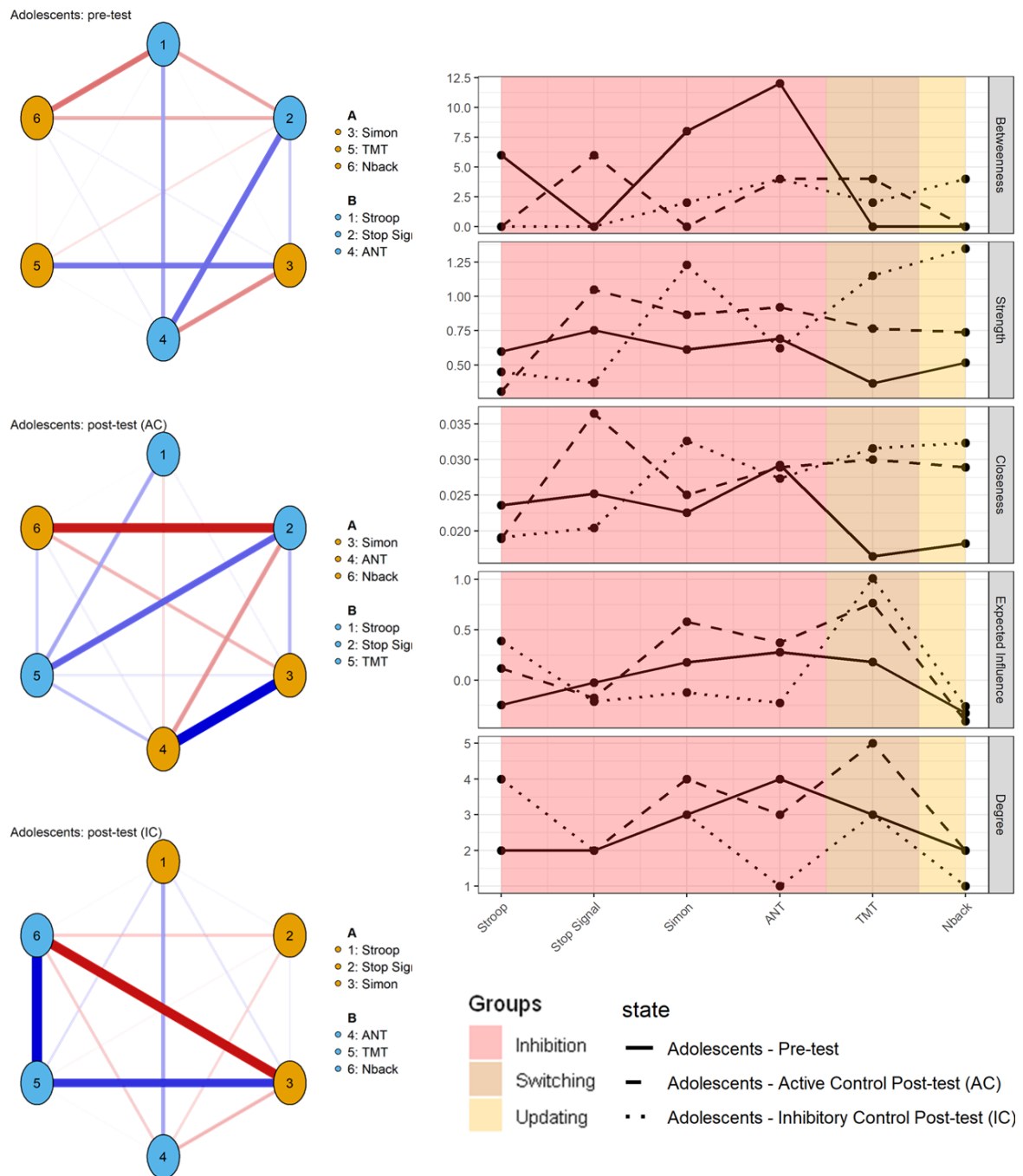


Figure 1.2: Networks for adolescents, before, after an active control training (AC) or an inhibitory control (IC) training (left panel) with the corresponding centrality indices (right panel). Color of nodes correspond to the communities. Each number in the networks corresponds to an EF task (see details in the legend).

nodes corresponding to executive functioning (stop signal, ANT and TMT); 2) Cluster B (in blue), which included 3 nodes corresponding to IC and updating (Stroop, Simon and Nback). In adolescents, the two clusters were as follows: 1) Cluster A (in orange), including 3 nodes corresponding to executive functioning (Simon, TMT and Nback); 2) Cluster B (in blue), including 3 nodes corresponding to IC (Stroop, stop signal and ANT). The only difference between children and adolescents' networks was the cluster switch of Stroop and TMT. Finally, the negative correlation between edge weights across networks ($r = -.51$) reflected the differences previously observed in network connectivity.

3.2 Training effects: pretest vs posttest

The changes in EF structure were first investigated using classical univariate repeated-measures ANOVAs applied to the two age groups and the two training groups separately (see section 4.5.7 of the General Method). These analyses detected a significant change in the stop signal ($p < 0.05$) and Stroop ($p < 0.05$) along with a marginal change in TMT ($p = 0.09$) for children after IC training. In adolescents, a significant change in the stop signal was detected following AC training ($p < 0.05$). All the other analyses failed to reach significance (all $ps > 0.14$).

Complementary analyses, including age and training groups as factors in order to investigate possible age- and training-specific effects, only revealed significant main effects of the age group for SST ($p = 1.3 \times 10^{-5}$) and for TMT ($p = 0.01$) but no interaction effects involving the age nor the training group (all $ps > 0.27$). Post-hoc analyses, with Tukey correction for multiple testing, revealed significant pre-post changes in children in IC group for SST ($p = 0.009$) and TMT ($p = 0.03$).

Of note, Welch Two Sample t-tests revealed no significant differences between the two training groups at pretest except for TMT in adolescents ($t(39.39) = -2.16$, $p < .05$) where adolescents affected to the IC training showed lower score (6.87 ± 3.63) than those who were affected to the AC training (9.62 ± 4.73). All other $ps > .17$.

These standard analyses were further investigated by comparing the network structure in the pretest and posttest for children (Figures 1.1 & 1.3) and adolescents (Figures 1.2 & 1.3).

3.2.1 Cognitive training in children

The children's 6-nodes-network had a different organization, with denser, more numerous and stronger connections after training compared to pretest, especially after the IC training. Almost all variables showed increasing strength (except for the stop signal task) and closeness (Figure 1.1). Stroop and TMT remained the most central nodes of the network after IC training. After AC training, most of the variables increased in strength and closeness, and N-back became the most central node in the network along with TMT. The centrality indices revealed poor connections at pretest in children (strength < 1 and closeness < 0.03) while at posttest, strength and closeness increased, but differently after AC and IC training.

The community analysis (Figure 1.1) detected two communities both pretest and after IC training and three communities after an AC training. After AC training, the three clusters were as follows: 1) Cluster A (in orange), including only ANT; Cluster B (in blue), including Stroop, stop signal and N-back and Cluster C (in green), including Simon and TMT. After IC training, the two clusters were: 1) Cluster 1 (in orange), including Stroop and TMT and Cluster B (in blue), including stop signal, Simon, ANT and Nback. Correlations between edge weights across networks were low both after AC ($r_{AC} = -.30$) and IC ($r_{IC} = -.23$) training indicating few similarities between networks before and after training.

3.2.2 Cognitive training in adolescents

In adolescents (Figure 1.2), the differences in network structure between pretest and after IC training are less important than in children (see Figure 1.2). Nevertheless, after IC training, almost all variables except Simon increased in strength and closeness. Analysis of EI and Degree highlights the centrality of Stroop and Nback, which have the highest scores in these indices. After AC training, fewer changes occurred with an increase in stop signal and Simon for both Strength and Closeness. However, these changes were less important than those after IC training. Community analysis revealed small cluster changes after training, with two nodes being switched after AC training (TMT and ANT) and after IC training (ANT and Simon; see details in Figure 1.2). As for centrality indices, changes in communities were less important in adolescents than in children.

Correlations between edge weights across networks between pretest and posttest were low in both AC ($r_{AC} = -.08$) and IC training ($r_{IC} = -.11$), supporting very few similarities between networks before and after training. In addition to the 6-node networks, a complementary analysis of balanced 3-node networks, where each node represented an EF (stop signal for IC, TMT for switching and N-back for updating; Figure 1.3), was performed. The stop signal, the IC task with the most significant progression after training (see pre-post changes in Table 3), was selected as IC measure. This analysis provided similar results to the previous analysis obtained with the 6-node network, namely greater network connections in childhood than in adolescence and similar network changes related to training and to development.

4 Discussion

In this study, we report the first NM analysis of EF structure changes with age and cognitive training. Based on the hypothesis that training mimics development and can therefore accelerate cognitive changes with age, we anticipated a switch from a centralized to a distributed EF network from childhood to adolescence (Baum et al., 2017; Miyake et al., 2000; Zink et al., 2020) as well as in children after IC but not AC training.

Quantitative and qualitative differences were detected in the EF network structure between children (9-10 years) and adolescents (16-17 years). The increased connections with age between children's and adolescents' networks between tasks tapping different EF domains support the previously reported increasing shared variance among EF variables dur-

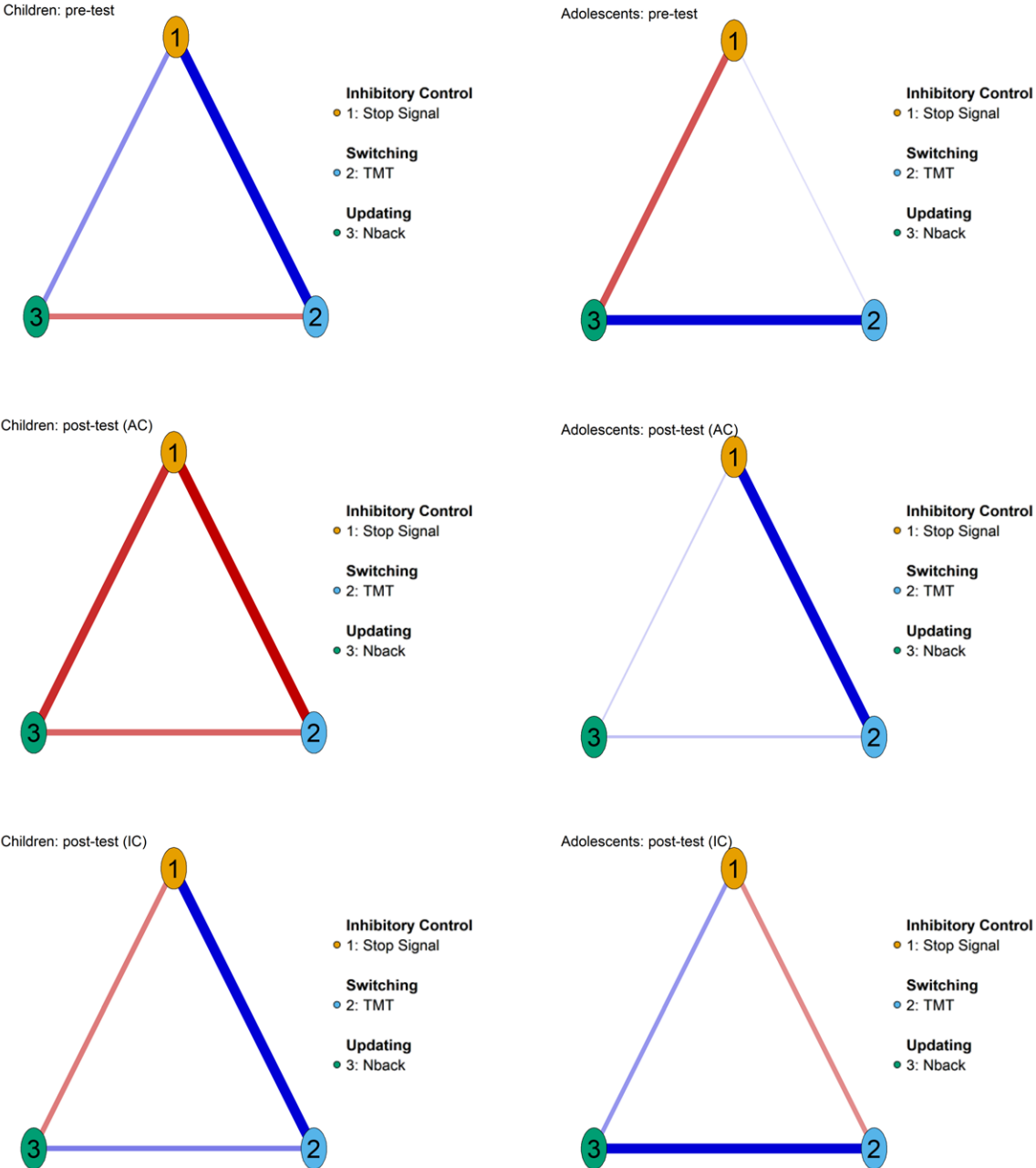


Figure 1.3: Three-nodes networks for children adolescents, before, after an active control training (AC) or an inhibitory control (IC) training.

ing development (Xu et al., 2013). This increased number of connections was confirmed by an increased overall centrality in adolescents compared to children. These findings are also consistent with a study on the development of EF structure from 7 to 15 years of age reporting increased centrality indices (closeness and strength) for EF tasks after 13 years of age (Hartung et al., 2020). Our results also support a recent cross-sectional study using network analysis to examine changes in EF organization from 3 to 85 years of age (Karr et al., 2022). This study reported an increase in inter-EFs connections (increasing strength and expected influence) from 15.5 years of age (Karr et al., 2022), consistently with our findings. However, this study also demonstrated that this increase was preceded by a decrease in the centrality indices from early childhood. Our two age groups are thus just around the point of inversion, it might thus be interesting in the future to extend our analyses with participants just at the point of inversion. Moreover, an accelerated longitudinal design study also suggested organizational changes between ages 8 and 14, along with change for each age group within a single year (cYounger et al., 2021). Thus, it might be relevant to narrow the age range in order to investigate finer developmental changes. Analysis of centrality also revealed that Stroop, stop signal and TMT—the first two on IC and the last one on switching—are central in the EF network of children. This is consistent with previous studies that reported that IC is central for children to employ other EFs (Best et al., 2011; Huizinga et al., 2006; Isquith et al., 2004). However, according to these studies, with age and EF development, IC becomes less central, while in adolescence and adulthood, working memory increases its role in regulating EFs (Best et al., 2011; Huizinga et al., 2006; Isquith et al., 2004). We thus expected N-back to be the most central node in adolescents. Instead, TMT and ANT—tapping on switching and attentional IC—were the central nodes of the network. Nevertheless, it should be noted that N-back had a high centrality in adolescents' graphs, and this centrality increased after 5 weeks of IC training, perhaps reflecting the increasing central role of working memory in EFs' regulation. Moreover, these results are consistent with a recent study that emphasized the increasingly critical role of Switching during the development, which would act as a mediator between IC and Updating from adolescence (Karr et al., 2022). On another hand, the community analyses revealed an organization of EFs in two clusters in both children (two clusters with mixed-EF tasks) and in adolescents (one cluster with IC tasks and a second cluster composed of three tasks measuring the three different EFs). Previous SEM studies reported a differentiation of EF organization between middle childhood and adolescence (Agostino et al., 2010; Friedman et al., 2016; Hartung et al., 2020; Lee et al., 2013; McAuley and White, 2011; Wu et al., 2011; Xu et al., 2013). It is important to note that the clusters obtained with community analysis are determined *a posteriori* (via a data-driven approach), while the factors obtained in SEM analysis are determined *a priori* (via a hypothesis-driven approach). Indeed, clusters derived from community analysis correspond to nodes with high mutual influence and are therefore dependent upon the data under analysis, while SEM clusters correspond to latent factors that were defined before the analysis. Hence, taken together, previous SEM studies and current NM analyses, which are based on complementary approaches, converge toward changes in EF structure from childhood, with a more general composition of EFs, to adolescence, with more specified EFs.

In addition to developmental changes, quantitative and qualitative changes in the EF structure were also found after training one EF, namely, IC. The results showed that after IC training in children, networks have increasingly stronger connections both within and

between EFs and are therefore more similar to adolescents' networks than before training. On the other hand, in adolescents, changes in the EF network were subtler. More precisely, after AC training, the number of connections decreased, but some edges increased in weight, whereas after IC training, the edge weights became much more important, reflecting a more integrated network. However, these lower changes in adolescents compared to children may also be interpreted in terms of reduced training effects in adolescents. Complementary analyses using classical repeated-measures ANOVAs (see Table 3 and Figures 48 & 49 in the General Method Section) indicated that adolescents did not improve their performances in the six EF tasks, while children improved their performances after IC training for stop signal, ANT and tendentially for TMT. The lack of progress in adolescents might reveal a ceiling effect (see Figure 27 in the General Method Section). Of note, the AC and IC trainings were similar in children and adolescents, with difficulty adapted at the individual level. Importantly, except for TMT in children, classical repeated-measures ANOVAs did not detect important transfer effects, while NM could highlight changes in the organization of EFs, including both trained and nontrained tasks (e.g., Stroop and stop signal), thus revealing transfer effects. The community analyses also provided insights into training-related reorganizations of EF structures. In children, networks had two communities before and after the IC training and three communities after the AC training, whereas in adolescents, there were two communities before and after both types of training; these communities had only slight changes in composition, once again reflecting the reduced effects of training in adolescents compared to children. However, it can be noted that in adolescents, after IC training, one of the two communities was composed of only IC tasks and the other of attentional IC, switching and updating tasks, thus highlighting EF-specific effects.

The present study has several limitations that call for caution when interpreting the results. First, sample size is a critical issue for the reliability of statistical analysis, particularly for NM analysis (Epskamp et al., 2018). Hence, despite the relatively large sample size used in this interventional longitudinal study in children and adolescents ($N > 120$), it is important to replicate the findings with confirmatory studies conducted on larger and independent samples. Of note, the recruitment and follow-up of typically developing school-aged children and adolescents enrolled in a 5-week longitudinal study with cognitive training on a tactile tablet raised sound logistical and practical issues which has constrained the sample size. Following recent recommendations for NM analysis with small sample size (i.e., approximately hundreds of participants), we limited the number of variables to 6 (Mansueto et al., 2020) as it allowed us to recover the global structure of the network even though the full network could not be measured. This criterion also led to an imbalance of the three EFs in the creation of the networks. Indeed, IC was overrepresented (4 nodes out of 6). As this was one being trained, it seemed important to look at the impact of training on the organization of this particular EF. Because such imbalance may bias the analysis, and particularly the estimation of the partial correlations, we completed our 6-node network analysis with a balanced 3-node network analysis with networks including one measure per EF. These 3-node network further confirmed the results provided by the 6-node network analysis, namely greater connections in childhood than in adolescence and similar network changes related to training and to development. A perspective is the inclusion of latent variables in the networks (Epskamp et al., 2017), which could allow us to observe the links, without *a priori*, between tasks within the same EF latent variable. Second, the behavioral changes

observed from the pre- to the post-training sessions might not be attributed only to the training *per se* but could also reflect a ‘regression to the mean’ effect (Barnett et al., 2005). This statistical phenomenon arises when a random variable –here task scores– is extreme at baseline but closer to the mean on follow-up or vice versa and typically affects longitudinal design such as the one used in the present study. However, it is unlikely that the difference in IC efficiency change from the pre- to the post-training sessions between the IC and AC training groups only reflects such a ‘regression to the mean’ effect because participants were randomly assigned to the two training groups, and thus, both groups were potentially equally affected by such an effect (Yudkin and Stratton, 1996).

NM provides an original and relevant way to investigate the effect of cognitive training on EF organization, complementary to more classical statistical approaches, such as univariate ANOVAs. Our study combining NM and classical ANOVAs appears to be relevant to analyses of developmental and training-related cognitive changes. Recent methodological developments, such as moderated network models (Haslbeck et al., 2020) or network model trees (Jones et al., 2020), could be an interesting perspective to further explore factors that could influence network organization after an intervention. Because EF neural networks are known to vary with age and to correlate with EF behavioral performance (Baum et al., 2017), a multimodal and multilevel approach combining network analysis at the behavioral level and the neural level (e.g., using resting-state functional magnetic resonance imaging; Zink et al., 2020), is likely an interesting direction to explore. Such an approach could provide a more complete view of EFs (Lydon-Staley et al., 2020) and could pave the way toward an integrative approach, including behavioral, neural and genetic and environmental levels.

STUDY 2: COMBINATION OF NETWORK AND LATENT MODELS TO ANALYZE THE ORGANIZATION OF EXECUTIVE FUNCTIONS ACROSS DEVELOPMENT

This study led to a manuscript in preparation: **Menu, I.**, Borst, G.* & Cachia, A.* (in prep.). Latent network analysis of executive functions across development.

In order to replicate our first study and to further explore changes in the organization of executive functions with age, a second study was conducted on the Texas Twin Project database. This project recruited school-age twins (preschool to 12th grade) enrolled in public schools in the Austin and Houston metropolitan areas. It was created with the goal of increasing the representation of low-income families and racial/ethnic minorities (Harden et al., 2013).

Study 2: Combination of network and latent models to analyze the organization of executive functions across development

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1 Introduction

As we have seen, network analysis has many advantages and complements well the previous findings of SEM studies. However, it would be interesting to compare and combine these two methods on the same sample.

The aim of this study was thus to investigate the organization of the three core EFs across development by using and comparing different methods of analysis: network models, latent models and latent variable network models.

First, in order to look at the links between the different tasks of the EFs without any *a priori* on the structure and to replicate our Study 1, EF network were estimated. A first study (Hartung et al., 2020) have used NM to investigate EF structure through development. This study, based on the Texas Twin Project cohort (7-15 years) found that the interconnection between tasks generally remained globally stable except for the inhibition tasks, whose shared-variance with the other EF domains was reduced with age, in line with the previous theory. Of note, in this study, the authors used 4 components of EFs: IC, updating, switching and working memory. In traditional EF models, only updating is a component of EFs, while working memory is not. By taking these two factors into account, the authors might have obtained different models' results due to the strong interconnections between these two elements. Another cross-sectional study used NM to examine changes in EF organization from 3 to 85 years of age (Karr et al., 2022). This study reported a differentiation of EFs from childhood to adolescence and a dedifferentiation during young adulthood, which accentuates at older adulthood (Karr et al., 2022). Moreover, an accelerated longitudinal design study also suggested organizational changes between ages 8 and 14, along with change for each age group within a single year (cYounger et al., 2021).

Then, latent variable models were constructed and compared in order to replicate the work of Karr et al., 2018 and Miyake et al., 2000. As we have seen in the introduction of Study 1, EF structure goes from a one-factor structure in early childhood with no clear separation among EF tasks (Shing et al., 2010; Wiebe et al., 2008; Willoughby et al., 2012; Xu et al., 2013) to a two- to four-factors structure at adolescence (Agostino et al., 2010; Friedman et al., 2016; Lee et al., 2013; McAuley and White, 2011; Wu et al., 2011; Xu et al., 2013). The meta-analysis from Karr et al., 2018, tested seven models of EF structure and found some evidence for greater unidimensionality of EFs among child/adolescent samples and both unity and diversity among adult samples.

Finally, to provide the most complete and accurate view of the evolution of EF organization with age, the two previous methods were combined to create a latent variable network model (LVNM, Epskamp et al., 2017). To date and to our knowledge, no study has used this methodology. This technique is extremely well suited for the study of EFs, as the factorial organization of EFs, although evolving with development, is generally accepted.

2 Material and Methods: the Texas Twin Project

This study was made possible by the collaboration with the Texas Twin Project (Harden et al., 2013) team, Prof. Elliot Tucker-Drob, Prof. Kathryn Paige Harden and Dr. Johanna Hartung who provided us age-weighted (co)variance matrices. More details about the Texas Twin Project can be found in (Engelhardt et al., 2016; Hartung et al., 2020).

2.1 Participants

Data were drawn from 1019 participants from the Texas Twin Project (Harden et al., 2013), a population-based sample that included children spanning the range of functioning so long as they were able to understand the instructions and complete the tasks encompassed in the protocol. For this reason, children with very severe disabilities and delays were not eligible to participate.

The average full scale intelligence quotient (FSIQ) of participants in the sample measured by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011) was 103.99, with a standard deviation of 14.09.

The current sample consisted of children in Grades 3 to 8 between 7.8 and 15.3 years of age ($M = 10.79$ years, $SD = 1.76$). This sample, of which 50.4% was female, included 479 twin pairs, 19 triplet sets, and 1 quadruplet set. In terms of race/ethnicity, 59.1% of the sample identified as non-Hispanic Caucasian, 15.0% as Hispanic, 6.7% as African American, 4.2% as Asian, 0.6% as another race or ethnicity, and 14.3% as multiple races or ethnicities.

2.2 Evaluation of EFs

We included 9 variables analyzed in the previous NM study (Hartung et al., 2020) derived from several tasks spanning the different EFs:

- Inhibitory control (IC)
 - **Animal Stroop**: participants were asked to verbally identify animals from line drawings. In the congruent condition, the face of the animal matches the body. In the incongruent condition, the face does not match the body and identification should be based on the body. In the neutral condition, the face area is blank, and identification should be based on the body (Wright et al., 2003). Dependent variable (DV) is the mean RT cost for incongruent conditions relative to congruent and neutral conditions.
 - **Stop signal auditory**: participants were asked to indicate which way an arrow points, but do not respond if a tone (stop signal) sounds after the arrow is presented (Verbruggen and Logan, 2008). DV is the mean RT cost for go trials relative to stop signal delay (time between arrow and stop signal presentation).

- **Mickey**: participants were asked to indicate on which side of a computer screen a cartoon Mickey Mouse face appears while ignoring any squares that flash on-screen before Mickey. In the congruent condition, a square flashes on the same side where Mickey appears. In the incongruent condition, a square flashes on the opposite side. In the neutral condition, squares flash on both sides (Lee et al., 2013). DV is the mean RT cost for incongruent trials relative to congruent and neutral trials.
- Cognitive flexibility (CF)
 - **Trail making**: participants were asked to connect circles containing numbers in numerical sequence and circles containing letters in alphabetical order. In the two simple conditions, only numbers or letters are presented. In the two alternating conditions, both numbers and letters are presented, and the circles should be connected in an alternating sequence (numbers–letters: 1-A-2-B, etc.; letters–numbers: A-1-B-2, etc.) (Salthouse, 2011). DV is the mean RT cost for alternating conditions relative to simple conditions.
 - **Plus-Minus**: participants were asked to complete simple addition and subtraction problems on paper. In the adding condition, participants should add 1 to each provided number. In the subtracting condition, they should subtract 1 from each number. In the alternating condition, they should alternate between adding 1 and subtracting 1 (Miyake et al., 2000). DV is the mean RT cost for alternating conditions relative to simple conditions.
 - **Local Global**: participants were asked to verbally identify letters and shapes composed of smaller letters and shapes. In the two local conditions, participants should name the small constituent letters or shapes. In the two global conditions, they should name the large overall letter or shape. In the alternating condition, they should alternate between naming the constituent and overall letters or shapes (Miyake et al., 2000). DV is the mean RT cost for alternating conditions relative to simple conditions.
- Working memory updating (WMU)
 - **2-Back**: participants were asked to watch a sequence of individual shapes and indicate when the current shape matches the shape from two trials prior (Jaeggi et al., 2010). DV is the total number of hits (correct matches) minus false alarms (nonmatches indicated).
 - **Running memory**: participants were asked to watch a sequence of single letters and identify the last n digits in order of their presentation (Broadway and Engle, 2010). DV is the total number of visually presented letters correctly recalled.
 - **Keeping track**: participants were asked to listen to words falling under four categories and recall the most recent word from a given category (Miyake et al., 2000). DV is the total number of verbally presented words correctly recalled.

2.3 Weighting function

Rather than grouping participants based on the moderator (here age) range, observations were weighted around focal points (i.e., specific values of the continuous moderator variable). This procedure, known as local structural equation modeling (LSEM), is thought to be beneficial for age-group analyses because parameter estimates have been shown to be more informative and less distorted with respect to age differences (Hildebrandt et al., 2016). Models (SEM but also NM or LVNM) can be estimated sequentially for each focal age point using weighted samples of observations (Hildebrandt et al., 2016).

The weighting function used in Hartung et al., 2020 was based on the recommendations of Hildebrandt et al., 2009. At each defined value of the age variable, called focal points, a Gaussian kernel function was used to weight observations, with the highest weight at the age point and decreasing weights for observations further from this age point. The focal age points ranged from 8.0 to 14.0 with 0.1 increments. These upper and lower limits were selected to reduce boundary bias based on the age distribution of the sample (Hildebrandt et al., 2016; Hildebrandt et al., 2009). In total, 61 weighted (co)variance matrices were obtained¹.

3 Sub-study 1: Network models

3.1 Method

Network models (NM) were constructed for each focal age point based on the (co)variance matrices of the same 9 EF variables described earlier. 61 networks were then estimated. Nodes of the network corresponded to the scores at the 9 cognitive tasks, which were grouped in three EFs. For each focal age point, network was estimated and its accuracy was assessed using precision and robustness measures (Borsboom et al., 2018) and standard graph centrality indices (degree, closeness and expected influence) were calculated.

NM was then used to analyze 1) the multiple relations (edges) between the different EF tasks (nodes) simultaneously, and 2) how these relations change during the development. Just as in Study 1, we used the successive steps procedure proposed for network analysis in psychology Fried et al., 2018: 1) network estimation; 2) network inference (topological characterization). The interrelation between the different variables was modeled with Gaussian Graphical Model (GGM; Lauritzen and Wermuth, 1989). The networks were characterized using both quantitative and qualitative measures.

Statistical analyses were performed using R-statistical software, version 3.6.3 (R Development Core Team, 2014). The NM were constructed and visualized using the package *qgraph* version 1.6.9 (Epskamp et al., 2012).

¹These were the matrices provided by the Texas Twin Project team that allowed for the following analyses. I did not perform this weighting or participate in any preprocessing of the data.

3.2 Results

Visually (see Figure 2.6), a differentiation of the EFs with age can be observed: while the network is initially very dense, with many intra- and inter-EF connections, the network becomes more and more sparse with age². In particular, the IC tasks that had a lot of weight in the network for the first focal age points, quickly separate from the rest of the nodes. On the contrary, it seems that WMU tasks gain more weight with age. Given the overlap between the results of the different centrality measures, we will describe only Degree and Expected Influence indices. Closeness results can be found in Appendix A3.

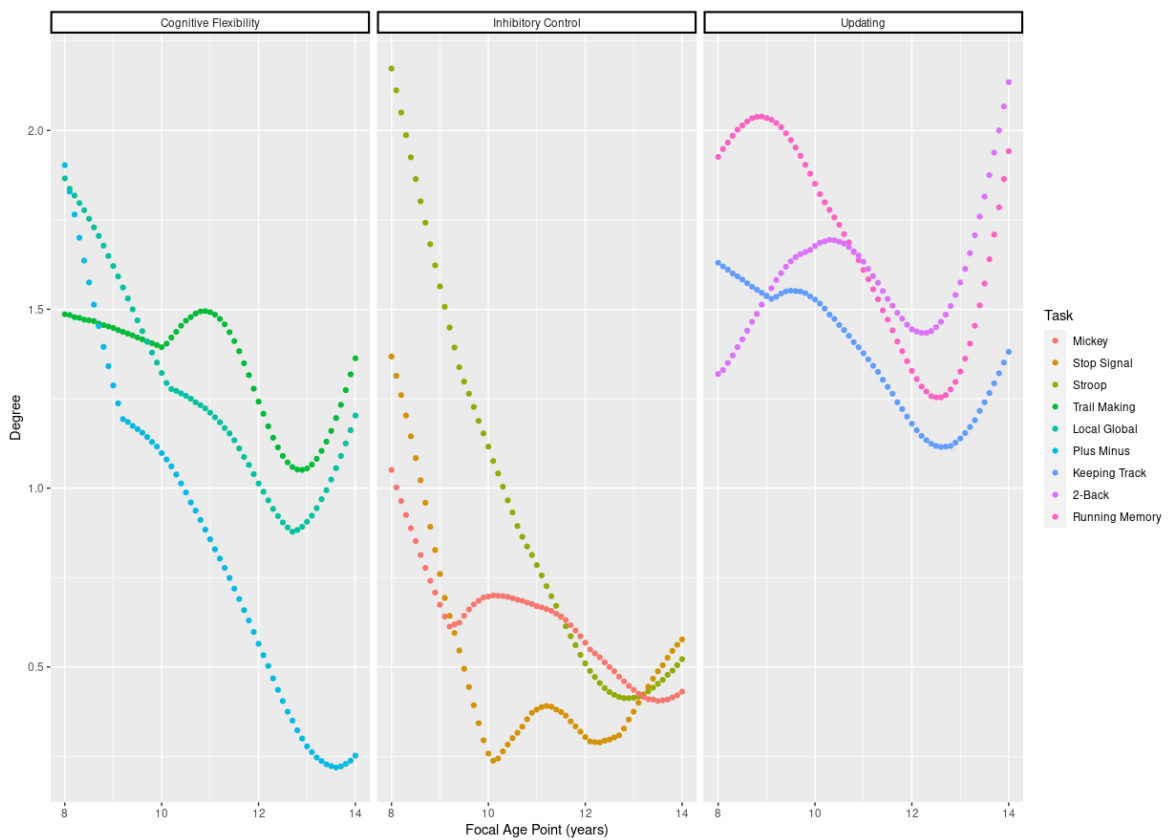


Figure 2.1: Degree of the 9 nodes in the network models across age.

As a reminder, Degree indexes the number of connections for each node of the network, weighted by the size of these connections, thus defining hubs (nodes with highest degree).

Degree of CF (left panel of Figure 2.1) varied according to the task. Plus Minus’s Degree dropped drastically through 9 y.o. and then continued to continuously drop through 13.6 y.o. and attaining a very low degree (0.22) before a small rebound. The Local Global followed a similar trajectory with some age lag (drastic drop until 9 y.o., degree rebound around 12.7 y.o.). Moreover, Local Global’s Degree never fell below 0.88. Finally, the Trail making followed another trajectory with a slow decrease until 10 before a rebound peaking at 10.9 y.o. preceding a new decrease until 12.9 y.o. and a last increase.

²For a visual animation, visit this link: <https://sites.google.com/view/irismenu/study-2-gifs>

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IC Degree varied again with the type of tasks (middle panel of Figure 2.1). Stroop's Degree was the highest at fist (2.17) and then decreased almost linearly with age until 12.58 y.o. and the value of 0.41 preceding a slight rebound. Stop signal Degree also strongly decreases until the focal age point of 10.1 and the value of 0.24 before slightly increasing with a high peak around 11.2 and a low peak around 12.3. Finally, Mickey's Degree also dropped from 1.05 at 8 y.o. to 0.61 at 9.2 y.o. before reincreasing slowly peaking at 0.70 at the focal age point of 10.2 and decreasing again slowly through 13.5 y.o.

WMU tasks are likely the most homogeneous in Degree developmental trajectories (right panel of Figure 2.1). 2-back and Running memory started by increasing in Degree peaking respectively at 1.70 at 10.3 y.o. and at 2.04 at 8.9 y.o. Then, their Degree decreased until 12.5 y.o. and the values of 1.25 for Running memory and 1.43 for 2-back. Starting 12.5, their Degree rapidly increases through focal age point 14. Keeping track followed a similar trajectory except for an initial low decrease from 8 to 9.1 y.o.

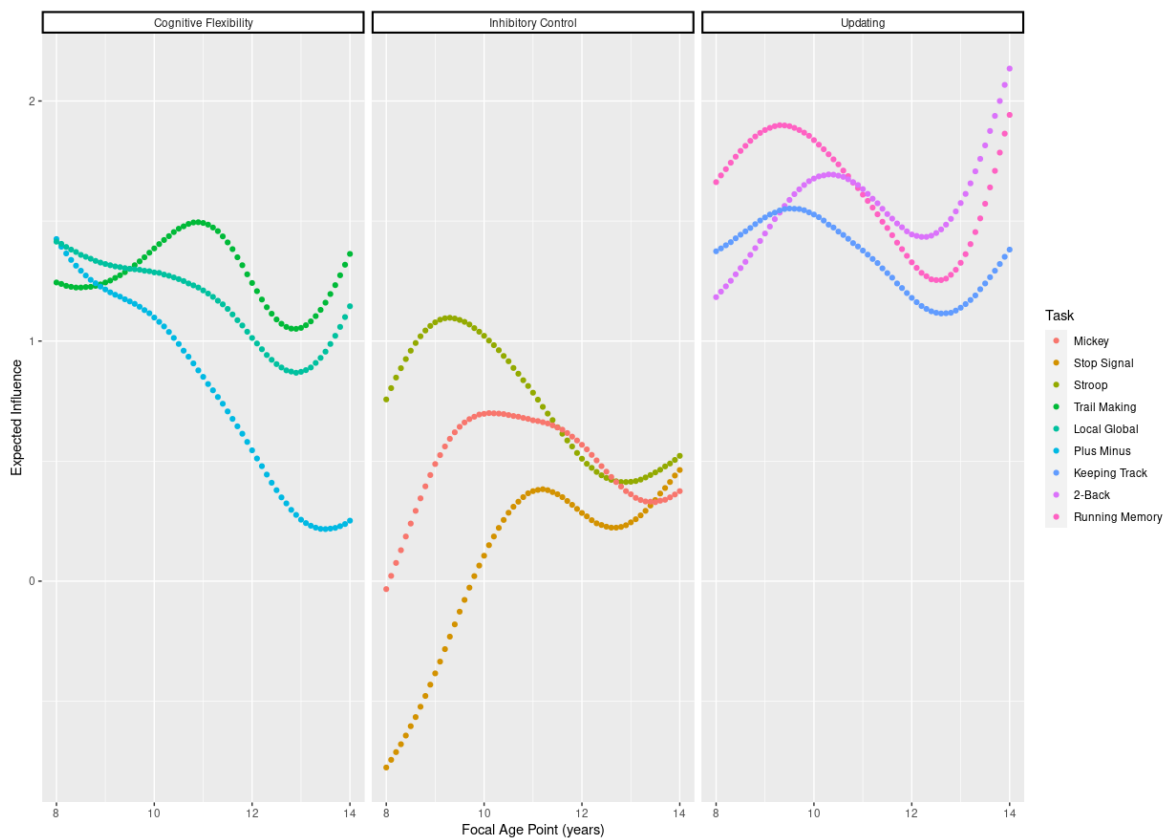


Figure 2.2: **Expected influence of the 9 nodes in the network models across age.**

As a reminder, contrary to Degree which takes the absolute value of the weights, Expected influence (EI) also takes into account the direction of the weight (negative or positive).

Regarding CF (left panel of Figure 2.2), Plus Minus task decreased slowly through age whereas Trail making's EI increased through the focal age of 10.9 before decreasing until 12.9 y.o. and reincreasing again. Local Global's EI decreased slowly until 12.9 y.o. before reincreasing again.

We can see in the middle panel of Figure 2.2 that the stop signal task has at the beginning a rather negative impact on the other variables of the network and that this weight increases almost linearly until 11.2 years when it stabilizes between 0 and 0.5. The other IC tasks follow the same dynamics but do not start from the same starting values. For example, the Mickey task has almost null expected influence values at the beginning which increase linearly to 0.70 shortly at 10.1 years.

Regarding WMU (right panel of Figure 2.2), all three tasks followed the WMU trajectories with an increase from 8 to 9-10 y.o., followed by a slight decrease until 12.5 y.o., preceding a strong increase until 14 y.o., especially for the 2-back and Running memory tasks.

4 Sub-study 2: Latent models

4.1 Method

To further investigate the factorial structure of EFs through development, we built and tested the seven factorial latent models described in Karr et al., 2018 (see Figure 2.3):

- *Unidimensional model*: one latent factor defined by the 9 EF variables (Common-EF)
- *CF-WMU Merged model*: two latent factors model, one referring to IC and one referring to CF and WMU merged
- *IC-WMU Merged model*: two latent factors model, one referring to CF and one referring to IC and WMU merged
- *IC-CF Merged model*: two latent factors model, one referring to WMU and one referring to CF and IC merged
- *Three-Factor Model*: three latent factors model, each referring to one EF (IC, WMU and CF)
- *Nested Factor Model*: three latent factors model, one referring to CF, another referring to WMU and a last one defined by the 9 EF variables (Common-EF)
- *Bifactor Model*: combination of the Three-Factor and the Unidimensional models: 4 latent factors, three referring to each EF (IC, WMU and CF) and a last one defined by the 9 EF variables (common-EF)

Each model was constructed and then fitted separately for each focal age point and compared to identify the model that best explain the data at each focal point. To find out which model provides the best fit for each of the 61 age points, the fit indices (AIC, BIC, RMSEA) were compared for each model for each focal age point. The respective factor loadings and details of the estimates for each model were then inspected.

The LM were constructed and estimated using the package *lavaan* version 0.6-7 (Rosseel, 2012).

Study 2: Combination of network and latent models to analyze the organization of executive functions across development

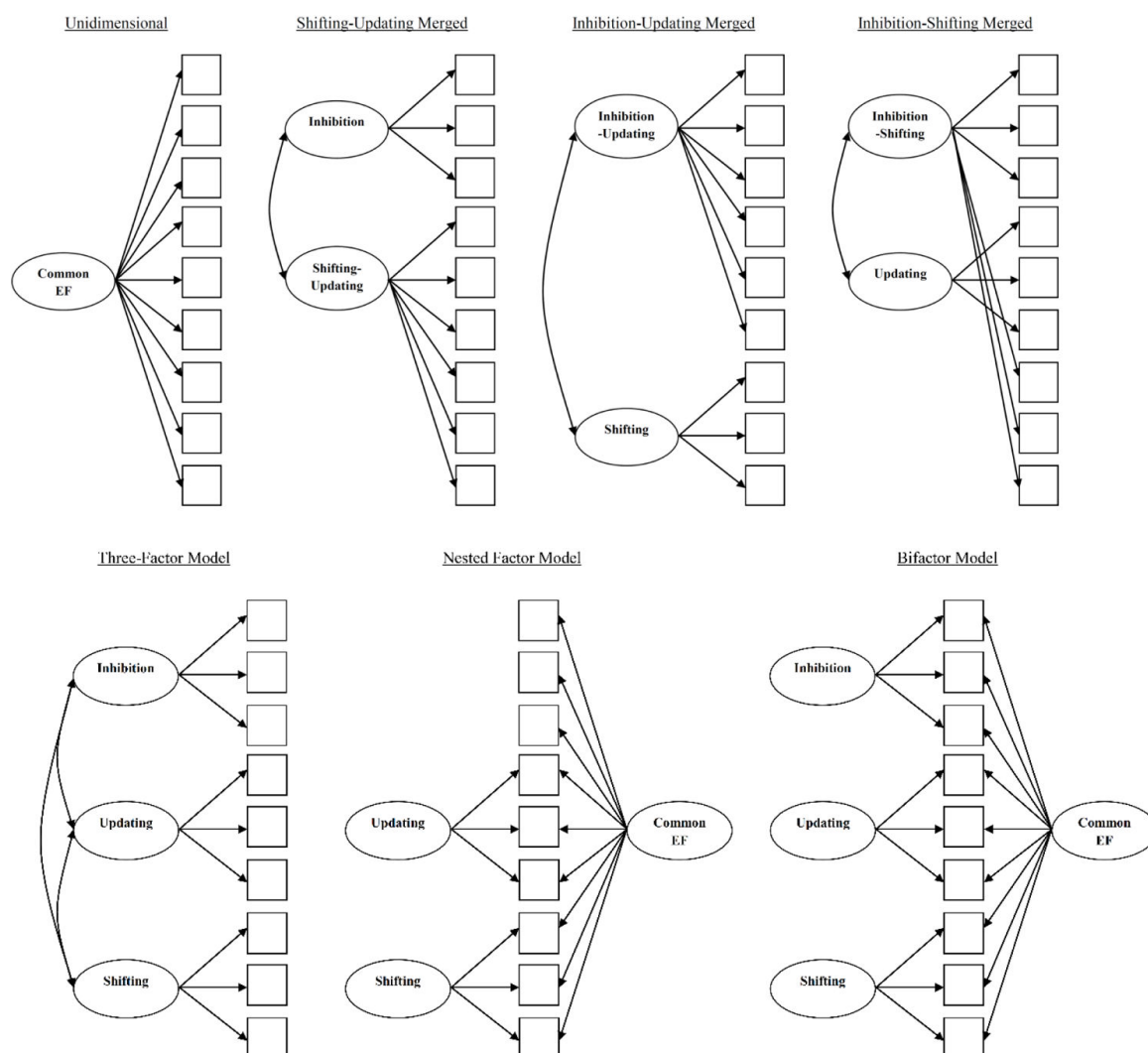


Figure 2.3: **Seven latent models of executive functions.** From Karr et al., 2018.

4.2 Results

4.2.1 Model fit

The fit results can be found in Figure 2.4. Within this sample, some models did not converge: in particular, the bifactorial model converges for few focal age points (20 out of 61). Similarly, the nested model did not converge for 19 focal age points, mostly located at the endpoints (between 8 and 8.9 years and between 12.4 and 13.9 years).

The bifactorial model is the one that presents the best fit indices between 8 and 8.5 years. Then, the nested model is the one that obtains the best fit indices. However, the fit variations between the different models were minimal.

Study 2: Combination of network and latent models to analyze the organization of executive functions across development

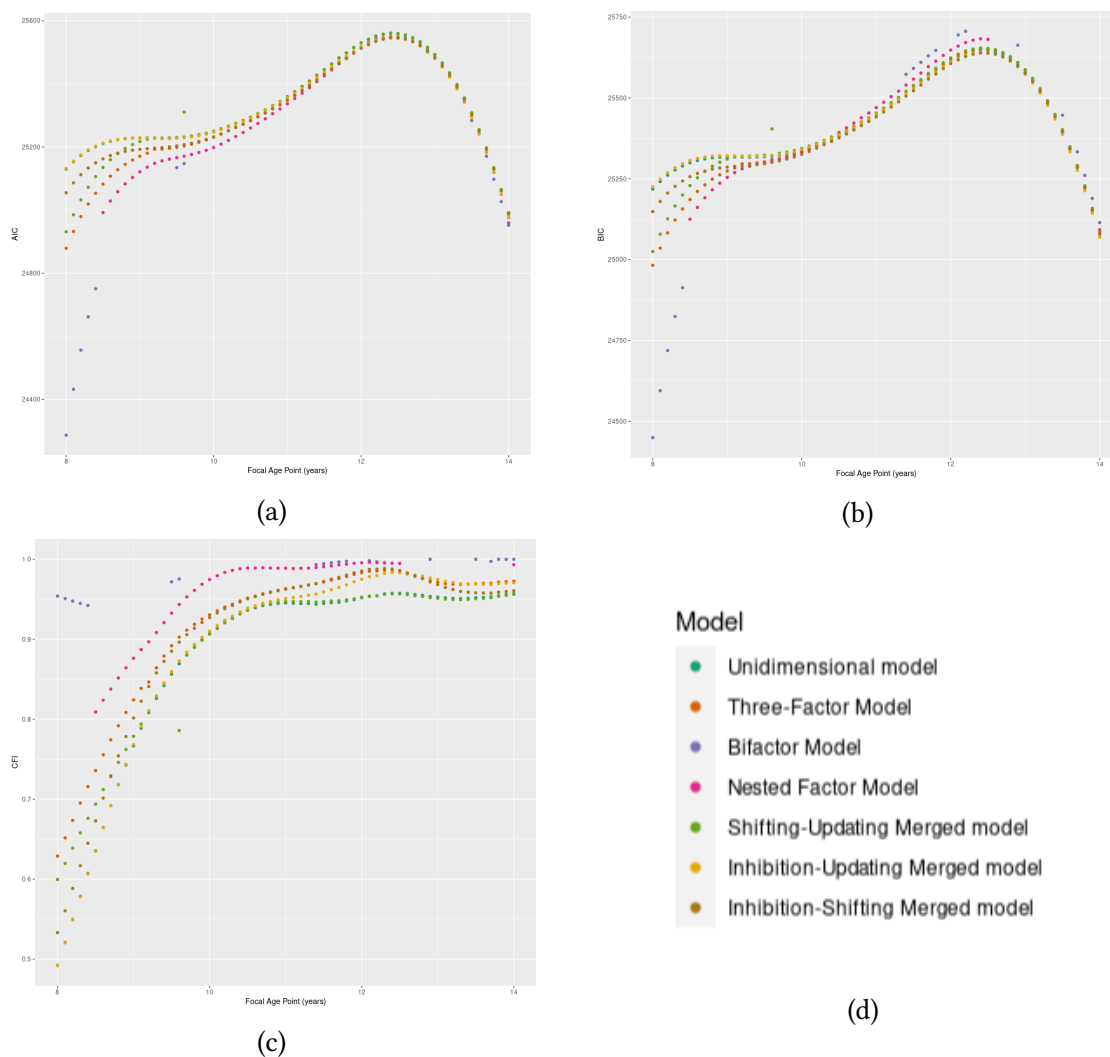


Figure 2.4: **Fit indices of the 7 latent models.** (a) = AIC (Akaike information criterion) for each model by focal age point. (b) = BIC (Bayesian information criterion) for each model by focal age point. (c) = RMSEA (root mean square error of approximation) for each model by focal age point. (d) = legend of the seven latent models.

4.2.2 Model results

In the following, we are presenting the results of the loadings obtained for the unidimensional models. On the one hand, this allows a comparison with the network analyses presented above and, on the other hand, the results are highly similar to the loadings obtained with the 3-factor models (see Appendix A4).

Concerning the loadings of IC variables, we see that the Stroop task has the highest loadings at age 8 and that this weight progressively decreases to stabilize around age 12. On the contrary, the loadings of Mickey and the stop signal gradually increase between 8 and 11 years of age and then stabilize (see Figure 2.5).

Regarding WMU, the loadings of the 3 tasks seem to evolve in the same way across age, with a slight increase between 8 and 9.5 years, a stabilization/slight decrease between 9.5 and 12 years followed by an increase between 12 and 14 years. Note that the loadings of Keeping track are lower than those of the other two tasks, especially between 12 and 14 years old where its loadings remain more stable.

Finally, concerning CF, the Plus-Minus loadings decrease almost linearly to 0 over time. Global Local loadings also decrease but to a much lesser extent and without approaching zero values. Finally, the Trail making loadings increase slightly between 8 and 11 years old before decreasing until 13 years old and then slightly decreasing (Figure 2.5).

Finally, while the Stroop task has the largest loadings at the beginning, we see that the loadings of this task and of the other inhibitory tasks approach 0 with time, while the loadings of the updating tasks take on more and more weight in the definition of a common executive factor (Figure 2.5).

5 Sub-study 3: Latent variable network models

5.1 Method

For each focal age point, following Epskamp et al., 2017, a latent variable network model (LVNM) derived from the classical three-factor model tested just above was constructed and estimated.

This LVNM allows to combine the two previous approaches by looking at the network at the level of the latent variables IC, WMU and CF, and not between the variables themselves. In the case of the unidimensional EF model, there is only one latent variable (common-EF), and therefore there is no possibility to create an LVNM (one cannot observe a network with only one node).

The LVNM were constructed and estimated using the package *lvnet* version 0.3.5 (Epskamp et al., 2017).

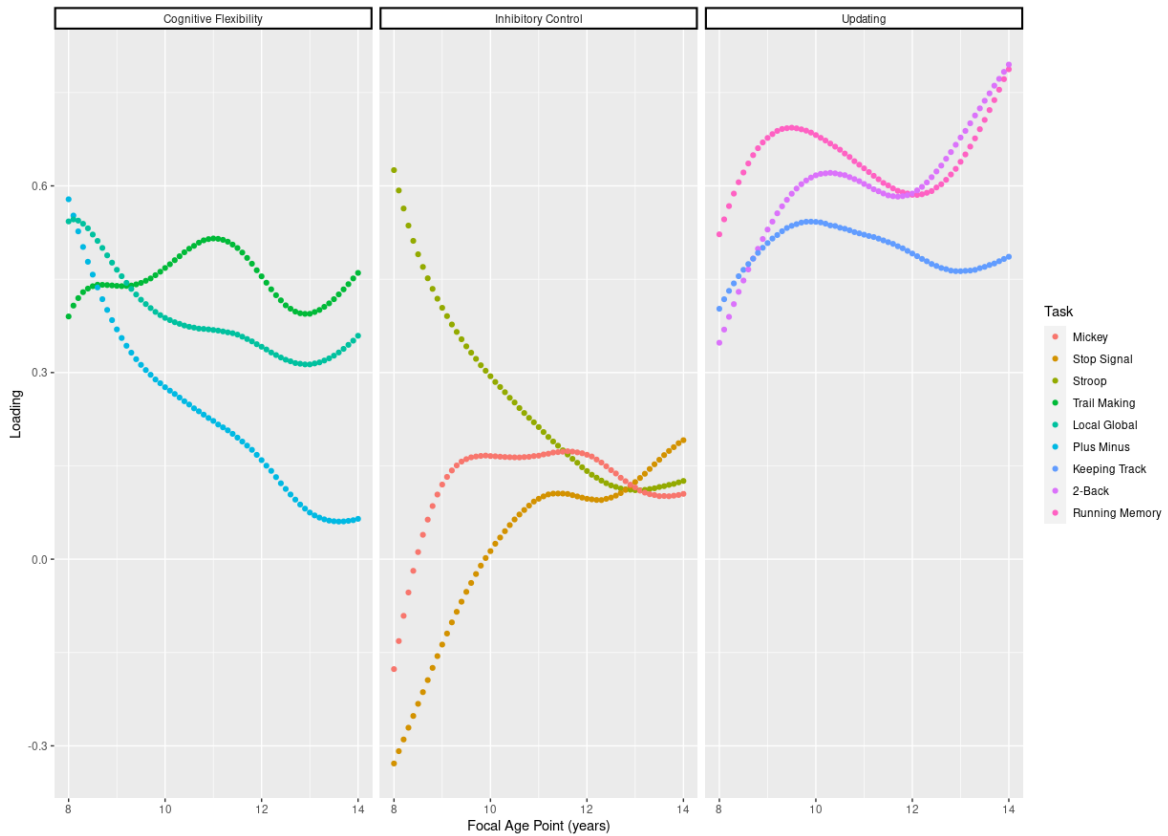


Figure 2.5: Loadings of the 9 EF variables in the unidimensional models across age.

5.2 Results

The visual inspection of the LVNM (see Figure 2.6) combined inspection of task loadings for each EF and of connectivity between EFs.

Interestingly, LVNM factor loadings are quite similar to the ones from the regular latent analysis. Thus, regarding CF, we see that Plus-Minus loadings decrease through age from 0.6 at the 8th focal age year to 0.1 at the 14th. Local global loadings remain almost stable and decrease way less than in SEM. Finally, trail making loadings increase almost linearly through 11.5 years and decrease then. Regarding WMU, we see the same "smoothing effect" with mexican hats pattern less identifiable. The biggest changes regard IC with broken loadings lines around 9 years. It seems that there is a mirroring effect of these factor loadings before this age. Indeed, Stroop loadings are at 8 years low (-1.1) and then increase through 8.9 years to -0.8 and are then at 0.8 at 9 years before an abrupt and then almost linear decrease.

Moreover, regarding the network between the three latent variables, we can see that, similarly, there is a break at 9 years of age. Regarding relations between EFs, connections between edges varied less homogeneously with time. Until 9 y.o., IC was negatively connected with CF before being connected with it more positively and strongly. Then, inter-EF connections remain low before an increase in connections between WMU and IC.

6 Discussion

These studies had two objectives. Theoretically, it aimed at characterizing the organization of EFs through development on a single cohort. Methodologically, it aimed at comparing different tools for EF modeling, and in particular to evaluate the validity of latent variable network modeling.

All three tools (latent models, network models and latent network models) gave very consistent and similar results. For example, the tasks that had substantial weight in the latent models were the same tasks that had large and strong connections in the network models. This suggests that the results obtained are therefore due to mechanisms observed in this sample and are therefore not attributable to the tool used. This consistency is not surprising in the sense that all three methodologies are based on the same sample and ask similar yet complementary questions. Indeed, whereas latent (factorial) analyses are more concerned with the hypothesis of a factorial organization, and thus of the weight of each variable for its associated factor, network analyses are interested in the free organization, without any *a priori*, of the variables with each other. NM thus make it possible to assess the links between a variable of one EF with the other variables of other EFs, which LM does not allow. On the contrary, LM make it possible to answer the big question of the factorial organization of EFs by directly testing and comparing different models with more or less latent factors. The LVNM analyses provide an additional level of information by looking at the links, without *a priori*, between the latent factors created by the researcher (here, the EFs).

Perhaps most surprisingly, a consistency between the different latent models across development was observed. With the exception of the first focal age points (until 10 y.o.), the seven models tested in this study give very similar fit indices. Note that at the first focal age points, some models have better fit indices than others, but, whatever the model, the fit indices reveal a poor fit. This seems surprising because, given the literature, one would expect that over the first few ages, a unidimensional model would show better fit indices than the other models and, that with age and entry into adolescence, an improvement in the fit of the 3-factor model could emerge. However, these homogeneous results, which are not very clear-cut and sometimes poor in fit, are consistent with Karr et al., 2018, which highlight models that are not so different and sometimes with poor fit.

Concerning the theoretical results themselves, this study highlights different things. Overall, whatever the statistical tool used, we see that the connections between the variables and/or the EFs themselves decrease over time. This is all the more obvious with the network analyses where we initially see a very integrated network with many inter- and intra-EF connections that decrease with age until we obtain a very sparse and segregated network. Considering each EF individually, for CF we see a segregation in intra (fewer and weaker connections between CF tasks) and inter (fewer and weaker connections between CF tasks and tasks of other EFs) even if the Trail making and Local Global tasks remain well connected to WMU tasks. This last point could be explained by the fact that these tasks solicit the WM (Brocki and Tillman, 2014; Chevalier et al., 2012) but we could have expected similar associations with the IC which is also involved during these tasks (Brocki and Tillman, 2014; Chevalier et al., 2012). Regarding IC, we observe a particular pattern

with initial negative loadings and connections of some tasks. These inter- and intra-EF connections then disappear quite early in the development with IC tasks, in the NMs, almost separated from the rest of the network and, in the CFAs, almost zero loadings. Thus, there seems to be a very early dissociation of IC from other EFs, maybe reflecting the nested organization observed in adults (Karr et al., 2018). On the contrary, for WMU, the intra-EF connections remain rather stable over time. The inter-EF connections decrease a little during development but it is the EF that has the most connections with the other EFs in our last age groups. This result is found in all models where loadings, edges between tasks or between latent variables increase in the later age groups. It would thus seem that the WMU is the EF that has a greater weight in late childhood, early adolescence. These results are consistent with previous results that stated that with age and EF development, IC becomes less central, while in adolescence and adulthood, WMU increases its role in regulating EFs (Best et al., 2011; Huizinga et al., 2006; Isquith et al., 2004).

At the task level, different observations can be made. For the WMU tasks, we see that the three tasks follow the same trajectory with just a small gap in childhood (peak at 9.5 years for Keeping track and Running memory, peak at 10.5 years for 2-back). These very similar patterns suggest that these three tasks solicit similar processes and thus point to a homogeneity of the measure. For the CF tasks, we see slightly different trajectories. The trajectory is almost linear for Plus-Minus, the trajectory follows a Mexican hat for the TMT task and an intermediate trajectory for the Local-Global task, which is more similar in dynamics to the Plus-Minus task. The use of TMT as a measure of CF is debated (for a review: Sánchez-Cubillo et al., 2009), as this task requires among others IC (Chaytor et al., 2006; Miner and Ferraro, 1998). Overall, these differences in trajectory suggest that these are different CF processes. Finally, concerning the IC tasks, the three tasks are initially different, especially the Stroop task, which has opposite loadings and correlations to the other two tasks. These differences decrease with time until a homogenization around age 12. These differences can also be explained for theoretical reasons: whereas the Stroop task corresponds to interference control, the Mickey and stop signal tasks correspond rather to response inhibition (Diamond, 2013). Thus, while the two components would initially be distinct, with the development of the IC, they would become increasingly integrated.

Before the age of 9, the patterns are very strange with results that mirror what would be expected. Several hypotheses can explain this. First, it could be due to the construction of the sample itself: if this is an under-represented age group in the sample, the results could be biased by the different sample size. It could also be due to the measures themselves: the difficulty of the tasks for this age group could explain our surprising results. Moreover, at these ages, EFs are currently being acquired and a large inter-individual variability can be observed which could, again, explain our strange results.

It would be very interesting to explore what happens during adolescence, after the age of 14 where this study ends. The period of adolescence is of great interest in EFs with notably the maturation of the PFC (Crone, 2009) and the acquisition of an almost adult executive performance (Huizinga and van der Molen, 2007; see 1.4). Generally, this study should be replicated with a longitudinal study from childhood (not too early in order to use the same tasks) to early adulthood with short time intervals. Indeed, we see very fine changes over short periods. This also raises the question of selecting age ranges for developmental

studies. In developmental psychology, it is common to have age intervals of several months (e.g., 12-13 years) to several years (e.g., 10-14 years). However, if the dynamics are so fine-grained over the course of a year, widening these age intervals could confound the results. It would be really necessary to replicate these results with a longitudinal approach with repeated and close measures in the EF domain or even in other cognitive domains.

A limitation of the study is that the data are from a twin study. Thus, a large proportion of the sample shares a significant genetic part, more than in a general population. It would therefore be necessary to replicate these results in an independent sample. However, the genetic question is interesting and it could be worthwhile to replicate and extend twin studies on EFs. In particular, it might be interesting to replicate the ACE models of Friedman et al., 2008 in our latent models but also to introduce these genetic and environment variables in the networks and in the LVNM. We could then see more finely the weight of genetics and environment on the tasks but also on the EF constructs.

Another perspective of this study would be to replicate it but with hot EF tasks. Indeed, it has been shown that cool and hot EFs follow different developmental trajectories (Prencipe et al., 2011; Welsh and Peterson, 2014; Zelazo and Carlson, 2012). It thus seems interesting to look at the organization of hot EFs to see if EF organization is similar according to the emotional load but also to see how it evolves over time. At periods such as adolescence, knowing how the organization of hot and cool EFs is done could allow us to understand the mechanisms at play and to contribute to the understanding of the observed gap between hot and cool executive functioning.

In conclusion, this study, by comparing the different methodological tools used in the literature, allows us to provide an update on the organization of EFs during development, from 8 to 14 years of age, and thus on the validity of the inferences previously made in the literature. The three approaches used gave consistent and complementary results. During development, these results highlighted an early differentiation of IC from other EFs, followed by a differentiation of CF, whereas WMU takes a more important role in the structure of EFs over time.

Study 2: Combination of network and latent models to analyze the organization of executive functions across development

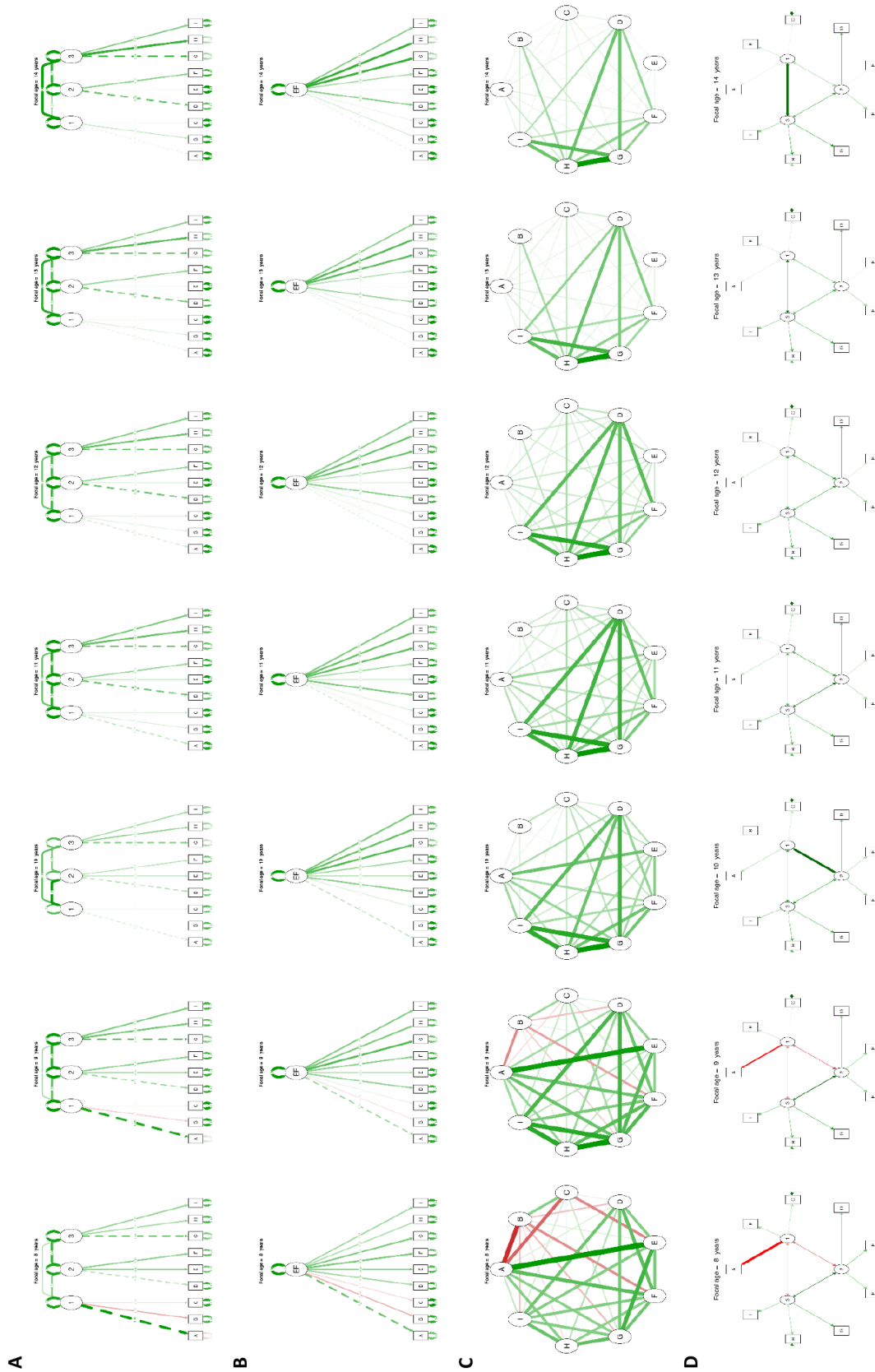


Figure 2.6: Overview of the different models studied at each focal age point year. Panel A = Three factors latent model. Panel B = One factor latent model. Panel C = Network model. Panel D = Latent variable network model. A = Stroop; B = Stop signal; C = Mickey; D = Trail making; E = Plus-minus; F = Local global; G = 2-back; H = Running memory; I = Keeping track.

Study 2: Combination of network and latent models to analyze the organization of executive functions across development

STUDY 3: SEM TO INVESTIGATE EF TRAINING TRANSFER EFFECTS

This study led to a manuscript: **Menu, I., Rezende, G., Le Stanc, L., Borst, G.* & Cachia, A.*** (under review). Inhibitory control training on executive functions of children and adolescents: a latent change score model approach.

After studying the changes in executive functions organization with development and with inhibitory control training, we wanted to investigate the impact of this training on the other two untrained executive functions, working memory updating and cognitive flexibility. The aim of this study was therefore to see whether, in addition to the organizational changes observed in Study 1, the inhibitory control training had benefited these two executive functions and what factors might have influenced these training transfer effects.

Study 3: SEM to investigate EF training transfer effects

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1 Introduction

Due to the fact that EFs are implicated in learning, academic achievement, psychiatric health and everyday functioning (see section 1.3 of the General Introduction; Best et al., 2011; Diamond, 2013), several intervention programs have tested the possibility of improving various aspects of EFs (for reviews, see Jolles and Crone, 2012; Karbach and Unger, 2014; Spierer et al., 2013). A recent meta-analysis suggested that training a single EF has nonsystematic effects on the improvement of untrained EFs (Kassai et al., 2019). For instance, some studies in which one EF is trained have reported no effects of the training (Enge et al., 2014; Talanow and Ettinger, 2018; Thorell et al., 2009), or only near transfer, i.e., improvement on the same EF (Bergman Nutley et al., 2011; Dunning et al., 2013; Zhao et al., 2015) or far transfer, i.e., improvement on another EF (Aydmune et al., 2019; Beauchamp et al., 2016; Jaeggi et al., 2011; Liu et al., 2015; Maraver et al., 2016; Söderqvist and Bergman Nutley, 2015). Interestingly, studies in which several EFs were trained have reported near transfer to specific EFs, including updating (Blakey and Carroll, 2015) and IC (Dowsett and Livesey, 2000) as well as far transfer effects on school abilities (Blakey and Carroll, 2015; Traverso et al., 2019).

Among these studies, many have focused on IC because of its importance for cognitive and socioemotional development (for a review, see Borst et al., 2015), academic success (e.g., Kim et al., 2013) and its impairment in many psychiatric disorders (e.g., Ajilchi and Nejati, 2017; Craig et al., 2016; Demetriou et al., 2019). IC is a multidimensional construct that can be divided in response inhibition and interference control (Diamond, 2013). IC training can target any of these dimensions and can affect them differently. For instance, IC training based on a playground activity (e.g., ‘Wesley says’) was found to improve preschool children performance in a Go/NoGo task (i.e., response inhibition) but not in a Stroop task (i.e., interference control) (Zhao et al., 2015). Such findings suggest that it may be preferable to train both facets of the IC to ensure near transfer effects. This IC dimension specific effect is not systematic. For instance, IC training composed of Simon and emotional Go/NoGo tasks (i.e., response inhibition) was found to transfer to interference control in an untrained Flanker task in adults (Millner et al., 2012).

Analyzing the extent to which training benefits other cognitive abilities, the extent to which it transfers to other domains, is crucial in order to evaluate the overall benefits of training. This is especially true for EFs, which are known to be important for many abilities. If a training targeting an EF allows to improve this EF (near transfer) but also the other EFs (far transfer), it is the whole EF core that is improved which can potentially impact many other abilities. The implications of such a transfer mechanism are therefore considerable. Moreover, studying transfer in the case of executive training could provide information at the theoretical level on the structural organization of EFs. For instance, the existence of near transfer, but not far transfer, could support the notion that training only impacts the specific part of the trained EF, which would therefore provide evidence of a factorial organization of EFs. On the contrary, the existence of a far transfer could support that training likely acts on the common part of EFs, which would thus be evidence for the unity of EFs.

The discrepancies in the near and far transfer effects following EF-, IC- or brain-training

in general (Simons et al., 2016) that have been reported in the literature may be explained by the fact that transfer effects vary with training time (Jaeggi et al., 2008) and individual differences in training receptivity (Jaeggi et al., 2011; Jaeggi et al., 2014). Of note, many studies have reported that individuals can respond differently to the same training intervention depending on their baseline level. Two (opposite) prominent mechanisms have been proposed to describe and explain such baseline effect (Karch and Unger, 2014). The ‘compensation’ effect states that individuals with high baseline abilities benefit the least from cognitive training because they are already functioning at an optimal level, which indicates that they have less room to improve, in contrast to individuals with lower baseline abilities. The ‘magnification’ effects (also referred as Matthew, or scissor, effect) states that individuals that are already performing very well will also benefit the most from cognitive interventions, because high-performing participants have more efficient cognitive resources to acquire and implement new abilities. In case of magnification, baseline cognitive performance positively correlates with training gains while in case of compensation, baseline cognitive performance negatively correlates with training gains.

Finally, transfer effect can depend on the statistical approach that is used to assess this potential transfer effect (Noack et al., 2014). Training studies typically use analysis of variance (ANOVA) or linear models to assess near and far transfer effects. These statistical approaches are intrinsically limited by the following three main issues: 1) dissociating the change in trained cognitive function from the change in untrained functions; 2) simultaneously and explicitly testing an entire set of possibly correlated variables; and 3) taking into account the complex error structure of longitudinal data (Noack et al., 2014). In the context of EF training, the unity and diversity of EFs also raise specific statistical issues, due to the fact that the changes of one EF (e.g., IC) are not entirely independent of the changes of the other EF (e.g., WMU and CF).

The cross-lagged panel model (CLPM; e.g., Biesanz, 2012) has been one of the most popular approaches for analyzing the interactions and reciprocal influences between variables over time. However, this model cannot investigate lasting effects, such as whether the change between two consecutive measurement time points is associated with further changes later in time (Mund and Nestler, 2019). An interesting alternative is the latent change score model (LCS; Kievit et al., 2018), which involve extensions of SEMs that have been developed for longitudinal, or repeated measures, data (McArdle, 2009). SEM, including LCS, allows for the simultaneous estimation of multiple relationships, including the specification of directed relations that correspond to hypothesized causal pathways. LCS has the advantage of combining the features of both growth models and CLPM (McArdle, 2009; McArdle and Hamagami, 2001; Steyer et al., 1997). Indeed, rather than investigating shifts in the rank order between two time points (as occurs in the CLPM), LCS models can examine the difference in a variable between two or more measurement time points (Castro-Schilo and Grimm, 2018). Differences between successive measurements are modeled in LCS as latent change factors. For instance, LCS models were recently used to test mutualism theory, which states that basic cognitive abilities directly and positively interact during development (Kievit et al., 2017). LCS models have shown that individuals with higher scores in one domain (e.g., vocabulary) exhibited greater gains in another domain (e.g., matrix reasoning) and vice versa (Kievit et al., 2017). Therefore, such an extended multivariate LCS model can provide a highly dynamic perspective on the analysis of second-

order interdependencies across time (Mund and Nestler, 2019).

In this context, this study aimed to evaluate the effect of 5 weeks of computerized IC training on trained (IC) and nontrained (updating and switching) EFs in children and adolescents by using LCS models. A dedicated LCS model was developed to assess the transfer effects 1) directly from the estimation of the training-related changes in both the trained and nontrained tasks and 2) indirectly from the effects of the initial levels of each EF on the training-related changes of the other EFs (crossed effects). To evaluate the extent to which the transfer or the lack of transfer effects that have been reported in some studies may be due to the statistical approaches that have been used to reveal such a transfer, we systematically compared the transfer effects (as revealed by LCS) compared to those effects revealed with the use of classical repeated-measures ANOVAs.

2 Material and Methods

2.1 Participants

Of the APEX cohort, 103 participants of the IC and AC training groups completed a minimum of 15 training sessions and were included in this study (pre-hoc inclusion criteria): 57 children (24 males, $M \pm SD = 9.79 \pm 0.55$ years, range = 9–10 years) and 46 adolescents (13 males, $M \pm SD = 16.56 \pm 0.50$ years, range = 15–17 years).

2.2 Pre- and post-training measures

IC efficacy was assessed from 1) the stop signal task by using the stop signal reaction time (SSRT), as recommended in previous studies (Verbruggen et al., 2019) and 2) the Stroop interference score calculated as the difference between the RT in congruent and incongruent trials. The CF or switching efficacy was obtained from the TMT by using the RT difference between TMT-B and TMT-A. The WMU or updating efficacy was obtained from the N-back task score by using the RT (in seconds) difference between the 2- and 1-back trials. This updating difference score was built to ‘normalize’ the RT, similarly to the difference scores used in the Stroop and TMT. A similar approach was used in Loughead et al., 2009. Of note, by using these definitions, lower EF scores corresponded to higher EF efficiency.

For each task, relative changes were screened and cleaned for possible aberrant values by using a nonparametric approach. Specifically, values lower than ‘median – 2.5 MAD’ or greater than ‘median + 2.5 MAD’ (MAD, or the median absolute deviation) were considered to be outliers.

2.3 Modeling framework

We fitted multivariate LCS models, as in previous studies (Kievit et al., 2017; McArdle, 2009; McArdle and Hamagami, 2001). Of note, the LCS model conceptualizes the difference

between successive measurements as latent change factors, which allowed us to directly model within-subjects changes as a function of structural parameters (McArdle and Hamagami, 2001). The basic equation of the LCS model specifies the score of individual i on test Y (stop signal, Stroop, TMT or N-back scores) at pre-training and post-training as a sum of the score at baseline (pre-training) and a change, or difference, score as follows:

$$Y_{i,post} = \beta Y_{i,pre} + \Delta Y_{i,post}$$

By setting the regression weight β to 1 (McArdle and Hamagami, 2001), the LCS allowed us to rewrite the change scores as follows:

$$\Delta Y_{i,post} = Y_{i,post} - Y_{i,pre}$$

These change scores were then modeled as indicators of a latent factor of change scores. The intercept provides approximately identical results as a paired-sample t-test when comparing differences across two measurement occasions; however, it provides two additional parameters (Kievit et al., 2017): the variance in the change scores (i.e., whether individuals change homogeneously or not over time) and the regression between the scores at pretest (baseline) and the change scores (i.e., whether change varies according to the baseline score).

We extended the basic univariate LCS model to a multivariate LCS model by modeling the change scores on three tasks ($Y1$, $Y2$ and $Y3$), which corresponded to the stop signal or the stroop, the TMT and the N-back scores, respectively, with the tasks being functions of three processes: a self-feedback process (β) and two coupling processes (γ), as follows:

$$\Delta Y1_{i,post} = \beta Y1_{i,pre} + \gamma_2 Y2_{i,pre} + \gamma_3 Y3_{i,pre}$$

The self-feedback parameter (β) reflects a combination of effects, including regression to the mean and a dampening effect induced by an end horizon for rapid development (i.e., individuals reaching their performance ceiling; Kievit et al., 2017). The coupling parameters (γ) demonstrate whether the change in $Y1$ is determined by the pretest scores in $Y2$ and $Y3$ (and vice versa; Kievit et al., 2017); thus, they index the degree to which the change in one EF is affected by the baseline level of another EF, above and beyond the self-feedback parameter.

We fitted a model that predicts multivariate coupling between the three EFs. We also added the number of training sessions as a covariate in the model. Additionally, we *a priori* anticipated that a higher baseline level in the stop signal and the Stroop would lead to larger differences in TMT and N-back scores and vice versa (see Figure 3.1).

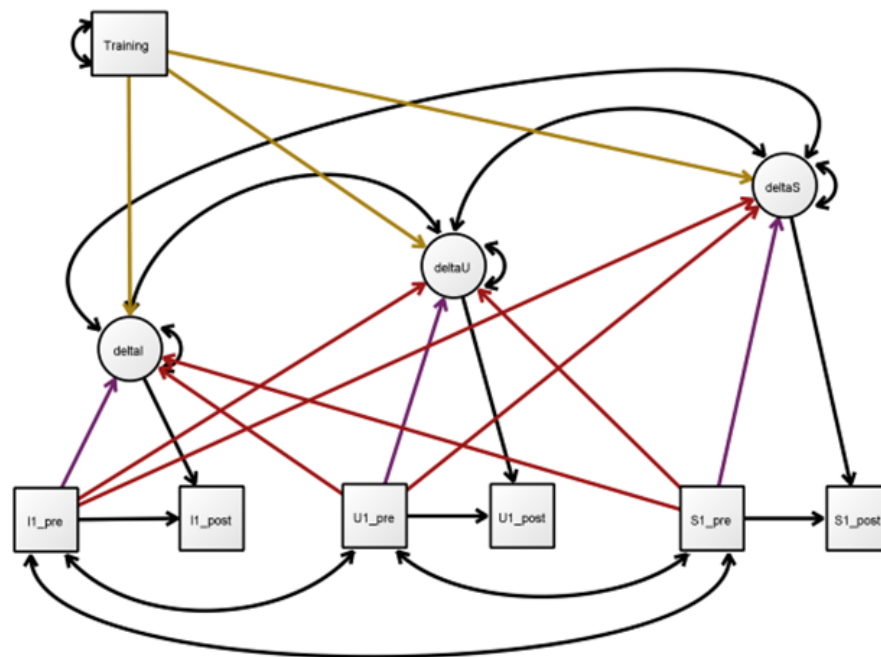


Figure 3.1: **Graphic illustration of the LCS model used to analyze the executive training data.** Training (i.e. number of training sessions) was entered as a covariate of the latent change scores for IC abilities (deltaI), updating abilities (deltaU) and switching abilities (deltaS). Circles indicate latent variables, and rectangles indicate observed variables. Thick single-headed arrows indicate regressions. Double-headed arrows indicate variance and covariance. The figure was computed with *ωnyx* software (von Oertzen et al., 2015).

2.4 Model fit and Comparison

LCS models were estimated with the *lavaan* software package (Version 6.8; Rosseel, 2012) in R by using full information maximum likelihood with robust standard errors to account for missingness and non normality.

Overall model fit was assessed by using standard indices (Schermelleh-Engel et al., 2003), including the chi-square test, the root-mean-square error of approximation (RMSEA; acceptable fit: < 0.08, good fit: < 0.05), the comparative fit index (CFI; acceptable fit: 0.95–0.97, good fit: > 0.97) and the standardized root-mean-square residual (SRMR; acceptable fit: 0.05–0.10, good fit: < 0.05).

2.5 Repeated-measures ANOVA

To evaluate the relevance of LCS, the same training data were also analyzed by using the classical univariate repeated-measures analysis of variance (ANOVA) as seen in section 4.5.7 of the General Method. Like for SEM analyses, ANOVAs were conducted separately for each of the four EF tasks for the two age groups and the two training groups. In order

to assess possible group-specific effects, complementary ANOVAs were run for each task, including age group (children vs adolescents) and training group (IC vs AC) in the models.

The repeated-measures ANOVAs were estimated using mixed-effects linear models. We used the package *lme4* (Bates et al., 2012) with the Time (pre- or post-training) as fixed effects and intercepts for subjects as random effects. P-values were obtained by using likelihood ratio tests of the full model, including the tested effect against the model without the tested effect.

3 Results

3.1 Repeated-measures ANOVAs

As we have seen in the section 4.5.7 of the General Method and in Study 1, the classical repeated-measures ANOVAs applied to the two age groups and the two training groups separately detected a significant change in the stop signal ($p < 0.05$) and Stroop ($p < 0.05$) along with a marginal change in TMT ($p = 0.09$) for children after IC training. In adolescents, a significant change in the stop signal was detected following AC training ($p < 0.05$). All the other analyses failed to reach significance (all $ps > 0.14$). Raw pre-training and post-training scores for the three EF tasks are shown in Table 3.

Complementary analyses, investigating possible interaction with age and training groups, revealed a significant main effect of the age group for stop signal ($p = 1.3 \times 10^{-5}$) and for TMT ($p = 0.01$). All other main and interaction effects, including for the analyses of Stroop and N-Back scores, were not significant (all $ps > 0.27$; see details of the analyses in section 4.5.7 of the General Method section).

Post-hoc analyses, with Tukey correction for multiple testing, revealed significant pre-post changes in children in IC group for SST ($p = 0.009$) and TMT ($p = 0.03$).

3.2 LCS models

Data were then analyzed by using LCS models. One task for each EF was included to have balanced models: stop signal or Stroop interference for IC abilities, N-Back for updating abilities and TMT for switching abilities.

Two LCS models were fitted and compared to investigate the age and training effects. In the first model, referred to as the ‘constrained model’, all of the parameters were constrained to be equal in the four groups (Children-IC_{pre} = Children-AC_{pre} & Adolescents-IC_{pre} = Adolescents-AC_{pre} & Children-IC_{post} = Children-AC_{post} & Adolescents-IC_{post} = Adolescents-AC_{post}), assuming the same training effects regardless of the training session and the age group. In the second model, referred to as the ‘free model’, the parameters were only constrained to be equal at the pretest period for each age group (Children-IC_{pre} = Children-AC_{pre} & Adolescents-IC_{pre} = Adolescents-AC_{pre}), assuming that the training effects were specific to the training session and the age group. In both models, the baseline scores were

constrained to be equal in each training group, assuming a similar level before training because the participants were randomly assigned to the different training groups but were left free in each age group, when assuming that children and adolescents do not have the same EF abilities before training.

With stop signal as IC measure, the free model fitted the data significantly better than the constrained model ($\chi^2 [54] = 135.58, p < 0.001$), thus indicating that the changes in EFs are not the same according to the type of training and participants' ages. Of note, the free model fit the data well according to the classical LCS metrics ($\chi^2 [30] = 23.65, p = 0.79$; RMSEA = 0.00, 90% confidence interval [CI] = [0.00, 0.11]; CFI = 1.00; SRMR = 0.11; Yuan-Bentler scaling factor = 0.84). Similarly, with Stroop as IC measure, the free model fitted the data significantly better than the constrained model ($\chi^2 [54] = 187.68, p < 0.001$), reflecting that the changes in EFs are not the same according to the type of training and participants' ages. The free model fit the data well according to the classical LCS metrics ($\chi^2 [30] = 18.92, p = 0.94$; RMSEA = 0.00, 90% confidence interval [CI] = [0.00, 0.03]; CFI = 1.00; SRMR = 0.11; Yuan-Bentler scaling factor = 0.91). For all of these reasons, the stop signal and Stroop free models were subsequently selected and further investigated in the different training and age groups. A summary of the fit indices of the two models for the two IC measures can be found in Table 3.1. Details of the model estimations can be found in Table 3.2 with stop signal as IC measure and in Table 3.3 with Stroop as IC measure.

IC measure	Model	χ^2	df	RMSEA	CFI	SRMR	Selected model
Stop signal	LCS constrained	157.676	84	0.185 [0.134-0.233]	0.000	0.305	
	LCS free	23.648	30	0.000 [0.000-0.113]	1.000	0.106	x
Stroop	LCS constrained	198.001	84	0.230 [0.184-0.275]	0.000	0.361	
	LCS free	18.921	30	0.000 [0.000-0.029]	1.000	0.108	x

Table 3.1: **Fit indices for the free LCS model and constrained LCS model.** A robust estimation of the parameters was used.

3.2.1 LCS model in children with stop signal as IC measure

Analysis of the free LCS model with the stop signal (Figure 3.2) at pretest in children revealed that TMT was marginally correlated with both Nback ($r = -0.73, SE = 0.44, z = -1.67, p = 0.10$) and stop signal ($r = 0.25, SE = 0.14, z = 1.79, p = 0.07$) scores.

In the experimental group (IC), the intercepts for the latent change score were significant for the stop signal (0.18, SE = 0.08, $z = 2.28, p < 0.05$) and N-back (-0.84, SE = 0.32, $z = -2.61, p < 0.01$) tasks and marginal for TMT (-18.53, SE = 9.99, $z = -1.86, p = 0.06$), thus indicating significant changes in all of the EF scores after IC training. The self-feedback parameters were significantly negative for the stop signal (-0.82, SE = 0.18, $z = -4.58, p < 0.001$) and TMT (-1.01, SE = 0.28, $z = -3.54, p < 0.001$) tasks and marginal for the N-back task (-0.28, SE = 0.16, $z = -1.81, p = 0.07$), thus indicating that higher initial scores (and thus a lower EF ability) on one EF task corresponded to greater gains on that task. An analysis of the coupling parameters, which indicated crossed effects between gains in one EF and initial performance in the two other EFs, showed that individuals with the larger improvement on the TMT had a higher stop signal score (i.e., a lower IC ability; 61.11, SE = 23.77, z

= 2.57, $p < 0.05$) and a lower N-back score (i.e., a better updating ability; -15.14, SE = 8.18, $z = -1.85$, $p = 0.06$) at baseline. Additionally, children with a higher TMT score (i.e., a poorer switching ability) at baseline improved more on the N-back (0.01, SE = 0.00, $z = 1.95$, $p = 0.05$). Finally, the number of training sessions was significantly related to latent change in TMT (1.04, SE = 0.44, $z = 2.37$, $p < 0.05$) and N-back (0.03, SE = 0.01, $z = 2.17$, $p < 0.05$) but not for the stop signal ($p = 0.83$) scores.

In the control training group (AC), there were no significant intercepts for the latent variables related to the EF score changes (all $ps > 0.65$), thus indicating no significant changes in EF scores after AC training. However, in contrast to the IC group, the latent change scores related to stop signal and to TMT were negatively correlated ($r = -0.17$, SE = 0.08, $z = -2.07$, $p < 0.05$), thus indicating that increased performance in stop signal following training was associated with a decreased performance in TMT following training. As in the IC group, all of the self-feedback parameters were significantly negative (all $ps < 0.01$). The coupling parameters were not significant (all $ps > 0.59$) except for updating; specifically, children who had a lower N-back score (i.e., a better performance) at pretest improved more in IC (-0.20, SE = 0.05, $z = -3.95$, $p < 0.001$).

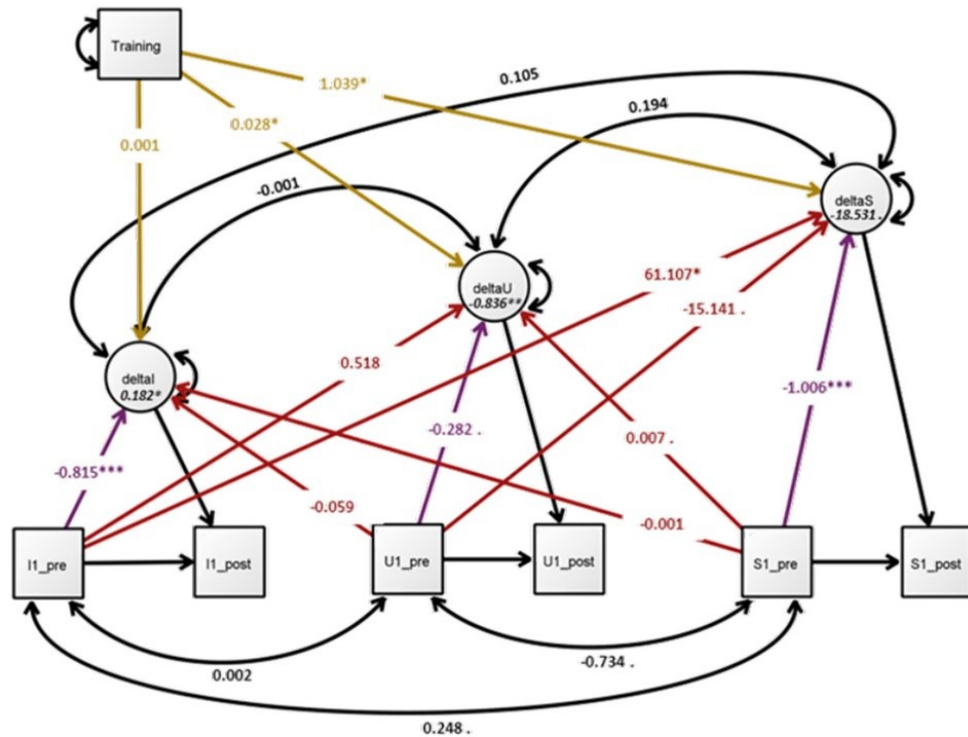
3.2.2 LCS model in adolescents with stop signal as IC measure

The analysis at the pretest of free LCS model with the stop signal in adolescents (Figure 3.3) did not reveal any significant correlation between any of the EF task scores (all $ps > 0.11$).

In the experimental group (IC), the latent change intercept for the stop signal was significant (0.14, SE = 0.07, $z = 2.05$, $p < 0.05$; all other $ps > 0.65$), thus indicating a significant change in stop signal scores after IC training, but not in the TMT or N-back scores. In addition, latent changes in N-back and TMT were correlated ($r = 0.11$, SE = 0.06, $z = 1.98$, $p < 0.05$). The self-feedback parameter of the stop signal was negative (-1.01, SE = 0.39, $z = -2.58$, $p < 0.05$), marginal for the TMT (-0.43, SE = 0.23, $z = -1.86$, $p = 0.06$) and failed to reach significance for the N-back ($p = 0.28$). The analysis of the coupling parameters indicated that adolescents with a greater N-back score (i.e., a lower updating ability) at baseline tended to improve more on the stop signal task (0.23, SE = 0.12, $z = 1.92$, $p = 0.06$). The other coupling parameters did not obtain significance (all $ps > 0.21$).

In the control training group (AC), there were only marginal latent change intercepts for N-back (-0.37, SE = 0.22, $z = -1.66$, $p = 0.10$; all other $ps > 0.33$), thus indicating no significant change in the EF scores after the AC session, except for N-back, which was a marginal change. Latent changes in stop signal and TMT were marginally correlated ($r = 0.03$, SE = 0.02, $z = -0.71$, $p = 0.09$), thus indicating that increased performance in SST following training was associated with increased performance in TMT following training, and vice versa. As in the children, all of the self-feedback parameters were significantly negative (all $ps < 0.01$), thus indicating that a lower efficiency on one EF task corresponded to greater gains on that task following training. An analysis of the coupling parameters revealed that individuals with a greater stop signal score at baseline (i.e., a lower IC ability) improved more on N-back following training (1.54, SE = 0.72, $z = 2.14$, $p < 0.05$); similarly, adolescents with a greater N-back score at baseline (i.e., a lower updating ability) improved more on the stop signal (0.15, SE = 0.07, $z = 2.33$, $p < 0.05$). A summary of the analyses can

IC group



AC group

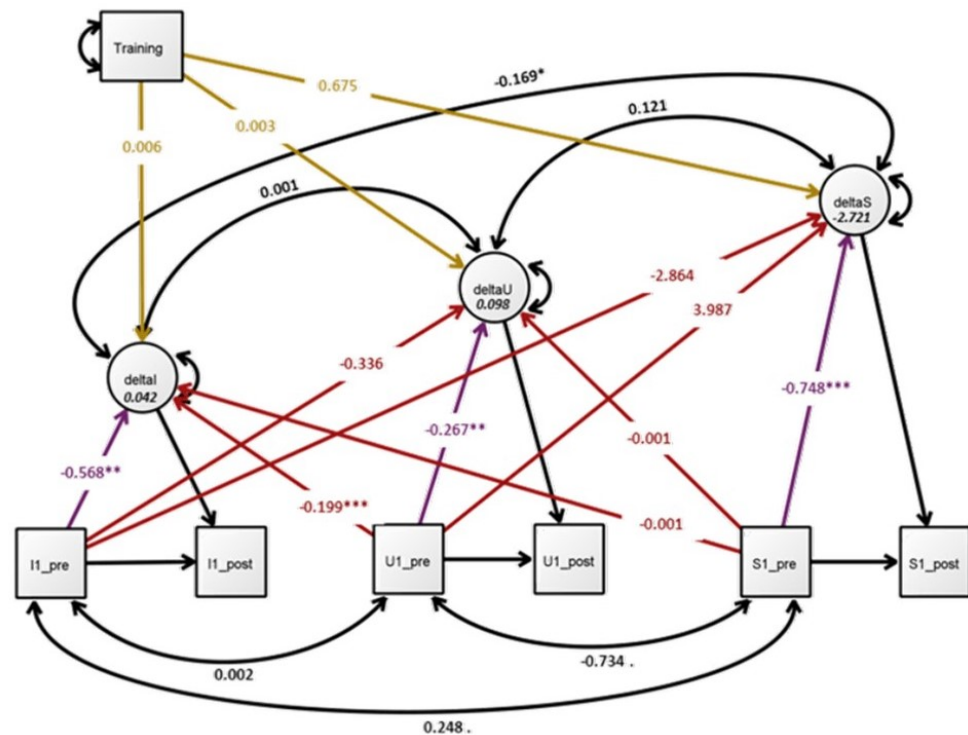
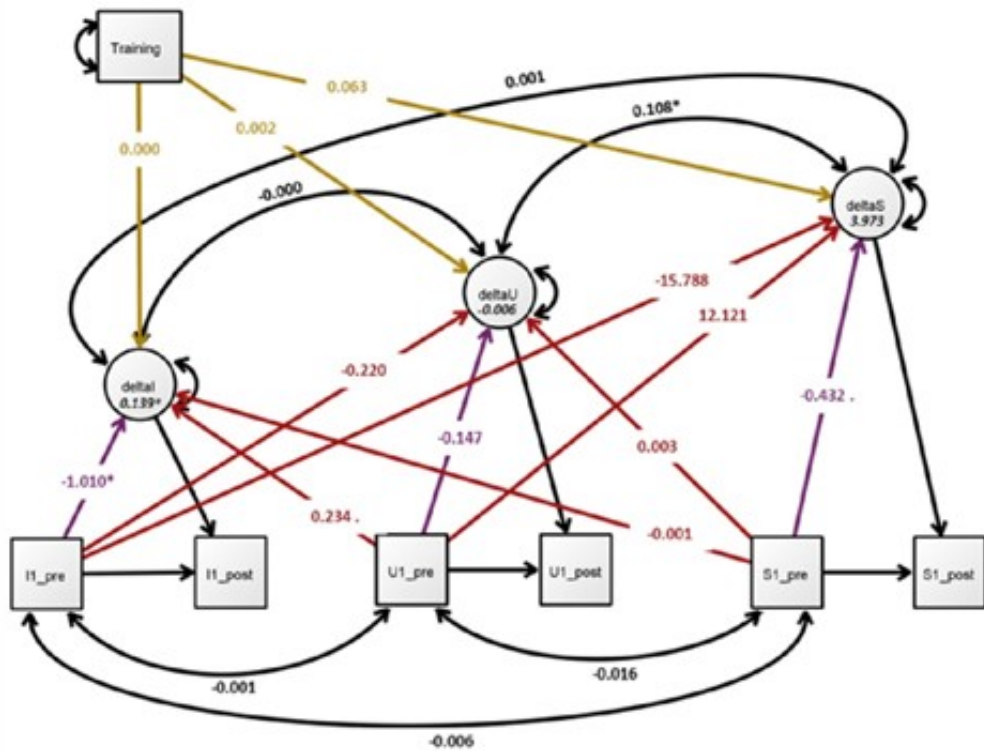


Figure 3.2: Estimated parameters for the LCS model in children without equality constraints between groups: IC group (experimental) on top and AC group (control) on bottom. Further results are given in Table 3.2. I1 = stop signal; U1 = N-back; S1 = TMT; pre = before training; post = after training.

IC group



AC group

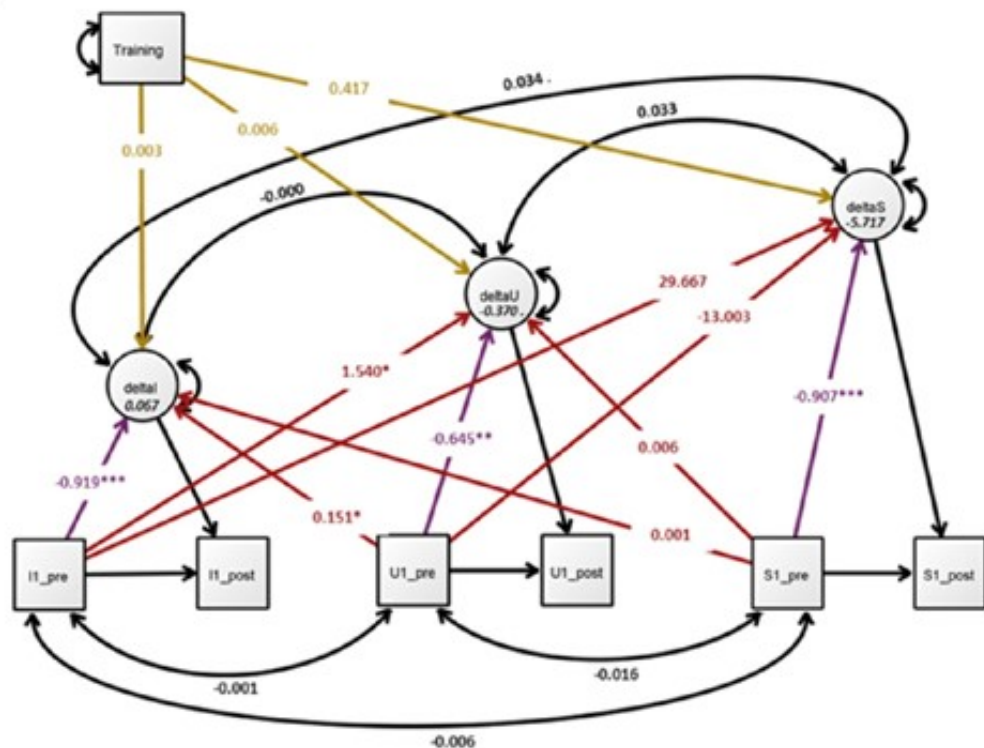


Figure 3.3: Estimated parameters for the LCS model in adolescents without equality constraints between groups: IC group (experimental) on top and AC group (control) on bottom. Further results are given in Table 3.2. I1 = stop signal; U1 = N-back; S1 = TMT; pre = before training; post = after training.

be found in Table 3.2.

3.2.3 LCS model in children with Stroop task as IC measure

Analysis of the free LCS model (Table 3.3) with the Stroop at pretest in children revealed that TMT was marginally correlated with Nback ($r = -0.75$, $SE = 0.43$, $z = -1.72$, $p = 0.09$).

In the experimental group (IC), the intercept for the latent change score was marginal for the N-back (-0.62 , $SE = 0.32$, $z = -1.95$, $p = 0.05$; all other $ps > 0.32$), thus indicating a marginal change in N-back scores after IC training, but not in the TMT or Stroop scores. The self-feedback parameters were significantly negative for the Stroop (-0.89 , $SE = 0.14$, $z = -6.48$, $p < 0.001$) and TMT (-1.12 , $SE = 0.25$, $z = -4.49$, $p < 0.001$) tasks and marginal for the N-back task (-0.27 , $SE = 0.14$, $z = -1.90$, $p = 0.06$), thus indicating that higher initial scores (and thus a lower EF ability) on one EF task corresponded to greater gains on that task. The analysis of the coupling parameters, which indicated crossed effects between gains in one EF and initial performance in the two other EFs, showed that individuals with the larger improvement on the TMT had a higher Stroop score (i.e., a lower IC ability; 25.01 , $SE = 12.14$, $z = 3.82$, $p < 0.05$) and a lower N-back score (i.e., a better updating ability; -14.70 , $SE = 7.81$, $z = -1.88$, $p = 0.06$) at baseline. Additionally, children with a higher TMT score (i.e., a poorer switching ability) at baseline improved more on the N-back (0.01 , $SE = 0.00$, $z = 2.58$, $p < 0.05$) and on the Stroop (0.01 , $SE = 0.00$, $z = 3.82$, $p < 0.001$) tasks. Finally, the number of training sessions was not significantly related to any of the EF latent changes.

In the control training group (AC), there was no significant intercept for the latent variables related to the EF score changes (all $ps > 0.10$), thus indicating no significant changes in EF scores after AC training. However, in contrast to the IC group, the latent change scores related to Stroop and to TMT were marginally correlated ($r = 0.30$, $SE = 0.16$, $z = 1.88$, $p = 0.06$), thus suggesting that increased performance in Stroop following training was associated with an increased performance in TMT following training. As in the IC group, all the self-feedback parameters were significantly negative (all $ps < 0.01$ except for N-back whose $p = 0.05$). The coupling parameters showed that individuals with the larger improvement on the Nback had a lower Stroop score (i.e., a lower IC ability; -0.51 , $SE = 0.28$, $z = -1.81$, $p = 0.07$) and a lower TMT score (i.e., a lower switching ability; -0.01 , $SE = 0.00$, $z = -1.78$, $p = 0.07$) at baseline. Additionally, children with a higher Stroop score (i.e., a poorer IC ability) at baseline improved more on the TMT (24.30 , $SE = 11.69$, $z = 2.08$, $p < 0.05$).

3.2.4 LCS model in adolescents with Stroop task as IC measure

The analysis at the pretest of the Stroop free LCS model in adolescents (Table 3.3) did not reveal any significant correlation between any of the EF task scores (all $ps > 0.11$).

In the experimental group (IC), the latent change intercept for the Stroop was marginal (0.08 , $SE = 0.05$, $z = 1.73$, $p = 0.08$; all other $ps > 0.47$), thus indicating a marginal change in Stroop scores after IC training, but not for the TMT or N-back scores. In addition, latent changes in N-back and TMT were correlated ($r = 0.10$, $SE = 0.04$, $z = 2.58$, $p < 0.05$). The self-feedback parameter was significantly negative for the Stroop (-0.88 , $SE = 0.14$, $z = -6.32$, $p <$

	Children												Adolescents											
	IC group				AC group				IC group				AC group											
	Estimate	SE	z	p	Estimate	SE	z	p	Estimate	SE	z	p	Estimate	SE	z	p								
Baseline effects (β)																								
Stop signal	-0.815 ± 0.178		-4.580	<0.001	-0.568 ± 0.168		-3.374	<0.01	-1.010 ± 0.391		-2.580	<0.05	-0.919 ± 0.157		-5.859	<0.001								
N-back	-0.282 ± 0.156		-1.813	0.070	-0.267 ± 0.102		-2.622	<0.01	-0.147 ± 0.136		-1.084	0.279	-0.645 ± 0.230		-2.804	<0.01								
TMT	-1.006 ± 0.284		-3.543	<0.001	-0.748 ± 0.208		-3.589	<0.001	-0.432 ± 0.233		-1.857	0.063	-0.907 ± 0.137		-6.633	<0.001								
Crossed effects (γ)																								
N-back → Stop signal change	-0.059 ± 0.057		-1.047	0.295	-0.199 ± 0.050		-3.954	<0.001	0.234 ± 0.122		1.917	0.055	0.151 ± 0.065		2.325	<0.05								
TMT → Stop signal change	-0.001 ± 0.001		-1.222	0.222	-0.001 ± 0.002		-0.546	0.585	-0.001 ± 0.002		-0.232	0.816	0.001 ± 0.001		0.596	0.551								
Stop signal → N-back change	0.518 ± 0.344		1.503	0.133	-0.336 ± 0.667		-0.503	0.615	-0.220 ± 0.465		-0.473	0.636	1.540 ± 0.720		2.140	<0.05								
TMT → N-back change	0.007 ± 0.003		1.952	0.051	-0.001 ± 0.005		-0.193	0.847	0.003 ± 0.003		1.096	0.273	0.006 ± 0.005		1.256	0.209								
Stop signal → TMT change	61.107 ± 23.767		2.571	<0.05	-2.864 ± 20.715		-0.138	0.890	-15.788 ± 31.260		-0.505	0.614	29.667 ± 25.768		1.151	0.250								
N-back → TMT change	-15.141 ± 8.176		-1.852	0.064	3.987 ± 7.953		0.501	0.616	12.121 ± 9.612		1.261	0.207	-13.003 ± 9.116		-1.426	0.154								
Number of sessions effects																								
Stop signal	0.001 ± 0.003		0.210	0.833	0.006 ± 0.004		1.401	0.161	0.000 ± 0.002		0.182	0.856	0.003 ± 0.003		0.915	0.360								
N-back	0.028 ± 0.013		2.171	<0.05	0.003 ± 0.020		0.163	0.870	0.002 ± 0.006		0.292	0.771	0.006 ± 0.010		0.581	0.561								
TMT	1.039 ± 0.440		2.361	<0.05	0.675 ± 0.782		0.864	0.388	0.063 ± 0.228		0.278	0.781	0.417 ± 0.259		1.610	0.107								
Covariances																								
Stop signal & N-back changes	-0.001 ± 0.002		-0.402	0.688	0.001 ± 0.002		0.295	0.768	0.000 ± 0.000		-0.966	0.334	0.000 ± 0.001		-0.708	0.479								
Stop signal & TMT changes	0.105 ± 0.078		1.342	0.180	-0.169 ± 0.082		-2.068	<0.05	0.001 ± 0.021		0.050	0.960	0.034 ± 0.020		1.711	0.087								
N-back & TMT changes	0.194 ± 0.219		0.889	0.374	0.121 ± 0.379		0.319	0.749	0.108 ± 0.055		1.981	<0.05	0.033 ± 0.072		0.459	0.646								
Stop signal & N-back baselines	0.002 ± 0.002		0.807	0.419	0.002 ± 0.002		0.807	0.419	-0.001 ± 0.000		-1.603	0.109	-0.001 ± 0.000		-1.603	0.109								
Stop signal & TMT baselines	0.248 ± 0.138		1.792	0.073	0.248 ± 0.138		1.792	0.073	-0.006 ± 0.036		-0.164	0.869	-0.006 ± 0.036		-0.164	0.869								
N-back & TMT baselines	-0.734 ± 0.440		-1.670	0.095	-0.734 ± 0.440		-1.670	0.095	-0.016 ± 0.067		-0.241	0.810	-0.016 ± 0.067		-0.241	0.810								
Intercepts																								
Stop signal change	0.182 ± 0.080		2.276	<0.05	0.042 ± 0.091		0.461	0.645	0.139 ± 0.068		2.045	<0.05	0.067 ± 0.069		0.974	0.330								
N-back change	-0.836 ± 0.320		-2.609	<0.01	0.098 ± 0.442		0.222	0.824	-0.006 ± 0.147		-0.041	0.967	-0.370 ± 0.223		-1.660	0.097								
TMT change	-18.531 ± 9.985		-1.856	0.063	-2.721 ± 18.407		-0.148	0.882	3.973 ± 8.683		0.458	0.647	-5.717 ± 7.757		-0.737	0.461								
Training sessions	19.889 ± 0.523		38.003	<0.001	20.3 ± 0.415		48.869	<0.001	23.457 ± 0.712		32.958	<0.001	22.783 ± 0.522		43.680	<0.001								

Table 3.2: Summary of the LCS analyses with stop signal as IC measure. Abbrev. SE: Standard error.

	Children						Adolescents					
	IC group		AC group		IC group		AC group		IC group		AC group	
	Estimate ± SE	z	P	Estimate ± SE	z	p	Estimate ± SE	z	p	Estimate ± SE	z	p
Baseline effects (β)												
Stroop	-0.886 ± 0.137	-6.481	<0.001	-0.646 ± 0.178	-3.628	<0.01	-0.877 ± 0.139	-6.318	<0.001	-0.953 ± 0.183	-5.200	<0.001
N-back	-0.268 ± 0.142	-1.895	0.058	-0.251 ± 0.131	-1.925	0.054	-0.118 ± 0.120	-0.981	0.326	-0.800 ± 0.207	-3.856	<0.001
TMT	-1.115 ± 0.248	-4.492	<0.001	-0.749 ± 0.169	-4.430	<0.001	-0.579 ± 0.208	-2.786	<0.01	-1.131 ± 0.155	-7.280	<0.001
Crossed effects (γ)												
N-back → Stroop change	-0.003 ± 0.083	-0.034	0.973	-0.077 ± 0.206	-0.374	0.708	0.134 ± 0.127	1.054	0.292	0.067 ± 0.146	0.462	0.644
TMT → Stroop change	0.005 ± 0.001	3.820	<0.001	-0.004 ± 0.004	-1.175	0.240	-0.003 ± 0.002	-1.618	0.106	-0.009 ± 0.004	-2.194	<0.05
Stroop → N-back change	0.191 ± 0.174	1.093	0.274	-0.507 ± 0.280	-1.812	0.070	-0.033 ± 0.221	-0.148	0.882	0.242 ± 0.309	0.784	0.433
TMT → N-back change	0.007 ± 0.003	2.576	<0.05	-0.006 ± 0.003	-1.784	0.074	0.003 ± 0.003	1.075	0.283	0.005 ± 0.005	0.868	0.385
Stroop → TMT change	25.011 ± 12.136	3.820	<0.05	24.295 ± 11.693	2.078	<0.05	23.150 ± 6.751	3.429	<0.01	28.118 ± 8.313	3.382	<0.001
N-back → TMT change	-14.699 ± 7.813	-1.881	0.060	6.167 ± 7.169	0.860	0.390	19.628 ± 4.259	4.608	<0.001	-22.373 ± 8.031	-2.786	<0.01
Number of sessions effects												
Stroop	0.003 ± 0.006	0.458	0.647	-0.018 ± 0.011	-1.639	0.101	-0.001 ± 0.002	-0.946	0.344	0.008 ± 0.006	1.211	0.226
N-back	0.021 ± 0.014	1.558	0.119	0.003 ± 0.017	0.180	0.857	-0.003 ± 0.006	-0.600	0.549	0.005 ± 0.010	0.516	0.606
TMT	0.570 ± 0.441	1.293	0.196	-0.033 ± 0.766	-0.043	0.965	0.198 ± 0.125	1.574	0.115	0.383 ± 0.236	1.622	0.106
Covariances												
Stroop & N-back changes	0.003 ± 0.002	1.206	0.228	-0.004 ± 0.004	-0.972	0.331	0.000 ± 0.001	0.197	0.844	0.000 ± 0.002	0.089	0.929
Stroop & TMT changes	0.029 ± 0.159	0.181	0.856	0.301 ± 0.160	1.877	0.061	-0.027 ± 0.025	-1.057	0.290	0.095 ± 0.037	2.551	<0.05
N-back & TMT changes	0.314 ± 0.220	1.431	0.152	0.151 ± 0.256	0.593	0.553	0.103 ± 0.040	2.576	<0.05	0.026 ± 0.066	0.395	0.693
Stroop & N-back baselines	0.008 ± 0.005	1.596	0.110	0.008 ± 0.005	1.596	0.110	-0.000 ± 0.001	-0.139	0.889	-0.000 ± 0.001	-0.139	0.889
Stroop & TMT baselines	-0.034 ± 0.333	-0.101	0.919	-0.034 ± 0.333	-0.101	0.919	0.110 ± 0.069	1.603	0.109	0.110 ± 0.069	1.603	0.109
N-back & TMT baselines	-0.747 ± 0.433	-1.723	0.085	-0.747 ± 0.433	-1.723	0.085	0.008 ± 0.068	0.113	0.910	0.008 ± 0.068	0.113	0.910
Intercepts												
Stroop change	-0.110 ± 0.111	-0.989	0.323	0.490 ± 0.299	1.638	0.101	0.084 ± 0.049	1.732	0.083	-0.038 ± 0.135	-0.285	0.776
N-back change	-0.618 ± 0.316	-1.953	0.051	0.168 ± 0.330	0.509	0.611	0.085 ± 0.146	0.580	0.562	-0.106 ± 0.205	-0.518	0.604
TMT change	5.215 ± 10.536	0.495	0.621	7.354 ± 16.747	0.439	0.661	-2.657 ± 3.698	-0.718	0.472	-0.208 ± 5.423	-0.038	0.969
Training sessions	20.704 ± 0.531	38.982	<0.001	20.300 ± 0.415	48.869	<0.001	24.304 ± 0.824	29.508	<0.001	22.783 ± 0.522	43.680	<0.001

Table 3.3: Summary of the LCS analyses with Stroop as IC measure. Abbrev. SE: Standard error.

0.001) and the TMT (-0.58 , $SE = 0.21$, $z = -2.79$, $p < 0.01$) but failed to reach significance for the N-back ($p = 0.33$). The analysis of the coupling parameters indicated that adolescents with the larger improvement on the TMT had a higher Stroop score (i.e., a lower IC ability; 23.15 , $SE = 6.75$, $z = 3.43$, $p < 0.01$) and a higher N-back score (i.e., a lower updating ability; 19.63 , $SE = 4.26$, $z = 4.61$, $p < 0.001$) at baseline. The other coupling parameters did not reach significance (all $ps > 0.28$).

In the control training group (AC), there were no significant latent change intercept (all $ps > 0.60$), thus indicating no significant change in the EF scores after the AC training. Latent changes in Stroop and TMT were positively correlated ($r = 0.10$, $SE = 0.04$, $z = 2.55$, $p < 0.05$), thus indicating that increased performance in Stroop following training was associated with increased performance in TMT following training, and vice versa. All the self-feedback parameters were significantly negative (all $ps < 0.001$), thus indicating that a lower efficiency on one EF task corresponded to greater gains on that task following training. The analysis of the coupling parameters indicated that individuals with the larger improvement on the TMT had a higher Stroop score (i.e., a lower IC ability; 28.12 , $SE = 8.31$, $z = 3.38$, $p < 0.001$) and a lower N-back score (i.e., a higher updating ability; -22.37 , $SE = 8.03$, $z = -2.79$, $p < 0.01$) at baseline. A summary of the analyses can be found in Table 3.3.

4 Discussion

This study reported the first multivariate LCS analysis of the effect on EFs of IC training in children and adolescents. When compared to repeated-measures ANOVAs, LCS models allowed us to identify the transfer of IC training on EFs and the modulation of such an effect as a function of individual differences in training receptivity.

Previous studies of transfer following executive training have shown mixed results. Some studies have reported far transfer (Aydmune et al., 2019; Beauchamp et al., 2016; Jaeggi et al., 2011; Liu et al., 2015; Maraver et al., 2016; Söderqvist and Bergman Nutley, 2015), other studies only near transfer (Bergman Nutley et al., 2011; Dunning et al., 2013; Zhao et al., 2015) and some studies no effect of the training at all (Enge et al., 2014; Talanow and Ettinger, 2018; Thorell et al., 2009). Our study, using a new statistical approach which can model more accurately the theory, could detect both near and far transfer effects following IC training. Hence, the mixed, and sometimes null, results reported in previous studies may be related to the choice of the statistical tools. The use of LCS in executive training therefore open new perspectives for both research and application.

Indeed, although the repeated-measures ANOVAs could only detect near transfer in the IC abilities of children, LCS detected near transfer in IC but also a far transfer effect in the updating abilities of children. The transfer detected in children with LCS is similar to previous IC training studies in children (Aydmune et al., 2019; Liu et al., 2015) and young adults (Beauchamp et al., 2016; Maraver et al., 2016). In adolescents, LCS, but not ANOVAs, detected significant changes in IC abilities after training. Of note, no far transfer effect could be detected in adolescents via ANOVAs or LCS. Such lack of transfer could be related with the EFs specialization with age, with decreased EF unity and increased EF diversity, thus leading to decreased common shared EFs (Agostino et al., 2010; Friedman et al., 2016;

Hartung et al., 2020; Lee et al., 2013; McAuley and White, 2011; Wu et al., 2011; Xu et al., 2013). Indeed, with age, EF structure progresses from a one-factor structure in early childhood with no clear dissociation between EFs (Shing et al., 2010; Wiebe et al., 2008; Willoughby et al., 2012; Xu et al., 2013) to a two- to four-factors structure at adolescence (Agostino et al., 2010; Friedman et al., 2016; Lee et al., 2013; McAuley and White, 2011; Wu et al., 2011; Xu et al., 2013). Hence, although in childhood, updating, switching and IC likely rely on similar underlying cognitive processes, in adolescence, EFs become more specialized and independent. This developmental change in EF organization (for a review: Lee et al., 2013) is supported by a recent brain imaging study reporting an increasing segregation of structural brain network modules with age, and this segregation mediates the effects of age on EFs (Baum et al., 2017). Such differentiation of EF organization from childhood to adolescence may also explain the stronger correlations observed in children compared to adolescents between EF tasks at baseline.

The LCS analysis also revealed that children and adolescents with lower initial EF abilities progress more than those individuals with higher initial EF abilities, thus confirming the results of previous studies that training provides greater benefits for children with lower EFs (Au et al., 2015; Diamond and Lee, 2011; Jaeggi et al., 2008). Such findings are in line with the ‘compensation account hypothesis’ (Karbach and Kray, 2021).

In addition, transfer effects (as measured by latent changes in updating and switching) depend not only on the initial levels in each of these EFs but also on the initial levels in the other EFs (cross-effects). Such cross-effects are consistent with a previous study on older adults that demonstrated that WM training led to both a larger training receptivity and marginally to larger transfer effects in planning, IC and fluid intelligence qualities in participants with lower cognitive abilities before training (Zinke et al., 2014). These cross-effects were less important in adolescents than in children. This age difference may be due to a lower training receptivity in adolescents. It may also be a consequence of the separation/specialization of EFs with age. Indeed, cross-effects are likely related to the common shared EFs; additionally, as previously mentioned, this common shared EFs decreases from childhood to adolescence with EF separation/specialization (Agostino et al., 2010; Friedman et al., 2016; Hartung et al., 2020; Lee et al., 2013; McAuley and White, 2011; Wu et al., 2011; Xu et al., 2013).

Finally, we observed a positive linear dose effect of the number of IC training sessions with the learning gains in updating and switching (but not in IC) in children. This finding is similar to previous studies demonstrating that direct benefits of EF training depend on the duration of training (Diamond and Ling, 2016; Jolles and Crone, 2012). Of note, in the present study, the dose effect was only found in nontrained EF tasks (far transfer). The lack of a dose effect in IC tasks may be related to a possible ceiling effect.

Ceiling effect may also contribute to the lack of transfer in adolescent (see Figure 27 in the General Method section, which suggests that 1) adolescents did not progress after the 4th session and 2) the Stroop task used for the IC training was too easy since participants reached the highest level quickly). This ceiling effect could be due, in part, by a decrease in motivation. Similarly, the decrease in performance on the training tasks in children can be explained by a decrease in motivation as well after more than 4 weeks of training. However, we did not have any quantitative measure of motivation, but only qualitative assessments

(auto-evaluation reports) and could not therefore test this hypothesis. For these reasons, it is not possible to disentangle the possible methodological issues from the developmental effects underlying the lack of transfer observed in adolescents. Of note, the separate analysis of the congruent and incongruent items in the Stroop task (see Appendix A6), revealed that the lack of change in Stroop interference score (RT difference between congruent and incongruent conditions) in the IC and AC groups correspond to different mechanisms: in IC group, RT decrease after training in both congruent and incongruent conditions, while in AC group, RT remain stable after training in both congruent and incongruent conditions.

It should be noted that LCS analyses yielded very similar findings regarding baseline effects, far transfer and crossed-effects using IC measured either by the stop signal task or the Stroop task, thus reflecting the robustness of our analyses. The main differences concerns the near transfer since LCS can detect IC change if the stop signal is used in the model but no IC change if the Stroop is used. Of note, no Stroop change could be detected with the classical ANOVAs nor the LCS.

Of note, LCS analysis detected changes after AC training. Several reasons may explain such training effects in the control group. First, participants in the AC group followed an active, and not a passive, 5-week training. Second, possible test-retest effects may have occurred. Finally, childhood and adolescence are developmental periods with intensive EF development, we cannot therefore rule out the possibility that the changes detected in the AC group are actually related to normal cognitive development. All these reasons support the use of an active control group to control for these different biases.

The present study had several limitations that warrant caution when interpreting the results. This study reports the first LCS analysis of EF training in children and adolescents. The SEM models uses robust estimates and have good fit, supporting the robustness of our findings. The sample size of the current study is in line with the classical criteria based on model complexity, with 3 – 10 participants per estimated parameter or variable (Bentler and Chou, 1987; Cattell, 1978). Like for all statistical methods, an increase in the sample size would increase the sensibility and specificity of the SEM analyses (Wang et al., 2021). Although statistically significant effects were detected, our findings should be replicated with a large and independent sample. In addition, such a 5-week longitudinal computerized-training study in children and adolescents is logistically complex to organize. Thus, only IC training could be investigated. Therefore, the training receptivity and transfer effects observed for IC should also be investigated in updating and switching training, which would allow us to evaluate to what extent the reported findings are EF training specific. Another issue of this study is the use of N-back to measure Updating. Indeed, this task is not a pure measure of Updating (Jaeggi et al., 2011; Kane et al., 2007), in particular the IC load increases with the number of lures (Kane et al., 2007). However, it is important to note that N-back task is classically used in the literature (Cohen et al., 1997; Gevins and Cutillo, 1993; Jaeggi et al., 2010) since it remains a valid indicator of working memory (Schmiedek et al., 2014). Finally, it may be interesting to have different tasks taping on the same EF, which would enable us to assess the EF change not at the task level but at the level of the EF construct, specifically by using latent variables for each EF. Such direct transposition of the model of Miyake et al., 2000 with latent variables into a longitudinal design would provide key data to investigate the near transfer effects.

In conclusion, our study shows that LCS modeling revealed transfer effects that were not detected with the use of classical univariate analysis of variance applied to the same data. This lower sensitivity of ANOVA may explain the lack of transfer effects that have been reported in EF training studies by using classical statistical approaches (Kassai et al., 2019). Due to its versatility, LCS can assess training transfer both directly (from the estimation of the training-related changes) and indirectly (from the effects of the initial level of each EF on the training-related changes of the other EFs).

STUDY 4: ASSOCIATIONS BETWEEN BRAIN, EFs AND TRAINING RECEPTIVITY

After showing that cognitive factors could play a role in the receptivity to inhibitory control training, we wanted to know if factors at a cerebral level were also involved in the gains after such training.

Study 4: Associations between brain, EFs and training receptivity

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1 Introduction

Executive functions are supported by a large cerebral network (see Section 2 of the Introduction). As reported previously, the three basic EFs (i.e., IC, WMU and CF) elicit frontal (e.g., dorsolateral PFC and ACC) and parietal (e.g., superior and inferior parietal lobes and precuneus) activations, suggesting a common EF (Collette et al., 2006; Niendam et al., 2012; Wager et al., 2004; Wager and Smith, 2003). However, while some regions would play an integrative and more common role, other regions would be more specialized for a specific EF (Collette et al., 2006; Luna et al., 2015; Nee et al., 2013; Niendam et al., 2012; Simmonds et al., 2008; Wager et al., 2004; Wager and Smith, 2003), reflecting on a cerebral level the unity and diversity of EFs. Of note, this cerebral organisation of EFs can vary with age (for a review, Fiske and Holmboe, 2019) but also with training.

Indeed, as seen in section 6.2.1.1 of the General Introduction, IC training has been shown to influence various brain characteristics (Jolles and Crone, 2012; Owen et al., 2010), such as the degree of activity in IC-related areas such as the prefrontal cortex, including IFG and ACC. For example, in adults, studies have shown that short term (i.e., 1 hour) and middle term (i.e., 5 to 10 hours over several weeks) IC training leads to functional changes in the inhibition brain network, particularly the prefrontal (Berkman et al., 2014; Manuel et al., 2013; Spierer et al., 2013) and parietal (Manuel et al., 2010) cortices. Moreover, this type of executive training not only improves FC between the IC network and other networks, but it also increases activity in specific areas (Hu et al., 2017). Delalande et al., 2020 also demonstrated an evolution of cortical thickness and cortical surface area in the same IC regions following an IC computerized training. Finally, one study combined functional and structural MRI to investigate functional and anatomical neuroplastic changes after an IC training using a stop signal task (Chavan et al., 2015) and highlighted that IC gains were associated with a neural activity decrease in the right pars opercularis and triangularis and in the left pars orbitalis of the IFG and a gray matter volume increase in the right pars orbitalis and modulations of white matter microstructure in the right pars triangularis.

As we have also seen previously, cognitive training does not benefit all participants in the same way and inter-individual differences are important. For example, we saw in the Study 3 that the initial cognitive level influenced the benefits of the training through a compensation phenomenon (Karbach and Kray, 2021). It has been shown that cerebral organization can also influence the receptivity to training (Baniqued et al., 2019; Baniqued et al., 2018; Chaddock-Heyman et al., 2020; Gallen et al., 2016). For example, higher brain networks' modularity measured in rsfMRI before a physical activity intervention was related to more important progress in EFs in children (Chaddock-Heyman et al., 2020) and older adults (Baniqued et al., 2018). Similarly, brain modularity was positively related to cognitive gains following numerical cognitive training targeting working memory and reasoning in young adults (Baniqued et al., 2019) and older adults (Gallen et al., 2016), and this was even more important for participants who performed more poorly initially (Baniqued et al., 2019). To date, and to our knowledge, only one study has investigated the neuroplastic anatomical characteristics underlying training receptivity (Chavan et al., 2015), and no study has explored this on a whole brain scale.

In this study, we wanted to see to what extent the anatomy of brain regions involved in

the EF efficacy were also involved in EF gains after cognitive training. To address this issue, we conducted two analyses. First, we examined the brain regions with grey matter volume associated with EF efficiency at baseline. Then, we studied the brain regions with changes in grey matter volume associated to efficiency progress in an EF task following cognitive training. We could then examine if the brain areas involved in EF efficacy corresponds to brain areas related to training receptivity.

2 Material and Methods

2.1 Participants

For the first analysis (brain areas involved in EFs tasks before any training), all participants in the APEX cohort were used (including the mindfulness and working memory training groups in order to have the largest possible sample size). The sample was then composed of 110 children (9.85 ± 0.52 years; 61 females) and 88 adolescents (16.71 ± 0.54 years; 53 females).

For the second question (brain areas whose changes are related to progress following cognitive training), only participants from the AC and IC groups and who completed a minimum of 15 training sessions were included, i.e., 57 children (9.79 ± 0.55 years; 33 females) and 48 adolescents (16.57 ± 0.50 years; 33 females).

2.2 EF measures

The same six cognitive measures were investigated as in Study 1, namely 4 measures of inhibitory control (stop signal reaction time, Stroop interference, Simon interference, ANT flanker score), 1 measure of cognitive flexibility (trail making test flexibility score) and 1 measure of working memory updating (N-back updating cost).

2.3 Pre-processing of anatomical MRI data

Voxel-Based Morphometry (VBM) was performed with CAT12 (<http://www.neuro.uni-jena.de/cat>). The analysis stream includes non-linear spatial registration to the 1.5mm³ MNI template, Gray Matter (GM), White Matter, and CerebroSpinal Fluid (CSF) tissues segmentation, bias correction of intensity non-uniformities, and segmentations modulation by scaling with the amount of volume changes due to spatial registration. We performed QC visual analysis: 1) we monitored the Noise Contrast Ratio (NCR) and Image Quality Rating (IQR) as two metrics of quality and we retained only images at a threshold below 4; 2) we sort the images by increasing IQR score and images with the higher IQR were visually inspected.

2.4 Statistical analyses

In order to investigate whether there were brain regions with grey matter volume associated with an EF score at pretest, we first performed whole brain voxel-wise analyses with one-sample t-tests using FSL, for pre-test performance at each task (SST, Stroop, Simon, ANT, TMT, N-back) and for each age group (children, adolescents) separately ($6 \times 2 = 12$ independent analyses). This analysis was performed on pre-training data, so there was no training group factor. The FSL tool Randomise, a non-parametric permutation testing ($n = 500$), was used for the voxel-wise analysis of MRI data (Winkler et al., 2014). The threshold for significance was $p < 0.05$, using threshold-free cluster enhancement (TFCE) method with family wise-error (FWE) correction for multiple comparisons (Smith et al., 2019).

In order to examine the local changes in brain volume related to changes in cognitive scores after training, we performed voxel-wise correlations between the differences in VBM maps (post-pre) and differences in cognitive scores (post-pre). Analyses were performed for each EF task, each age group and each age group separately ($6 \times 2 \times 2 = 24$ independent analyses). Randomise with 500 permutations was used and the threshold was still $p < 0.05$ using TFCE with FWE correction for multiple comparisons.

3 Results

3.1 Neural basis of EFs

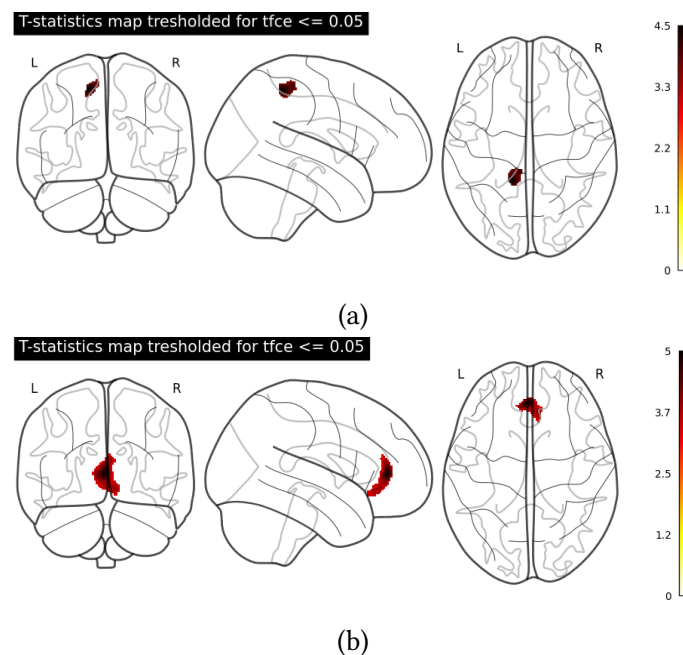


Figure 4.1: Brain voxels involved in (a) Stroop and (b) Trail making test performance at pre-test in adolescents.

In children, the analyses revealed no significant association between local grey matter volume with any of the 6 EF scores at pre-test after TFCE correction (all $ps > .08$). TFCE-corrected images of the uncorrected results are available in Appendix A7.

In adolescents, the analyses revealed a significant association between the grey matter volume in, on one hand, the left ACC and the TMT performance at pre-test and, on the other hand, the left precuneus and the Stroop performance at pre-test (see Figure 4.1). No other significant association after TFCE correction was detected (all $ps > .18$). TFCE-corrected images of the uncorrected results are available in Appendix A7.

3.2 Neural basis of training receptivity

In children, a large area of voxels was identified as significantly related to cognitive change in Stroop but after AC training only ($p < .01$). This area covered a large part of the left medial frontal gyrus (MFG) as well as the inferior frontal gyrus (IFG) and the cingulate gyrus (see Figure 4.2). For the other tasks and training group, no significant results after TFCE correction could be identified (all $ps > .06$). TFCE-corrected images of the uncorrected results are available in Appendix A8.

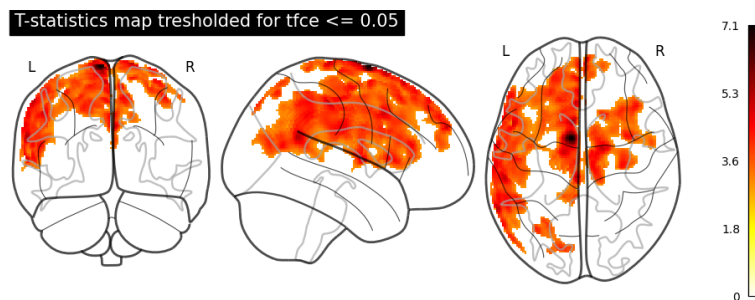


Figure 4.2: **Brain voxels involved in Stroop progress following an AC training in children.**

In adolescents, several regions were found to be significantly related to cognitive change in Stroop after both AC and IC ($ps < .05$) training (see Figure 4.3). The regions corresponded to the left insula, the left IFG and the left and right ACC for the IC group (see Figure 4.3a) and to a part of the right middle temporal gyrus for the AC group (see Figure 4.3b). Some voxels or the left ACC and middle frontal gyrus were also associated with cognitive change in Trail making test after AC training ($p < .05$). For the other tasks, in this age group, no significant results after TFCE correction could be identified (all $ps > .09$). TFCE-corrected images of the uncorrected results are available in Appendix A9.

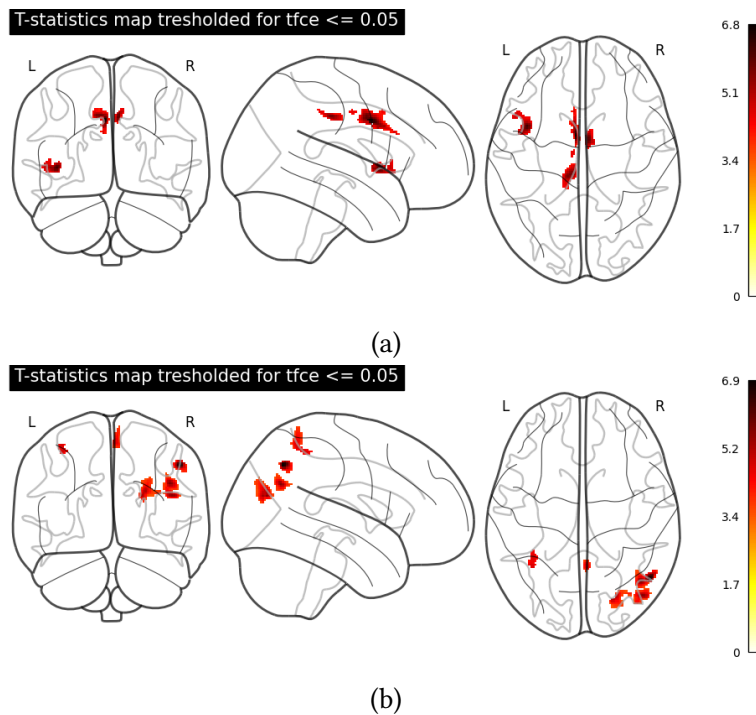


Figure 4.3: Brain voxels involved in Stroop progress following (a) an IC or (b) an AC training in adolescents.

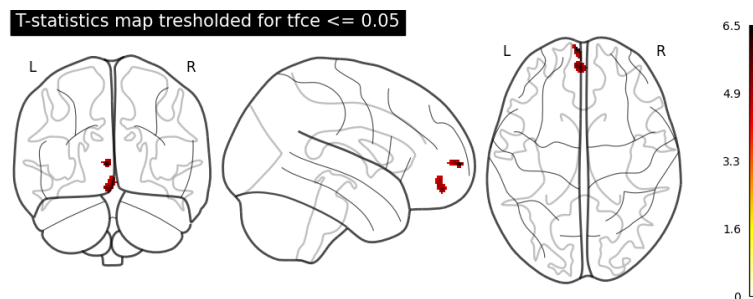


Figure 4.4: Brain voxels involved in Trail making test progress following an AC training in adolescents.

4 Discussion

The aim of this study was to examine whether the brain areas involved in executive functioning were the same as the regions involved in responsiveness to cognitive training.

To test this hypothesis, we first looked at which brain areas were significantly associated with each of our 6 executive tasks, in children and in adolescents separately. On all six EF tasks, regions were shown to be significantly associated with TMT and Stroop and in adolescents only. Because these regions were located in the left ACC and left precuneus, these results are consistent with those previously observed in the literature (Collette et al., 2005; Dajani and Uddin, 2015; Dosenbach et al., 2006; Gläscher et al., 2012; Kim et al., 2012;

Leber et al., 2008; Niendam et al., 2012). We anticipated associations between our EF tasks and brain areas previously described as EFs' brain bases such as the IFG (Aron, 2006; Aron et al., 2003; Obeso et al., 2013; Rubia et al., 2001), or the Putamen (Pas et al., 2019; Pas et al., 2017; Vink et al., 2005). However, this lack of results may be explained by the small sample size for whole brain association studies. Indeed, it has recently been shown that it would require samples of at least 1000 subjects for such analyses (Marek et al., 2022). In smaller cohorts, a solution to observe brain-behavior association in smaller cohorts would be to employ more suitable methods such as machine learning models (Genon et al., 2022). Of note, we have performed preliminary machine learning analyses with a linear Ridge model but they were inconclusive (see Appendix A10.1).

Then, we examined the local changes in brain volume associated with cognitive changes after IC or AC training. In children, a large number of brain regions, including the medial-frontal and inferior-frontal gyrus (IFG), were shown to be related to change in stop signal after AC training. However, at the cognitive level, changes were not shown to be significant in this group (see Table 3). In adolescents, interestingly, different brain regions were shown to be associated with change in Stroop after IC (insula, IFG, ACC) and after AC (middle temporal gyrus) training. These regions, although not detected in the first part of our analyses, correspond to the brain bases previously identified in the literature. Indeed, executive performance has been shown to be related to ACC (e.g., Aron et al., 2014; Houdé et al., 2010), insula (e.g., Molnar-Szakacs and Uddin, 2022; Varjačić et al., 2018), IFG (e.g., Bunge et al., 2002; Houdé et al., 2010). Thus, it seems that there is an overlap between the brain bases of EFs and the brain bases of training receptivity. However, given the small sample size, replication of these results on a larger, independent sample is needed. Moreover this sample size also does not allow to obtain good results with methods such as machine learning models as suggested by Genon et al., 2022 (see Appendix A10.2).

Overall, we obtained more brain-behavior associations in our second analyses than in the first ones, even if the samples were at least a third smaller ($N \sim 90-110$ for the first analyses, $N \sim 30$ for the second ones). This may seem surprising given recent results supporting the need for very large samples to observe brain-behavior associations. In reality, Marek et al., 2022 paper paves two different paths for future brain-behavior studies in neuroscience: (1) the need for large consortia to have very large sample sizes, or (2) the need for more precise, theoretically guided, noise-minimizing, signal-maximizing experimental designs (Gratton et al., 2022). For example, in clinical populations where behavior may have less variability due to its measurement (patient/control) but also due to the greater homogeneity of measurements in clinical populations than in normal populations, much smaller sample sizes may be sufficient to find nontrivial effect sizes (Libedinsky et al., 2022). As well, the use of repeated measures data, personalized for each subject (post - pre image) allowed us to increase our statistical power for our second analysis, even for brain-wide data. Having repeated measures designs allows control for inter-individual variability at the level of brain organization and can thus allow for precision analyses at the individual level (Gordon et al., 2017). Indeed, the methods used by Marek et al., 2022, while popular, do not take into account the fact that the functional organization of the brain differs from one person to another; individualized localization tools allow to obtain much better brain-behavior associations (DeYoung et al., 2022).

An interesting perspective would be to look at whether these brain effects vary with sex, especially in adolescents. Indeed, it has been shown that there are differential effects of brain anatomy on EFs according to sex in the same cohort of participants (Delalande et al., 2020). Sex-specific analyses could thus reduce noise and refine the question (Gratton et al., 2022), potentially leading to more personalized results.

Other factors could have a moderating role on these brain-behavior associations such as socioeconomic status or culture. For example, SES has been shown to be correlated with structural brain development and functional connectivity segregation, with higher SES being associated with more protracted brain development and more efficient cortical networks in adulthood (Tooley et al., 2021). In addition, different associations between cerebral activity and cognition have been observed across cultures (Han and Ma, 2014; Han and Northoff, 2008). Moreover, a recent study has highlighted a moderating effect of culture on the SES relationship with brain and cognition (Walhovd et al., 2022). Thus, it may be interesting to replicate our analyses in other cultures and socioeconomic backgrounds to see if these effects would be universal or moderated by environmental factors. In general, it would be of great interest to perform multilevel analyses to look at the different factors supporting learning while controlling for the presence of these other factors. A perspective to increase reliability and validity for brain, environmental or behavioral data is the use of SEM which, thanks to latent variables, allows to reduce the measurement error of the constructs of interest (DeYoung et al., 2022).

Furthermore, several studies have shown that brain organization (resting state functional MRI data) is associated with training responsiveness (Baniqued et al., 2019; Baniqued et al., 2018; Chaddock-Heyman et al., 2020; Gallen et al., 2016). It could thus be interesting to explore different imaging modalities, both at the anatomical level with cortical surface area or thickness, and at the functional level, at rest or related to a task, in order to understand the different factors that, within the same brain level, support learning. This could allow us to understand the precise mechanisms that are put in place and then propose the most personalized interventions possible. In addition, it was shown that overall, over the course of development, EFs goes from a global to a local cerebral organization (Fiske and Holmboe, 2019). This may explain the more important results identified in adolescents even though they seem to have benefited less from the training according to their cognitive results (see Figure 27). Moreover, it could be interesting to replicate these developmental findings from a global to a local organization, and to compare them with training results on the same sample to see if training would accelerate development (Jolles and Crone, 2012).

In conclusion, this study replicated the role of the left ACC for EFs in adolescents and highlighted the role of brain regions typically involved in executive functioning (such as insula, ACC, IFG) for receptivity to inhibitory control training. This latter result suggests that brain anatomical features of the EF brain network would also be a factor supporting executive learning.

STUDY 5: MACHINE LEARNING METHODS TO INVESTIGATE BRAIN AGING CHANGES FOLLOWING TRAINING

We were able to observe that the brain regions whose plasticity was associated with receptivity to learning corresponded to regions of the executive function brain network. These results, together with those of Study 1, support the hypothesis that training could accelerate development and lead us to test this hypothesis at the cerebral level.

Study 5: Machine learning methods to investigate brain aging changes following training

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1 Introduction

Several authors propose that cognitive training could “speed-up” the development, so that neurocognition in children would be more mature after than before training (Bryck and Fisher, 2012; Diamond and Lee, 2011; Fong et al., 2012; Jolles and Crone, 2012). Galván, 2010 also pointed out that development and learning should not be considered two separate constructs as the development is driven by interaction between both pre-specified biological maturation and also experience (Stiles, 2011). Finally, some findings also suggest that training may not mimic but rather interferes and deviates the typical developmental trajectory (Denney, 1984; Hertzog et al., 2008; Jolles and Crone, 2012).

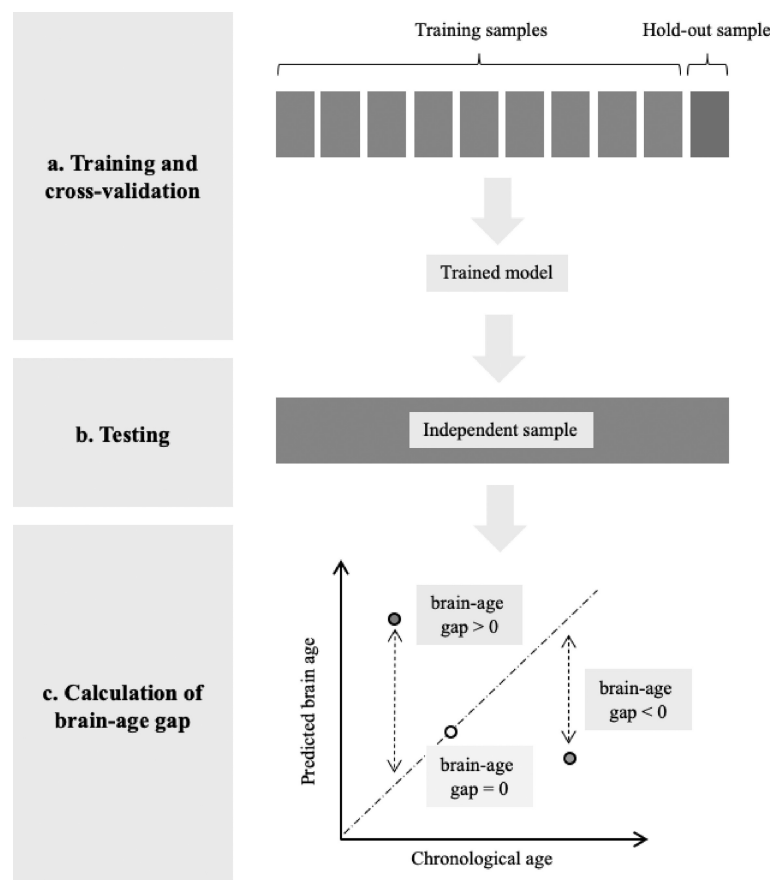


Figure 5.1: **Machine learning method for brain age prediction.** From Baecker et al., 2021b.

An interesting and original approach to test this hypothesis at the cerebral level is to calculate the brain age (i.e., predict age from cerebral information such as grey matter volume, etc.) before and after training to see if the training has indeed accelerated development (by increasing the brain age compared to the chronological age). Indeed, for the past few years and the development of machine learning, age prediction from brain imaging data has become popular (Baecker et al., 2021b).

The principle is quite simple: on a subset of data, a computer learns to predict the age

of subjects from an image of their brain and this learning is tested on another independent data set. Using such models, correlations of .90 were observed between the predicted brain age and the real chronological age (e.g., Ashburner, 2007; Dosenbach et al., 2010). It is then possible to look at the difference between the predicted brain age and the real chronological age for each subject. This brainAGE¹ (brain Age Gap Estimation, also called brain-PAD or brain-predicted age difference) can be negative (brain age < chronological age) or positive (brain age > chronological age) (see Figure 5.1).

This tool has been used extensively in psychiatry and studies have shown a larger brainAGE (i.e., a brain age greater than chronological age) is associated with schizophrenia (Hajek et al., 2019; Lee et al., 2021; Schnack et al., 2016; Shahab et al., 2019), bipolar disorder (Hajek et al., 2019; Shahab et al., 2019), autism spectrum disorder, ADHD (Kaufmann et al., 2019), Alzheimer (Beheshti et al., 2018; Gaser et al., 2013), epilepsy (de Bézenac et al., 2021; Sone et al., 2021) and even mortality (Cole et al., 2018). In clinical practice, the brainAGE could then be used to estimate the general state of health of the brain, to detect disorders before they appear (prevention), to help in diagnosis and in treatment recommendations (Baecker et al., 2021b). BrainAGE has also been used longitudinally but for clinical issues. For example, brainAGE was reduced after neurosurgery in epilepsy patients (de Bézenac et al., 2021) and after the intake of ibuprofen in healthy subjects (Le et al., 2018). However, to date and to our knowledge, no study has looked at the effect on brainAGE of more ecological interventions such as cognitive training.

Fewer studies on brainAGE have been conducted in healthy subjects. In healthy adults (45-80 years old), brainAGE has been shown to be related to performance in CF, planning and fluid intelligence (Cole, 2020). In the aging population, a link between brainAGE and various cognitive measures (processing speed, CF, visual attention, etc.) has nevertheless been demonstrated (Boyle et al., 2021). Brain age also seems to be related to lifestyle. For example, in 50-years-old adults, long-term meditation practitioners had a 7.5-year younger brain age than control participants (Luders et al., 2016).

Therefore, this study aimed to address three questions. First, *does the brain matures with cognitive training?* We hypothesized that the brainAGE in post-test would be superior than the brainAGE in pre-test and that this difference would be more important in the experimental IC training group than in the control AC training group. Then, the second question is whether *the brain development is related to cognition?* We hypothesized that the brainAGE at pre-test would be a predictor of EF performance at pre-test. Finally, *is the brain aging after cognitive training related to gains following training?* We hypothesized that the difference between the brainAGE at post-test and the one at pre-test will be a predictor of EF performance difference, and that this effect will be more important in the experimental IC training group than in the control AC training group.

¹brainAGE refers to the difference between the predicted brain age and the real chronological age. *brain age* refers to the predicted brain age. *brainAGE difference* or Δ brainAGE refers to the difference of brainAGE post-pre training.

2 Material and Methods

2.1 Brain age prediction

2.1.1 Training data

To calculate the brain age, it is necessary to have independent training data and test data. Our test data being the APEX cohort, it was necessary to find independent cohorts that could constitute our training data. Two different cohorts were used: ADHD200 (Milham et al., 2012; http://fcon_1000.projects.nitrc.org/indi/adhd200/) and ABIDE2 (Di Martino et al., 2017; http://fcon_1000.projects.nitrc.org/indi/abide/abide_II.html).

ADHD200 is a cohort of control and ADHD subjects. For this study, we included control participants only so a total of 474 participants (246 boys, 228 girls) of mean age 12.25 years [7.09-21.83 years]. MRIs were acquired across 7 sites. ABIDE2 is a cohort of control and ASD subjects. As for ADHD200, we included control participants only so a total of 658 subjects (440 boys, 218 girls) of mean age 16.31 years [5.89-64.00 years]. The acquisition of MRI data were done over more than 15 sites.

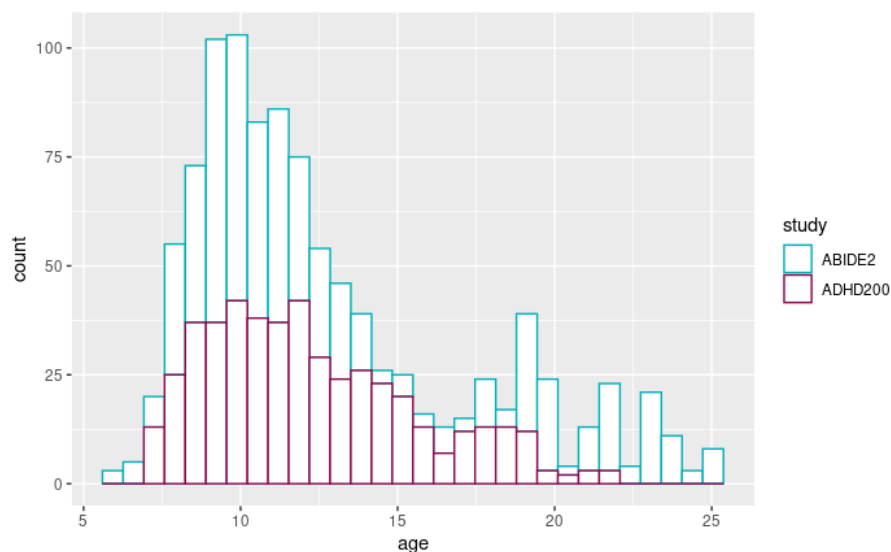


Figure 5.2: Age distribution across the three training datasets (ABIDE2 and ADHD200) with a threshold at 25 years of age.

In total, our training data was constituted of 1132 healthy participants (686 boys, 446 girls) of mean age 14.61 years [5.89-64.00 years]. However, because of the age distribution over 25 years and the test data targeting children and adolescents, we decided to exclude from the training set the 102 participants from ABIDE2 over 25 years. The final training data included 1030 healthy participants (612 boys, 418 girls) of mean age 12.78 years [5.89-25.00 years] (see Figure 5.2).

2.1.2 Test data

To predict brain age at pretest, in order to have the largest possible sample size, all participants in the APEX cohort were used (including the mindfulness and working memory training groups, see Figure 5.3a). Of note, before training, the sample was then composed of 110 children (9.85 ± 0.52 years; 61 females) and 88 adolescents (16.71 ± 0.54 years; 53 females). For the statistical group analyses, only participants from the AC and IC groups and who completed a minimum of 15 training sessions were included (see Figure 5.3b), i.e., 57 children (9.79 ± 0.55 years; 33 females) and 48 adolescents (16.57 ± 0.50 years; 33 females).

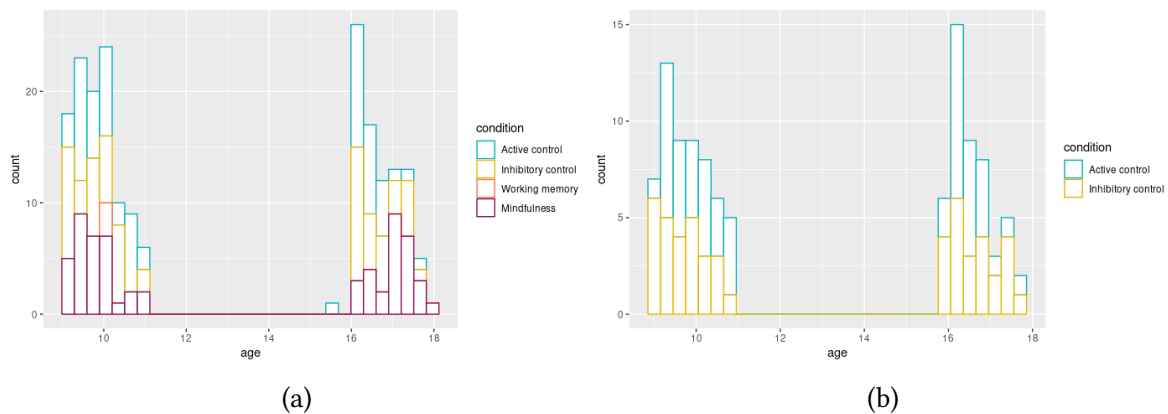


Figure 5.3: **Age distribution across the APEX dataset.** (a) = all participants included for the brain age prediction; (b) = participants who met inclusion criteria and that are included for the following statistical analyses.

2.1.3 Preprocessing and derived anatomical features

Voxel-Based Morphometry (VBM) was performed with CAT12 (<http://www.neuro.uni-jena.de/cat>). The analysis stream includes non-linear spatial registration to the 1.5mm³ MNI template, Gray Matter (GM), White Matter, and CerebroSpinal Fluid (CSF) tissues segmentation, bias correction of intensity non-uniformities, and segmentations modulation by scaling with the amount of volume changes due to spatial registration. Moreover, CAT12 computes GM volumes averaged on the Neuromorphometrics atlas that includes 284 brain cortical and sub-cortical ROI. We performed QC visual analysis: 1) we monitored the Noise Contrast Ratio (NCR) and Image Quality Rating (IQR) as two metrics of quality and we retained only images at a threshold below 4; 2) we sort the images by increasing IQR score and images with the higher IQR were visually inspected.

2.1.4 Machine learning models

We tested six machine learning models, three linear models (Ridge, ElasticNet, linear Support vector regression), two non linear models (Gradient boosting, Random forest) and one deep learning model (Multilayer perceptron).

These models were optimized in the training set (i.e., ADHD200 + ABIDE2) using a 5-fold cross-validation randomized hyperparameter search. No residualisation was applied. Global scaling based on total intracranial volume was done.

Next, we recomputed the machine learning models using the entire training dataset (ADHD200 + ABIDE2) and the optimal parameters and used it to predict brain age for the test dataset (APEX).

These models were conducted on GM volumes derived from VBM analyses, either at local level (using voxel-wise analysis of modulated normalized VBM maps) or regional level (averaging VBM maps in regions of interest of the Neuromorphometrics atlas).

To select the best model, R^2 , MAE and MSE of the different models were compared. R^2 corresponds to the variance explained by the regression divided by the total variance (see equation 5.1), MAE (mean absolute error) to the expected value of the absolute error (see equation 5.2) and MSE (mean square error) to the expected value of the squared (quadratic) error (see equation 5.3).

$$R^2 = 1 - \frac{\sum_{i=1}^n brainAGE_i^2}{\sum_{i=1}^n (age_{chronolo,i} - \overline{age}_{chronolo,i})^2} \quad (5.1)$$

$$MAE = \frac{1}{N} \sum_{i=1}^n |brainAGE_i| \quad (5.2)$$

$$MSE = \frac{1}{N} \sum_{i=1}^n brainAGE_i^2 \quad (5.3)$$

2.2 EF measures

Six EF measures were investigated, namely 4 measures of inhibitory control (Stop signal reaction time, Stroop interference, Simon interference, ANT flanker score), 1 measure of cognitive flexibility (trail making test flexibility score) and 1 measure of working memory updating (N-back updating cost).

2.3 Statistical analysis

To investigate if brainAGE, i.e. difference between brain and chronological ages, changed following training, repeated-measures ANOVAs were estimated using mixed-effects linear models. We used the package *lme4* (Bates et al., 2012) with Time (pre- or post-training) as fixed effect and intercepts for subjects as random effects. To see if these effects were specific to the type of training, mixed-effects linear models with Time (pre- or post-training) and Training group (IC or AC training) as fixed effects and intercepts for subjects as random effects were run. P-values were obtained by using likelihood ratio tests of the full model,

including the tested effect against the model without the tested effect.

To investigate if brainAGE was related to EF performance at pre-test, ANCOVAs were estimated using each of the 6 EF tasks performance at pre-test as dependant variable and with an interaction between brainAGE and Age group (children or adolescents) as independent variables.

Finally, to investigate if brainAGE difference was related to EF progress following cognitive training, ANCOVAs were estimated using each of the 6 EF tasks performance progression (post-pre) as dependant variable and with an interaction between Δ brainAGE (i.e., brainAGE at post-test - brainAGE at pre-test), Age group (children or adolescents) and Training group (IC or AC training) as independent variables.

3 Results

3.1 Brain age prediction

All results for the different models are presented in Table 5.1 for age predictions from ROIs and in Table 5.2 for age predictions from voxel-wise analyses. The parameters for each model can be found in Appendix A11.

	All participants			Children			Adolescents		
	R ²	MAE	MSE	R ²	MAE	MSE	R ²	MAE	MSE
Ridge	0.82515225	1.15530548	1.44110153	-4.91160575	1.01764460	1.26400227	-8.36683554	1.32738158	1.63573025
ElasticNet	0.80791494	1.20893627	1.51046739	-3.84432429	0.91564348	1.14422578	-11.24178492	1.57555226	1.86998279
Support vector regression	0.79205662	1.27168347	1.57158223	-4.80137829	1.01704746	1.25216257	-11.59356306	1.58997848	1.89666027
Random forest	0.59233451	1.73585395	2.20047546	-6.20034560	1.07190927	1.39499225	-28.62463319	2.56578479	2.90898665
Gradient boosting	0.65380571	1.53922720	2.02779715	-6.56571054	1.05555827	1.42994714	-22.44139571	2.14381336	2.58765856
Multilayer perceptron	0.65427997	1.63373225	2.02640769	-10.24663390	1.40243872	1.74343758	-18.04364458	1.92284917	2.33233146

Table 5.1: Brain age prediction results from ROIs by type of model and age groups.

	All participants			Children			Adolescents		
	R2	MAE	MSE	R2	MAE	MSE	R2	MAE	MSE
Ridge	0.75755503	1.39488996	1.69695822	-10.78503303	1.48801945	1.78468070	-7.74467458	1.27847808	1.58047294
ElasticNet	0.67402584	1.57247986	1.96768756	-8.35890277	1.26278856	1.59040448	-18.42885425	1.95959398	2.35580225
Support vector regression	0.53812123	2.15872601	2.34222470	-12.86163346	1.78705308	1.93554080	-25.81850436	2.62331716	2.76778604
Random forest	0.55344451	1.87119280	2.30304420	-9.17981113	1.34120063	1.65868908	-28.73933120	2.53368300	2.91461259
Gradient boosting	0.54583713	1.83691799	2.32257831	-8.38950308	1.21029624	1.59300239	-30.38574921	2.62019518	2.99420470
Multilayer perceptron	-2.22669827	5.14274797	6.19075667	-16.26096743	2.09637182	2.15987039	-280.46927422	8.95071816	8.96666065

Table 5.2: Brain age prediction results from voxel analysis by type of model and age groups.

Among these models, we selected those that, by imaging modality, presented the best results. Thus, for prediction from ROIs, the Ridge model was selected ($R^2 = 0.83$, MAE = 1.16, RMSE = 1.4, see Figure 5.4) and, for prediction from voxel analysis, the Ridge model was also selected ($R^2 = 0.76$, MAE = 1.39, RMSE = 1.70, see Figure 5.5). These two age prediction models will therefore be the ones used for the further analyses.

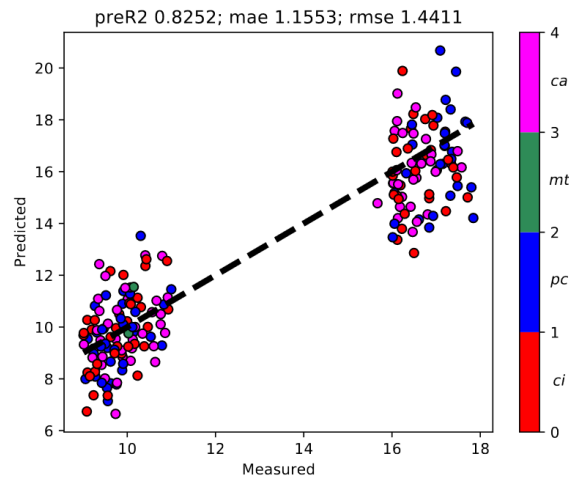


Figure 5.4: **Brain age prediction from ROIs with Ridge model.** The color of the dots indicates the training group (see legend on the right). The x-axis corresponds to the predicted brain age and the y-axis to the measured chronological age.

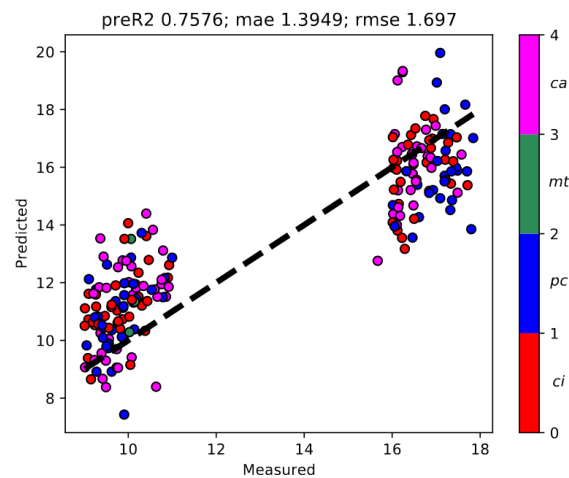


Figure 5.5: **Brain age prediction from voxel analysis with Ridge model.** The color of the dots indicates the training group (see legend on the right). The x-axis corresponds to the predicted brain age and the y-axis to the measured chronological age.

Note that, although most of the models show very good fit indices (with large R^2), these indices drop drastically when we look at the results by age group. The correct R^2 on the whole sample are due to the fact that there was indeed a differentiation between the group of children and adolescents, but within these two age subgroups, the prediction of brain age is rather poor according to this index. However, we can note a MAE lower than 1.5 for many of the models, i.e. a brain age predicted with less than 1.5 years precision.

3.2 Does the brain ages with cognitive training?

3.2.1 Results from brain age prediction from ROIs measure with Ridge model

Regardless of the type of training followed, repeated-measures ANOVA highlighted a marginal difference between the brainAGE at pre-test (-0.2077 ± 1.4253) and the brainAGE at post-test (-0.3190 ± 1.4905) ($\chi^2 = 2.84$, $p = 0.09$). In addition, the interaction between the training group (IC vs. AC) and the time session (pre- vs. post-test, see Figure 5.6) was marginal ($\chi^2 = 3.18$, $p = 0.07$).

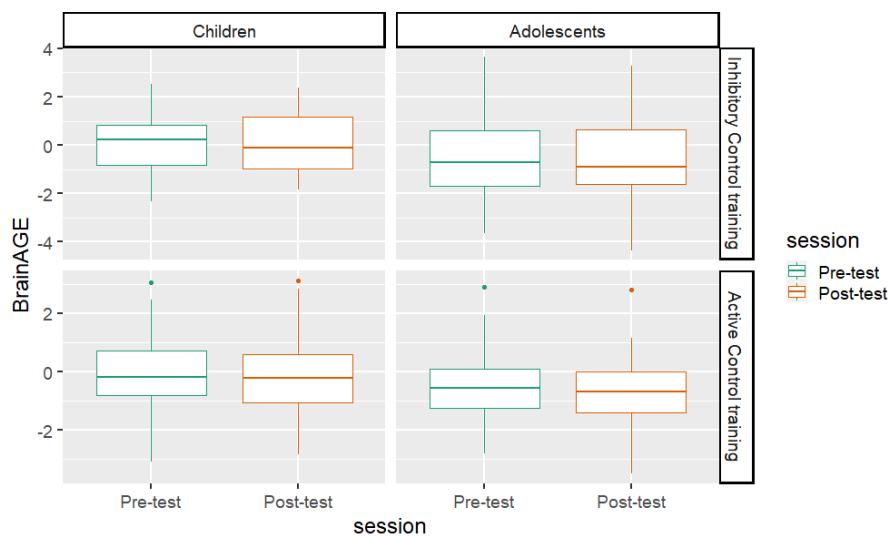


Figure 5.6: **BrainAGE by training group and session (from ROIs measure with Ridge model).**

3.2.2 Results from brain age prediction from voxel-wise analyses with Ridge model

Regardless of the type of training followed, repeated-measures ANOVA failed to detect any difference between the brainAGE at pre-test (0.5091 ± 1.6154) and the brainAGE at post-test (0.5005 ± 1.6607) ($\chi^2 = 0.02$, $p = 0.88$). In addition, the interaction between the training group (IC vs. AC) and the time session (pre- vs. post-test, see Figure 5.6) failed to reach significance as well ($\chi^2 = 1.47$, $p = 0.23$).

3.3 Does the brainAGE predicts EF performance?

3.3.1 Results from brain age prediction from ROIs measure with Ridge model

To investigate whether brainAGE could predict executive functioning, we performed ANCOVAs with EF tasks performance at pre-test as dependant variable and with an interaction between brainAGE and Age group (children or adolescents) as independent variables. These

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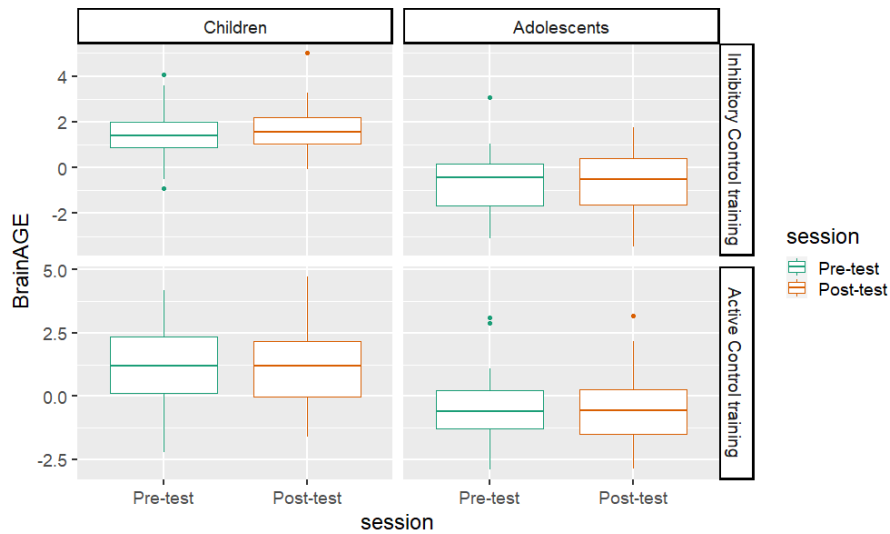


Figure 5.7: **BrainAGE by training group and session (from voxel-wise analyses with Ridge model).**

analyses revealed that, for the Simon task, there was a marginal interaction between age group and brainAGE ($F(1,113) = 3.68, p = 0.06$, see Figure 5.8) and a significant main effect of brainAGE ($F(1,113) = 7.53, p < .01$) on the Simon score interference at pre-test while main effect of age group failed to reach significance ($p = .18$).

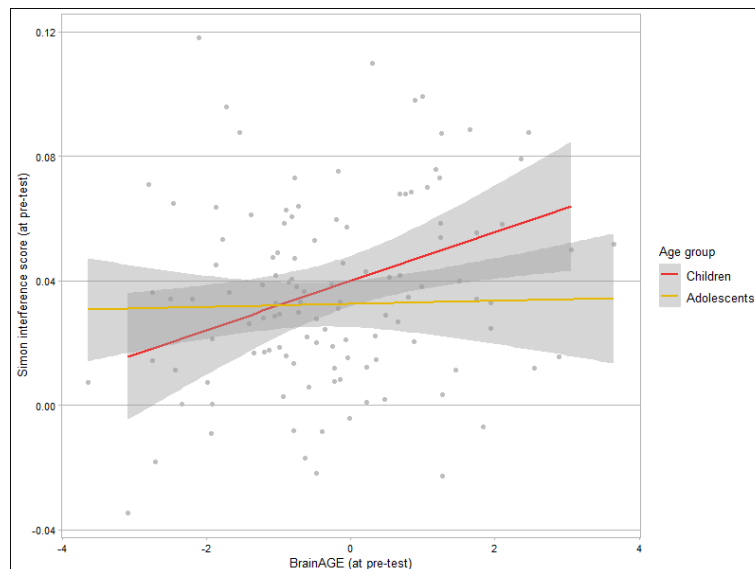


Figure 5.8: **BrainAGE effect on Simon interference score at pre-test by age group.**

No significant other interaction or main effects of brainAGE on any of the 5 other EF tasks at pre-test were observed (all $ps > .26$).

3.3.2 Results from brain age prediction from voxel-wise analyses with Ridge model

There were significant main effects of brain age ($F(1,100) = 4.02, p < .05$, see Figure 5.9) while the other main and interaction effects of brainAGE and age group failed to reach significance (all $ps > .54$).

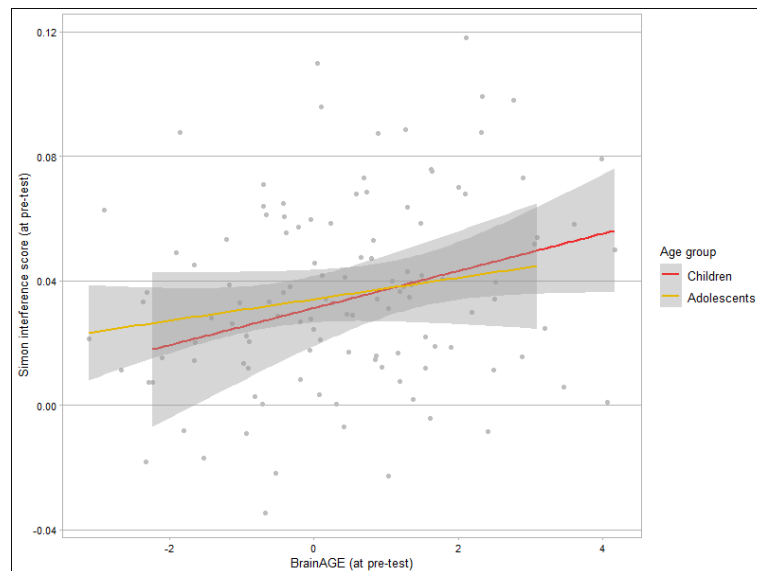


Figure 5.9: **BrainAGE effect on Simon interference score at pre-test.**

No significant other interaction or main effects of brainAGE on any of the 5 other EF tasks at pre-test were observed (all $ps > .23$).

3.4 Does the change in brainAGE predicts cognitive gains following training?

3.4.1 Results from brain age prediction from ROIs measure with Ridge model

To investigate whether Δ brainAGE (i.e., brainAGE at post-test - brainAGE at pre-test) could predict EF gains (i.e., EF score at post-test - EF score at pre-test, for each EF task) following AC or IC training, we performed ANCOVAs with EF tasks performance progression (post-pre) as dependant variable and with an interaction between Δ brainAGE, Age group (children or adolescents) and Training group (IC or AC training) as independent variables. These analyses revealed a marginal triple interaction Age group * Training * Δ brainAGE was found marginal for the stop signal task progress ($F(1,91) = 3.63, p = 0.06$, see Figure 5.10a) and the N-back progress ($F(1,100) = 2.76, p = 0.10$, see Figure 5.10b). Post-hoc Tukey analyses revealed significant differences in Δ brainAGE effect on N-back progress between children from the IC and AC training groups ($t(100) = -3.03, p < .05$) but not in adolescents ($p = .97$). On the other hand, the same analyses conducted on stop signal progress did not reveal any significant difference between the two training groups (all $ps > .36$).

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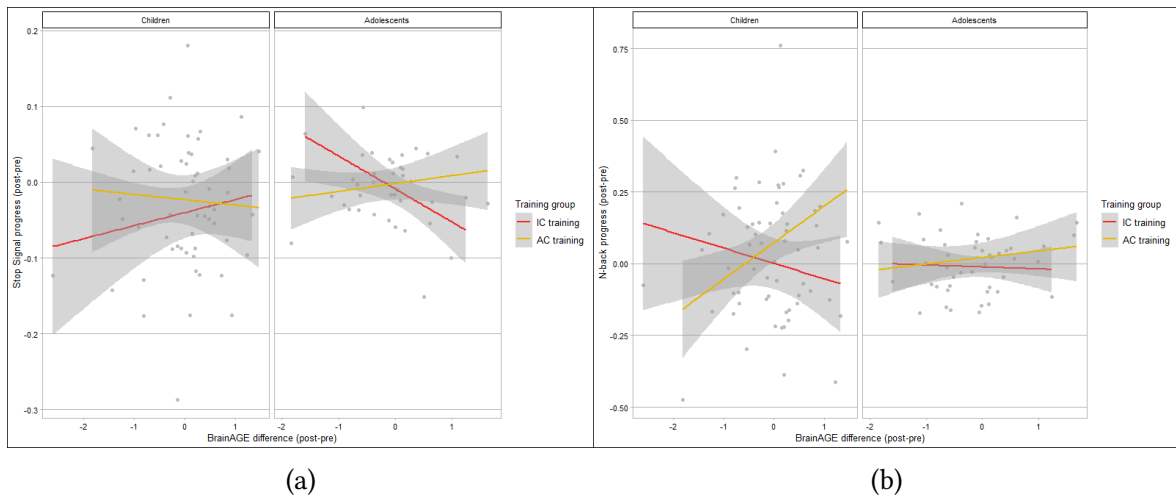


Figure 5.10: **BrainAGE difference effect on (a) stop signal and (b) N-back progress by age and training group.**

All other main and interaction effects of age and training groups failed to reach significance (all $ps > .11$).

All other interaction or main effects of brainAGE difference failed to reach significance ($ps > 0.16$).

3.4.2 Results from brain age prediction from voxel-wise analyses with Ridge model

An interaction Training (IC vs. AC) * Δ brainAGE was found marginal for the Stroop task progress ($F(1,104) = 2.95$, $p = .09$, see Figure 5.11). Post-hoc Tukey analyses revealed significant differences in Δ brainAGE effect on Stroop progress between participants from the IC and AC training groups ($t(104) = -2.20$, $p < .05$).

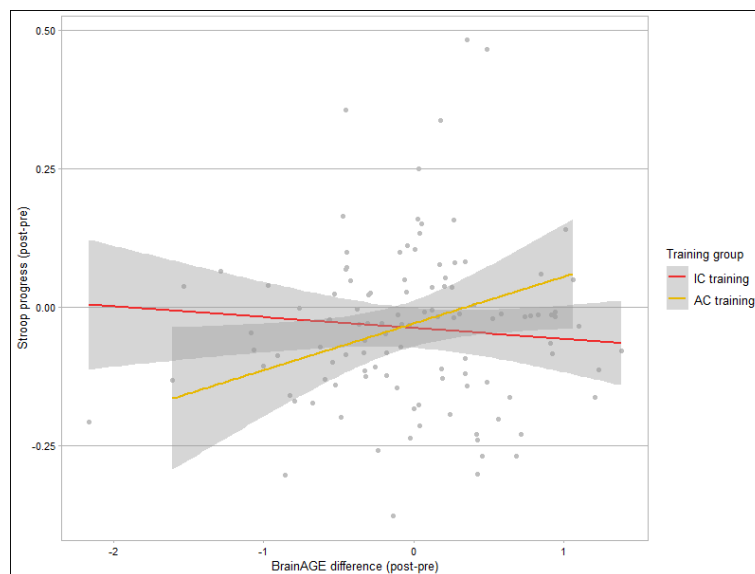


Figure 5.11: **BrainAGE difference effect on Stroop progress by training group.**

All other interaction or main effects of Δ brainAGE on EF tasks progress failed to reach significance ($ps > 0.13$).

4 Discussion

This study aimed to predict brain age to test different hypotheses. First of all, it aimed to see if cognitive training could accelerate development (Jolles and Crone, 2012), i.e. whether the gap between the predicted brain age and the real chronological age increased after training. Although our models provided a good prediction of age, similar to previous studies (e.g., Ball et al., 2021), no significant effect of training was observed. There are several reasons for this lack of results. First, although our prediction of brain age is quite good, its accuracy (approx. 1.5 years) is most likely not sufficient to highlight a difference between two measurement times spaced 5 weeks apart. It would therefore be necessary either to improve the accuracy of the prediction of brain age and/or to increase the delay between the pre- and post-test. This methodology is therefore not ideal for short duration cognitive training. However, this approach could be relevant to examine the impact of longer-term training or learning, such as learning to read or cognitive remediation training.

Second, this study aimed to see if brain age could predict executive functioning. With the Ridge prediction model from the ROIs data, an effect on the Simon task performance of the difference between the predicted brain age and the real chronological age, different in children and adolescents, was demonstrated. Notably, children with a larger brainAGE (i.e., a brain age more important than their chronological age) had poorer inhibitory abilities (i.e., higher interference scores on the Simon task). The same results were observed with the Ridge prediction model from the voxel-wise analysis. However, the fact that the cerebral cortical volume was not related to EF performance (see Study 4) may lead us to believe that these results could hardly be generalized. It is possible that in young populations such as the APEX cohort, the variability in cognitive and brain development does not allow the use of an index such as brain age as a marker of executive functioning. It is also possible that brain age, calculated from a combination of anatomical and functional, would be a better marker of EF functioning and development. Thus, it would be necessary to replicate our analyses on a sample with more variability in age, and not just two groups of participants concentrated in two narrow age ranges, but also with a prediction of brain age on several variables, maybe combined, and not just cortical volume. However, it is possible that by combining different modalities, noise can be added and that the interpretation of the results is more difficult (to know which is the result of functional and which is the result of anatomical features for example; Groves et al., 2012). Another perspective would be more theory-driven and calculate participants' brain age from more *a priori* specified brain characteristics, more related to EFs. In particular, a brain age calculated on brain features of the EF network (PFC striatum, etc.) could prove to be a better indicator of executive performance. By integrating markers of segregation (such as ROI volume or surface area) and integration (such as functional or structural connectivity), a brain age reflecting the development of the EF brain network could indeed be calculated.

Finally, the last goal of this study was to see if variations in brain age following cognitive training could predict executive progress following this cognitive training. With the

prediction of brain age from ROI data and a Ridge model, the difference in brain age was predictive of progress following cognitive training on the stop signal and N-back. For these two tasks, the effects of Δ brainAGE varied according to the age group and the type of training followed. In the case of N-back, brainAGE difference does not seem to play any role in N-back progress in adolescents. But, in children, results seem to show that the greater the progress in WMU are likely to be observed if the brain "got older" following IC training and if the brain "got younger" following AC training. In the case of stop signal, brainAGE difference seemed to be a poor indicator of IC progress following the AC training. On the other hand, following IC training, in children, the more the brain "got younger", the greater the progress in IC following the 5 weeks of training, whereas in adolescents, the opposite effect was found (the more the brain "got older", the greater the progress in IC). These results, suggest differentiated effects according to age. While a brain that is "getting younger" would be linked to more progress following training in childhood, in adolescence on the contrary, progress would be more linked to a brain that is "getting older". It would be necessary to look at the brain areas that drive these results. In particular, it seems that brain age is not predicted in an equivalent way by all the cerebral regions (Ball et al., 2021). If our brain age is computed in an important way by a developing region from childhood to adolescence, our results could be driven by the overrepresentation of a developing region. In the same way as mentioned above, it could be interesting to calculate the brain age from characteristics of the EF brain network but also from the learning brain network (striatum, etc.). Moreover, as we have previously seen in Study 3, progress following IC training is variable from one individual to another. More personalized analyses of individual trajectories would be necessary to shed more light on the neurocognitive mechanisms at play during IC training. With the prediction of brain age from the voxel-wise analysis and a Ridge model, the brainAGE difference was predictive of progress following cognitive training on the Stroop task. The effect of brainAGE difference varied with the type of training but there was no difference of age. This effect of brainAGE difference seemed to be more important following AC training (the more the brain "got younger", the greater the progress in Stroop) as it was almost null following IC training. Thus, given our results fluctuating from one prediction model to another as well as the small sample size, these results should be interpreted with caution and need to be replicated before being generalized.

Another reason that could explain our results is a bias, systematically observed in the estimation of brain age, which makes that the brain age is underestimated for the oldest subjects and overestimated for the youngest (Aycheh et al., 2018; Cole et al., 2017; Le et al., 2018). Potential explanations for this bias include regression toward the mean (Liang et al., 2019) and nongaussian distribution of subject ages (Smith et al., 2019). When the brain age gap is used as a biomarker for psychopathology or cognition development, this bias can introduce a confounding effect of chronological age (Niu et al., 2020).

The question of the development of the brainAGE deserves to be investigated. While most studies using brain age are performed in adults, the calculation of brain age in childhood raises questions. Indeed, the brain is still developing up to age 25, and there are maturation lags between brain regions (Bethlehem et al., 2022). This lag in brain maturation according to the regions also raises the question of the data to be included in training: it could then be more relevant to have a training set very similar to the test-set or, on the contrary, to have a training set that is as broad as possible. Secondly, although most studies

Study 5: Machine learning methods to investigate brain aging changes following training

present brainAGE as a potential marker of pathologies (e.g., Shahab et al., 2019) or cognitive difficulties (e.g., Cole, 2020), little is known about the stability of brainAGE during development. Notably, little association between cross-sectional brain age and longitudinal changes in brain age was observed, rather brain age in adulthood was shown to be associated with very early life factors such as birth weight (Vidal-Pineiro et al., 2021). It could be very interesting to look at the variations of brainAGE during development or at least longitudinally and if these variations are influenced by the data included in the model. This could give us information about the plasticity or the fixed character of this index which is increasingly used as a psychiatric and psychological marker.

In conclusion, although we were not able to use brainAGE to test the hypothesis of brain aging after training, our promising first results associating brainAGE with executive performance and gains after IC training suggest that longitudinal brainAGE can be a very interesting tool for development and training.

STUDY 6: RELATIONSHIPS OF BRAIN, GENES AND INHIBITORY CONTROL THROUGH COGNITIVE TRAINING AND DEVELOPMENT - A MULTILEVEL ANALYSIS

This study led to a manuscript in preparation: **Menu, I.**, He, Q., Victor, J., Rezende, G., Le Stanc, L., Vidal, J., Oppenheim, C., Duchesnay, E., Chaumette, B., Houdé, O., Borst, G. & Cachia, A. (in prep.). Do neuroplasticity and genetic factors contribute to cognitive training in children and adolescents?

After investigating the effects of development and inhibitory control training at the cognitive and brain levels, we wanted to examine how these different levels of analysis, cognitive and cerebral, as well as genetic, interact to explain inter-individual differences in training receptivity.

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1 Introduction

Various studies have been conducted to stimulate IC (Diamond and Lee, 2011; Hu et al., 2017; Jaeggi et al., 2011; Liu et al., 2015; Zhao et al., 2015). Although studies reported cognitive gains following IC training (Manuel et al., 2010; Maraver et al., 2016; Peckham and Johnson, 2018; Thorell et al., 2009), inter-individual differences persist in training receptivity.

At the cognitive level, as we have seen in Study 3, the impact of the baseline level is a critical predictive factor of training receptivity often studied to investigate who benefits the most from the training proposed. The "compensation account" hypothesis postulates that individuals who are already high performers will benefit the least from cognitive training because they are already functioning at an optimal level. This leaves them less room to improve, in contrast to individuals who have more fragile baseline performance (Karchach and Kray, 2021; Karchach and Unger, 2014; Lövdén et al., 2012b; Titz and Karchach, 2014). Indeed, several studies of EF training have found greater benefits for children and older adults than for young adults (see for review: Karchach and Unger, 2014) but also for children with low working memory or with ADHD (Diamond, 2011).

At the brain level, as seen in Study 4, direct links between cerebral organization and training receptivity have also been demonstrated: brain network organization predicted cognitive gains after training in children (Chaddock-Heyman et al., 2020), in young adults (Baniqued et al., 2019) and in older adults (Baniqued et al., 2018; Gallen et al., 2016).

Finally, at the genetic level, a first indirect link between genetic polymorphism and training receptivity was proposed by Rueda et al., 2005a. Children with poorer initial performance on attentional conflict were more likely to show training effects than others (compensation account hypothesis). Moreover, DAT1, a gene implicated in the dopamine system, polymorphism explained attentional conflict scores at pre-test. The link between DAT1 polymorphism and training receptivity was thus really indirect. But one study did establish a direct link between genetic factor and training receptivity while controlling for baseline and showed that BDNF polymorphism mediated the effect of a physical training intervention on EFs in older adults (Leckie et al., 2014).

However, to date, no study has been able to put all the levels together by investigating simultaneously the effects between these different factors and training receptivity. This lack of studies can be explained firstly by a methodological difficulty. Indeed, classical regression analyses allow to highlight the effect of one or more independent variable(s) on a dependent variable, or correlations between different variables. However, as soon as we investigate several levels, these classical analyses do not allow answering all the questions we might have and to create all the needed connections. It is then necessary to use more complex statistical analyses for multilevel modeling (Hoffman and Walters, 2022). Mediations can be used to highlight links between three different levels of data but are not sufficient in the case of an experimental design involving training: it would be necessary to carry out these mediations before and after the intervention, while controlling their effect on each other but also the effect of baseline, etc.

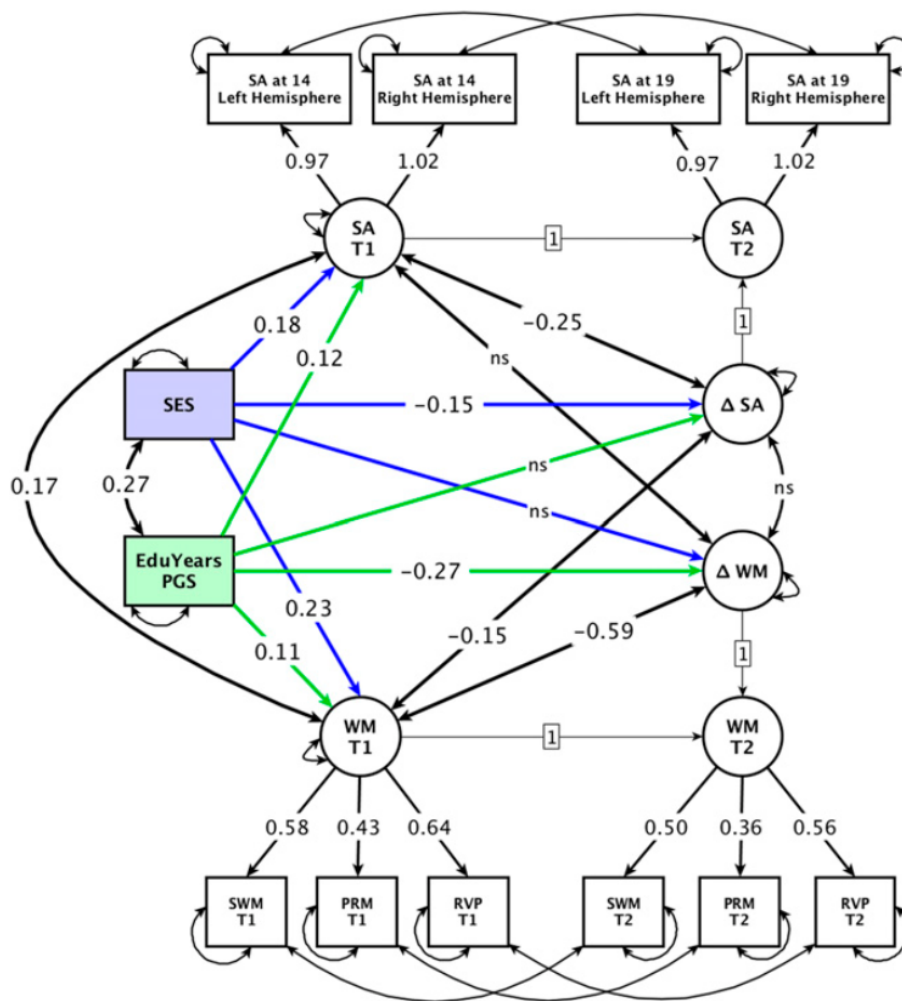


Figure 6.1: Path diagram of a strict measurement invariant BLCS model with the change of surface area and working memory from 14 to 19. From Judd et al., 2020.

Such multilevel modeling is possible with structural equation modeling (SEM) analyses that allow to test simultaneously and globally the existence of several hypothetical relationships. SEM can be used in multi-level and longitudinal data. Indeed, latent change score (LCS) models, extensions of SEM seen in Study 3, have been developed for longitudinal data (McArdle, 2009) and can examine the difference in a variable between two or more measurement time points rather than investigating shifts in the rank order between two time points (Castro-Schilo and Grimm, 2018). Differences between successive measurements are then modeled as latent change factors. This modeling can easily and accurately investigate complex and critical training issues, such as 1) the estimation of inter-individual differences in the initial levels and in training-related changes and 2) the characterization of complex (and possibly nonlinear) change trajectories, along with the determination of the factors influencing these trajectories (McArdle, 2009; McArdle and Nesselrode, 2014). This model can be extended for a multilevel characterization as in a bivariate latent change score (BLCS) to investigate cross-level coupling (Kievit, 2017). For instance, we can quantify the extent to which cognitive changes between pre- and post-training are a function of brain structure and cognition at pretest (Kievit et al., 2018). In a previous study, this type

of modeling demonstrated that environment (SES index) and genetic (PRS based on educational attainment) were important for cognitive (working memory) and brain (surface area of the two brain hemispheres) development through adolescence (Judd et al., 2020; see Figure 6.1). This study, looking at changes during normal development, uses a modeling that is also suitable for examining changes following cognitive training such as our IC training.

The aim of the present study was thus, through a multilevel SEM similar to the one used in (Judd et al., 2020), to put all the pieces together and to investigate which cognitive, cerebral, and genetic factors contribute to inter-individual differences in training receptivity in our APEX cohort of healthy children and adolescents after a 5-weeks computerized IC (experimental group, IC) or control (active control group, AC) training.

At the brain level, we *a priori* focused on the ACC and the IFG as they were shown to be associated with IC abilities (see fMRI meta-analyses: Criaud and Boulinguez, 2013; Simmonds et al., 2008; Swick et al., 2011) and to present changes in structure (cortical thickness and surface; Delalande et al., 2020) and in functional connectivity (Hu et al., 2017) after an IC training. We also focused on striatal regions, including caudate nucleus and putamen, since these regions were shown to be classically involved in learning (Seger, 2006, 2008; Seger and Cincotta, 2005a; Seger and Cincotta, 2005b) and in IC (Beste et al., 2018).

At the neurobiological level, given the polygenic architecture of IC, diffuse across very many variants (Donati et al., 2019; Hatoum et al., 2022), polygenic risk scores (PRSs; Wray et al., 2007) seem to be the most relevant to study the genetic impact on variability in IC training receptivity. PRSs are quantitative scores that index, for each individual subject in a study sample, their aggregate genetic risk for a trait of interest. Specifically, a PRS is computed as the weighted sum counting all risk alleles for a selected set of single nucleotide polymorphisms (SNPs) carried by an individual. The weight used for each risk allele is the SNP log odds ratio estimated out of sample in a large GWAS of the given trait.

Thus, multilevel SEM will be able to investigate how cognitive (basal stop signal and color-word Stroop efficiency), cerebral (grey matter volume in left and right ACC, left and right IFG, left and right caudate, left and right putamen), and genetic (PRS) factors contribute to inter-individual differences in training gain in our cohort of children and adolescents after a 5-weeks computerized training.

2 Methods

2.1 Participants

Of the APEX cohort, 176 participants (102 children and 74 adolescents) had given their consent for the genetic part of the study and were included for the PRS calculation. For the multilevel modeling, we included APEX participants who completed at least 15 sessions of the AC or the IC training, i.e., 57 children (9.79 ± 0.55 years; 33 females) and 48 adolescents (16.57 ± 0.50 years; 33 females).

2.2 IC evaluation in pre- and post-training sessions

In this study, we focused on the tasks completed before and after training that were trained, namely the stop signal and color-word Stroop task. As described in the Method section of this manuscript (see section 8), we estimated the stop signal reaction time (SSRT) using the integration method with replacement of go omissions as recommended in literature (Verbruggen et al., 2019) while the Stroop interference score was calculated as the difference between the reaction time (RT) for successful incongruent CPCM trials and the RT for successful congruent trials. For each task, relative changes were screened and cleaned for possible aberrant values by using a nonparametric approach. Specifically, values lower than 'median - 2.5 MAD' or greater than 'median + 2.5 MAD' (MAD, or the median absolute deviation) were considered to be outliers.

2.3 MRI acquisition

2.3.1 Anatomical MRI acquisition

High-resolution isotropic 3T sagittal MRI data (1 x 1 x 1 mm) were acquired for both children and adolescents, before and after training. MRI data in children were acquired at the Cyceron biomedical imaging platform (Archieva, Philips Medical System, Netherlands). MRI data of adolescents were acquired at the CIREN biomedical imaging platform (General Electric Healthcare). The parameters of the sequences were optimized in each site to obtain similar acquisition at Cyceron (TE = 3.3 ms; TR = 7.2 ms; flip angle = 9°; matrix size = 256 x 240 mm; field of view = 256 mm) and at CIREN (TE = 3.2 ms; TR = 8.2 ms; flip angle = 11°; matrix size = 256 x 256 mm; fields of view = 256 mm).

2.3.2 MRI data analyses

Local grey matter volumes were automatically assessed on the whole brain based on the standard voxel-based morphometry (VBM) approach using the Computational Anatomy Toolbox (CAT12) (<http://www.neuro.uni-jena.de/cat/>) as described in Studies 4 & 5. Local grey matter volume of the eight regions of interest (ROIs) were extracted: left (lACC) and right anterior cingulate cortex (rACC), left (lIFG) and right inferior frontal gyrus (rIFG), left (lCaudate) and right caudate (rCaudate), left (lPutamen) and right putamen (rPutamen). Both absolute (raw) and relative (after spatial normalization with global scaling using Total Intracranial Volume; TIV) volumes of these 8 ROIs were computed.

2.4 Genotyping and imputation

Genotyping data was generated for all individuals using the genome-wide genotyping array Infinium PsychArray (Illumina, San Diego, California, United States). The genetic data of one participant could not be calculated because of insufficient salivary volume. We per-

formed quality control with PLINK (v1.9, www.cog-genomics.org/plink/1.9/; Purcell et al., 2007) on the raw genotyping data to exclude single nucleotide polymorphisms (SNPs) with a minor allele frequency <2%, genotyping missing rate >5% and Hardy–Weinberg Equilibrium p value < 10⁻⁶. Only autosomal SNPs were kept. The software KING was used to compute and check sex, relatedness and ancestry (Manichaikul et al., 2010). After filtering, 157 children and adolescents were confirmed with European ancestry, and all passed the quality filtering.

2.5 Polygenic risk score

Polygenic risk score calculates the aggregate genetic risk for a phenotype of interest for each subject in a study sample (test data) as the weighted sum of all risk alleles for a selected set of single nucleotide polymorphisms (SNPs). The SNP log odds ratio estimated out of sample in a large GWAS (train data) of the given phenotype is used as the weight for each risk allele.

Here, the PRS for each APEX participant was calculated using PRSice (v2.2.8; Choi et al., 2020) with the summary statistics of latest GWAS related TMT-alphanumeric (Watanabe et al., 2019, see Appendix A12), freely available online on the Atlas of GWAS Summary Statistics website (<https://atlas.ctglab.nl/>). The sample size and number of SNPs for this data set are in Table 6.1. The P-value threshold was automatically determined by testing a wide range of thresholds to capture the best fit PRS possible (Choi et al., 2020). Linear regression models were used to determine the relationships between the two IC tasks (stop signal and color-word Stroop tasks) and their respective PRS, adjusted on age, sex and ten top principal components that reflects population structure identified as covariates by KING. The Empirical P-value for the linear regression was adjusted by using 1,000 permutations. Empirical $P < 0.05$ was considered as significant.

Data set	Reference	Sample size	Number of SNPs
TMT-B	Watanabe et al., 2019	84,259	9,267,643

Table 6.1: Data set used for polygenic risk score calculations.

2.6 Statistical analyses

2.6.1 Multi-level model

A multilevel model (see Figures 6.3 & 6.4) was created to combine four existing common models.

First, this model incorporates a latent change score model (LCS, see Study 3; Kievit, 2017; McArdle, 2009; McArdle and Nesselrode, 2014) at the cognitive level, for each IC task (color-word Stroop or stop signal, down Figures 6.3 & 6.4 in yellow and black). LCS model conceptualizes the difference between successive measurements as latent change fac-

tors, which allowed us to directly model within-subjects changes (McArdle and Hamagami, 2001). Similarly, our multilevel model also integrates a LCS model at the brain level, for each ROI (lACC, rACC, lIFG, rIFG, lCaudate, rCaudate, lPutamen, rPutamen, down Figures 6.3 & 6.4 in yellow and black). Cross-effects (down Figures 6.3 & 6.4 in red) were modeled in order to investigate the possible role of the cognitive baseline on the ROI volume change and of the ROI volume baseline on the cognitive change (Kievit, 2017). Moreover, this model also includes a mediation model at pretest level where the PRS predicts the IC score at pretest and the grey matter volume at pretest (down Figures 6.3 & 6.4 in blue). Finally, a mediation model at the level of latent change was included with PRS predicting cognitive and cerebral LCS change (down Figures 6.3 & 6.4 in green).

To make sure that training effects were specific to the IC-training group, we run a model comparison. Indeed, two types of multilevel models were fitted for the eight ROIs of interest by age group. In the first model, referred to as the ‘constrained model’, all of the parameters were constrained to be equal in the two groups ($IC_{pre} = AC_{pre}$ & $IC_{change} = AC_{change}$), assuming the same training effects regardless of the training group. In the second model, referred to as the ‘free model’, the parameters were only constrained to be equal at the pretest period ($IC_{pre} = AC_{pre}$), assuming that the training effects on change were specific to the training group. In both models, the baseline scores were constrained to be equal, assuming a similar level before training because the participants were randomly assigned to the different training groups. We then compared these two models with a χ^2 comparison test.

2.6.2 Model fit and comparison

The multilevel models were estimated with the *lavaan* software package (Version 6.8; Rosseel, 2012) in R, for each age group separately, using full information maximum likelihood with robust standard errors to account for missingness and non-normality. Overall model fit was assessed using standard indexes (Schermelleh-Engel et al., 2003): the chi-square test, the root-mean-square error of approximation (RMSEA; acceptable fit: $< .08$, good fit: $< .05$), the comparative fit index (CFI; acceptable fit: $.95-.97$, good fit: $> .97$), and the standardized root-mean-square residual (SRMR; acceptable fit: $.05-.10$, good fit: $< .05$).

3 Results

3.1 Association of polygenic risk for cognitive flexibility with Inhibitory Control

We calculated polygenic score for executive functioning using the summary statistics from the trail making test (time to complete the alphanumeric part, TMT-B) in 84,259 adults of the UK Biobank 2 study (UKB2; Watanabe et al., 2019). We found that common genetic variation predisposing to executive functioning significantly contributed, in our independent subsample of 157 children and adolescents, to response inhibition measured by stop

signal reaction time (SSRT) (empirical $P = 0.01$, $r^2 = 7.19\%$, coefficient = -10.00 , $se = 2.82$) but not to interference control measured by Stroop interference score (empirical $P = 0.51$, $r^2 = 2.09\%$, coefficient = 43.23 , $se = 25.05$). Hence, for the remaining analyses, only PRS associated to the SSRT was investigated. The corresponding PRS barplot can be found in Figure 6.2. Detailed results can be found in Table 6.2.

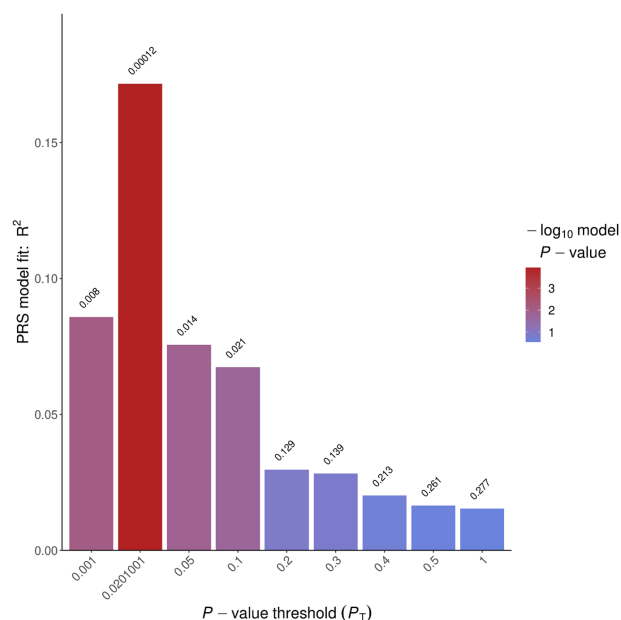


Figure 6.2: Barplot of the stop signal PRS at different p-value thresholds.

Discovery	Target	Threshold	PRS.R2	Beta	SE	P	Num SNP	Adjusted P (Bonferroni)	Adjusted P (Holm)	Empirical P
TMT-B	Stop signal	0.0201	0.1716	-26.45	6.5260	0.0001	7453	0.0002	0.0002	0.0035
TMT-B	Stroop	0.0071	0.0219	-9.2501	6.6784	0.1698	3441	0.3396	0.1698	0.8019

Table 6.2: The association of the polygenic risk score (PRS) for TMT with IC measures. Beta is the coefficient. SE is the standard error. The coefficient and standard error are standardized.

3.2 Multilevel model

To investigate to which extent cognitive, cerebral, and genetic factors contributed to cognitive training receptivity, we designed and estimated a multilevel model designed to combine two LCS models to investigate change induced by training, one at the cognitive level of the stop signal and one at the brain level of grey matter (GM) volume of a given ROI of the IC brain network (lACC, rACC, lIFG, rIFG, lCaudate, rCaudate, lPutamen, rPutamen), and two mediation models to investigate whether the genetic effect of PRS on response inhibition was mediated by a cerebral variable, the GM volume of one of the 8 ROI, at both pre-test and latent change levels (see Methods section above).

Since we were interested in factors involved in cognitive gains following training, we focused on models showing (1) training effects specific to the IC-training group, (2) good

fit indices to ensure the robustness of our estimations, (3) a significant learning-related cognitive change.

3.2.1 Raw volumes (without spatial normalization)

In children, we ran 8 models corresponding to the 8 ROIs and we found that the model with left ACC was the only model with training effects specific to the IC-training group (χ^2 [11] = 41.06, $p < 0.001$), fitted the data well according to the classical SEM metrics (Schermelleh-Engel et al., 2003: χ^2 (7) = 11.28, $p = .13$, RMSEA = .13, 90% confidence interval (CI) = [0.00, 0.27]; CFI = 0.98; SRMR = 0.15, Yuan-Bentler scaling factor = .76) and showed a significant learning-related cognitive change ($p < .01$, $R^2 = 0.86$).

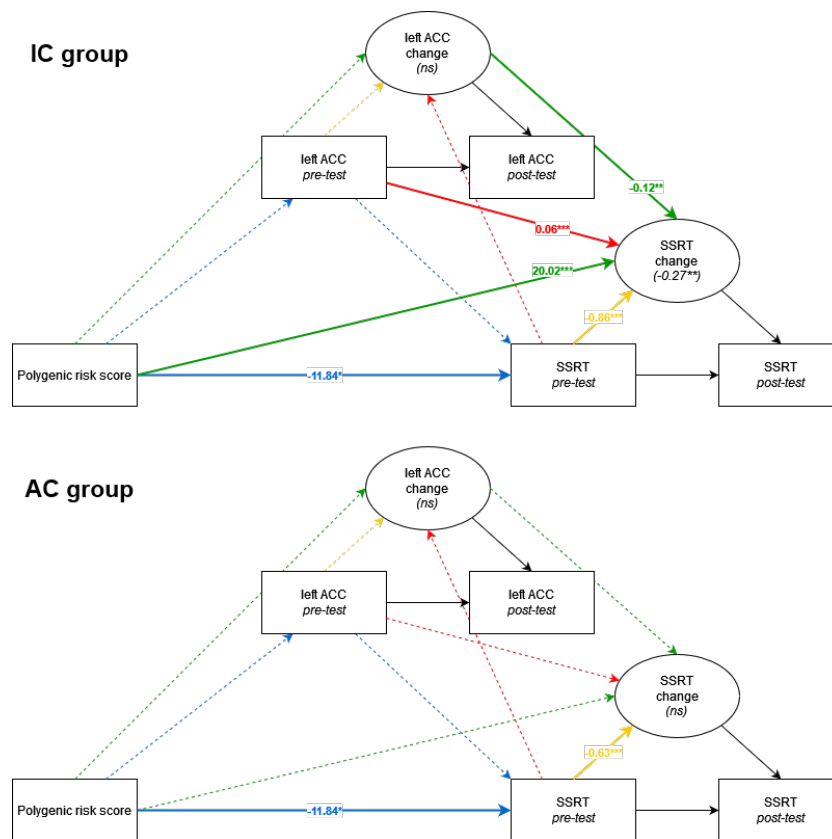


Figure 6.3: **LCS model estimations.** Top = children of the experimental (IC) training group; Bottom = children of the control (AC) training group. Plain lines represent $p < .05$, dotted lines represent $p \geq .05$.

At pre-test, this model estimation (see Figure 6.3) revealed a significant influence of genes (PRS) on response inhibition (SSRT; -11.84 , SE = 4.82, $z = -2.45$, $p < .05$). There were no significant effect of PRS on lACC GM volume ($p = .36$) nor of lACC GM volume on SSRT at pre-test ($p = .18$).

In the experimental IC group, there was a significant latent change score for the stop signal (-0.27 , SE = 0.10, $z = -2.70$, $p < .01$), indicating significant changes in SSRT after IC training. Among factors contributing to this change of stop signal, at the cognitive level,

there was a significant baseline effect (-0.86 , $SE = 0.12$, $z = -7.49$, $p < .001$), indicating that the higher the initial cognitive scores (and thus the lower the IC efficiency) on stop signal, the greater the gain on that task. At the brain level, significant effects of both IACC GM volume baseline (0.06 , $SE = 0.01$, $z = 4.56$, $p < .001$) and latent change of IACC GM volume (-0.12 , $SE = 0.05$, $z = -2.65$, $p < .01$) were observed, reflecting an effect of both neural architecture at baseline and plasticity. Finally, at the genetic level, a significant effect of PRS on change for stop signal was detected (20.02 , $SE = 4.30$, $z = 4.65$, $p < .001$), indicating that the higher the risk of having good executive functioning (i.e., low PRS), the greater the change after IC-training. Of note, there were no significant latent change of the IACC GM volume ($p = .59$) and this change of IACC was not impacted by either cerebral baseline IACC GM volume ($p = .85$), genetic PRS ($p = .26$), nor cognitive stop signal baseline performance ($p = .88$).

In the AC training group, there was no significant latent change for the stop signal ($p = .11$), i.e., no significant cognitive change following this placebo training. Among factors contributing to change of stop signal, only the baseline parameter was significantly negative for the stop signal (-0.63 , $SE = 0.10$, $z = -6.22$, $p < .001$). All other factors failed to reach significance ($ps > .16$). Of note, there were no significant change of the IACC GM volume ($p = .29$) and this change of IACC was not impacted by either cerebral baseline IACC GM volume ($p = .15$), genetic PRS ($p = .51$), nor cognitive stop signal baseline level ($p = .64$).

In adolescents, none of the model estimation completed the three criteria, namely training effects specific to the IC-training group, good fit indices to ensure the robustness of our estimations, and a significant learning-related cognitive change. Fit indices for all ROIs in children and adolescents are available in Appendix A13. All model estimates for all ROIs are available in Appendix A14.

3.2.2 Global-scaled ROI volumes (with spatial normalization)

In children, among the 8 ROIs, the model estimation with lPutamen as the ROI was the one that met all the criteria. Indeed, training effects were specific to the IC-training group ($\chi^2 [11] = 27.47$, $p < 0.01$), fitted the data well according to the classical SEM metrics (Schermelleh-Engel et al., 2003: $\chi^2 (7) = 7.82$, $p = .35$, $RMSEA = .06$, 90% confidence interval (CI) = $[0.00, 0.24]$; CFI = 0.99; SRMR = 0.12, Yuan-Bentler scaling factor = .87) and showed a significant learning-related cognitive change ($p < .001$, $R^2 = 0.78$).

At pre-test, this model estimation revealed a significant influence of genes (PRS) on response inhibition (SSRT; -10.33 , $SE = 4.98$, $z = -2.07$, $p < .05$). There were no significant effect of PRS on lPutamen GM volume ($p = .31$) nor of lPutamen GM volume on SSRT at pre-test ($p = .35$).

In the experimental group (IC, upper part of Figure 6.4), there was a significant latent change score for the stop signal (0.54 , $SE = 0.10$, $z = 5.23$, $p < .001$), indicating significant changes in stop signal score after IC training. Among factors contributing to this change of stop signal, at the cognitive level, there was a significant baseline effect (-1.02 , $SE = 0.14$, $z = -7.28$, $p < .001$), indicating that the higher the initial scores (and thus the lower the IC efficiency) on stop signal, the greater the gain on that task. At the brain level, significant effects of both lPutamen GM volume baseline (-0.07 , $SE = 0.02$, $z = -3.97$, $p < .001$) and latent

Study 6: Relationships of brain, genes and inhibitory control through cognitive training and development - a multilevel analysis

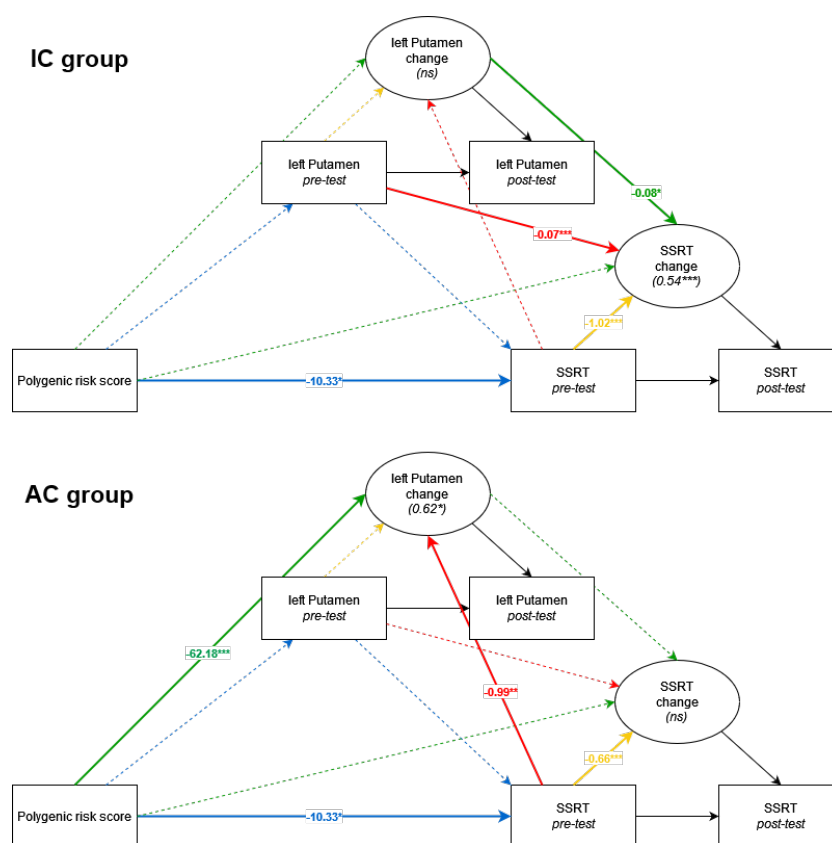


Figure 6.4: **LCS model estimations.** Top = children of the experimental (IC) training group; Bottom = children of the control (AC) training group. Plain lines represent $p < .05$, dotted lines represent $p \geq .05$.

change of lPutamen GM volume (-0.08 , $SE = 0.03$, $z = -2.32$, $p < .05$) were observed, reflecting an effect of both neural architecture at baseline and plasticity. Finally, at the genetic level, no significant effect of PRS on change for stop signal was detected ($p = .24$). Of note, there were no significant latent change of the lPutamen GM volume ($p = .21$) and this change of lPutamen was not impacted by either cerebral baseline lPutamen GM volume ($p = .28$), genetic PRS ($p = .31$), nor cognitive stop signal baseline performance ($p = .77$).

In the control training group (AC, bottom part of Figure 6.4), there was no significant latent change score for the stop signal ($p = .25$), i.e., no significant cognitive change following this placebo training. Among factors contributing to latent change of stop signal, only the cognitive baseline parameter was significantly negative for the stop signal (-0.55 , $SE = 0.16$, $z = -3.54$, $p < .001$). All other contributing factors failed to reach significance ($ps > .52$). Of note, this time there were a significant latent change of the lPutamen GM volume (0.62 , $SE = 0.24$, $z = 2.59$, $p < .05$) and this latent change of lPutamen was impacted by genetic PRS (-62.18 , $SE = 7.44$, $z = -8.36$, $p < .001$) and baseline cognitive stop signal level (-0.99 , $SE = 0.35$, $z = -2.88$, $p < .01$) but not by cerebral baseline lPutamen GM volume ($p = .23$).

In adolescents, none of the model estimation completed the three criteria. Fit indices for all ROIs in children and adolescents are available in Appendix A13. All model estimates for all ROIs are available in Appendix A14.

4 Discussion

This study used a multilevel SEM model to investigate the role of cognitive, brain, and genetic factors on receptivity to IC training (i.e., cognitive gain) in children and adolescents.

In children, some effects at the three different levels have been demonstrated. We found an effect of the basal cognitive level in line with the compensation hypothesis (e.g., Karbach and Unger, 2014), i.e., the children who benefit the most from the training are those who have the most difficulties initially (see Study 3). At the genetic level, we observed an effect of the PRS on the cognitive gains following training. This is consistent with previous studies that have shown a role of single nucleotide polymorphisms in training receptivity (Leckie et al., 2014; Rueda et al., 2005a). Here, since the PRS was calculated from a cognitive flexibility score (Trail making test) and was associated with the initial level of stop signal, this result suggests that the genetic basis of EFs would be involved for training receptivity. Again, this is consistent with the two studies that showed that polymorphism of genes involved in EFs (DAT1 and BDNF) were linked to post-training gains. At the brain level, we could detect an effect of the baseline brain ROIs volume and volume changes (i.e., plasticity) on cognitive gain. These results are the first to show an effect of brain anatomy on the benefits following training, and complement the brain basis of training receptivity with the previously described effects of cerebral network organization (Baniqued et al., 2019; Baniqued et al., 2018; Chaddock-Heyman et al., 2020; Gallen et al., 2016).

In adolescents, like all of our findings on APEX where cognition is involved (see Studies 1 & 3), the results were very limited. It would have been very interesting to have results in this age group, as it would have allowed us to compare our model with Judd's model (Judd et al., 2020) which covered similar age ranges. This longitudinal study of adolescents seen at 14 and then at 19 years of age had demonstrated through multilevel SEM that developmental changes in WM and cortical surface were under the influence of socioeconomic (SES index) and genetic (PRS) factors. Although in their study, baseline effects, cross-effects, and cognition-brain relationships at the pretest and latent change levels were bidirectional (whereas we modeled them as causal to be able to infer mediation effects), our two models were very similar and deal with theoretically related variables (IC and WM), so it might have been interesting to compare them.

Interestingly, among the 8 ROIs tested, two were found to have effects on cognitive gain: the left ACC and the left putamen, two key regions for IC. Indeed, various studies have reported the link between ACC cortical thickness and IC performance (Elderkin-Thompson et al., 2008; Takeuchi et al., 2010; Westlye et al., 2010). Functionally, ACC activity increases with age and development, similarly to IC performance measured by a Stroop task (Adelman et al., 2002). This region has also been shown to be more prominently activated during other IC tasks like Simon (Kharitonova et al., 2013) and Go/No-Go (Pornpattananangkul et al., 2016), having a central role in conflict detection and being increasingly activated when errors are committed (Braver et al., 2001). Therefore, both anatomy and function of ACC are related to IC performance. On the other hand, the activation of striatum, including the putamen, was shown to be related to response inhibition during the Stop signal task (Vink et al., 2005). Striatum, and particularly the putamen, are associated with motor response suppression (Pas et al., 2017) and inhibition anticipation (Pas et al., 2021; Pas et al., 2019;

Zandbelt and Vink, 2010). Thus, while ACC is a general region for IC, putamen is more specific for the stop signal task.

To get insight on raw and normalized brain changes, we conducted analyses using absolute or relative volumes (normalized by total intracranial volume; TIV). We observed slightly different but complementary results. The issue of spatial normalization of anatomical brain imaging data has been debated for a long time (Mills et al., 2016; O'Brien et al., 2011). Most often, a corrective factor, frequently TIV, is used as a regressor in VBM studies. If global differences related to sex, body height, and head size are not thoroughly controlled, these factors can bias the comparison. TIV is under the influence of genetic (early; the Alzheimer's Disease Neuroimaging Initiative (ADNI) et al., 2012; the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium and Early Growth Genetics (EGG) Consortium, 2012) and environmental factors (Caspi et al., 2020). In a developmental perspective, there is less consensus with studies correcting regional brain volume (Herting et al., 2014; Urošević et al., 2012), other studies using the raw volumes of brain structures (Goddings et al., 2014; Raznahan et al., 2011; Wierenga et al., 2014), and some studies reporting both analyses (Coupé et al., 2017; Dennison et al., 2013). As our volume measurements were very close in time (5 weeks) and the observed changes in brain volume were very limited (see Study 4), there are likely very few changes in the TIV explaining our results.

This study is the first to use a non-psychiatric phenotype to generate PRS and thus, paves the way for a new area of investigation: using non-psychiatric but related to IC outcomes to calculate PRS and emphasize relationships at the genome level. In particular, associating non-psychiatric and EF-related PRS with IC performance in healthy populations may advance our understanding of the overlap among genetic factors contributing to cognitive variability. Although PRSs do not provide the molecular specificity of single locus studies, they can provide important insights into broader aspects of genetic architectures. These broader relationships are important for informing newer analytic approaches exploiting functional hypotheses for improved power at finer scales.

Our results should be interpreted with caution given the small sample size and would need to be replicated on a larger independent sample before being generalized. Despite the large number of parameters, our models presented good fit indices, suggesting a reasonable robustness of the results within our sample. At the genetic level, extremely large sample sizes for reliable single variant studies or alternative approaches will be needed to advance understanding of the molecular genetic contributions to IC performance and training receptivity.

To conclude, this study paves the way for multilevel modeling to answer the question of intervention outcomes. This could be used to investigate the factors supporting learning, as in this study, but also, in clinical practice, to understand the evolution of a pathology, particularly following a therapeutic intervention, and thus participating in the development of a more precise and personalized medicine.

PART III: GENERAL DISCUSSION

This thesis had sub-goals in psychology and in methodology. In psychology:

- To study at the cognitive level the changes in the organization of executive functions following inhibitory control training and throughout development
- To investigate the factors at different levels (cognitive, cerebral and genetic) influencing inter-individual differences in the direct benefits and transfer effects of the same training
- With the underlying hypothesis that training could accelerates development

To this end, this thesis also had methodological objectives:

- To apply advanced statistical models to model the change following cognitive training
- To develop models that can link the different levels of observation
- To use machine learning models to test the hypothesis that training may change the brain age

1 On executive functions

EFs are important for academic learning (e.g., Diamond, 2013) but also for mental and physical health (for a review, Snyder et al., 2015). The number of publications on EFs and the diversity of the fields of study that are interested in them (psychology, psychiatry, neuroscience, cognitive science) can reflect the central role that they play in our lives. Thus, their development is of crucial importance.

1.1 EF organization

1.1.1 Through development

To have a better knowledge of EFs, their characteristics and their development, the question of their factorial organization is crucial. This question was particularly developed after the work of Miyake et al., 2000 who revealed, in adults, a three-factor organization of EFs (IC, WMU and CF) in three distinct but correlated factors which would each be composed of a common base (unity of EFs) and a unique part (specificity of EFs) (Miyake and Friedman, 2012). Following these findings, many studies have focused on the factorial organization of EFs at the developmental level (for reviews, see Karr et al., 2018; Lee et al., 2013). The recent meta-analysis and literature review by Karr et al., 2018 highlighted an organization ranging from one factor in childhood to a 3-factors (IC, WMU, CF) or nested (bifactor without IC) organization in adulthood. Within this framework, we investigated the organization of EFs during development (Studies 1 and 2). For these studies, we used different modeling techniques allowing to scrutinize the structure of EFs using both theory- and data-driven approaches.

In Study 1, we were able to demonstrate a segregation of EFs from childhood to adolescence with a network analysis (i.e., data-driven approach without *a priori*) on the APEX cohort. These results are consistent with a differentiation of EFs (e.g., Hartung et al., 2020) and a specialization of processes (Anderson and Nelson, 2005) with age.

In Study 2, we investigated the developmental organization of EFs in the Texas Twin Project (Harden et al., 2013) cohort using three complementary methods: network models, latent models, and latent network models. These three analyses revealed consistent and complementary results supporting a differentiation of EFs with development. Moreover, we were able to see that the weight of the different EFs varied with time, with the IC having a central role in childhood and then giving its central place to the WMU in early adolescence, in line with previous studies (Huizinga et al., 2006).

These results, consistent across the two studies, of different sample sizes but also different cultural background and with different experimental designs (i.e., different EF tasks), support the idea that EFs become segregated with age. These results are consistent with the developmental differentiation hypothesis that suggest that the structure of a child's development is unitary early in infancy but becomes more differentiated with age (Anderson and Nelson, 2005). As this hypothesis stated that the higher the differentiation, the higher the cognitive abilities (Anderson and Nelson, 2005), this highlights the importance of studying such factorial organization. Moreover, this differentiation may explain the different developmental trajectories between EFs (e.g., Best et al., 2009) as well as the segregation of brain networks with age (e.g., Baum et al., 2017). These results may also raise questions about the genetic bases of EFs, where it could be envisaged that there are genes associated with the common core of EFs and others associated with the specific part of each EF. At the interventional and clinical level, this suggests that there may be different sensitive periods for the development of the common-EF part and for each specific-EF individually. Further research is needed to investigate how higher-level EFs such as planning fit into this structural organization. Taken together, these findings will also provide a better understanding and insight into dysexecutive disorders in a clinical context.

There are some limitations to these studies. First of all, these two studies are cross-sectional with rather small sample sizes per age group. In addition, we saw in Study 2 that there appeared to be significant dynamics of change across the age groups proposed in Study 1. Further studies with a longitudinal design and more closely spaced repeated measures are thus needed.

1.1.2 During training

In addition to studying the organization of EFs throughout development, we were also interested in changes in EF organization after cognitive training. Thus, in Study 1, we were able to examine the effects of two types of training (targeting IC vs. active control) on the organization of EFs in a group of children and a group of adolescents.

In children, we found that the organizational changes following IC training were consistent with those occurring during development, with a network of children post-IC-training having similarities with the network of adolescents pre-training. These results are thus

consistent with the hypothesis that training may accelerate development (Jolles and Crone, 2012).

In adolescents, it appears that training had much less impact on EF structure than in children. As previously mentioned, this lack of results can be explained by the fact that adolescents seem to have benefited much less from training, reaching a plateau very early.

To confirm these results and to look at whether this lack of results in adolescence is due to poorly adapted training or to a developmental specificity, replication studies are needed. In addition, these studies need to be replicated within a longitudinal design to ensure that training does not deviate from the normal developmental trajectory (Jolles and Crone, 2012).

1.2 Training EFs

In Study 1, we were able to report that cognitive training could accelerate the development of EFs at the organizational level. However, in addition to looking at the results of such training at the group level, it is important to consider several things.

1.2.1 Inter-individual differences

Firstly, as we saw in Studies 3 and 6, inter-individual differences in training receptivity exist. In particular, we noticed that the children and adolescents who had the lowest basal level were the ones who benefited the most from the training, in line with the compensation hypothesis (Karbach and Unger, 2014). But these inter-individual differences were not solely explained by this cognitive level baseline. In Study 6, in addition to this cognitive factor, we observed an effect of genetic and brain factors. Indeed, in children who followed the IC training, within the same multilevel SEM model, the change in stop signal was explained by the pre-test score in stop signal, the polygenic risk score calculated from a TMT measure, as well as the initial volume and volume change (i.e., neuroplasticity) of the left ACC and the left putamen. These results are in agreement with the literature that had previously highlighted the influence of cognitive (e.g., Karbach and Unger, 2014), cerebral (e.g., Baniqued et al., 2019), and genetic (e.g., Leckie et al., 2014) factors in training responsiveness.

Together, these results point to the need for more personalized training. To this end, further studies are needed to identify the factors that contribute to the benefits of training and to perform cluster analyses to see if it is possible to draw up learner profiles. Then, on the basis of the properties of these profiles, it could be possible to propose the most adapted training to participants according to their learning characteristics.

Such approaches have already been adopted in medicine, for example in the context of "personalized" or "precision" mental medicine. For example, by using this type of approach, patients with depression can be subdivided into four neurophysiological subtypes ("biotypes") defined on the basis of distinct functional brain connectivity profiles (Drysdale et al., 2017). The use of these biotypes also improved the prediction of response to a therapeutic intervention (prognostic biomarker) and thus allowed the identification of the best

type of treatment for a given patient (Bzdok and Meyer-Lindenberg, 2018).

1.2.2 Transfer effects

In addition to direct benefits, training can also be valued according to the extent of its generalization. These transfer effects are also important at the theoretical level as they provide additional information on the relationship between the cognitive function trained and the cognitive function that benefited from the transfer. Above all, they make it possible to evaluate the total benefits of a cognitive training and thus to assess its overall impact.

In Study 3, we were able to show that transfer effects following IC training in children depended both on the baseline level of the EF that benefited from the transfer, the baseline level of other EFs, and the number of training sessions. In view of the development of the organization of EFs towards segregation, it is reasonable to think that offering the same training later on, once the EFs are already differentiated, transfer effects could be more reduced. On the contrary, offering WMU training at a time when WMU has a more important role in the organization of EFs (see Study 2), could lead to larger transfer effects. Taking into account the development of EF structure could thus maximize the transfer effects of training one EF to other EFs.

However, transfer effects are not limited to benefits on other EFs but could be assessed by measures of academic learning, which could represent the ultimate target. In this project, we did not have measures of academic performance, but it might be interesting to see if executive training could lead to improvements in academic abilities with a latent change score model and to see to what extent these improvements are related to transfer effects on other EFs. However, we can already hypothesize that such training could benefit academic learning, as learning relies on executive abilities. Ideally, several EFs should be trained at the same time in order to consolidate the common EF base and thus increase the chances of transfer to academic learning (e.g., Traverso et al., 2019).

Finally, the motivational factor could play a role for transfer effects since it is known to be involved in direct benefits (Jaeggi et al., 2014; Smid et al., 2020; Strobach and Karbach, 2021). In the training evaluated here, the sessions were adaptive according to the participants' performance level, in particular to keep them motivated (Green and Bavelier, 2008). However, it would have been very interesting to have quantitative measures of motivation in order to directly test the effect of motivation on transfer effects.

1.2.3 Sensitive periods

It is acknowledged that there are sensitive periods, i.e. developmental periods during which certain capacities are easily modulated by experience, for learning (e.g., White et al., 2013). This could also be the case for cognitive training, although current results are not entirely conclusive (Park and Mackey, 2022). Cognitive training has been proposed for childhood and adolescence according to this logic of periods of opportunity. Indeed, children would be more receptive than young adults to learning due to their increased neuroplasticity capacity (Kray and Ferdinand, 2013) and it was demonstrated that this type of numeric EF

training benefits 8-12 year olds more than younger 4-5 year olds (Diamond and Lee, 2011). Adolescence may be another sensitive period for interventions targeting EFs due to the behavioral, cognitive, and brain developments taking place during this time (Blakemore and Choudhury, 2006).

The different studies presented in this manuscript have shown that children benefited more from IC training at the cognitive level, even though Study 4 reported results at the cerebral level in adolescents. However, as already mentioned above, this discrepancy in results may also be due to training methodological problems in adolescents (progression cessation rather quickly).

Replication studies should be proposed to specify the periods of opportunity in order to know which are the most relevant times to obtain both direct benefits and transfer effects. Given the development of both performance and organization of EFs, it is possible that these periods could vary according to the composition of the training and the EFs targeted by it.

2 Neuroimaging studies

This PhD research was also an opportunity to analyse neuroimaging data and to investigate the links between brain, EFs and IC training. In particular, we were able to show in Study 4 that the brain regions whose plastic changes (here changes in local grey matter volume) were linked to changes in EFs (differences in scores after vs. before training) were regions identified in the literature as EF network regions (i.e., insula, anterior cingulate cortex, inferior frontal gyrus). We also tried to look at whether the initial volume of brain regions was related to executive abilities before any training. These analyses yielded fewer insights than our longitudinal analyses, but the result obtained was consistent with the literature (e.g., left precuneus associated with Stroop performance, Banich et al., 2000; Takeuchi et al., 2015).

However, it must be kept in mind that these brain-behavior associations are not reflecting causal relationships. We wrongly use the terminology of brain bases, which suggests a causality (see Genon et al., 2022). These discussions on the terminology used are part of a broader process of rethinking brain-behavior associations research following a replicability crisis in neuroimaging that questioned the way to conduct research (Genon et al., 2022).

2.1 Neuroscience at the time of big data

More and more consortia with neuroimaging data are being set up, such as the Human Connectome Project (Van Essen et al., 2012), UK-Biobank (Sudlow et al., 2015) or the Adolescent Brain Cognitive Development consortium (Casey et al., 2018). In parallel, studies have recently been published to emphasize the need for very large sample sizes (> 1000 participants) to be able to draw reliable conclusions on brain-behavior associations (Marek et al., 2022). While neuroimaging studies have traditionally involved smaller numbers of participants (25-100 subjects, Gratton et al., 2022), this shift to big data can also be perceived

in the methodologies used in neuroimaging, with the development of machine learning models that can be trained on large cohorts (Abraham et al., 2014). It is certain that the development of these consortia will allow scientific questions to be asked and analyses to be carried out that would not be possible with small sample sizes. However, it is important to ensure that it is not just these methods and consortia that guide research. It can seem that sometimes the data is used as a starting point to find a suitable research question, while the scientific method requires starting with the theory in order to pose a question and hypotheses before conducting analyses to answer the question (Bergmann and Spence, 1941). Furthermore, as stated in the discussion section of Study 4, if the research questions are asked precisely and a relevant design is proposed, then the signal can be maximized and the noise minimized and it is not necessary to have samples of thousands of participants to produce reliable results (Gratton et al., 2022). In particular, as we have seen in Study 4, in the case of longitudinal data, it is possible to control for inter-individual variability at the cerebral organization level (Gordon et al., 2017), which makes it possible to obtain reliable results while reducing the sample size.

In conclusion, it is undeniable that big data brain imaging studies and these new tools have allowed and will continue to allow new valuable findings, such as the development of brain charts (e.g., Bethlehem et al., 2022), but they should not however become the standard and prevent the results of smaller studies from being considered.

2.2 Diversity of tools and frameworks

In addition to sample size, other research practices may explain the differences in results and thus the challenge of replicability.

In particular, different preprocessing and analysis practices can lead to very different outcomes. As an example, 70 research teams were given the same neuroimaging data with the same 9 hypotheses to test and their final results were extremely variable (Botvinik-Nezer et al., 2020). Given these findings, one possibility would be to offer recommendations with unified pipelines across teams in conjunction with shared data and analysis codes. However, these choices of pipelines and processing tools are also influenced by the research question. For example, VBM is most commonly used for voxel-wise analysis in the context of statistical parametric mapping, whereas FreeSurfer is best suited for investigating cortical thickness (Ashburner and Friston, 2000; Fischl, 2012). It should also be kept in mind that the study of certain populations may require different analysis tools. For example, neuroimaging in children may require a greater correction of movements (Kaplan et al., 2022).

Finally, it is also important to take into account that neuroimaging is a recent field of research where innovations are regular and can interfere with the standardization of practices. There is thus a balance to be found between the standardization of analysis pipelines, the precision of research questions and the ongoing evolution of tools.

2.3 Towards multivariate studies

In future neuroimaging studies, it might be interesting to integrate the different brain features and not limit the analysis to one of them. Indeed, it is known that cortical area and thickness have different genetic etiologies (Panizzon et al., 2009) and may reveal different outcomes in the analysis of psychiatric disorders for example (Rimol et al., 2012). The analysis of these two variables therefore provides complementary information. Simply combining these different variables can however create noise and erase the specific effects of each variable. Ideally, one should assess each of these influences individually or use adapted tools for multivariate analyses such as latent factors. This type of analysis, often used for diffusion modalities, allows to create a latent variable from the different diffusion variables (e.g., McCormick et al., 2022). This kind of modeling would allow to look at the influences of each variable but also more globally at the latent modality level. Such multivariate and multimodal analysis would allow a good understanding of the brain mechanisms underlying the phenotypes of interest.

These multimodal and multivariate analyses could also be used to investigate the relationship between structure and function. There are several studies supporting the hypothesis that structure precedes function (Batista-García-Ramó and Fernández-Verdecia, 2018; Cohen et al., 2008; Damoiseaux et al., 2006; Honey et al., 2009; Mantini et al., 2007; Passingham et al., 2002; Rykhlevskaia et al., 2008; Vincent et al., 2007). This hypothesis comes from the fact that functional connectivity at rest is constrained by the anatomical configuration of the brain (Batista-García-Ramó and Fernández-Verdecia, 2018; Honey et al., 2009). With the integration of different variables from different modalities, it would also be possible to look at how early brain constraints such as sulcal patterns might compel other anatomical features such as volume and especially its neuroplastic variations. By understanding the links between these different cerebral features, it could be possible in the future to know which variable to consider according to the question asked. For example, if we know that changes after an intervention occur first at the structural level and then at the functional level, it might be more relevant to look first at the anatomical variations.

2.4 Machine learning

With the expansion of big data, the application of machine learning algorithms on brain imaging data has developed (Abraham et al., 2014). At the methodological level, these models make it possible to obtain more generalizable and stable results. By performing cross-validation and thus ensuring that the observed brain-behavior associations are not sample-dependent, the possibility of generalizing them to other data sets is increased, the ideal being to perform cross-validation on independent samples (Genon et al., 2022). With the evolution of consortia, and especially in the field of psychopathology, these models allow generalization across acquisition sites and thus obtain robust results that can then be used for clinical purposes (Chen et al., 2020b; de Pierrefeu et al., 2018a). An important prospect for the future of research and clinic is the development of meta-matching, an approach that allows to translate predictive models from large datasets to related but new phenotypes in smaller datasets (He et al., 2022).

2.5 Brain age

The development of machine learning in neuroimaging has led to the development of a new notion, the brain age. In Study 5, we were able to estimate the brain age of the children and adolescents participants with an accuracy of about 1 year from structural imaging data. Our preliminary results show that brain age gap estimation (brainAGE = brain age - chronological age) can be related to pre-test executive performance and to training responsiveness. However, these results are preliminary and it would be necessary to replicate them in independent samples.

2.5.1 Challenges for brain age prediction

In the midst of its development, brain age prediction is currently facing many challenges. In particular, on the issue of replicability, we know that the estimation of brain age can vary according to the data used to train the model (de Lange et al., 2022; Franke and Gaser, 2019), according to the modalities used (Franke and Gaser, 2019) but also according to the spatial level (e.g., ROIs vs. voxel; Baecker et al., 2021a) and finally according to the algorithm (Lee et al., 2021). If neuroimaging is recent, brain age is even more so. Studies calculating brain age are numerous but based on different characteristics and parameters and it will be necessary to explore these differences in detail to understand precisely what these brain ages represent. This exploration may help to establish guidelines for the models, variables and parameters to be used.

Finally, a challenge that may be important is brain age prediction by region of interest. It is known that in certain pathologies, certain regions are more affected than others (e.g., post-traumatic stress disorder and amygdala and prefrontal cortex, Koenigs and Grafman, 2009), and that for certain cognitive abilities, certain regions play a more important role (e.g., prefrontal cortex for EFs, Diamond, 2000). Predicting age from specific brain regions could thus make it possible to identify differences at the brain level that would be erased at the whole brain scale.

2.5.2 Development of brainAGE

Another axis of research, already mentioned in Study 5, would be to study the development of brain age and in particular its deviation from chronological age in a longitudinal design. Once a consensus has been reached on the methods and characteristics to be used to estimate brain age at the different stages of life, it will then be possible to study its variation during development and to produce brainAGE charts. As we know that the brain age can be impacted by surgical interventions (de Bézenac et al., 2021) or drugs (Le et al., 2018), it is possible to consider that its estimation can vary during the development. Creating a reference at the developmental level could allow to investigate the effects of the environment (pathology, learning, culture, etc.). The dynamics of brainAGE during development could also question the idea of brainAGE as a brain marker, or at least it could clarify what it indicates (trait/fix or state/plastic marker). Notably, it was demonstrated that brainAGE was partly determined by very early factors such as birth weight (Vidal-Pineiro et al., 2021).

Large longitudinal studies are therefore needed to disentangle early from plastic markers and to characterize the development of brainAGE so that it can be used for further clinical or research purposes.

2.5.3 Translational perspectives

BrainAGE is already being used in a clinical framework, but it is likely that once methodological studies have converged on how to model it, it could become a more standard tool. In the clinical context, brainAGE could be used for diagnosis, prognosis and management (Baecker et al., 2021b, see Figure 50). In the development of precision medicine, it can be combined with other brain, cognitive, biological and environmental measurements to propose the most appropriate medicine possible. Within this context, an estimation of age based on indices on different organs (body age) could allow us to understand the impact of a pathology on the whole human body but also to evaluate the state of each organ in order to adapt the medical treatment (see <https://people.eng.unimelb.edu.au/azalesky/project3.html>). Such approach with multi-scale data could also be adapted to the field of learning in a personalized education approach.

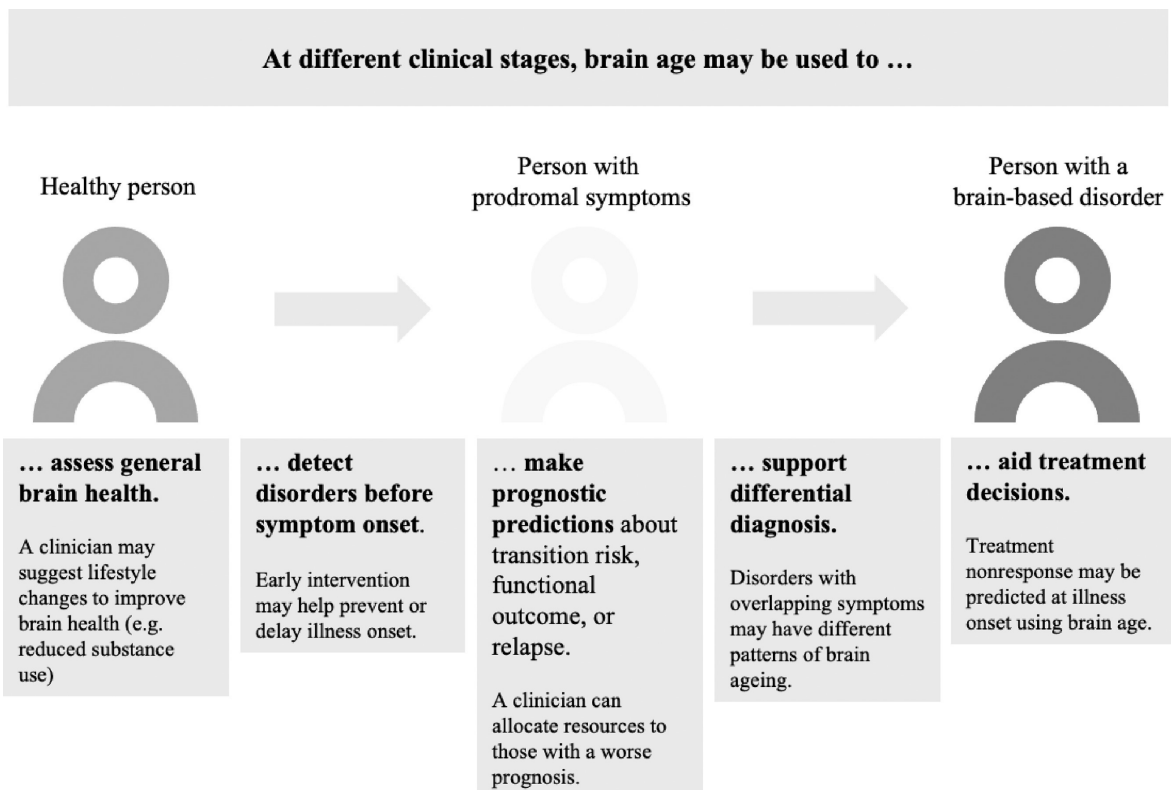


Figure 50: **Potential clinical applications of brain age at different stages of the patient lifecycle.** From Baecker et al., 2021b.

3 Genetic studies

Finally, we investigated in this PhD research the influence of genetic factors. The polymorphism of several genes, in particular of the dopaminergic system, has been shown to be related to performance in EFs (Croyley et al., 2006). However, it is quite certain that there are not a small number of genes whose polymorphism alone would determine our executive abilities but that the influence is rather polygenic (Donati et al., 2019; Hatoum et al., 2022). This polygenic influence has encouraged us to use statistical tools such as the polygenic risk score (PRS, Choi et al., 2020), rather than a candidate gene approach. Candidate gene approach also requires an *a priori* hypothesis on biological functioning and thus increases the risk of arbitrariness which can lead to contradictory results (Tabor et al., 2002), as seen in the General Introduction (see section 3.2.3). Of note, given our sample size, it was impossible to perform a genome wide association study (GWAS). We also wanted to follow a "genome-first" approach in which genome sequencing is done in a large population with subsequent determination of its association with the phenotypes of interest, here EFs. In a "phenotype-first" approach, the sequencing is done on a population presenting impairments of the phenotype of interest, allowing to determine which genetic variants could be associated with the phenotype. This approach is not adapted to study of EFs, which are highly variable in the normal population and are almost always associated with other symptoms in pathological populations.

Thus, in Study 6, the calculation of a PRS from a TMT score allowed the demonstration of an effect of genetics (indexed by the PRS) both on initial IC performance measured by the stop signal but also on the benefits in stop signal following training. These results, combined with those of Study 4, seem to indicate an overlap between the cerebral or genetic bases of EFs and those of training receptivity.

3.1 PRS : the top of the iceberg

Even though PRS have the huge advantage of taking into account the polygenic dimension by considering the influences of several genes at the same time, they do not yet take into account epistasis, i.e. the interaction of genes between them (Moore and Williams, 2009). Moreover, to calculate PRS, it is necessary to rely on GWAS independent from the target sample (Choi et al., 2020). However, current GWAS are far from representing the universal contribution of all SNPs for a given phenotype. In particular, it is necessary to integrate data from populations that are still poorly represented (Tam et al., 2019; see Figure 51).

Genetics, although a long-standing source of interest, has only recently been studied at the genome level and the first studies calculating PRS were published in the late 2000s (Wray et al., 2007). There is no doubt that in the coming years, we will see the emergence of analysis methods to consider the different parts of the iceberg that are not yet handled. In particular, among the analyses that are developing, we can mention genomic SEM (Grotzinger et al., 2019), that incorporates genetic covariance structure into multivariate GWAS discovery, or multivariate analyses that combine several phenotypes, revealing an important pleiotropy (Hindley et al., 2022).

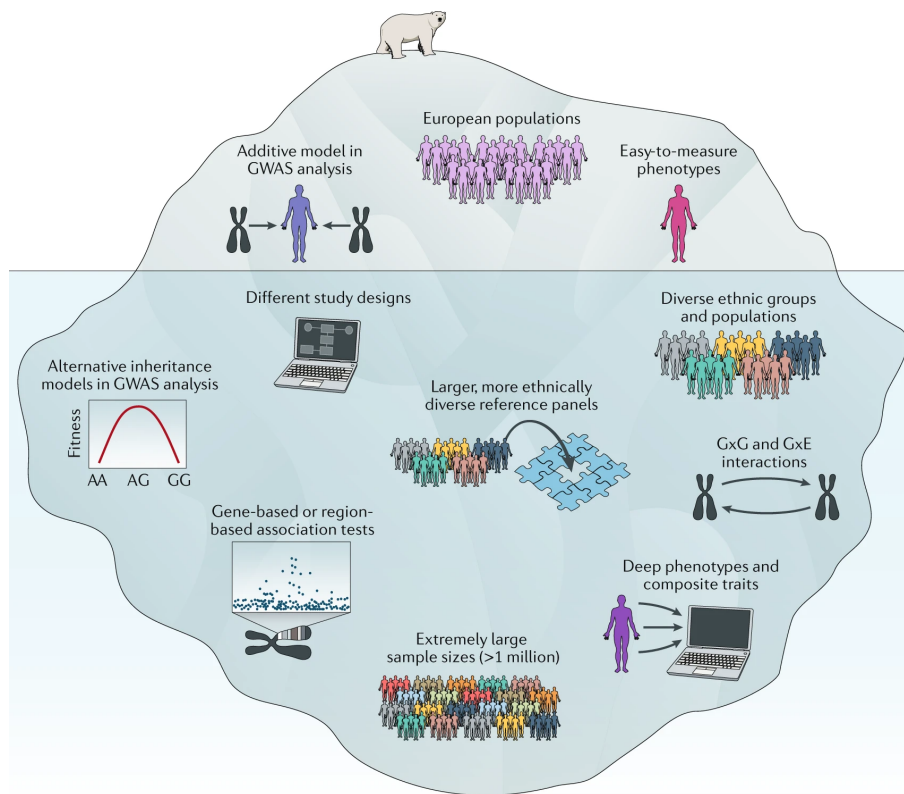


Figure 51: **GWAS, the top of the iceberg.** From Tam et al., 2019.

3.2 Why studying genetics

Genetic studies are important for fundamental research in order to understand the neuro-biological mechanisms underlying what can be observed at the brain or behavioral level. In addition, in the clinical context, genetic assessments are being increasingly used, both for diagnostic purposes and for the understanding of mechanisms underlying a pathology (e.g., which pathways are affected and what treatment should be proposed knowing this). The degree of analysis is increasingly refined at the genetic level, looking not only at the number of chromosomes or certain candidate genes, but also at more detailed variables such as copy number variants (Kaminsky et al., 2011). Thus, the development of research can serve clinical practice to understand the pathways of action of certain pathologies at the group level but also at the individual level as part of precision medicine.

Moreover, genetics can also be seen as a factor of inequalities. Indeed, knowing that genetics matters for educational and professional success, it could be important to keep in mind the inequalities carried by our DNA, which very often come from and interact with socio-economic background (Abdellaoui et al., 2022), to distance ourselves from meritocracy and promote a fairer society (Harden, 2021). Thus, genetics could be seen as a social outcome and studying it could help to provide insight into inter-individual differences and maybe could contribute to move toward a more equitable society.

3.3 Ethic considerations

It is necessary to be careful as, even if our intentions are good, eugenics is not that far away. Of course, it is not a matter here of identifying genes that would allow better performance in order to promote them, but rather of understanding the underlying mechanisms in order to help those who experience difficulties.

In particular, it is important to remember that the influence of genetics remains limited ($R^2 = 7.19\%$ in our Study 6, and usually between 1 and 6 % for psychiatric disorders Mistry et al., 2018). Moreover, although not studied here, there are also epigenetic mechanisms that modulate gene expression, notably under the influence of the environment (Ibrahim et al., 2018).

It is part of the researcher's responsibility in presenting and promoting these results to emphasize this and not to present inter-individual variations as simply innate. For example, in our Study 6, although we showed that PRS is a factor that explains initial CI performance (up to 7 %) and changes in IC after training, it is not the only factor that plays a role. It is therefore important to use statistical approaches such as SEM or NM that allows to analyze all the factors, and not only the genetic one, at the same time.

4 On the importance of integrating environment

Among the factors that play an important role on, among others, EFs and their development, are environmental factors, including culture and socio-economic status (e.g., Lawson et al., 2018; Roos et al., 2017).

4.1 The need of diversity in population studies

In psychology in general, there is a serious lack of studies on non-WEIRD (Western, educated, industrialized, rich and democratic) populations (Nielsen et al., 2017). However, effects observed in WEIRD populations are not always replicated in non-WEIRD populations, putting forward a cultural factor (e.g., Caparos et al., 2012). Notably, as presented in section 4.2 of the General Introduction, executive capacities may differ from one culture to another (for a review: Roos et al., 2017). Indeed, cultural habits may encourage the development of certain cognitive abilities and explain inter-individual variability (Yanaoka et al., 2022). Moreover, for genetic studies, as explained above, the distribution of SNPs can vary according to ancestry (Tam et al., 2019) and it is therefore relevant to have an idea of gene-behavior associations in not only europeans populations. Nevertheless, it is important to be aware that even in non-European populations, diversity is not always represented (e.g., Han population mostly represented in the studies on Chinese populations). Lastly, it is important to be careful not to generalize results obtained in one population to all human beings.

4.2 Limits on studying SES

In addition to culture, within the same genetic population, there are differences due to the environment and in particular to socioeconomic status (SES). Indeed, SES is known to be related with executive abilities (for review and meta-analysis, see Lawson et al., 2018) but also with brain development (e.g., Tooley et al., 2021). However, studies focusing on SES differences may present different results (e.g., Lawson et al., 2018) particularly due to measurement diversity. In a recent literature review, 147 unique measures of SES were found, and in almost 80% of studies, SES was not defined (Antonoplis, 2022). This variability in measurement may play into the variations in results. These difficulties are sometimes added to those of data acquisition with, for example, the difficulty in France of obtaining salary information.

Moreover, SES effects on brain and cognition seem to be rather complex, with the important variability in results between cohorts with different cultural backgrounds, with no consistent association of SES with either brain or cognition (Walhovd et al., 2022).

Given the crucial role that SES plays in cognitive and brain development, it seems important to address these variables and to converge on one or several ways to measure it. Until this consensus is reached, it would be advisable for further studies to precisely define their measures of SES, for example by describing how the variables that compose and the ways to calculate the index used.

5 Methodological issues

In this PhD project, a methodological objective was also involved.

5.1 Development of models for longitudinal designs

First, different models have been proposed to investigate longitudinal changes. Thus, network model in Study 1 and latent change scores (LCS) models in Studies 3 and 6 allowed to highlight results that could not have been highlighted with a classical statistical approach. In particular, in Study 1, networks were used to model the organization of EFs without *a priori* and allowed to test the hypothesis of training accelerating development on EF organization. In studies 3 and 6, the LCS allowed us to look at the change as a latent variable and to look at the factors that could influence it. LCS present the advantages of assessing training-related changes without the use of classical change scores (post-pre), which do not estimate causal effects (Tennant et al., 2019), of allowing to investigate inter-individual differences in the initial levels and in training-related changes and of determining the factors influencing the change trajectories.

The LCS was specifically developed for longitudinal studies with at least two measurement times. Other models have been developed for this type of study such as the latent growth curve model (LGCM). LGCM integrates within-person and between-person models of individual growth into a single structural framework, allowing for the description

of a single individual's developmental trajectory, the capture of individual differences in these trajectories over time, and the study of development at the group level (Duncan and Duncan, 2004).

5.2 Development of multilevel models

A model was also devised to study longitudinal changes at different levels (Study 6). This model, combining classical models such as the LCS and mediation models, allowed the integration of cognitive, genetic and brain variables within the same model.

The factors underlying a phenomenon are often complex, present at different levels of observation and interacting with each other. This is why it is important to study the relationships between these different variables, while controlling for these different relationships. Integrating these different modes of observation and levels of analysis is necessary in order to understand the intra- and inter-level mechanisms that take place and thus, more globally, the relationship between the structure and dynamics of psychological systems (Borsboom, 2022). The development of these multilevel models are part of a larger movement to connect variables, components, that were traditionally studied separately. This is also reflected in the growing popularity of network analyses (Borsboom, 2022) that can integrate different levels of measurement (Isvoranu et al., 2019) as well as SEM (Judd et al., 2020). Indeed, inter- and intra-level analyses require adapted and more complex tools than simple correlations or regressions, which can constitute a methodological barrier.

5.3 Methodological considerations

These methodological tools are still in evolution. Even if SEMs were introduced in the field of social sciences in the 1970s (Duncan, 1975) and applied to the issue of EFs as early as 2000 (Miyake et al., 2000), the different models presented in this thesis are still being developed and appropriated by psychological research. This is even more true for newer models such as networks (Borsboom, 2022). Tutorials and recommendations are developing (e.g., Epskamp and Fried, 2018) and it is likely that in the coming years, more precise standards and adapted recommendations will emerge.

5.3.1 The importance of theory

An important thing to consider when building a model is the theory. Even with a limited number of variables, the number of possible models is enormous and there is no question of estimating and comparing all these models but rather of relating them to the theory. We must preserve ourselves from being guided by the data. Even if tools such as the Loadings Comparison Test, which can predict whether a data set is rather structured in factors or in networks (Christensen and Golino, 2020), it is above all the scientific and psychological questions that must guide the choice of variables and models.

For example, as we saw in Study 2, the different models produced similar yet complementary results. The comparison of these different models was interesting in view of the question (i.e., the development of the EF organization). However, in the context of our Study 3, it would have made little sense to use network analyses to answer the question of transfer and the factors influencing it. Thus, it is the scientific question and theory that must guide practice but also interpretation.

5.3.2 Limitations on path models

Most models are evaluated by their fit indices. However, while some may be good, others may indicate a not so great fit of the model. It is the researchers' responsibility not to pick out the fit indices that would support a good fit of the data and use them to justify a poorly fitted model (Stone, 2021).

Moreover, there is currently a critical discourse on SEMs that these models are too complex to be used as a descriptive tool but are not complex and flexible enough to be used as predictive tools (e.g., Foster, 2010; Rohrer et al., 2022). For example, it has been suggested that, in contradiction to common practice, observing a good fit for, say, a mediation model, would not be sufficient to be able to make causal inferences (Rohrer et al., 2022). To make causal inferences, it would be necessary to be able to ensure that there is no reverse causality or that confounding variables are not involved (Rohrer et al., 2022).

In conclusion, it is also important to keep in mind that no analysis is inherently better than the others and thus that no single statistical analysis should rule out others (Wagenmakers et al., 2022).

6 Perspectives

After reviewing the different results of this thesis and discussing the different methods and levels of measurements used in this research, several perspectives emerge.

6.1 For future APEX-like studies

6.1.1 Sample

First, as we have seen in several of the studies presented in this manuscript, the relatively small sample size, although important for a longitudinal project with multilevel data acquisition, has often been a limitation. Thus, increasing the number of participants could allow for analyses that were limited here by the small sample size (e.g., machine learning analyses for Study 4, inclusion of an additional level of measurement for Study 6).

Most importantly, it seems crucial to have a more diverse sample at the socio-economic level. This may allow us to look at and control for the effects of SES on EFs and training but also potentially a better generalization of our results. As mentioned earlier, it could

also be interesting to replicate our study in other cultures because we know that cultural factors play a role in the EF performance (Roos et al., 2017) and question their sole definition (Yanaoka et al., 2022).

It could also be interesting to test such cognitive training on younger populations, maybe as early as preschool like Tools of the Mind (Diamond et al., 2019). Identifying the most sensitive age group could make it possible to offer the training at the moment when it could bring the most benefits. However, if results are to be compared across different age groups, methodological adjustments may be necessary, particularly in terms of the tasks used (Simpson and Carroll, 2019).

Finally, in the context of clinical application, as initiated with part of the APEX project, which was conducted on 9-10 year old children born prematurely, it could be very relevant to test the effects of such executive training on populations with executive difficulties, who might benefit particularly from such training. Testing EF training in different clinical populations could, depending on its results, open the way to targeted interventions for executive difficulties. Moreover, depending on the direct benefits but also of transfer effects for example on other symptoms, this could provide information on the organization of a pathology's symptoms and help characterize it a little more precisely.

6.1.2 Other types of training

The APEX project had the great interest of comparing an inhibitory control training and an active control training. The inclusion of this active control group allowed control for experimenter and test-retest (Diamond and Ling, 2016) effects. However, in the future it may be interesting to include a passive control group to be able to distinguish the effects of any training from EF training.

In addition, it might be interesting to test trainings targeting the other EFs and even targeting several EFs at the same time. It could be valuable to compare the results of these different training sessions, both on the organization of the EFs as well as on the direct benefits and transfer effects.

Finally, proposing Stroop and stop signal tasks every day does not seem very adapted in a context other than experimental. It would be interesting to test trainings that could be integrated into everyday life, such as trainings based on sports (Diamond and Lee, 2011), mindfulness meditation (Gabriela Rezende's PhD at LaPsyDE), school games (Letang et al., 2021) or video games (Chiara Andreola's PhD at LaPsyDE, Andreola et al., 2022). It is likely that these more adapted and gamified trainings would increase the adherence and motivation of the participants, which could enhance the benefits (see Katz et al., 2014).

6.1.3 EF measures

To address some of the perspectives developed in this section, it might also be interesting to reconsider the different tasks proposed in the cognitive battery before and after training.

6.1.3.1 To examine EF organization through development In particular, it seems extremely relevant to integrate several measures for each EF in order to be able to look at the organization of the EFs and test the different Karr et al., 2018 models (see Study 2). For each EF, measurements of the different subcomponents should be available (e.g., response inhibition and motor inhibition tasks to measure IC). Ideally, this executive battery should be pre-tested and a confirmatory factor analysis conducted to test and confirm the factorial organization at different ages of life (e.g., childhood, adolescence, adulthood). However, care should be taken not to multiply the tasks in order to respect correct and child-friendly administration times, especially in a longitudinal design.

6.1.3.2 Hot and cool EFs It might also be interesting to conduct a parallel study on hot EFs, which involve the emotional system and have a distinct developmental trajectory from cool EFs (e.g., Zelazo and Carlson, 2012). To date, and to our knowledge, no study has investigated training hot EFs or looking at the effects of cognitive training on these functions. Furthermore, to date and to our knowledge, no study has looked at the organization of hot EFs. It might be interesting to compare trajectories during development or after training of hot and cool EFs. As these do not have the same developmental trajectories, we could expect different effects of training, but also different organization of EFs during development.

6.1.4 Implement a delayed post-test

It would be interesting to repeat these different executive measures, but also the brain imaging and perhaps epigenetic measures, several weeks or even months after the training has been stopped. First, it would allow us to investigate the stabilization of all these changes during this delayed post-test, which is more than relevant to evaluate the overall effects of a cognitive training. Moreover, this would also allow us to study the temporal dynamics taking place at different levels after a cognitive training. For example, we have seen that there is a hypothesis that anatomical changes constrain functional changes (e.g., Batista-García-Ramó and Fernández-Verdecia, 2018). We could thus imagine observing different dynamics at the group level (structural and then functional changes over time) but also at the individual level (those who have shown greater structural changes following training could be also those who could show greater and more stable functional changes over time).

6.1.5 Deeper investigation of training characteristics

We are used to looking at the effects of a training session by comparing pre- and post-test but it could be relevant to look at the effects of the training as the sessions progress and the program progresses.

At the cognitive level, it may be relevant to look at the intra-individual variability from one session to another or within a session (Aristodemou et al., 2022; Könen and Karbach, 2015) and the individual progression curves. On one hand, at the group level, this could allow us to understand the mechanisms that come into play during cognitive training. In

particular, this could allow us to identify how long it would take for the progression to reach its peak and thus determine the ideal number of sessions. On the other hand, at the individual level, as we have seen in Study 3, there is a large inter-individual variability in the benefits of training, especially according to the baseline cognitive level (e.g., Lövdén et al., 2012a). There may also be different individual trajectories with subjects who progress rapidly and then stabilise, others who progress linearly or others who are not responsive to training at all. Looking at individual trajectories could thus allow for individualization of training durations.

At the brain level, it could be very relevant to perform repeated anatomical and functional measurements to see how training can affect the brain (Simplex project at LaPsyDE). In particular, this could allow us to see if training has an impact from the first sessions or if a minimal number of sessions is necessary before observing an effect. In particular, we could see which brain characteristics are impacted by training and according to what timing, and we could hypothesize that changes would first be observed at the structural level and then at the functional level (Batista-García-Ramó and Fernández-Verdecia, 2018) and, by linking them to individual progression curves, to understand the neuro-cognitive mechanisms that support learning. The implementation of the delayed post-test could allow us to see if these effects persist even after the training has ended.

6.2 Towards a precise definition of EFs

Overall, in future EF studies, it will be necessary to specify what is meant by EFs. Indeed, as seen in the introduction, EFs suffer from a lack of precision. While multiple terminologies are used for similar or very similar processes, shortcuts are sometimes used. Moreover, the fact that these concepts are very similar leads to a real methodological difficulty: which task should be used to measure a precise concept?

All these imprecisions and difficulties lead to two observations and recommendations. First, it is necessary to investigate each of the components of EFs and precise their definition, and for this, it is also necessary to understand how EFs are organized and related to each other. This will allow, in a second step, to specify the measurement spectra of the different tasks. A given task should no longer be able to be used in one experiment to measure one EF and in another to measure another EF.

This work will certainly be long and cannot be done one theory separated from another, at a single level of observation. It will have to be done collectively, by integrating cognitive, developmental, cerebral, genetic, environmental, and cultural data, and by using statistical tools that will make possible to finely investigate the links between the different levels of observation.

6.3 Potential clinical applications

At the EF level, gathering knowledge to understand at the fundamental level their organization, their development and the factors that influence them is important for the care

of pathologies in which these EFs are impacted (e.g., Thomas et al., 2009). By linking this knowledge with that of other symptoms, it could also allow us to understand the mechanisms that are at play in these pathologies.

In terms of cognitive training, training programs such as APEX could be proposed, not as a treatment but as a preventive tool (Diamond, 2013). Thus, training targeting EFs could be proposed to at-risk populations, for example those diagnosed but without detected executive difficulties, those with initial but undiagnosed EF difficulties or those who present symptoms in which EFs are known to play a role, such as IC for auditory hallucinations (Jardri et al., 2016).

Finally, at the methodological level, the tools used in this research can be used in the clinical context. Networks are already widely used in clinical studies, whether in depression (Mullarkey et al., 2019), post-traumatic stress disorder (Hansen et al., 2021) or psychosis (Isvoranu et al., 2017). But the longitudinal and multilevel models presented in Studies 3 and 6 could also be used to study the effects of a therapeutic intervention and the mechanisms that influence the benefits of that intervention. They could also be used to investigate the evolution of a pathology in conjunction with the mechanisms influencing the development of symptoms.

6.4 Towards a personalized education

At the educational level, we know that EFs have an important supporting role in learning (e.g., Mulder et al., 2017). Training EFs could then allow to compensate or prevent the difficulties of some students. In particular, we could propose training aimed at improving the EFs in children who have difficulties in certain learning areas such as reading (Andreola et al., 2022). Such training could also be proposed as a preventive measure to children with initial difficulties in EF in order to ensure that their executive base is sufficiently solid to allow the implementation of school learning.

Overall, this research is in line with precision education or personalized instruction (Watson and Watson, 2016). It has been known for a long time that not all children learn in the same way, and that some have more learning difficulties than others (Watson and Watson, 2016). Identifying the factors that support learning could make it possible to propose a more personalized education adapted to each learning child. These personalized education approaches are at the core of certain pedagogies such as Montessori (Cossentino, 2010).

6.5 Ethical questions

However, we must be careful because as soon as we talk about personalized education and the identification of learning profiles of children, we can think of categorization and potential educational inequalities. The aim of personalized education is not to stigmatize, but to offer an education adapted to each child so that everyone can expect the same results and in this sense promote equality.

It is also important to emphasize that this work must be done in conjunction with the

actors of education: the teachers. They are the experts in education and school learning and they are the ones who see the students learning on a daily basis. It is not possible to move forward without them in the field of education and bridges must be built in this sense. This can be constructed with collaborative research (Letang et al., 2021) and curricula such as the *DU Neuroeducation* in which I was involved during my thesis, where researchers in psychology and neuroscience of education bring their knowledge to the actors of education in order to co-create the school of tomorrow.

Furthermore, it is important to note that this research does not aim to go towards a search for EF excellence for healthy populations. Rather, this thesis is part of fundamental research: to understand EFs, their development, their training and to propose statistical methods to be able to do so rigorously. There is absolutely no question of encouraging excellence in EFs, inter-individual variability is natural and should be preserved.

7 Being a researcher in psychology nowadays

To conclude this manuscript, I would like to briefly present some more general considerations about psychological research nowadays.

7.1 The growth of psychological science

When we introduce ourselves as researchers in psychology, we can observe that there is often a gap between the public's perception of psychology and the current research in this field. In particular, and this is especially true in France, psychology is often associated with psychoanalysis while we are getting further and further away from it. We are moving towards a scientific psychology, based on mathematical proof. This can be seen with the creation of scientific societies like the Association for Psychological Science (<https://www.psychologicalscience.org/>), the Society for the Improvement of Psychological Science (<https://improvingpsych.org/>), or the Society for Mathematical Psychology (<https://mathpsych.org/>). We can hope that this will contribute to a greater credibility to this field of research which sometimes suffers from misconception without dismissing the complementarity of approaches between scientific psychology and literary approaches of mental phenomena.

7.2 The development of new tools

This scientific progression of psychology can also be seen in the methods now used in research. In particular, studies using SEM or networks, initially developed by other disciplines, are multiplying and spreading on different research questions in psychology thanks to the appropriation of these methods by several actors of the discipline. This evolution in psychometrics is linked to a new vision of human beings as complex systems that evolve over time and that involve different levels of observation and analysis, sweeping aside the conventional analyses in which the different psychological components were studied indi-

vidually (Borsboom, 2022).

In general, statistics are becoming more and more important with the development of psychological methods. In particular, among the statistics not mentioned in this PhD, Bayesian statistics are likely to become more and more widely used and with them the p-values more and more abandoned.

7.3 Improving psychological researchers' training

The evolution of the discipline and these new tools are changing the way of conducting psychological research. It is necessary to integrate into researchers' training courses on these methods and tools so that they can understand them, appropriate them and use them. It would also be useful to include courses on modeling theory and not just statistics, as scientific models are lacking in psychology (van Rooij, 2022). Finally, we must not fall into another extreme: as stated several times, theory remains at the heart of research and there is no intention of abandoning theoretical and practical training in favor of methodological and statistical training.

7.4 Collaborative framework

This emerging science is also part of a broader context of open science with the creation of consortia, data sharing and increasingly open access codes and analysis tools. This dynamic can allow questions to be asked that could not be answered alone in one's laboratory, especially for "smaller" laboratories with reduced funding. However, one must be careful not to forget to ask scientific questions with rigor and not just let oneself be carried away by the open access data. For this, knowing what it is to acquire data allows one to have experience of the scientific method. In the same way, concerning the open access codes and analysis tools, it is important to make sure that one understands what is being done in order to correctly interpret the results. In conclusion, open science, both for data and for codes, is an important resource but should not guide the entire future of research.

7.5 The future of doing research in psychology

Thus, it appears that research in psychology will be carried out more and more in collaboration with other researchers in psychology but also in other disciplines, allowing for interdisciplinarity to develop. These collaborations will also be made with other specialists: as for education, research and especially its clinical applications must also be made in collaboration with experts in the field: the clinicians.

The replicability crisis (e.g., Anvari and Lakens, 2018) has been a major issue in psychological research and since then, many actions have been taken. In particular, pre-registration (Nosek et al., 2018) and pre-registered reports (Nosek and Lakens, 2014) have developed a lot to fight against p-hacking. Although more difficult, we also see a trend of publishing negative results to fight against publication bias (Hubbard and Armstrong,

1997). It is likely that more and more rigorous studies will emerge in terms of design and analysis, and hopefully also at the theoretical level.

To conclude I would say: what an exciting time to do research in psychology!

CONCLUSION

Throughout this thesis, we have investigated the effects of inhibitory control training and development at different levels of observation: cognitive, cerebral and genetic.

Regarding the organization of executive functions, we were able to show a differentiation of executive functions with development, supporting the hypothesis of differentiation of processes with age and acquisition of these processes (Anderson and Nelson, 2005). We have also been able to see that the different executive functions do not play the same role in this organization during development, at the beginning the inhibitory control being very central and then leaving its place to the working memory updating. We could also demonstrate that these developmental changes were fairly similar to changes following 5 weeks of computerized inhibitory control training in children, supporting the hypothesis that training accelerates development (Jolles and Crone, 2012). However, such results have not been replicated in the adolescent sample. Further studies are needed to determine whether these results are due to a developmental characteristic or to the proposed training.

In terms of inhibitory control training benefits, we were able to see that inter-individual differences in training could be explained by cognitive, brain and genetic factors. Notably, participants with initial lower inhibitory abilities were found to benefit most from an inhibitory control-targeted intervention, supporting the compensation hypothesis (Karchach and Kray, 2021). In addition, children who were at lower genetic risk for poor executive functioning also showed the most progress. Thus, an overlap seems to exist between the genetic basis of executive functions and the genetic basis of responsiveness to training. Similar overlap was also observed at the brain level. Further studies are needed to integrate environmental variables into this multilevel modeling.

This thesis is also taking place in the context of an evolution of psychological research which becomes more precise and interdisciplinary, with the development of analytical methods such as network, structural equations or machine learning models, and more integrative, with the simultaneous integration of different levels of observation. These methodological developments allow crucial questions in developmental psychology to be answered and variables to be considered not isolated but as part of an integrated human system.



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APPENDICES

A1 General introduction: Segregation and integration

Over the last twenty years, neuroimaging research has established two fundamental principles of brain organization: *segregation*, the segregated or modular distribution of anatomical and/or functional specialization within brain regions, and *integration*, the functional and/or effective connectivity between brain regions (Friston, 2009).

A1.1 Study of brain segregation

A1.1.1 Anatomical segregation

The idea of specialized regions for a brain function is not new. Phrenology, developed by Franz Joseph Gall (1758-1828), is a well-known theory: each part of the brain would be involved in a cognitive capacity or a personality trait and, the more developed this capacity or this trait is, the more important the associated brain region would be. According to Gall, it would then be possible to discover the intellectual capacities and personality traits of a person only from the analysis of the bumps in his skull, such as the famous "math bump". Some aspects of this theory, such as the organization of the brain into functional regions or the link between the anatomy of the brain and its functioning, have since been validated experimentally on numerous occasions, in humans and animals. However, the main concern with this theory is that there is no link between the shape of the skull and the shape of the brain.

At the end of the 19th century, the French physician Paul Broca (1824-1880) proposed a clinical proof establishing a link between a precise cerebral region and a specific cognitive function. One of his patients, Monsieur Leborgne, suffered from aphasia and presented a lesion in the third convolution of the left frontal lobe, now called Broca's area. This lesion associated with the functional deficit allowed Broca to establish a link between this area of the brain and language production. Since Broca, lesional studies have increased in order to understand the link between a given function and a specific brain structure. These studies are the first brick in the study of brain segregation but have the disadvantage of being applicable only to bimodal functions (aphasia vs. no aphasia) and, before the arrival of neuroimaging, of only being performed post-mortem. Today, these studies are often performed on patients who have suffered a brain lesion after a head injury or a stroke and can be observed with neuroimaging tools while the patient is alive. However, for complex functions such as EFs, these studies do not allow the analysis of normal inter-individual variability.

The development of neuroimaging tools has accelerated the development of brain segregation studies. At the anatomical level, the scanner first allowed *in vivo* lesional studies to be performed (see above). But it is really the development of cerebral MRI that has been a

game changer for research. Structural MRI allows the precise characterization of the cerebral anatomy. It is then possible to study the volume, surface or thickness of regions of interest (see Figure A1) and look at the link between these characteristics and phenotypic variables (e.g., executive performance).

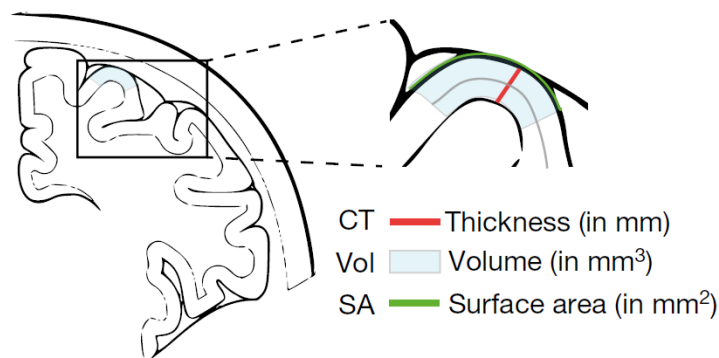


Figure A1: **Schematic representation of thickness, volume and surface of a brain area.** From Bethlehem et al., 2022.

As represented in Figure A1, cortical volume is a combination of thickness and surface area. Thus, a change in volume can reflect either a change in thickness, a change in surface area, or both. Over the lifespan, it was demonstrated that volume changes were primarily explained by changes in thickness rather than surface area (Storsve et al., 2014). However, it is possible to assess cortical thickness and cortical area separately (Dale et al., 1999; Dale and Sereno, 1993). These two components of cortical volume, area and thickness, result from well-differentiated ontogenic stages during corticogenesis (Lichtenstein et al., 2009) and appear to have independent genetic etiologies (Dale and Sereno, 1993).

Of note, other neuro morphometrics can be extracted from structural MRI such as white matter surface area (Fischl and Dale, 2000), sulcal length, depth (Im et al., 2006) and morphology (Ono (M.D.) et al., 1990), gyrification index (Schaer et al., 2012), or fractal dimensionality (Madan and Kensinger, 2016). Whereas some of these metrics such as volume, surface or thickness can evolve with time, events, environment and learning, others such as sulcal morphology remain unchanged over time. The former are called plastic markers (they reflect a situation at a given moment; e.g., Draganski et al., 2004) and the latter are called fixed or stable markers (they remain the same over time; Sun et al., 2012).

A1.1.2 Functional segregation

In addition to the anatomical results, functional neuroimaging methods made it possible to highlight the regions that were particularly activated during the performance of a task or action.

Functional MRI allows an indirect observation of brain activity using the BOLD (blood-oxygen-level dependent) signal, which reflects local and transitory variations in the quantity of oxygen transported by hemoglobin as a function of neuronal activity in the brain. This technique is indirect and is based on the idea that any neuronal activation will be ac-

accompanied by a local increase in blood flow in order to cover the metabolic needs related to this activation. Classically, to see the regions particularly activated for a cognitive function, the participant is asked to perform a task requiring this function while in the MRI. This may require adaptations, especially for tasks that are not compatible with the technical characteristics of MRI (powerful magnet, lying patient who must keep his head still), such as writing (Palmis et al., 2020).

Electroencephalography (EEG) allows less constraints in the tasks that can be performed. Indeed, since it is only a helmet connected to a computer and placed on the head of the participant, the latter is much freer of his/her movements than in the MRI where he/she must remain laid down and immobile. For this same reason, EEG is used a lot in young populations, as early as the first days of life (de Hevia et al., 2014). However, EEG does not provide the same information as MRI, having a much lower spatial resolution although a better temporal resolution (Logothetis, 2008). Thus, fMRI allows us to map more precisely the local brain regions activated during the execution of a task and we will therefore focus mostly on fMRI studies in this introduction.

Of note, other techniques have been used to map brain function such as magnetoencephalography (Hillebrand et al., 2005) or transcranial magnetic stimulation (Hallett, 2007).

A1.2 Study of brain integration

Integration refers to the connectivity between brain regions (Friston, 2009). Two types of connectivity can be distinguished: structural (or effective) connectivity and functional connectivity.

A1.2.1 Structural connectivity

Structural connectivity (SC) can be defined as the description of the anatomical connections between network nodes (i.e., brain regions, neurons) and relates often to reconstructed anatomical projections derived from diffusion MRI (dMRI), directed anatomical pathways derived from neural tract tracing, or synaptic connections between individual neurons (van den Heuvel and Sporns, 2013), mostly using diffusion tensor imaging (DTI). DTI provides a three-dimensional model of diffusion distribution within each voxel quantifying the diffusivity along three orthogonal axes.

The most common metric extracted from DTI studies (see Figure A2) are:

- *Fractional anisotropy (FA)*: measure of the directionality of diffusion that ranges from 0-1 with higher values reflecting highly ordered diffusion which occurs primarily in one direction and lower values reflecting isotropic diffusion which is more distributed in each direction.
- *Mean diffusivity (MD)*: mean of the diffusivity along the three axes.

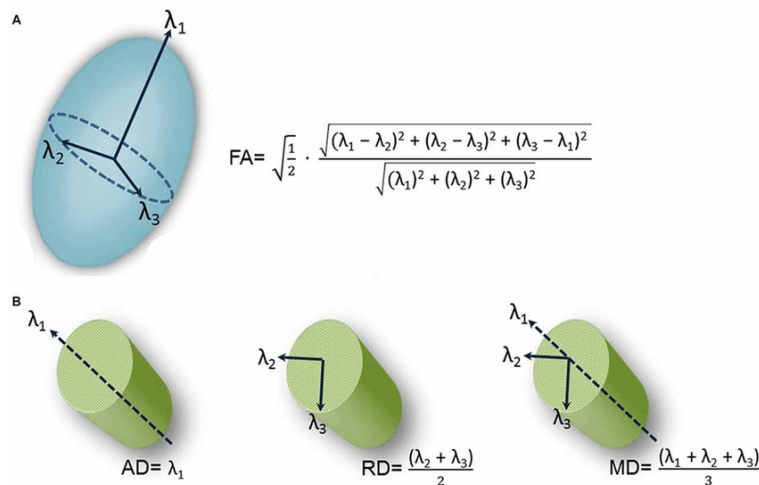


Figure A2: **Schematic representation of DTI-derived metrics.** From DeSouza et al., 2016.

- *Axial diffusivity (AD)*: diffusivity in the direction of the primary axon orientation (within the voxel), represented by the principal diffusion axis in the tensor.
- *Radial diffusivity (RD)*: mean of the diffusivity along the secondary and tertiary axes reflecting diffusion perpendicular to the axon bundle.

Developmental studies hypothesized that changes in FA and RD reflect changes in myelination and/or axonal packing and diameter (Krogsrud et al., 2018; Lebel et al., 2008), whereas changes in AD might be related to axon straightening (Giorgio et al., 2010).

A1.2.1.1 Main white fiber tracts With the analyses of cerebral white matter fibers, main routes have been identified, connecting different brain regions (see Figure A3).

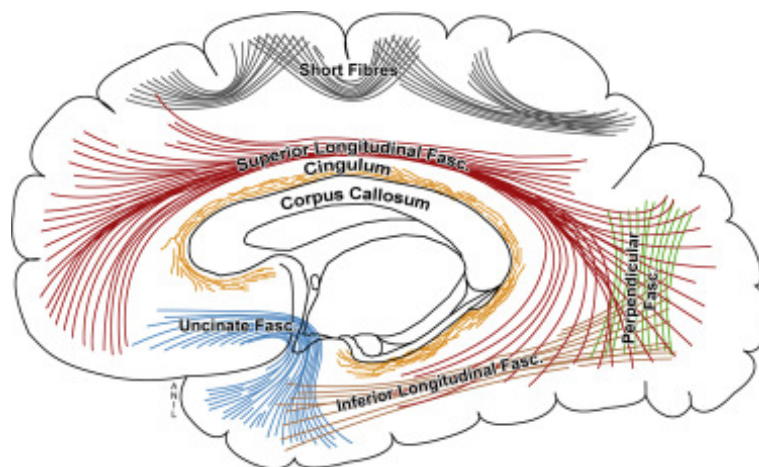


Figure A3: **Main white matter fiber tracts.** Fasc. = fasciculus. From Gupta, 2017.

The most well known bundle might be the corpus callosum, connecting the two cerebral hemispheres (in white in Figure A3). The forceps major is a subpart of this corpus callosum

which connects the posterior portions of the occipital lobes with each other. The cingulum is the main route connecting frontal regions to the hippocampus (in yellow in Figure A3). The superior longitudinal fasciculus (SLF) connects parietal and lateral prefrontal cortices (in red in Figure A3). The inferior longitudinal fasciculus (ILF) is the main route connecting occipital and temporal-occipital areas of the brain to the anterior temporal areas (in orange in Figure A3). The uncinate fasciculus (UF) links the anterior temporal lobes to the anterior prefrontal and lateral orbitofrontal cortex (in blue in Figure A3).

A1.2.2 Functional connectivity

On the other hand, functional connectivity reflects how the activities of different brain regions are linked. This functional connectivity, measured as the statistical dependence between time series of two network nodes (e.g., brain regions, neurons; van den Heuvel and Sporns, 2013) can be observed by activation (fMRI) or resting state functional MRI (rsfMRI) sequences.

From these works are derived the field of connectome, the comprehensive network map of the connections of a species' nervous system (Sporns, 2012; Sporns et al., 2005). A principal aim of connectome studies is to unravel the architecture of brain networks and to explain how the topology of networks shape and modulate brain function. Brain networks can be mathematically described as graphs, composed of sets of nodes (neuronal elements) and edges (their interconnections) whose pairwise couplings can be summarized in the network's connection matrix and whose arrangement defines the network's topology (van den Heuvel and Sporns, 2013). The term connectotype or functional fingerprint has been introduced to point out interindividual variations in terms of connectivity profile (Miranda-Dominguez et al.; Miranda-Dominguez et al., 2014; Sripada et al., 2019).

The study of the functional connectome has confirmed the organization of brain networks around the segregation and integration main principles (Bullmore and Sporns, 2012; Mišić et al., 2014; Park et al., 2019; Rubinov and Sporns, 2010). At the network level, segregation refers to local, within-module processing with sets of nodes that are highly interconnected within a single module but have few connections to nodes in other modules. Integration on the other hand refers to global processing and inter-module connectivity.

A1.2.2.1 Three core neurocognitive networks The brain is thus organized into a number of large networks based on shared function. The correlations of these networks during resting-state fMRI scans varies across individuals and is an indicator of individual differences in abilities.

Of the many stable functional networks identified in the human brain, three are particularly important for understanding cognitive functioning and dysfunctioning and are often designated as the 'core' neurocognitive networks (Menon, 2011). These three networks are the central executive network (CEN), the default mode network (DMN) and the salience network (SN; see Figure A4; Greicius et al., 2003; Seeley et al., 2007). Importantly, these networks show close correspondence in independent analyses of resting and task-related connectivity patterns, suggesting that intrinsically coupled functional networks are also

systematically engaged during cognition (Smith et al., 2009).

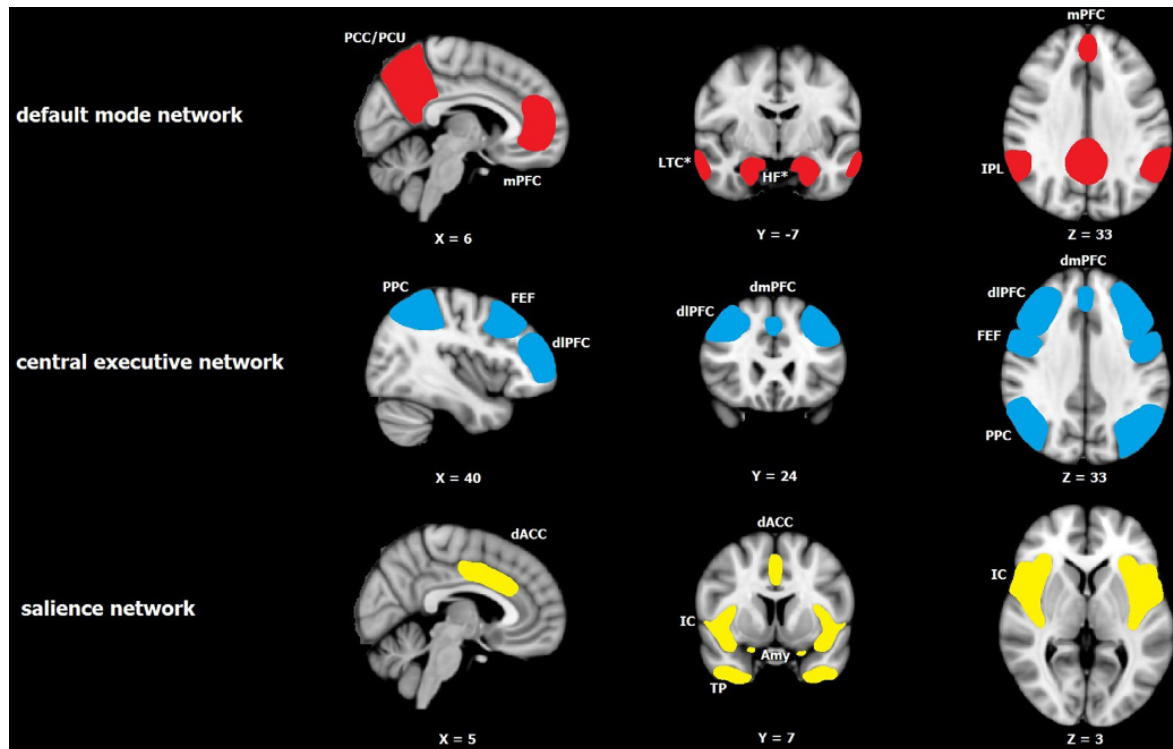


Figure A4: **Representation of the default mode network (top, in red), the central executive network (middle, in blue) and the salience network (bottom, in yellow).** mPFC = medial prefrontal cortex; PCC/PCu = posterior cingulate cortex/precuneus; IPL = inferior parietal lobule; LTC = lateral temporal cortex; HF = hippocampal formation; dIPFC = dorsolateral prefrontal cortex; PPC = posterior parietal cortex; dmPFC = dorsomedial prefrontal cortex; FEF = frontal eye fields; IC = insular cortex; dACC = dorsal anterior cingulate cortex; TP = temporal pole; Amy = amygdala. From Mulders et al., 2015.

The default mode network (DMN) reflects the permanent intrinsic functional activity of the brain. This network arose from research based on rsfMRI sequences. In contrast to *activation* fMRI, which aims to capture in real time the regions recruited during a task, *resting* fMRI is a modality free of stimuli. These sequences are acquired while the participant is in a particular mental state of conscious rest, during which he/she is given the instruction to remain calm, perfectly still, eyes closed but wide awake and to let his/her thoughts go. This instruction is necessary for the process of spontaneous cognition, characteristic of this resting mental state. This basic state, which does not require any attentional resources, is called the *default mode* (Raichle et al., 2001). A resting state network corresponds to a set of brain regions whose temporal decays of the BOLD signal measured in the conscious resting state are synchronized.

This DMN consists of two core regions: the medial prefrontal cortex (mPFC) and the posterior cingulate cortex/precuneus (PCC/PCu), with the inferior parietal lobule (IPL) also being reported consistently. The lateral temporal cortex (LTC) and the hippocampal formation (HF) are often found as being strongly related to the DMN, and are likely to constitute a subsystem within the DMN (Mulders et al., 2015). The central executive network (CEN)

is engaged during a cognitively demanding task requiring attention (Fox et al., 2006). This CEN is centered on the dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC), and also includes the dorsomedial prefrontal cortex (dmPFC) and frontal eye fields (FEF) (Mulders et al., 2015). The salience network (SN) is related to the degree of subjective salience, whether cognitive, homeostatic, or emotional. It is composed of the insular cortex (IC), dorsal anterior cingulate cortex (dACC), temporal pole (TP) and amygdala (Amy) (Mulders et al., 2015).

These three networks are interdependent. Indeed, it was demonstrated that the SN drives the switching between the DMN and the CEN (Goulden et al., 2014). Models of pathology have also proposed a theory of triple network dysfunction where the regulation between the three networks are impaired (Menon, 2011).

A1.2.2.2 Development of functional connectivity Many authors have focused on the development of functional connectivity in infancy (Gao et al.; Grayson and Fair, 2017; Hoff et al., 2014; Power et al., 2010; van den Heuvel et al., 2018) and even *in utero* (Dubois et al., 2015; Thomason et al., 2014; van den Heuvel and Thomason, 2016; Wheelock et al., 2019). Hierarchical organization of functional resting networks is already present in the newborn (Teeuw et al., 2019). However, between the early years of life and adulthood, significant maturational changes in resting networks occur continuously (Collin and van den Heuvel, 2013; Dennis and Thompson, 2013; Khan et al., 2018; Menon, 2013; Power et al., 2010; Vértes and Bullmore, 2015). This functional connectivity has been shown to be predictive of brain maturity (Dosenbach et al., 2010; Qin et al., 2015). This network organization evolves drastically during the first two years of life to be more spatially structured and distributed and continues to do so through childhood and adolescence (for a review: Grayson and Fair, 2017). This local to distributed principle is supported by the decrease in functional connectivity between different functionally distinct regions and the increase in functional connectivity between functionally related regions resulting in improved functional communication (i.e. functional integration; Dosenbach et al., 2010; Fair et al., 2008; Fair et al., 2009; Fair et al., 2007; Marek).

In contrast, while some resting networks are already well established and mature at birth, with a topology similar to the one found in adults (e.g. sensorimotor or auditory networks; Bo et al., 2014; Gao et al., 2015), others take longer to develop (Shen, 2015). For example, the DMN structure differs in children compared to adults: even if the connections between the same regions from one hemisphere to the other are strong in childhood, the overall network goes from a sparse network in childhood to a more integrated one in adults (Fair et al., 2008), going from a local to a distributed organization, related to the development of neural systems underlying cognition (Fair et al., 2009).

A2 Study 1: Networks accuracy

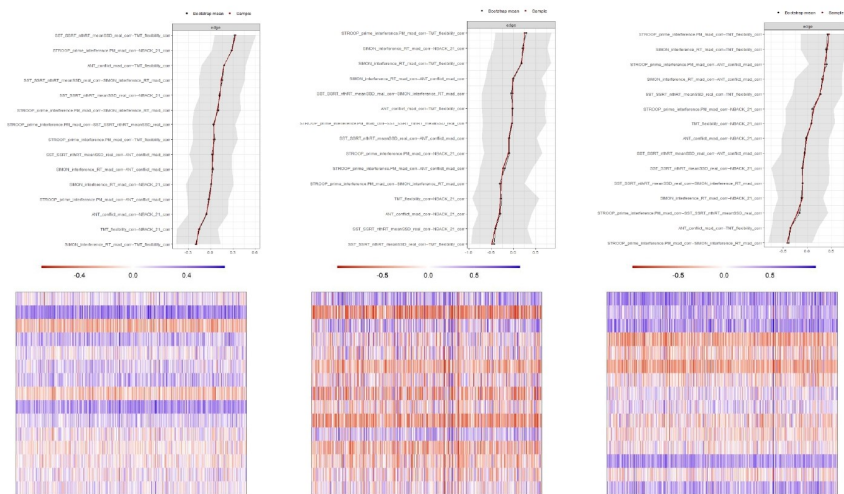


Figure A5: **Accuracy of children's networks.** (Top) 95% bootstrapped CIs (nBoots = 500) for each network edge weight before (left), after active control training (center) and after inhibitory control training (right). (Down) Stability across bootstrap iterations (nBoots = 500) (rows: edges, columns: iterations) for the estimated networks before (left), after active control training (center) and after inhibitory control training (right).

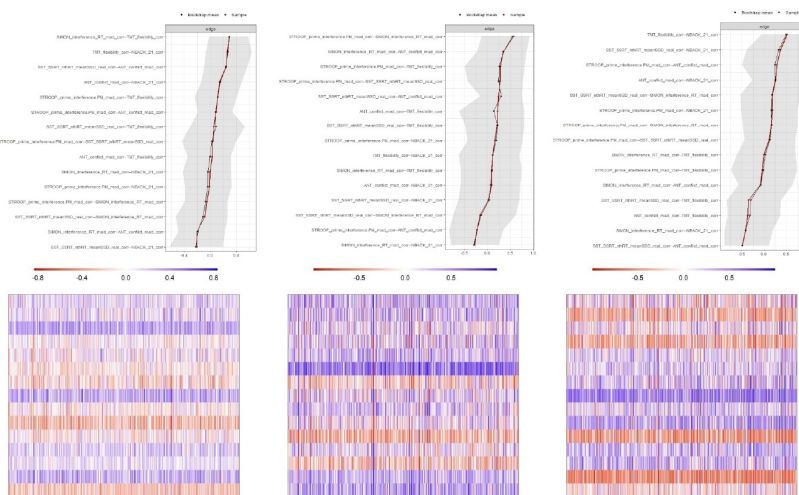


Figure A6: **Accuracy of adolescents' networks.** (Top) 95% bootstrapped CIs (nBoots = 500) for each network edge weight before (left), after active control training (center) and after inhibitory control training (right). (Down) Stability across bootstrap iterations (nBoots = 500) (rows: edges, columns: iterations) for the estimated networks before (left), after active control training (center) and after inhibitory control training (right).

A3 Study 2: Closeness of network models

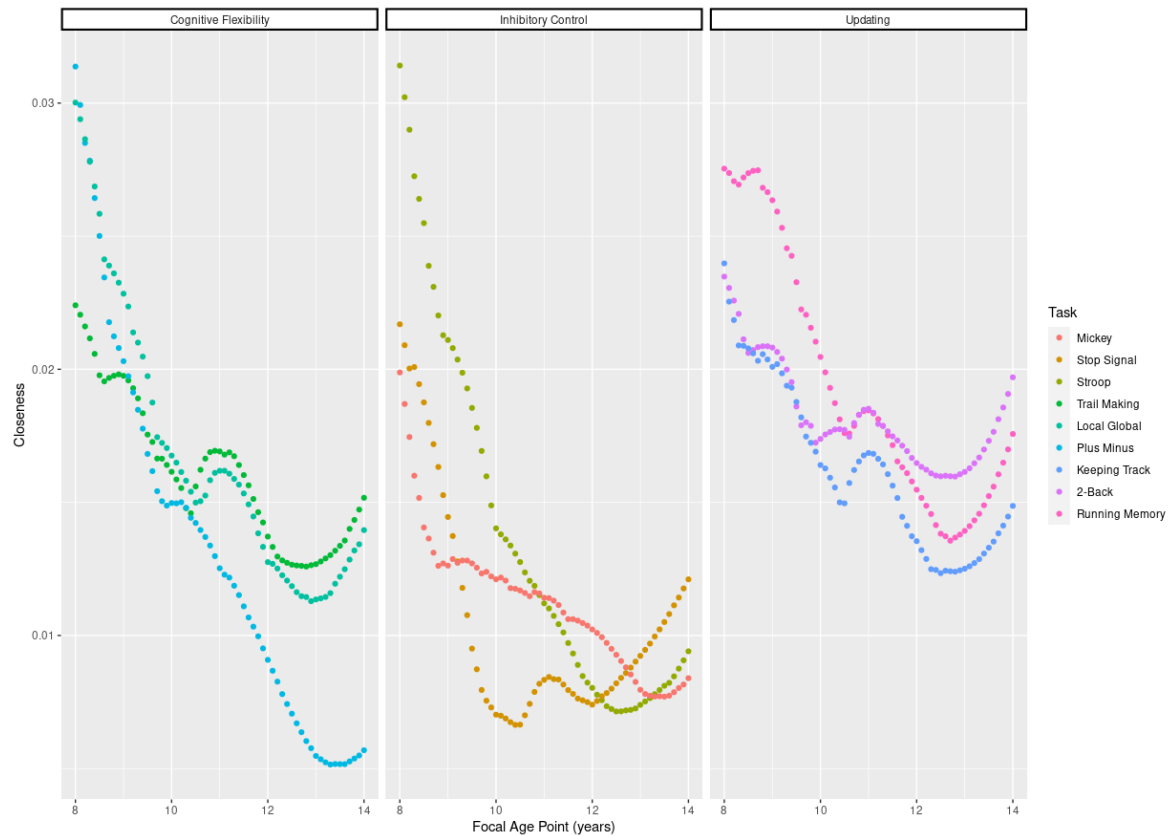


Figure A7: Closeness of the 9 nodes in the network models across age.

Closeness centrality (the inverse of the total length of all the shortest paths between the selected node and all other nodes in the network), a measure of how strongly a node is connected indirectly with the network. Higher closeness centrality indicates that a task is related to more other tasks, and strength indicates that a task is related more strongly with other tasks.

A4 Study 2: Loadings for the 3-factors and the unidimensional models.

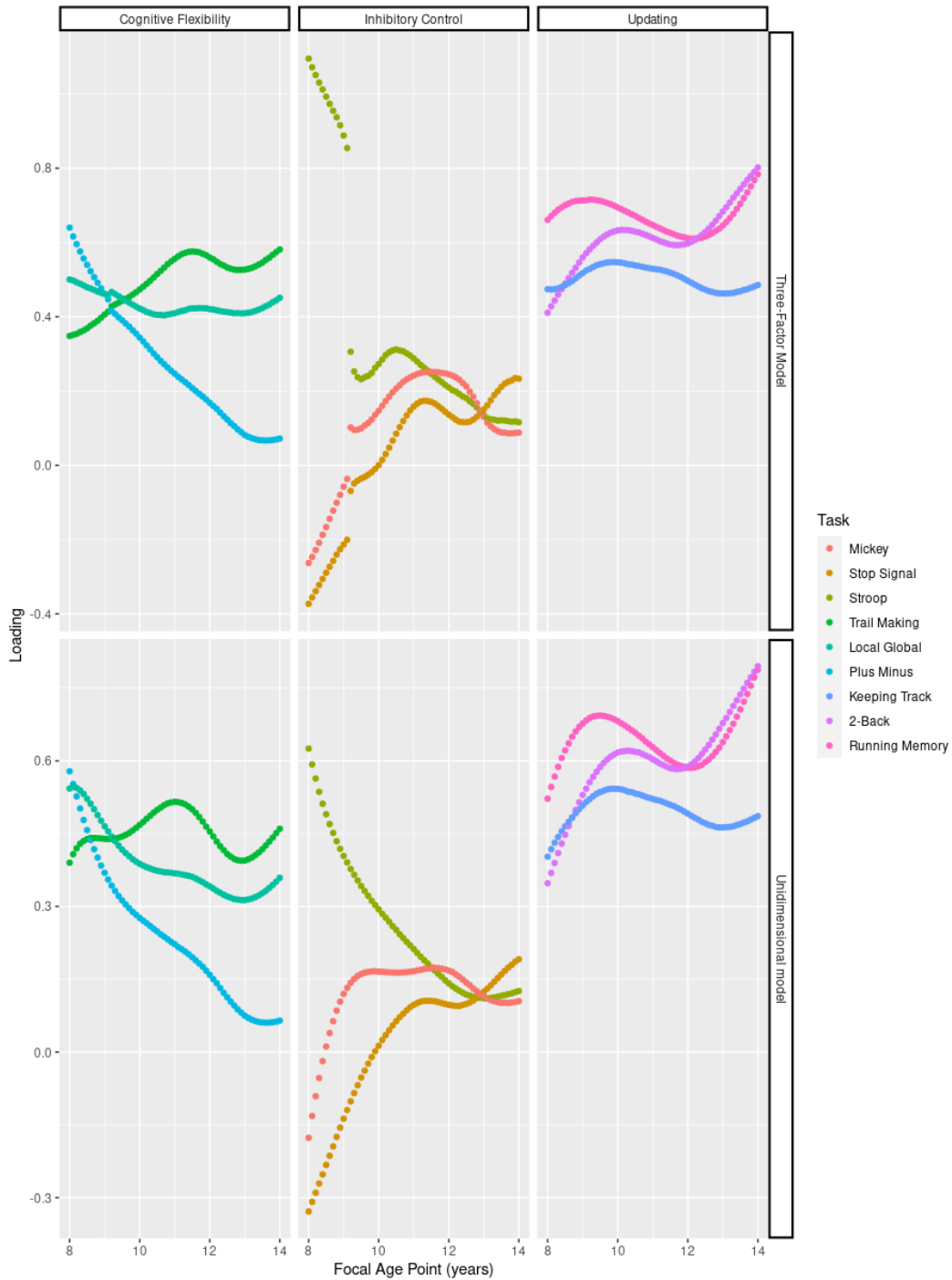


Figure A8: Loadings of the 9 EFs variables for the 3-factors (*above*) and unidimensional (*below*) models across age.

A5 Study 3: LCS analyses with N-back accuracy as Updating measure.

Model	2	df	RMSEA	CFI	SRMR	Selected model
LCS constrained	249.957	84	0.277 [0.233-0.322]	0.000	0.946	
LCS free	23.462	30	0.000 [0.000-0.110]	1.000	0.114	x

Table A1: Fit indices of LCS analyses with N-back accuracy as Updating measure.

In children, the results remained very similar while in adolescents, more changes were observed. Most differences were related to statistical power. Of note, the differences almost exclusively concern variables involving the N-back.

In children, after IC training, the latent change for TMT was marginal ($p = 0.06$) with RT and not significant with accuracy scores ($p = 0.20$). In addition, the effect of the number of training sessions on latent changes in Updating and Switching were not more significant with accuracy scores ($ps > .15$). Finally, baseline correlation between TMT and N-back along with self-feedback parameter of the Nback that were previously marginal with the RT difference score become significant with the accuracy scores. After AC training, latent change is detected for the N-back with the accuracy scores ($p < .05$) but not the RT ($p = 0.82$). However, the correlations between the latent changes in SST and TMT were significant with the RT but not with the accuracy score. Other effects remained similar.

In adolescents, after IC training, significant latent changes were detected in N-back and TMT with accuracy scores (all $ps < 0.01$) but not RT (all $ps > .65$). In addition, the correlation between TMT and N-back latent was significant with RT but not with accuracy scores. Two crossed-effect implicating N-back, that were not significant with the RT (all $ps > 0.21$), were significant with the accuracy scores ($p < 0.05$), namely the effect of stop signal baseline level on N-back change and the effect of N-back baseline level on TMT change. After AC training, significant latent changes were detected in stop signal and N-back with accuracy scores ($p < 0.05$) that were not detected with RT ($ps > .09$). Of note, the effect of stop signal baseline level on N-back latent change was significant with the RT ($p < 0.05$) but not with the accuracy scores ($p = 0.11$).

	Children						Adolescents					
	IC group			AC group			IC group			AC group		
	Estimate ± SE	z	p	Estimate ± SE	z	p	Estimate ± SE	z	p	Estimate ± SE	z	p
Baseline effects (β)												
Stop signal	-0.905 ± 0.153	-5.911	<0.001	-0.585 ± 0.177	-3.314	<0.01	-1.173 ± 0.455	-2.580	<0.05	-1.081 ± 0.206	-5.239	<0.001
N-back	-0.734 ± 0.082	-8.960	<0.001	-0.751 ± 0.137	-5.474	<0.001	-1.033 ± 0.049	-21.104	<0.001	-0.909 ± 0.070	-13.071	<0.001
TMT	-0.716 ± 0.153	-4.663	<0.001	-0.629 ± 0.168	-3.741	<0.001	-0.244 ± 0.154	-1.577	0.115	-0.802 ± 0.187	-4.279	<0.001
Crossed effects (γ)												
N-back → Stop signal change	-0.120 ± 0.045	-2.633	<0.01	-0.163 ± 0.084	-1.938	0.053	0.043 ± 0.051	0.837	0.402	-0.127 ± 0.036	3.516	<0.001
TMT → Stop signal change	-0.000 ± 0.001	-0.362	0.717	-0.002 ± 0.001	-1.632	0.103	-0.000 ± 0.003	-0.137	0.891	0.001 ± 0.001	0.970	0.332
Stop signal → N-back change	0.266 ± 0.285	0.935	0.350	-0.671 ± 0.421	-1.596	0.111	0.394 ± 0.185	2.136	<0.05	-0.360 ± 0.223	-1.610	0.107
TMT → N-back change	-0.010 ± 0.001	-6.832	<0.001	-0.000 ± 0.003	-0.007	0.994	0.001 ± 0.002	0.532	0.595	-0.000 ± 0.001	-0.192	0.847
Stop signal → TMT change	31.716 ± 19.736	1.607	0.108	10.074 ± 14.506	0.694	0.487	-30.893 ± 20.689	-1.493	0.135	22.912 ± 29.364	0.780	0.435
N-back → TMT change	5.753 ± 8.281	0.695	0.487	5.228 ± 6.985	0.748	0.454	-11.279 ± 3.679	-3.065	<0.01	-11.928 ± 10.213	-1.168	0.243
Number of sessions effects												
Stop signal	-0.000 ± 0.003	-0.099	0.921	0.003 ± 0.004	0.660	0.509	-0.000 ± 0.001	-0.268	0.789	0.005 ± 0.003	0.722	0.471
N-back	0.003 ± 0.008	0.395	0.693	0.009 ± 0.012	0.766	0.444	-0.002 ± 0.002	-1.146	0.252	0.002 ± 0.003	1.774	0.076
TMT	0.881 ± 0.611	1.442	0.149	0.912 ± 0.684	1.334	0.182	-0.185 ± 0.157	-1.179	0.239	0.376 ± 0.291	1.293	0.196
Covariances												
Stop signal & N-back changes	0.000 ± 0.001	0.395	0.693	0.002 ± 0.002	0.836	0.403	-0.000 ± 0.000	-0.643	0.520	-0.000 ± 0.000	-0.722	0.470
Stop signal & TMT changes	0.154 ± 0.092	1.669	0.095	-0.166 ± 0.129	-1.292	0.196	0.018 ± 0.024	0.749	0.454	0.018 ± 0.019	0.988	0.323
N-back & TMT changes	-0.037 ± 0.153	-0.239	0.811	-0.147 ± 0.188	-0.783	0.434	-0.009 ± 0.013	-0.669	0.503	-0.066 ± 0.030	-2.213	<0.05
Stop signal & N-back baselines	-0.001 ± 0.002	-0.471	0.637	-0.001 ± 0.002	-0.471	0.637	-0.000 ± 0.001	-0.254	0.799	-0.000 ± 0.001	-0.254	0.799
Stop signal & TMT baselines	0.235 ± 0.131	1.790	0.073	0.235 ± 0.131	1.790	0.073	0.011 ± 0.046	0.233	0.816	0.011 ± 0.046	0.233	0.816
N-back & TMT baselines	-0.974 ± 0.445	-2.190	<0.05	-0.974 ± 0.445	-2.190	<0.05	0.072 ± 0.083	0.859	0.390	0.072 ± 0.083	0.859	0.390
Intercepts												
Stop signal change	0.271 ± 0.095	2.852	<0.01	0.226 ± 0.120	1.892	0.058	0.153 ± 0.057	2.708	<0.01	0.223 ± 0.086	2.598	<0.01
N-back change	0.687 ± 0.179	3.836	<0.001	0.552 ± 0.269	2.048	<0.05	0.969 ± 0.058	16.583	<0.001	0.825 ± 0.118	6.981	<0.001
TMT change	18.476 ± 14.269	-1.295	0.195	-16.073 ± 16.039	-1.002	0.316	21.186 ± 5.998	3.532	<0.001	5.502 ± 13.282	0.414	0.679
Training sessions	19.074 ± 0.583	37.712	<0.001	20.300 ± 0.415	48.869	<0.001	22.609 ± 0.875	25.824	<0.001	22.783 ± 0.522	43.680	<0.001

Table A2: Estimated parameters for the LCS model in children without equality constraints between groups with N-back accuracy as Updating measure.

A6 Study 3: Reaction time (in s) at the Stroop task by trial condition.

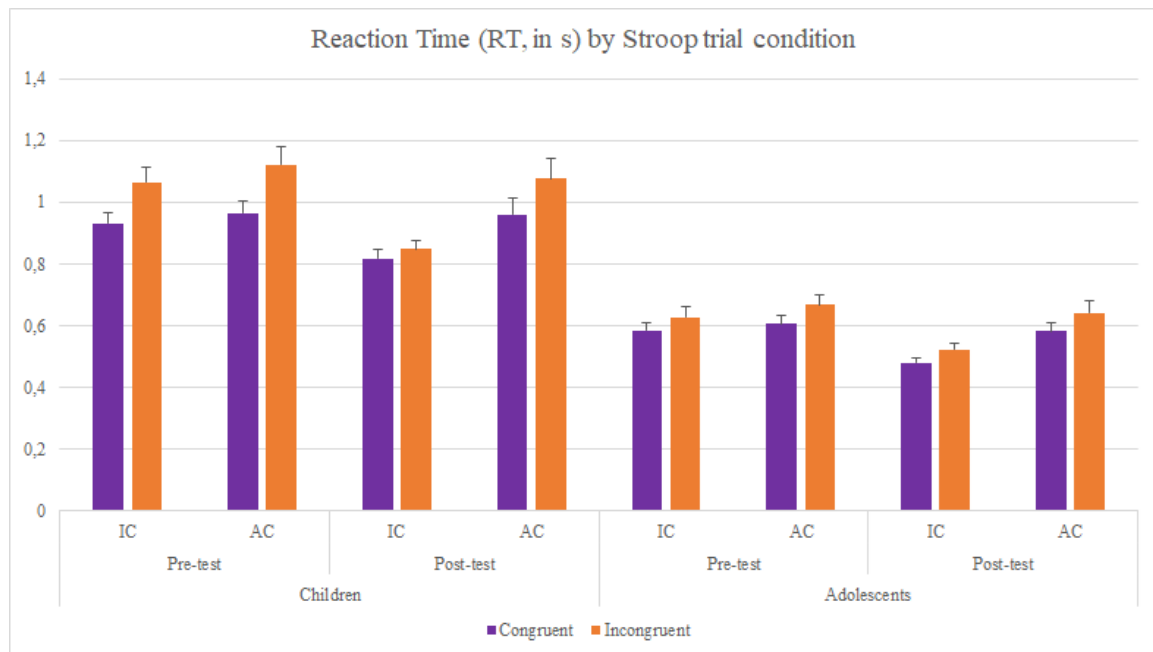


Figure A9: Reaction time (in s) at the Stroop task by trial condition.

A7 Study 4: Brain voxels involved in the 6 EF tasks base- line in children and adolescents.

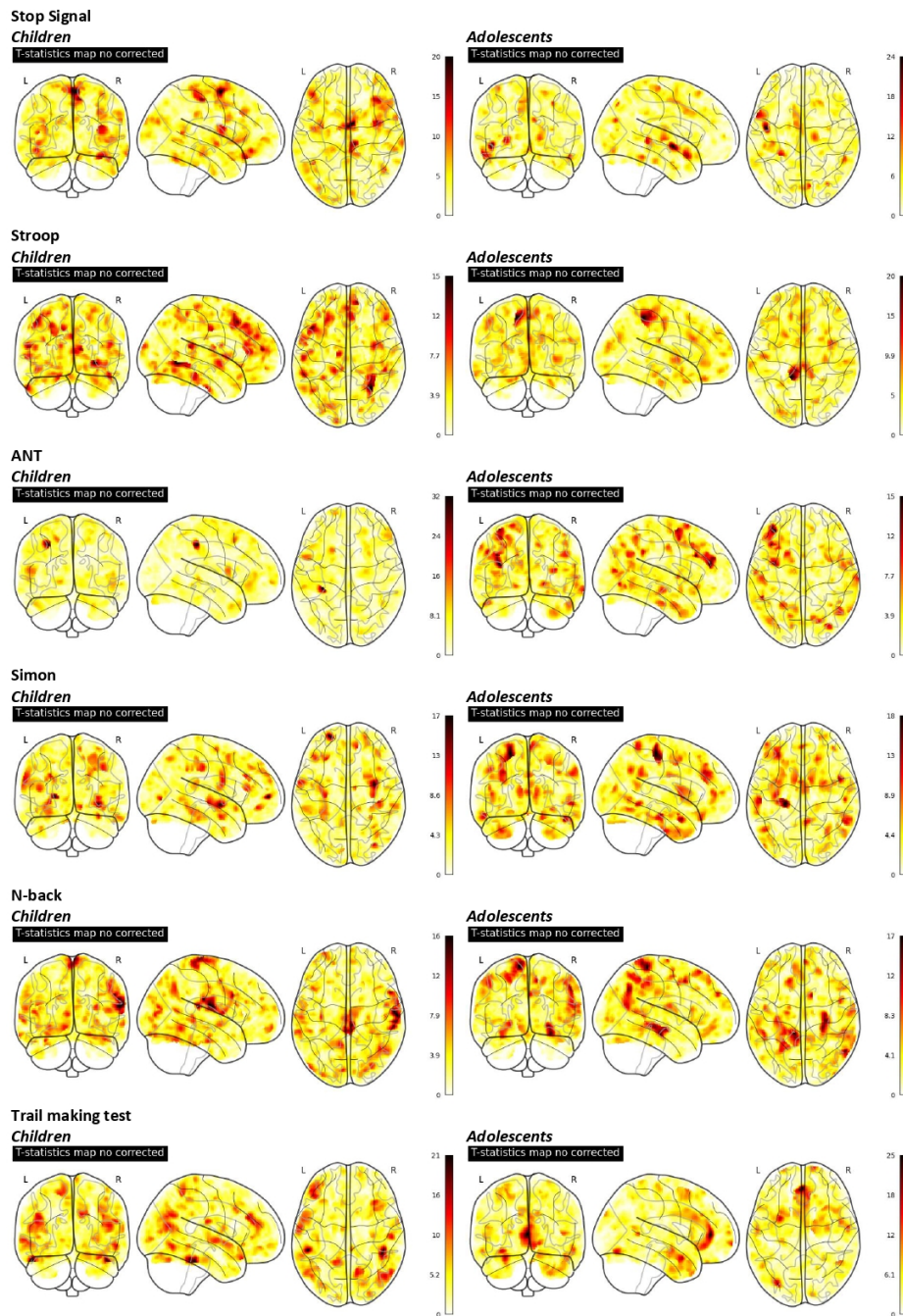


Figure A10: Brain voxels involved in the 6 EF tasks baseline in children and adolescents.

A8 Study 4: Brain voxels involved in the 6 EF tasks progress following IC and AC training in children.

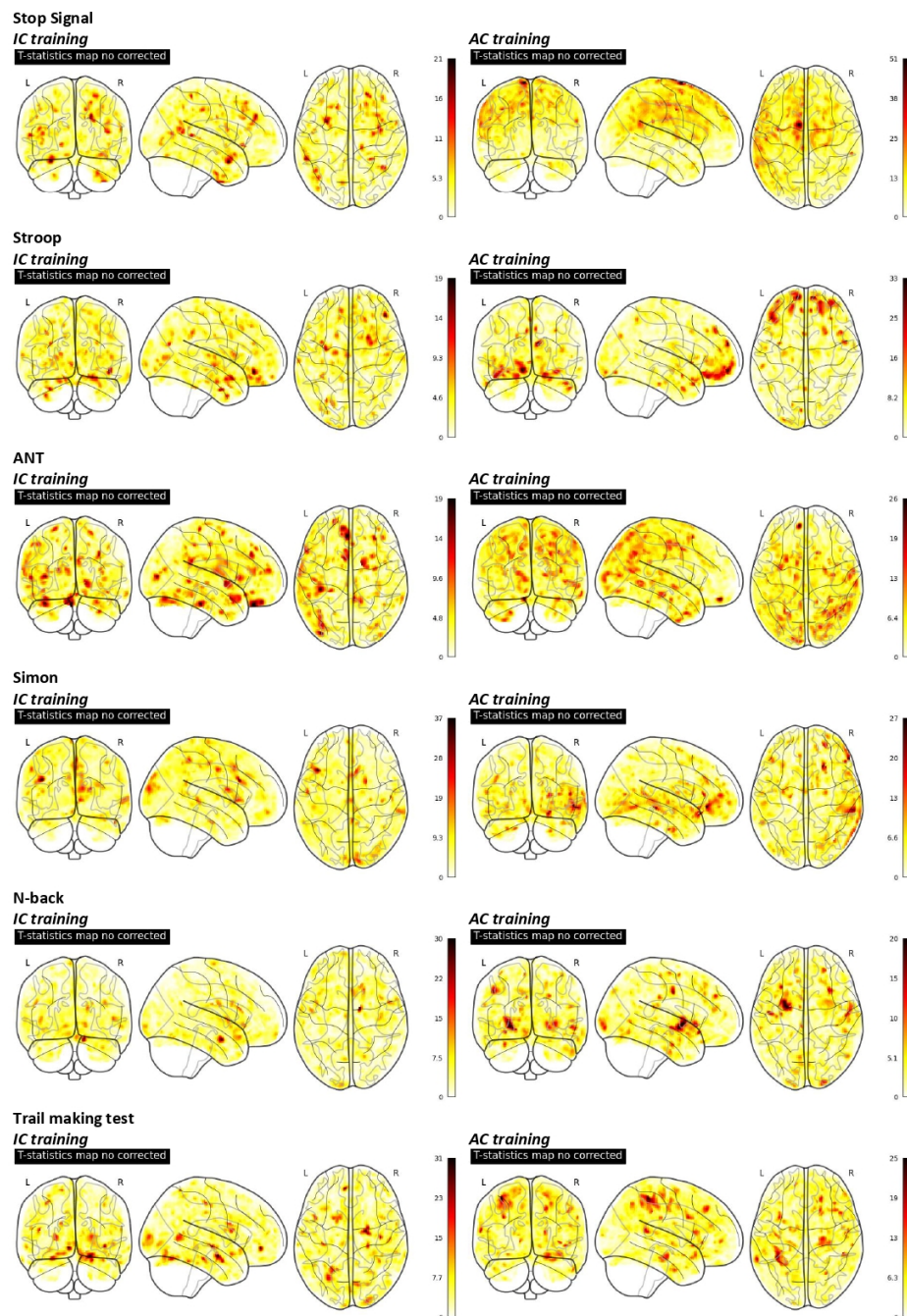


Figure A11: Brain voxels involved in the 6 EF tasks progress following IC and AC training in children.

A9 Study 4: Brain voxels involved in the 6 EF tasks progress following IC and AC training in adolescents.

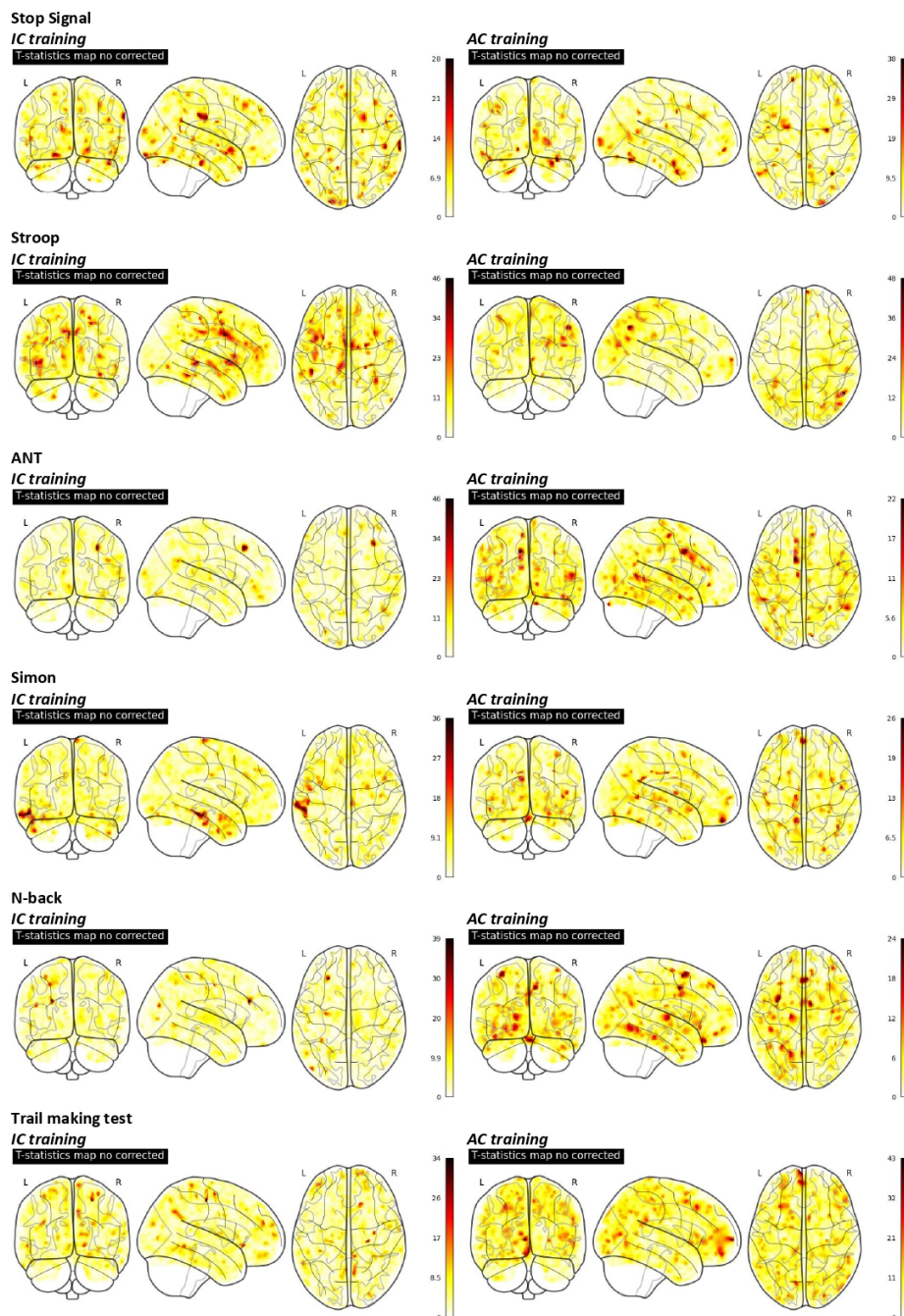


Figure A12: Brain voxels involved in the 6 EF tasks progress following IC and AC training in adolescents.

A10 Study 4: Complementary machine learning analyses

A10.1 Neural bases of EFs

	All participants			Children			Adolescents		
	R ²	MAE	MSE	R ²	MAE	MSE	R ²	MAE	MSE
Stop signal									
Ridge	-0,029372	0,058205	0,074054	-0,254220	0,060181	0,077687	-2,429664	0,055364	0,068495
ElasticNet	0,192108	0,051552	0,067401	-0,098254	0,054969	0,072332	-0,806913	0,046640	0,059601
Support vector machine	-0,106907	0,063703	0,076098	-0,176704	0,068363	0,080822	-4,457897	0,057005	0,068740
Random forest	0,203745	0,050244	0,066380	-0,101005	0,053888	0,070708	-0,395273	0,045005	0,059611
Gradient boosting	0,169452	0,051621	0,068195	-0,128551	0,054607	0,073707	-0,522246	0,047329	0,059382
Multilayer perceptron	-2,827082	0,102528	0,139801	-3,498620	0,099971	0,136230	-16,039109	0,106204	0,144780
Stroop									
Ridge	-0,205998	0,105788	0,132158	-0,150571	0,101964	0,127211	-0,460673	0,110197	0,137640
ElasticNet	-0,005715	0,096185	0,121093	-0,017610	0,097412	0,120968	-0,053489	0,094770	0,121238
Support vector machine	-0,028701	0,096257	0,122452	-0,050336	0,096158	0,120863	-0,034452	0,096370	0,124259
Random forest	-0,046368	0,097954	0,123722	-0,062372	0,096617	0,120707	-0,084187	0,099496	0,127108
Gradient boosting	-0,027616	0,097210	0,122497	-0,024286	0,098124	0,122212	-0,142524	0,096155	0,122824
Multilayer perceptron	-1,172045	0,139184	0,179705	-0,955325	0,152154	0,193869	-2,253150	0,124230	0,161843
ANT									
Ridge	-0,091586	0,033294	0,042831	-0,193735	0,033472	0,042361	-0,816981	0,033065	0,043427
ElasticNet	0,031401	0,031955	0,041235	-0,104392	0,031561	0,039977	-0,386726	0,032462	0,042801
Support vector machine	-0,359711	0,040523	0,048409	-0,087411	0,039434	0,046875	-3,910609	0,041924	0,050317
Random forest	-0,006226	0,031850	0,041086	-0,170277	0,031454	0,040478	-0,240003	0,032359	0,041856
Gradient boosting	-0,048281	0,031958	0,041999	-0,229351	0,031104	0,040356	-0,285998	0,033058	0,044023
Multilayer perceptron	-8,473383	0,089002	0,125166	-6,513376	0,097307	0,138665	-30,162582	0,078310	0,105268
Simon									
Ridge	-0,422963	0,028025	0,035736	-0,501263	0,029443	0,037978	-0,679035	0,026509	0,033169
ElasticNet	-0,030427	0,024685	0,030801	-0,215701	0,025512	0,031937	-0,134673	0,023801	0,029537
Support vector machine	-0,048415	0,025028	0,031189	-0,222942	0,026012	0,032475	-0,096482	0,023974	0,029752
Random forest	-0,066498	0,025090	0,031415	-0,254269	0,025464	0,032201	-0,183349	0,024690	0,030551
Gradient boosting	-0,067336	0,025031	0,031293	-0,229206	0,025766	0,032627	-0,231853	0,024246	0,029801
Multilayer perceptron	-14,457539	0,087649	0,118302	-20,876344	0,084849	0,110427	-27,988714	0,090645	0,126183
Trail making test									
Ridge	0,044869	7,789444	10,138706	-0,379226	7,626890	10,190166	-2,586358	7,991093	10,074504
ElasticNet	0,267771	6,896336	8,921844	-0,125373	7,102925	9,062393	-0,885653	6,640060	8,744354
Support vector machine	0,240897	6,615937	9,068357	-0,241113	6,621107	9,138306	-0,272605	6,609524	8,980828
Random forest	0,168796	6,914576	9,421571	-0,363657	6,598327	9,116646	-0,329444	7,306886	9,786639
Gradient boosting	0,239966	6,610877	9,110109	-0,241957	6,889302	9,384133	-0,361176	6,265489	8,758273
Multilayer perceptron	-0,115040	8,181444	10,883553	-0,770791	7,856809	10,572735	-1,100718	8,584155	11,257206
N-back									
Ridge	-0,340531	0,161339	0,207508	-0,268017	0,155869	0,201949	-1,607575	0,168966	0,215020
ElasticNet	-0,033895	0,137942	0,181431	-0,032553	0,131881	0,178108	-0,290067	0,146393	0,185965
Support vector machine	-0,076188	0,139474	0,184911	-0,079908	0,134273	0,180145	-0,268383	0,146727	0,191357
Random forest	-0,154004	0,145537	0,191468	-0,166047	0,138050	0,184398	-0,265356	0,155978	0,200912
Gradient boosting	-0,086789	0,141058	0,185100	-0,089202	0,135639	0,179221	-0,249156	0,148615	0,192998
Multilayer perceptron	-0,485550	0,167376	0,215124	-0,374035	0,160247	0,211601	-2,283428	0,177316	0,219942

Table A3: Machine learning analyses of neural bases of EFs.

A10.2 Neural bases of training receptivity

	Children						Adolescents					
	IC training			AC training			IC training			AC training		
	R ²	MAE	MSE	R ²	MAE	MSE	R ²	MAE	MSE	R ²	MAE	MSE
Stop signal	-0,0342	0,3133	0,3236	0,2838	0,2708	0,2866	-0,6900	0,1789	0,1812	-1,2807	0,1665	0,1695
Stroop	-0,1055	0,1785	0,2097	-0,1046	0,1894	0,2262	-0,1641	0,0890	0,1155	-1,0537	0,1175	0,1344
Simon	-0,3162	0,0387	0,0450	-0,0924	0,0477	0,0576	-0,0046	0,0425	0,0494	-0,7410	0,0396	0,0443
ANT	-0,0360	0,1091	0,1188	-0,0920	0,0999	0,1157	-1,5627	0,0370	0,0409	-0,4556	0,0496	0,0536
TMT	-1,8057	26,7296	28,3089	-0,2125	22,3102	24,3514	-0,7708	6,2024	7,1662	-0,4258	9,6524	10,7065
N-back	-0,8323	0,2115	0,2532	-0,3646	0,1540	0,1959	-1,5705	0,0703	0,0812	-0,8068	0,0777	0,0872

Table A4: Machine learning analyses of neural bases of training receptivity.

A11 Study 5: Best parameters

	ROIs	mwp1
Ridge	$\alpha = 100.00$	$\alpha = 0.001$
ElasticNet	$\alpha/l_1 = 0.50$	$\alpha/l_1 = 0.10$
Support vector regression	$C = 10.00$	$C = 10.00$
Random forest	criterion = 100.00	criterion = 100.00
Gradient boosting	loss = 100.00	loss = 100.00
Multilayer perceptron	$\alpha = 0.0001$	$\alpha = 0.0001$

Table A5: **Best parameters of machine learning models.**

A12 Study 6: Manhattan plot of the GWAS for TMT-B.

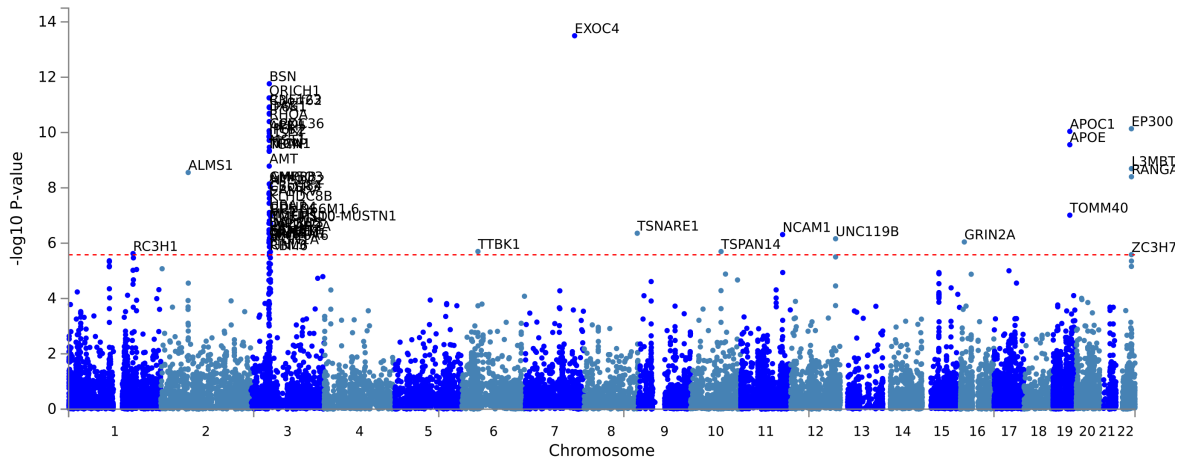


Figure A13: **Manhattan plot of the GWAS for TMT-B.** Input SNPs were mapped to 19046 protein coding genes (distance 0). Genome wide significance (red dashed line in the plot) was defined at $P = 0.05/19046 = 2.625e-6$.

A13 Study 6: Fit indices of the multilevel model for the eight ROIs

A13.1 Raw volumes (without spatial normalization)

A13.1.1 In children

	Model comparison				Fit indices					
	Chi2 difference	df	p-value	Selected model	Chi2	p-val	Yuan-Bentler scaling factor	RMSEA	CFI	SRMR
lACC	41,056	11	2,36E-05	free	11,278	0,127	0,758	0,131 [0,000-0,266]	0,984	0,147
rACC					<i>the model did not converge</i>					
lIFG	24,198		0,012	free	11,440	0,121	0,782	0,136 [0,000-0,272]	0,980	0,183
rIFG	37,579	11	9,21E-05	free	7,144	0,414	0,808	0,025 [0,000-0,215]	0,999	0,144
lCaudate	63,459	11	2,10E-09	free	15,938	0,026	0,733	0,186 [0,061-0,309]	0,970	0,192
rCaudate	21,123	11	0,032	free	13,839	0,054	0,752	0,165 [0,000-0,293]	0,977	0,192
lPutamen	23,593	11	1,46E-02	free	7,247	0,404	0,791	0,032 [0,000-0,215]	0,998	0,142
rPutamen	14,156	11	2,25E-01	constraint	<i>did not meet criteria 1</i>					

Table A6: Fit indices of the multilevel model for the eight ROIs in children (without spatial normalization).

A13.1.2 In adolescents

	Model comparison				Fit indices					
	Chi2 difference	df	p-value	Selected model	Chi2	p-val	Yuan-Bentler scaling factor	RMSEA	CFI	SRMR
lACC	17,595	11	0,091	constraint	<i>did not meet criteria 1</i>					
rACC					<i>the model did not converge</i>					
lIFG	12,683	11	0,315	constraint	<i>did not meet criteria 1</i>					
rIFG	20,524	11	3,87E-02	free	10,996	0,139	0,867	0,182 [0,000-0,376]	0,961	0,361
lCaudate	6,870	11	8,10E-01	constraint	<i>did not meet criteria 1</i>					
rCaudate	12,566	11	0,323	constraint	<i>did not meet criteria 1</i>					
lPutamen	17,890	11	0,084	constraint	<i>did not meet criteria 1</i>					
rPutamen	24,747	11	9,93E-03	free	5,022	0,657	0,741	0,000 [0,000-0,220]	1,000	0,151

Table A7: Fit indices of the multilevel model for the eight ROIs in adolescents (without spatial normalization).

A13.2 Global-scaled ROI volumes (with spatial normalization)

A13.2.1 In children

	Model comparison				Fit indices					
	Chi2 difference	df	p-value	Selected model	Chi2	p-val	Yuan-Bentler scaling factor	RMSEA	CFI	SRMR
lACC	23,558	11	1,47E-02	free	12,550	0,084	0,748	0,148 [0,000-0,278]	0,976	0,107
rACC					<i>the model did not converge</i>					
lIFG	22,443	11	0,021	free	8,239	0,312	0,823	0,073 [0,000-0,235]	0,994	0,112
rIFG	26,681	11	5,13E-03	free	24,506	0,001	0,710	0,304 [0,157-0,466]	0,907	0,301
lCaudate	42,895	11	1,13E-05	free	18,701	0,009	0,682	0,205 [0,095-0,321]	0,963	0,169
rCaudate	11,959	11	0,367	constraint	<i>did not meet criteria 1</i>					
lPutamen	27,466	11	3,91E-03	free	7,818	0,349	0,873	0,061 [0,000-0,235]	0,994	0,120
rPutamen	20,116	11	4,38E-02	free	13,024	0,072	0,803	0,160 [0,000-0,294]	0,944	0,136

Table A8: Fit indices of the multilevel model for the eight ROIs in children (with spatial normalization).

A13.2.2 In adolescents

	Model comparison				Fit indices					
	Chi2 difference	df	p-value	Selected model	Chi2	p-val	Yuan-Bentler scaling factor	RMSEA	CFI	SRMR
lACC	18,638	11	0,068	constraint	<i>did not meet criteria 1</i>					
rACC					<i>the model did not converge</i>					
lIFG	19,318	11	0,056	constraint	<i>did not meet criteria 1</i>					
rIFG	19,782	11	4,84E-02	free	6,135	0,524	0,816	0,000 [0,000-0,265]	1,000	0,158
lCaudate	7,9749	11	7,16E-01	constraint	<i>did not meet criteria 1</i>					
rCaudate	19,935	11	0,046	free	5,492	0,600	0,926	0,000 [0,000-0,262]	1,000	0,172
lPutamen	22,926	11	0,018	free	6,340	0,501	0,986	0,000 [0,000-0,297]	1,000	0,179
rPutamen	15,672	11	1,54E-01	constraint	<i>did not meet criteria 1</i>					

Table A9: Fit indices of the multilevel model for the eight ROIs in adolescents (with spatial normalization).

A14 Study 6: Model estimates of the multilevel model for the eight ROIs

A14.1 Raw volumes (without spatial normalization)

A14.1.1 In children

	IACC	rACC	lIFG	rIFG	lCaudate	rCaudate	lPutamen	rPutamen
<i>baseline mediation</i>								
COG_T1~PRS	-11.836*		-11.807**	-10.461*	-10.237*	-10.940*	-10.251*	
NEU_T1~PRS	-48.870		-33.374	-4.813	24.502	11.493	40.460	
COG_T1~NEU_T1	-0.020		-0.036	0.000	-0.010	0.005	-0.015	
<i>delta mediation</i>								
ΔCOG~PRS	20.020***		10.601	11.424**	1.705	-1.310	4.492	
ΔNEU~PRS	20.449		10.305	27.151	10.063	-5.861	-12.072	
ΔCOG~ΔNEU	-0.118**		-0.023	-0.070	-0.187*	-0.291*	-0.087*	
<i>baseline effects</i>								
ΔCOG~COG_T1	-0.861***		-0.909***	-0.963***	-1.072***	-1.197***	-0.995***	
ΔNEU~NEU_T1	0.010		0.077	-0.086	-0.077	-0.008	-0.105	
<i>crossed effects</i>								
ΔCOG~NEU_T1	0.058***		0.054*	0.089***	0.078***	0.090***	0.032	
ΔNEU~COG_T1	0.050		-0.188	0.141	0.233	-0.234	0.151	
<i>intercepts</i>								
ΔCOG	-0.267**		-0.071	-0.216*	-0.041	-0.052	0.045	
ΔNEU	-0.201		-0.368	0.291	0.153	0.088	0.464	
<i>R2</i>								
ΔCOG	0,857		0,727	0,789	0,877	0,876	0,746	
COG_T1	0,106		0,116	0,063	0,065	0,067	0,073	
ΔNEU	0,045	<i>the model did not converge</i>	0,143	0,258	0,164	0,094	0,077	<i>did not meet criteria 1</i>
NEU_T1	0,014		0,015	0	0,013	0,003	0,028	
<i>baseline mediation</i>								
COG_T1~PRS	-11.836*		-11.807**	-10.461*	-10.237*	-10.940*	-10.251*	
NEU_T1~PRS	-48.870		-33.374	-4.813	24.502	11.493	40.460	
COG_T1~NEU_T1	-0.020		-0.036	0.000	-0.010	0.005	-0.015	
<i>delta mediation</i>								
ΔCOG~PRS	-7.321		-6.819	-12.475*	-3.369	-7.900	-1.645	
ΔNEU~PRS	-6.702		-1.732	-19.037**	-10.032*	-9.124*	-61.294***	
ΔCOG~ΔNEU	-0.083		-0.314***	-0.326**	0.387	-0.055	0.076	
<i>baseline effects</i>								
ΔCOG~COG_T1	-0.633***		-0.604***	-0.701***	-0.691***	-0.663***	-0.573***	
ΔNEU~NEU_T1	-0.039		-0.015	-0.028	0.016	0.005	0.033	
<i>crossed effects</i>								
ΔCOG~NEU_T1	-0.010		-0.017	-0.018	-0.025	-0.009	-0.009	
ΔNEU~COG_T1	0.131		0.085	-0.242	0.041	-0.203	-0.822*	
<i>intercepts</i>								
ΔCOG	0.211		0.222*	0.250*	0.236	0.184	0.157	
ΔNEU	0.229		0.082	0.233	-0.049	0.043	0.193	
<i>R2</i>								
ΔCOG	0,395		0,584	0,511	0,476	0,393	0,396	
COG_T1	0,144		0,152	0,1	0,103	0,106	0,112	
ΔNEU	0,078		0,011	0,2	0,176	0,123	0,5	
NEU_T1	0,023		0,025	0,001	0,021	0,005	0,046	

Table A10: Multilevel SEM estimates per ROI in children (raw volumes). Significance levels: . < .10 ; * < .05 ; ** < .01 ; *** < .001. Abbr.: IC = inhibitory control, AC = active control, l = left, r = right, ACC = anterior cingulate cortex, IFG = inferior frontal gyrus. COG = stop signal reaction time. NEU = raw grey matter volume of the ROI. PRS = polygenic risk score. T1 = pre-test. Δ = latent change.

A14.1.2 In adolescents

	IACC	rACC	lIFG	rIFG	lCaudate	rCaudate	lPutamen	rPutamen	
IC group	<i>baseline mediation</i>								
	COG_T1~PRS				0.614				0.486
	NEU_T1~PRS				-37.711				-65.830
	COG_T1~NEU_T1				0.008				0.004
	<i>delta mediation</i>								
	ΔCOG~PRS				-5.880**				-7.323*
	ΔNEU~PRS				-4.787				-16.508
	ΔCOG~ΔNEU				0.155*				0.008
	<i>baseline effects</i>								
	ΔCOG~COG_T1				-1.272***				-1.191***
	ΔNEU~NEU_T1				-0.138*				0.101
	<i>crossed effects</i>								
	ΔCOG~NEU_T1				0.063***				0.011
	ΔNEU~COG_T1				-0.166				-1.523
	<i>intercepts</i>								
	ΔCOG				-0.048				0.144
	ΔNEU				0.566				-0.121
	<i>R2</i>								
	ΔCOG				0,756				0,611
	COG_T1				0,015				0,003
ΔNEU				0,336	<i>did</i>	<i>did</i>	<i>did</i>	0,308	
NEU_T1				0,03	<i>not</i>	<i>not</i>	<i>not</i>	0,101	
<hr/>									
AC group	<i>baseline mediation</i>								
	COG_T1~PRS				0.614	<i>criteria</i>	<i>criteria</i>	<i>criteria</i>	0.486
	NEU_T1~PRS				-37.711	<i>1</i>	<i>1</i>	<i>1</i>	-65.830
	COG_T1~NEU_T1				0.008				0.004
	<i>delta mediation</i>								
	ΔCOG~PRS				-4.809				-1.817
	ΔNEU~PRS				-29.493*				44.646*
	ΔCOG~ΔNEU				-0.083				-0.105***
	<i>baseline effects</i>								
	ΔCOG~COG_T1				-1.281***				-1.333***
	ΔNEU~NEU_T1				-0.105**				-0.078
	<i>crossed effects</i>								
	ΔCOG~NEU_T1				-0.011				-0.020**
	ΔNEU~COG_T1				0.948				0.280
	<i>intercepts</i>								
	ΔCOG				0.255**				0.309***
	ΔNEU				0.351*				0.302
	<i>R2</i>								
	ΔCOG				0,785				0,872
	COG_T1				0,015				0,003
ΔNEU				0,35				0,251	
NEU_T1				0,014				0,049	

Table A11: **Multilevel SEM estimates per ROI in adolescents (raw volumes)**. Significance levels: . < .10 ; * < .05 ; ** < .01 ; *** < .001. Abbr.: IC = inhibitory control, AC = active control, l = left, r = right, ACC = anterior cingulate cortex, IFG = inferior frontal gyrus. COG = stop signal reaction time. NEU = raw grey matter volume of the ROI. PRS = polygenic risk score. T1 = pre-test. Δ = latent change.

A14.2 Global-scaled ROI volumes (with spatial normalization)

A14.2.1 In children

	IACC	rACC	lIFG	rIFG	lCaudate	rCaudate	lPutamen	rPutamen
<i>baseline mediation</i>								
COG_T1~PRS	-13,063*		-12,855**	-10,497*	-9,949*		-10,325*	-10,509*
NEU_T1~PRS	-64,31		-48,016	-18,974	10,903		27,334	22,661
COG_T1~NEU_T1	-0,034.		-0,045*	-0,001	-0,011		-0,020	0,001
<i>delta mediation</i>								
ΔCOG~PRS	11,140		4,951	11,260.	4,554		10,010	11,889
ΔNEU~PRS	33,914**		-3,884	30,896*	9,791		-17,043	-9,981
ΔCOG~ΔNEU	-0,095		-0,003	-0,136	-0,332*		-0,080*	-0,070
<i>baseline effects</i>								
ΔCOG~COG_T1	-0,927***		-1,122***	-1,097***	-0,943***		-1,024***	-0,991***
ΔNEU~NEU_T1	0,110.		0,030	-0,071	-0,044		0,061	-0,142.
<i>crossed effects</i>								
ΔCOG~NEU_T1	0,018		-0,042	-0,092*	0,044.		-0,068***	-0,069***
ΔNEU~COG_T1	0,528		0,038	0,064	0,226		0,257	-0,087
<i>intercepts</i>								
ΔCOG	0,003**		0,423**	0,643**	0,024		0,535****	0,518***
ΔNEU	-1,055*		-0,168	0,262	0,056		-0,351	0,646
<i>R2</i>								
ΔCOG	0,70		0,73	0,78	0,78		0,78	0,744
COG_T1	0,13		0,14	0,06	0,06		0,08	0,063
ΔNEU	0,20	<i>the</i>	0,03	0,29	0,12	<i>did</i>	0,05	0,127
NEU_T1	0,04	<i>model</i>	0,04	0,01	0,00	<i>not</i>	0,02	0,008
		<i>did</i>				<i>meet</i>		
		<i>not</i>				<i>criteria</i>		
		<i>converge</i>				<i>1</i>		
<i>baseline mediation</i>								
COG_T1~PRS	-13,063*		-12,855**	-10,497*	-9,949*		-10,325*	-10,509*
NEU_T1~PRS	-64,314		-48,016	-18,974	10,903		27,334	22,661
COG_T1~NEU_T1	-0,034.		-0,045*	-0,001	-0,011		-0,020	0,001
<i>delta mediation</i>								
ΔCOG~PRS	-8,046.		-7,666	-10,691*	-3,822		-1,035	-7,749
ΔNEU~PRS	-6,186		0,279	-18,987**	-8,981.		-62,184***	-30,412
ΔCOG~ΔNEU	-0,105.		-0,242***	-0,216**	0,471*		0,086	0,001
<i>baseline effects</i>								
ΔCOG~COG_T1	-0,633***		-0,622***	-0,660***	-0,655***		-0,550***	-0,649***
ΔNEU~NEU_T1	-0,055		0,005	-0,024	0,010		-0,047	-0,100
<i>crossed effects</i>								
ΔCOG~NEU_T1	-0,027		-0,039	-0,032	-0,038		-0,024	-0,018
ΔNEU~COG_T1	-0,000		-0,008	-0,348	-0,033		-0,994**	-0,134
<i>intercepts</i>								
ΔCOG	0,340*		0,329**	0,312*	0,277*		0,221	0,230
ΔNEU	0,394		0,015	0,242	-0,010		0,623*	0,515
<i>R2</i>								
ΔCOG	0,40		0,55	0,46	0,51		0,41	0,396
COG_T1	0,17		0,17	0,10	0,10		0,12	0,100
ΔNEU	0,07		0,00	0,13	0,14		0,59	0,093
NEU_T1	0,07		0,06	0,02	0,01		0,03	0,013

Table A12: **Multilevel SEM estimates per ROI in children (global-scaled volumes).** Significance levels: . < .10 ; * < .05 ; ** < .01 ; *** < .001. Abbr.: IC = inhibitory control, AC = active control, l = left, r = right, ACC = anterior cingulate cortex, IFG = inferior frontal gyrus. COG = stop signal reaction time. NEU = global-scaled grey matter volume of the ROI. PRS = polygenic risk score. T1 = pre-test. Δ = latent change.

A14.2.2 In adolescents

	IACC	rACC	lIFG	rIFG	lCaudate	rCaudate	lPutamen	rPutamen
IC group	<i>baseline mediation</i>							
	COG_T1~PRS			0,501		0,537	1,484	
	NEU_T1~PRS			-32,220		1,194	-50,272	
	COG_T1~NEU_T1			0,003		-0,012	-0,006	
	<i>delta mediation</i>							
	ΔCOG~PRS			-8,780**		-10,599*	-7,781*	
	ΔNEU~PRS			8,166		18,762**	-12,496	
	ΔCOG~ΔNEU			0,106		0,132	-0,025	
	<i>baseline effects</i>							
	ΔCOG~COG_T1			-1,180***		-1,094***	-1,263***	
	ΔNEU~NEU_T1			-0,109		-0,104	-0,166***	
	<i>crossed effects</i>							
	ΔCOG~NEU_T1			0,039		0	0,001	
	ΔNEU~COG_T1			-0,479		-1,058	-1,118*	
	<i>intercepts</i>							
	ΔCOG			0,038		0,186.	0,199	
	ΔNEU			0,469		0,468	0,921***	
	R2							
	ΔCOG			0,69		0,653	0,648	
	COG_T1			0,002		0,015	0,020	
ΔNEU	<i>did</i>	<i>the</i>	<i>did</i>		<i>did</i>		<i>did</i>	
NEU_T1	<i>not</i>	<i>model</i>	<i>not</i>	0,224	<i>not</i>	0,372	0,611	<i>not</i>
	<i>meet</i>	<i>did</i>	<i>meet</i>	0,033	<i>meet</i>	0	0,088	<i>meet</i>
<i>criteria</i>								
COG_T1~PRS	<i>1</i>	<i>converge</i>	<i>1</i>	0,501	<i>1</i>	0,537	1,484	<i>1</i>
NEU_T1~PRS				-32,220		1,194	-50,272	
COG_T1~NEU_T1				0,003		-0,012	-0,006	
AC group	<i>delta mediation</i>							
	ΔCOG~PRS			6,297		-6,005	-2,953	
	ΔNEU~PRS			-29,390**		6,553	23,369*	
	ΔCOG~ΔNEU			0,010		0,162.	0,069	
	<i>baseline effects</i>							
	ΔCOG~COG_T1			-1,356***		-1,328***	-1,441***	
	ΔNEU~NEU_T1			-0,144*		-0,085*	-0,077*	
	<i>crossed effects</i>							
	ΔCOG~NEU_T1			0,033*		0,004	0,008	
	ΔNEU~COG_T1			0,562		-0,501	0,484	
	<i>intercepts</i>							
	ΔCOG			0,071		0,196*	0,194*	
	ΔNEU			0,575*		0,416*	0,257	
	R2							
	ΔCOG			0,806		0,805	0,802	
	COG_T1			0,002		0,014	0,012	
	ΔNEU			0,363		0,206	0,261	
	NEU_T1			0,015		0	0,042	

Table A13: **Multilevel SEM estimates per ROI in adolescents (global-scaled volumes)**. Significance levels: . < .10 ; * < .05 ; ** < .01 ; *** < .001. Abbr.: IC = inhibitory control, AC = active control, l = left, r = right, ACC = anterior cingulate cortex, IFG = inferior frontal gyrus. COG = stop signal reaction time. NEU = global-scaled grey matter volume of the ROI. PRS = polygenic risk score. T1 = pre-test. Δ = latent change.

PUBLICATIONS

Menu, I., Rezende, G., Le Stanc, L., Borst, G.* & Cacia, A.* (accepted). A network analysis of executive functions before and after computerized cognitive training in children and adolescents. *Scientific reports*.

In revision

Menu, I., Rezende, G., Le Stanc, L., Borst, G.* & Cacia, A.* (in revision). Effects of inhibitory control training on executive functions of children and adolescents: a latent change score model approach.

In preparation

Menu, I., He, Q., Victor, J., Rezende, G., Le Stanc, L., Vidal, J., Oppenheim, C., Duchesnay, E., Chaumette, B., Houdé, O., Borst, G. & Cacia, A. (in prep.). Do neuroplasticity and genetic factors contribute to cognitive training in children and adolescents?

Menu, I., Borst, G., & Cacia, A. (in prep.). Latent network analysis of executive functions across development.

Omont, S., **Menu, I.**, Salvia, E., Houdé, O., Oppenheim, C., Cacia, A.* & Borst, G.* (in prep.). Lateralization effects of the inhibition brain network with development and training.

Rezende, G., Le Stanc, L., **Menu, I.**, Cassotti, M., Aïte, A., Salvia, E., Houdé, O., Borst, G. & Cacia, A. (in prep.). Differential effects of mindfulness meditation and cognitive training on cool and hot inhibitory control in children and adolescents.

RÉSUMÉ DE LA THÈSE

Contexte

Les facteurs soutenant les apprentissages sont multiples et à différents niveaux du vivant : moléculaires (génétique), cérébraux (réseaux neuronaux), psychologiques et environnementaux (pédagogiques, socio-économiques, culturels...). En apportant des indications sur les capacités et les contraintes du cerveau qui apprend, la psychologie et les neurosciences cognitives peuvent aider à étudier les mécanismes sous-tendant l'efficacité de différents types d'apprentissage. Cela nécessite une approche interdisciplinaire associant à la fois la psychologie du développement et les neurosciences cognitives de l'éducation, pour constituer et analyser ce type de données, et les mathématiques appliquées, pour développer et appliquer des algorithmes de traitement automatique sur ces bases de données, en particulier l'analyse de données multiniveaux (gène-cerveau-comportement) afin de relier les différents niveaux d'observation.

Un domaine essentiel de l'apprentissage est celui des fonctions exécutives (FEs), à savoir les fonctions permettant à un individu de réguler intentionnellement sa pensée et ses actes afin d'atteindre des objectifs (Diamond, 2013). Trois FEs de base sont généralement distinguées : la mise à jour en mémoire de travail (MAJ en MDT), le contrôle inhibiteur (CI) et la flexibilité cognitive (FC), formant trois facteurs distincts (*diversité des FEs*) mais néanmoins corrélés (*unité des FEs* ; Miyake et al., 2000). Chaque FE serait donc composée d'une partie commune aux trois FEs (*part commune*) et d'une partie spécifique à la FE en question (*part spécifique*; Miyake and Friedman, 2012). Cette organisation évoluerait au cours du développement avec une organisation plutôt unidimensionnelle avec un seul facteur commun au cours de l'enfance à une organisation à deux ou trois facteurs à l'âge adulte, les FEs devenant de en plus spécifiques avec l'âge (Karr et al., 2018).

Dès leur première année de vie, les bébés présentent des formes basiques de FEs (Diamond, 1990), mais les composantes essentielles (CI, MAJ en MDT et FC) se développent essentiellement au cours des années préscolaires (Hughes, 1998) puis tout au long de l'enfance (Davidson et al., 2006), de l'adolescence (Huizinga and van der Molen, 2007) jusqu'au début de l'âge adulte (Anderson et al., 2001; Ferguson et al., 2021).

Ces fonctions sont principalement sous-tendues par le cortex préfrontal qui se développe

pendant l'enfance et l'adolescence (Best et al., 2009) et, bien que chaque FE recrute des régions cérébrales spécifiques, il y a un chevauchement important des régions cérébrales recrutées par les trois FEs, celles-ci activant toutes des régions préfrontales et pariétales, ce qui plaide en faveur de composantes communes à ces fonctions (unité des FEs ; Greene et al., 2008). De plus, différentes études ont montré une augmentation de l'activité des cortex préfrontal et pariétal avec l'âge (Kwon et al., 2002; Paus et al., 2008). Une hypothèse serait que, de manière similaire à l'organisation des FEs au niveau comportemental (d'une organisation à 1 facteur à une organisation à 3 facteurs), le développement des FEs serait lié à la ségrégation des modules du réseau (Baum et al., 2017). Cela conduirait au fait que, chez l'adulte, les FEs fonctionneraient de manière hiérarchique : alors que certaines régions joueraient un rôle intégratif et plus commun, d'autres seraient plus spécialisées pour une FE particulière (Collette et al., 2006; Luna et al., 2015; Niendam et al., 2012; Simmonds et al., 2008; Wager et al., 2004; Wager and Smith, 2003), reflétant au niveau cérébral l'unité et la diversité des FEs.

Ces fonctions sont aussi sous influence génétique. Une revue de 2014 (Logue and Gould, 2014) a conclu que les FEs sont différentiellement altérées par les systèmes monoaminergiques et cholinergiques et par les polymorphismes associés à ces systèmes de neurotransmetteurs. La FC est associée aux polymorphismes COMT, DRD2/ANKK1 et DRD4, tandis que le CI est lui lié au polymorphisme du gène 5-HT2A. Ainsi, outre le système dopaminergique, sur lequel de nombreuses études se sont concentrées, plusieurs études ont montré que les systèmes glutamatergique et GABAergique influencent les capacités exécutives (Dauvermann et al., 2017; Logue and Gould, 2014; Thomas et al., 2017). Il semble donc que l'architecture génétique des FEs se répartisse sur de très nombreux variants (polygéniques).

D'autres facteurs jouent également un rôle important sur les FEs et leur développement, notamment les facteurs environnementaux, dont la culture et le statut socio-économique (Lawson et al., 2018; Roos et al., 2017).

Du fait de leur grande importance pour les acquisitions scolaires telles que la lecture ou les mathématiques (Diamond, 2013), pour le développement cognitif et socio-émotionnel (Borst et al., 2015) mais aussi pour la santé physique et mentale (Snyder et al., 2015), plusieurs programmes d'intervention ont été proposés pour améliorer différents aspects des FEs, notamment la MDT (Klingberg, 2010; Maraver et al., 2016) et le CI (Hu et al., 2017; Jaeggi et al., 2011; Liu et al., 2015; Xu et al., 2020; Zhao et al., 2015). Ces études, menées chez

des enfants, des adolescents et des jeunes adultes, ont montré qu'il est possible d'entraîner les FE et ont soulevé la question de la possibilité de transférer les effets de l'entraînement d'une FE à d'autres domaines exécutifs ou cognitifs. En effet, la plupart des études visent à déterminer dans quelle mesure l'entraînement des FEs, et du CI en particulier, peuvent se transférer à des tâches non entraînées dans le même domaine cognitif ou la même FE (transfert proche) ou dans d'autres domaines cognitifs ou FEs (transfert lointain). Alors que certaines études ont rapporté un effet de transfert proche et lointain chez les enfants d'âge préscolaire (pour le transfert proche : Zhao et al., 2015 et pour le transfert lointain : Liu et al., 2015; Rueda et al., 2005b), d'autres études n'ont montré aucun effet de transfert de l'entraînement du CI Enge et al., 2014; Talanow and Ettinger, 2018; Thorell et al., 2009).

Parallèlement, des études ont également examiné l'effet de l'entraînement au CI sur différentes caractéristiques cérébrales (Jolles and Crone, 2012; Owen et al., 2010), et ont pu mettre en évidence des changements fonctionnels (activité fonctionnelle) dans les régions du réseau cérébral du CI, en particulier les cortex préfrontaux (Berkman et al., 2014; Chavan et al., 2015; Manuel et al., 2013; Spierer et al., 2013) et pariétaux (Manuel et al., 2010). Une étude a notamment mis en évidence une évolution des caractéristiques neuro-plastiques (épaisseur et surface corticale) dans ces mêmes régions, après un entraînement au CI (Delalande et al., 2019). Enfin, ce type d'entraînement permet non seulement d'augmenter l'activité dans des zones spécifiques, mais aussi d'améliorer la connectivité entre le réseau lié à l'inhibition et d'autres réseaux (Hu et al., 2017).

Ce projet de thèse se situe au carrefour des neurosciences cognitives, de la psychologie du développement et des statistiques appliquées, financé par une bourse pour des projets interdisciplinaires (CNRS PRIME 80).

Dans ce contexte, ce projet de recherche a plusieurs objectifs :

- **L'analyse statistique longitudinale avancée des changements exécutifs associés au développement et à l'entraînement cognitif.** Le premier objectif du projet était d'étudier le changement de l'organisation des FEs au niveau cognitif au cours du développement et après un entraînement au CI. Le développement de l'organisation de ces fonctions cognitives de base est au cœur de plusieurs recherches (Hartung et al., 2020). De plus, certaines données suggèrent que l'entraînement cognitif pourrait accélérer le développement (Jolles and Crone, 2012). L'adaptation et l'amélioration des méthodes statistiques telles que les modèles d'équations structurelles (SEM) ou

les modèles en réseau (NM) permettent de tester directement la structure des FEs. Ainsi, le premier objectif de cette thèse était d'étudier l'organisation des FEs avec ces nouveaux outils et l'hypothèse que l'entraînement est un accélérateur de développement.

- **Des modèles d'apprentissage automatique pour tester l'hypothèse selon laquelle l'entraînement peut modifier l'âge du cerveau.** La prédiction de l'âge à partir de données d'imagerie cérébrale est devenue populaire (Baecker et al., 2021b). Nous avons utilisé cet outil pour déterminer si l'entraînement modifiait l'âge du cerveau et si ces changements étaient liés aux progrès cognitifs. L'adaptation et l'application des algorithmes aux données d'imagerie ont été réalisées en collaboration avec Edouard Duchesnay et Julie Victor, CEA/Neurospin.
- **Analyse multiniveau des données génétiques, cérébrales et cognitives.** Nous avons cherché à développer un modèle d'équations structurelles (SEM) multiniveaux afin d'intégrer les différents niveaux d'observation (cerveau, génétique, cognition) pour avoir une image complète de l'impact du développement et de l'entraînement sur les FEs.
- **La finalisation de l'acquisition d'une base de données multi-modalité et multi-niveau pour caractériser l'apprentissage.** Ce projet de recherche sur des données d'entraînement s'appuyait sur les projets APEX-Enfant et APEX-Ado (Apprentissages EXécutifs et cerveau chez l'enfant d'âge scolaire et chez l'adolescent). Ces projets visaient à tester à différents âges l'impact d'un apprentissage exécutif ciblé sur le contrôle inhibiteur (CI) et d'un apprentissage métacognitif plus général, la pleine conscience (PC). Les données pour l'entraînement CI étaient déjà acquises. L'un des objectifs de ce projet de doctorat était aussi de contribuer à l'acquisition des données de l'entraînement PC (thèse de Gabriela Rezende), en particulier dans le recrutement des participants, l'acquisition de données génétiques, IRM et cognitives.

Le projet APEX

Ces travaux de recherche se sont appuyés sur le projet APEX (financement ANR-14-CE30-0014-01 APEX, CPP : ID-RCB 2015-A00383-46 et ID-RCB 2015-A00811-48), un programme d'entraînement informatisé au contrôle inhibiteur (CI).

Dans le cadre du projet APEX, 201 participants ont été recrutés : 110 enfants (33 garçons, $M \pm SD = 9,84 \pm 0,53$ ans, [9-10 ans]) et 91 adolescents (20 garçons, $M = 16,71 \pm 0,53$ ans, [15-17 ans]).

Ces participants ont été répartis aléatoirement dans 3 groupes d'entraînement, le groupe contrôle inhibiteur (CI; 37 enfants et 32 adolescents), le groupe contrôle actif (CA; 40 enfants et 28 adolescents) et le groupe méditation pleine conscience (PC; 33 enfants et 31 adolescents). A noter que 3 enfants ont également pris part à un entraînement à la mémoire du travail mais cet axe du projet a été interrompu en raison de contraintes pratiques.

Les séances d'entraînement se faisaient sur une tablette tactile, au domicile de l'enfant ou de l'adolescent, sur une période de 5 semaines. Chaque session d'entraînement durait environ 15 minutes. Pour le groupe CI, chaque session d'entraînement était constituée d'une tâche de Stroop couleur et d'une tâche de stop signal. Pour le groupe CA, les sessions étaient composées d'un "jeu de questions générales", avec des questions de culture générale, et d'un "jeu de questions spécifiques", avec des questions plus scolaires. Pour le groupe PC, chaque séance était composée de deux exercices de méditation guidée. Dans cette thèse, nous nous sommes focalisés sur les entraînements CA et CI. Dans ces deux types d'entraînement, la difficulté des séances était progressivement augmentée et adaptée en temps réel à la courbe d'apprentissage de chaque participant afin de maintenir sa motivation et d'éviter une automatisation.

Avant et après l'entraînement, les participants prenaient part à une batterie cognitive composée de 21 tâches visant à évaluer différentes facettes des FE. Au cours de cette thèse, nous nous sommes intéressés à six d'entre elles :

- la tâche de Stroop couleur (Stroop, 1935), dont la performance était mesurée par l'interférence au Stroop (temps de réaction - TR pour les essais incongruents - TR pour les essais congruents)
- la tâche de stop signal (Verbruggen and Logan, 2008), mesurée par le stop signal reaction time (SSRT) calculé selon la méthode intégrative recommandée par Verbruggen et al., 2019
- la tâche de Simon (Lu and Proctor, 1995), mesurée par le Simon effect (TR pour les essais incongruents - TR pour les essais congruents)
- l'attention network task (ANT; Fan et al., 2002), mesurée par l'effet d'interférence (TR pour les essais incongruents - TR pour les essais congruents)
- la tâche de n-back (Cohen et al., 1994), mesurée par le TR moyen au niveau $n = 2$ - le

TR moyen au niveau $n = 1$

- le trail making test (TMT; Reitan and Wolfson, 1992), dont l'efficacité était mesurée par le temps pour compléter la planche B - le temps pour compléter la planche A

Des analyses statistiques univariées classiques (analyses de variance, ANOVA) ont mis en évidence des changements significatifs dans les tâches de stop signal et de Stroop ainsi qu'un changement marginal à la tâche de TMT chez les enfants après l'entraînement CI. Chez les adolescents, un changement significatif en stop signal a été détecté après l'entraînement CA.

En plus de cette batterie cognitive, les participants réalisaient en pré- et post-test une imagerie par résonance magnétique (IRM) cérébrale multimodalités (anatomique/ fonctionnel/ diffusion).

Enfin, en pré-test, des prélèvements génétiques salivaires ainsi que des questionnaires de mesures environnementales et culturelles étaient collectés.

Etude 1

Cette étude a donné lieu à un article : **Menu, I.**, Rezende, G., Le Stanc, L., Borst, G.* & Cachia, A.* (accepté). A network analysis of executive functions before and after computerized cognitive training in children and adolescents. *Scientific reports*.

Dans une première étude, nous nous sommes intéressés à l'organisation des FE au cours du développement (de l'enfance à l'adolescence) et avec l'entraînement cognitif (pre- vs. post-test).

En utilisant des modèles d'équations structurelles (SEM), Miyake et al., 2000 avait proposé, chez l'adulte, un modèle des FE avec une structure hiérarchique, où trois facteurs latents représentent chaque FE (CI, MAJ en MDT et FC). Au cours du développement, il a été montré que cette structure des FE évolue d'un seul facteur au cours de la petite enfance, sans séparation claire entre les différentes tâches des FE (Shing et al., 2010; Wiebe et al., 2008; Willoughby et al., 2012; Xu et al., 2013) à deux à quatre facteurs à l'adolescence (Agostino et al., 2010; Friedman et al., 2016; Lee et al., 2013; McAuley and White, 2011; Wu et al., 2011; Xu et al., 2013). Ainsi, alors que pendant l'enfance, la MAJ en MDT, la FC et

le CI reposent sur des processus cognitifs sous-jacents similaires, à l'adolescence, les FEs deviennent plus spécialisées et indépendantes (Hartung et al., 2020; Karr et al., 2018).

Les FEs étant impliqués dans l'apprentissage, la réussite scolaire, la santé mentale et la vie quotidienne (Best et al., 2011; Diamond, 2013), plusieurs programmes d'intervention ont testé la possibilité d'entraîner divers aspects des FEs, notamment le CI (Diamond, 2013; Hu et al., 2017; Jaeggi et al., 2011; Liu et al., 2015; Xu et al., 2020; Zhao et al., 2015). Toutefois, à ce jour, aucune étude n'a évalué dans quelle mesure un entraînement des FEs pouvait modifier l'organisation de ces FEs.

Dans cette première étude, nous avons donc examiné comment la structure des FEs était modifiée par l'entraînement au CI chez les enfants et les adolescents en utilisant un modèle en réseaux. Dans cette modélisation, les systèmes peuvent être représentés comme des nœuds reliés entre eux par des arêtes (plus les arêtes sont épaisses, plus l'interconnexion est forte). Appliquée aux FEs, cette modélisation permet d'identifier les nœuds (ici, chaque nœud correspond à une tâche de FEs) qui jouent un rôle central dans l'ensemble du réseau (ici, différentes tâches FE). En utilisant une telle approche, nous avons cherché à déterminer si l'entraînement accélère le développement des FEs ou le modifie qualitativement en s'écartant de la trajectoire développementale observée de l'enfance à l'adolescence (Jolles and Crone, 2012).

Pour ce faire, des réseaux basés sur les matrices de corrélation des scores aux 6 tâches de FE ont été construits pour les enfants et les adolescents avant l'entraînement (pré-test) et après l'entraînement (entraînement au CI : post-test CI ; entraînement CA : post-test CA). Six réseaux (3 par tranche d'âge) ont donc été estimés. Ces réseaux comprenaient 6 nœuds avec 4 mesures portant sur différents aspects du CI (Stroop pour le contrôle de l'interférence, Stop Signal et Simon pour l'inhibition de la réponse et Attentional Network Task pour l'inhibition attentionnelle), 1 mesure de FC (Trail making test) et 1 mesure de MAJ en MDT (N-back).

Des différences quantitatives et qualitatives ont été détectées dans la structure des réseaux des FEs entre les enfants (9-10 ans) et les adolescents (16-17 ans). Notamment, les connexions entre les différentes tâches des FEs étaient de plus en plus nombreuses avec l'âge. Ces résultats sont cohérents avec une augmentation de la variance partagée entre les FEs avec le développement (Xu et al., 2013).

En plus de ces changements développementaux, des changements quantitatifs et quali-

tatifs au niveau de la structure des FEs ont également été constatés après l'entraînement au CI. Les résultats ont montré qu'après l'entraînement au CI chez les enfants, les réseaux ont des connexions de plus en plus fortes à la fois entre les tâches d'une même FE et entre les tâches des différentes FEs. Le réseau post-test était donc plus similaire à celui des adolescents que celui avant l'entraînement. En revanche, chez les adolescents, les changements au niveau du réseau des FEs étaient plus subtils. Plus précisément, après l'entraînement CA, le nombre de connexions a diminué mais le poids de certaines arêtes a augmenté, alors qu'après l'entraînement CI, le poids des arêtes est devenu beaucoup plus important, reflétant un réseau plus intégré. Cependant, ces changements plus faibles chez les adolescents par rapport aux enfants peuvent également être interprétés en termes d'effets réduits de l'entraînement chez les adolescents.

Pour conclure, les modèles de réseaux constituent un outil original et pertinent pour étudier les effets d'un entraînement cognitif sur l'organisation des FEs, en complément d'approches statistiques plus classiques telles que les ANOVA univariées.

Etude 2

Cette étude a donné lieu à un article en préparation : **Menu, I.**, Borst, G.* & Cachia, A.* (en préparation). Latent network analysis of executive functions across development.

Afin de répliquer notre première étude et d'explorer davantage les changements développementaux dans l'organisation des FEs, une deuxième étude a été menée sur la base de données du Texas Twin Project. Ce projet a recruté 1019 jumeaux de la maternelle à la terminale, âgés de 7,8 à 15,3 ans ($M = 10,79$ ans, $ET = 1,76$), inscrits dans des écoles publiques des régions d'Austin et de Houston, Texas, Etats-Unis (Harden et al., 2013).

Afin d'examiner les liens entre les différentes tâches des FE sans aucun *a priori* sur la structure et pour reproduire notre étude 1, un réseau des FEs a tout d'abord été estimé. Ensuite, des modèles factoriels à variables latentes ont été construits et comparés afin de répliquer les travaux de Karr et al., 2018 et Miyake et al., 2000. Enfin, pour fournir la vision la plus complète et la plus précise de l'évolution de l'organisation des FEs avec l'âge, ces deux méthodes ont été combinées pour créer un modèle de réseau de variables latentes (LVNM, Epskamp et al., 2017). À ce jour et à notre connaissance, aucune étude n'a util-

isé cette méthodologie. Cette technique est extrêmement bien adaptée à l'étude des FEs, car l'organisation factorielle des FEs, bien qu'évoluant avec le développement, fait plutôt consensus.

Globalement, quel que soit l'outil statistique utilisé, nous avons pu constater que les connexions entre les variables et/ou les FEs elles-mêmes diminuaient avec le temps. Cela était d'autant plus visible avec les analyses de réseau où il y avait initialement un réseau très intégré avec de nombreuses connexions inter- et intra-FEs qui ont diminué avec l'âge jusqu'à obtenir un réseau très clairsemé et ségrégué. Parmi les FEs, nous avons pu observer que le CI, qui semblait avoir un rôle central dans l'organisation des FEs avant 10 ans, se dissociait des autres FEs assez précocément. A l'inverse, la MAJ en MDT prenait un rôle de plus en plus central dans la structure des FEs avec le développement.

En conclusion, cette étude, en comparant les différents outils méthodologiques utilisés dans la littérature, a permis de faire le point sur le développement de l'organisation des FEs de 8 à 14 ans. Les trois approches utilisées ont donné des résultats cohérents et complémentaires. Au cours du développement, ces résultats ont mis en évidence une différenciation précoce du CI par rapport aux autres FEs, suivie d'une différenciation de la FC, tandis que la MAJ en MDT prend un rôle plus important dans la structure des FEs au cours du développement.

Etude 3

Cette étude a donné lieu à un article : **Menu, I.**, Rezende, G., Le Stanc, L., Borst, G.* & Cachia, A.* (en révision). Inhibitory control training on executive functions of children and adolescents: a latent change score model approach.

Après avoir étudié les changements d'organisation des FEs avec le développement et avec l'entraînement au CI, nous avons voulu étudier l'impact de cet entraînement sur les deux autres FEs non entraînées, la MAJ en MDT et la FC. Le but de cette étude était donc de voir si, en plus des changements d'organisation observés dans l'étude 1, l'entraînement au CI avait bénéficié à ces deux FEs et quels facteurs pouvaient influencer ces effets de transfert.

Pour cela, un modèle de score de changement latent (LCS) dédié a été développé. Les modèles LCS sont des extensions des SEM qui ont été développés pour les données

longitudinales (McArdle, 2009). Ces modèles permettent d'étudier facilement et précisément des questions complexes et importantes pour des données d'entraînement, telles que l'estimation des différences interindividuelles dans les niveaux initiaux et dans les changements liés à l'entraînement, ou encore la caractérisation de trajectoires de changement complexes (et éventuellement non linéaires), ainsi que la détermination des facteurs influençant ces trajectoires. Appliqués à l'entraînement des FEs, les modèles LCS permettent d'évaluer les effets de transfert 1) directement à partir de l'estimation des changements liés à l'entraînement dans les tâches entraînées et non entraînées et 2) indirectement à partir des effets des niveaux initiaux de chaque FE sur les changements liés à l'entraînement des autres FEs (effets croisés).

Alors que les ANOVA à mesures répétées n'avaient détecté qu'un transfert proche dans les capacités de CI des enfants, le modèle LCS a détecté un transfert proche en CI mais aussi un effet de transfert lointain dans les capacités de MAJ en MDT chez les enfants. Le transfert détecté chez les enfants avec les modèles LCS est cohérent avec les résultats d'études précédentes sur l'entraînement au CI chez les enfants (Aydmune et al., 2019; Liu et al., 2015) et les jeunes adultes (Beauchamp et al., 2016; Maraver et al., 2016). Chez les adolescents, les modèles LCS, mais pas les ANOVA, ont permis de détecter des changements significatifs dans les capacités de CI après l'entraînement. Il est à noter qu'aucun effet de transfert n'a pu être détecté chez les adolescents via les ANOVA ou les LCS. Ce manque de transfert pourrait être lié à la spécialisation des FEs avec l'âge, avec une diminution de l'unité des FEs et une augmentation de la diversité des FEs, conduisant ainsi à une diminution de la part commune des FEs (Agostino et al., 2010; Friedman et al., 2016; Hartung et al., 2020; Lee et al., 2013; McAuley and White, 2011; Wu et al., 2011; Xu et al., 2013). Ces résultats chez l'adolescent peuvent aussi s'expliquer par une plus faible implication des adolescents à l'entraînement au CI, ceux-ci ne progressant plus après la 4ème séance.

Par ailleurs, chez les enfants, les effets de transfert observés dépendaient non seulement du niveau initial dans la FE ayant bénéficié du transfert, mais aussi des niveaux initiaux dans les autres FEs (effets croisés). De tels effets croisés sont cohérents avec une étude précédente sur des adultes plus âgés qui a démontré qu'un entraînement ciblant la MDT a conduit à la fois à de plus grands bénéfices en MDT et marginalement à des effets de transfert plus importants en planification, en CI et en intelligence fluide chez les participants qui présentaient initialement des capacités cognitives plus faibles (Zinke et al., 2014).

Enfin, nous avons observé un effet positif du nombre de séances d'entraînement au CI

sur les gains d'apprentissage en MAJ en MDT et en FC chez les enfants. Ce résultat est cohérent avec les résultats de précédentes études démontrant que les bénéfices directs de l'entraînement aux FEs dépendent de la durée de l'entraînement (Diamond and Ling, 2016; Jolles and Crone, 2012). Il convient de noter que, dans notre cas, l'effet de dose n'a été constaté que dans les tâches de FEs non entraînées (transfert lointain). L'absence d'effet dose dans les tâches du CI pourrait être liée à un éventuel effet plafond.

Enfin, le modèle LCS a également révélé que les enfants et les adolescents ayant des capacités exécutives initiales plus faibles progressaient davantage que les individus ayant des capacités en FEs initialement plus élevées, confirmant ainsi les résultats d'études antérieures selon lesquels l'entraînement bénéficie plus aux participants ayant un fonctionnement exécutif plus faible (Au et al., 2015; Diamond and Lee, 2011; Jaeggi et al., 2008) conformément à l'hypothèse de compensation (Karbach and Kray, 2021).

Pour conclure, notre étude montre que la modélisation LCS a révélé des effets de transfert qui n'ont pas pu être détectés avec l'utilisation de modèles d'analyse de variance classiques appliqués aux mêmes données. Cette sensibilité plus faible de l'ANOVA peut expliquer le manque d'effets de transfert rapportés dans les études d'entraînements exécutifs utilisant des approches statistiques classiques (Kassai et al., 2019).

Etude 4

Après avoir montré que les facteurs cognitifs pouvaient jouer un rôle dans la réceptivité à l'entraînement au CI, nous avons voulu savoir si des facteurs au niveau cérébral étaient également impliqués dans les bénéfices après un tel entraînement.

Dans cette étude, nous avons voulu voir dans quelle mesure l'anatomie des régions cérébrales impliquées dans les FEs était également impliquée dans les progrès exécutifs suivant un entraînement cognitif. Pour aborder cette question, nous avons effectué deux analyses.

Tout d'abord, nous avons examiné les régions du cerveau dont le volume de matière grise était associé à la performance exécutive initiale. Sur les 6 tâches des FEs, des régions cérébrales ont été identifiées seulement chez les adolescents pour la tâche de Stroop (pre-cuneus) et de TMT (ACC). Chez les enfants, aucune région cérébrale n'était associée aux tâches exécutives.

Ensuite, nous avons étudié les régions cérébrales dont les changements de volume de matière grise sont associés à la progression dans les tâches des FEs après l'entraînement cognitif. Nous avons pu observer que des modifications de régions cérébrales étaient associées à des gains à la tâche de Stroop (chez les enfants du groupe CA et chez les adolescents des deux groupes d'entraînement) ainsi qu'à la tâche de TMT (chez les adolescents du groupe CA). Les régions détectées correspondaient à des régions du réseau cérébral des FEs comme l'ACC, l'IFG ou l'insula (Houdé et al., 2010; Molnar-Szakacs and Uddin, 2022). Ainsi, il y aurait un chevauchement entre les régions impliquées dans les FEs et celles impliquées dans la réceptivité à l'entraînement au CI.

Etude 5

Nous avons pu observer que les régions cérébrales dont la plasticité était associée à la réceptivité à l'apprentissage correspondaient à des régions du réseau cérébral des FEs. Ces résultats, ainsi que ceux de l'étude 1, soutiennent l'hypothèse selon laquelle l'entraînement pourrait accélérer le développement et nous amènent à tester cette hypothèse au niveau cérébral.

Une approche intéressante et originale pour tester directement cette hypothèse au niveau cérébral est de calculer l'âge du cerveau (c'est-à-dire de prédire l'âge à partir de données cérébrales telles que le volume de matière grise, etc.) avant et après l'entraînement pour voir si celui-ci avait effectivement accéléré le développement en augmentant le brainAGE, à savoir la différence entre l'âge du cerveau et l'âge chronologique.

Pour calculer l'âge du cerveau, nos données de test étant la cohorte APEX, il était nécessaire de trouver des cohortes indépendantes qui pourraient constituer nos données d'entraînement. Deux cohortes différentes ont été utilisées : ADHD200 (Milham et al., 2012 ; http://fcon_1000.projects.nitrc.org/indi/adhd200/) et ABIDE2 (Di Martino et al., 2017 ; http://fcon_1000.projects.nitrc.org/indi/abide/abide_II.html).

Nous avons testé cinq modèles d'apprentissage automatique (de *machine learning*), trois modèles linéaires (Ridge, ElasticNet, linear Support Vector Regression), deux modèles non linéaires (Gradient boosting, Random forest) et un modèle de *deep learning* (Multilayer perceptron). Ces modèles ont été optimisés sur l'ensemble des données d'entraînement (c'est-à-dire ADHD200 + ABIDE2). Ensuite, nous avons recalculé ces modèles avec l'ensemble des données d'entraînement (ABIDE2, ADHD200) et les paramètres optimaux obtenus et les

avons utilisés pour prédire l'âge du cerveau pour l'ensemble des données test (la cohorte APEX) à partir des volumes de matière grise dérivés des analyses VBM, soit au niveau local (par voxel), soit au niveau régional (par région d'intérêt). Que ce soit au niveau local ou régional, le modèle Ridge était celui qui a donné la meilleure estimation de l'âge cérébral.

Nous avons ensuite essayé de déterminer si le cerveau mûrissait avec l'entraînement cognitif. Nous avons émis l'hypothèse que le brainAGE au post-test serait supérieur au brainAGE au pré-test et que cette différence serait plus importante dans le groupe expérimental ayant suivi l'entraînement CI que dans le groupe témoin d'entraînement CA mais nos résultats n'ont pas été concluants.

Ensuite, nous avons cherché à savoir si le développement du cerveau était lié à la cognition avant tout entraînement. Nous avons émis l'hypothèse que le brainAGE serait un prédicteur de la performance exécutive au pré-test. Sur nos six tâches des FEs, seule la performance à la tâche de Simon était prédite par le brainAGE. Notamment, les participants ayant un brainAGE plus important (âge cérébral > âge chronologique) avaient de moins bonnes performances à cette tâche.

Enfin, nous avons voulu savoir si le "vieillessement" du cerveau après l'entraînement cognitif était lié aux gains après l'entraînement. Nous avons émis l'hypothèse que la différence entre le brainAGE au post-test et celui au pré-test serait un prédicteur de la différence de performance aux tâches des FEs, et que cet effet sera plus important dans le groupe CI que dans le groupe CA. Nous avons pu voir que cela était le cas pour la tâche de N-back chez les enfants mais n'avons pas pu généraliser ces résultats à d'autres tâches ou tranches d'âge.

En conclusion, nos résultats préliminaires associant brainAGE et performances exécutives initiales ou gains après l'entraînement au CI suggèrent que le brainAGE utilisé de manière longitudinale peut être un outil très intéressant pour étudier des apprentissages plus longs, comme celui de la lecture.

Etude 6

Cette étude a donné lieu à un article en préparation : **Menu, I.**, He, Q., Victor, J., Rezende, G., Le Stanc, L., Vidal, J., Oppenheim, C., Duchesnay, E., Chaumette, B., Houdé, O., Borst, G. & Cachia, A. (en préparation). Do neuroplasticity and

genetic factors contribute to cognitive training in children and adolescents?

Après avoir étudié les effets du développement et de l'entraînement au CI au niveau cognitif et cérébral, nous avons voulu examiner comment ces différents niveaux d'analyse, cognitif et cérébral, mais aussi génétique, interagissaient pour expliquer les différences interindividuelles de réceptivité à l'entraînement.

Bien que des études aient rapporté des gains cognitifs à la suite d'un entraînement au CI (Manuel et al., 2010; Maraver et al., 2016; Peckham and Johnson, 2018; Thorell et al., 2009), des différences interindividuelles persistent dans la réceptivité à l'entraînement.

Au niveau cognitif, l'impact du niveau de base est un facteur prédictif important de la réceptivité à l'entraînement souvent étudié pour déterminer qui bénéficie le plus d'un entraînement proposé. L'hypothèse de "compensation" postule que les individus qui sont déjà très performants bénéficieront le moins d'une formation cognitive car ils fonctionnent déjà à un niveau optimal. Cela leur laisse moins de marge de progression, contrairement aux individus dont les performances initiales sont plus fragiles (Karchach and Unger, 2014; Lövdén et al., 2012b; Titz and Karchach, 2014). En effet, plusieurs études sur l'entraînement des FE ont trouvé des bénéfices plus importants pour les enfants et les adultes plus âgés que pour les jeunes adultes (Karchach and Unger, 2014) mais aussi pour les enfants ayant une plus faible mémoire de travail ou étant atteint de trouble déficitaire de l'attention avec ou sans hyperactivité (Diamond, 2011).

Au niveau cérébral, des liens directs entre l'organisation cérébrale et la réceptivité à l'entraînement ont également été démontrés : l'organisation des réseaux cérébraux a permis de prédire les gains cognitifs après entraînement chez l'enfant (Chaddock-Heyman et al., 2020), chez le jeune adulte (Baniqued et al., 2019) et chez l'adulte plus âgé (Baniqued et al., 2018; Gallen et al., 2016).

Enfin, au niveau génétique, un premier lien indirect entre polymorphisme génétique et réceptivité à l'entraînement a été proposé par Rueda et al., 2005a. Les enfants qui avaient de moins bonnes performances initiales en conflit attentionnel étaient plus susceptibles de bénéficier de l'entraînement que les autres (hypothèse de compensation). De plus, le polymorphisme de DAT1, un gène impliqué dans le système dopaminergique, expliquait les scores de conflit attentionnel au pré-test. Les auteurs ont alors émis l'hypothèse d'un lien entre le polymorphisme de DAT1 et les bénéfices tirés de l'entraînement. Une autre étude a montré que le polymorphisme de BDNF médiait, en contrôlant pour le niveau de

base, l'effet d'un entraînement sportif sur les FEs chez les adultes plus âgés (Leckie et al., 2014).

Cependant, à ce jour, aucune étude n'a pu rassembler tous les niveaux d'analyse en étudiant simultanément les relations entre ces différents facteurs et la réceptivité à l'entraînement chez les mêmes participants.

L'objectif de cette étude était donc, par le biais d'un modèle SEM multiniveau, de rassembler toutes les pièces du puzzle et d'examiner quels facteurs cognitifs, cérébraux et génétiques contribuaient aux différences interindividuelles de réceptivité à l'entraînement dans notre cohorte APEX d'enfants et d'adolescents après un entraînement informatisé de 5 semaines au CI (groupe expérimental) ou contrôle (groupe contrôle actif, CA).

Le modèle SEM multiniveau combinait deux modèles LCS, un au niveau cognitif modélisant le changement à la tâche de Stroop couleur ou de stop signal, et un au niveau cérébral modélisant le changement de volume de matière grise dans une de 8 régions d'intérêt (ACC gauche et droit, l'IFG gauche et droit, noyau caudé gauche et droit, putamen gauche et droit). Il incluait aussi deux modèles de médiation, un au niveau du pré-test et un au niveau du changement, permettant de voir si nos variables cérébrales avaient un rôle de médiateur entre notre variable génétique et nos variables cognitives. Ainsi, le SEM multiniveau nous permet d'étudier comment les facteurs cognitifs (niveaux initiaux en stop signal et à la tâche de Stroop couleur), cérébraux (volume de matière grise dans l'ACC gauche et droit, l'IFG gauche et droit, le caudate gauche et droit, le putamen gauche et droit) et génétiques (score de risque polygénique, PRS) contribuent aux différences interindividuelles dans les bénéfices suivant l'entraînement dans notre cohorte d'enfants et d'adolescents après un entraînement informatisé de 5 semaines.

Chez les enfants, des effets aux trois différents niveaux ont été démontrés. Nous avons pu observer un effet du niveau cognitif de base en accord avec l'hypothèse de compensation (Karbach and Kray, 2021), c'est-à-dire que les enfants qui bénéficiaient le plus de l'entraînement étaient ceux qui avaient le niveau initial le plus faible. Au niveau génétique, nous avons observé un effet du PRS sur les gains cognitifs après l'entraînement. Ceci est cohérent avec les études précédentes qui ont montré un rôle des polymorphismes de nucléotides simples dans la réceptivité à l'entraînement (Leckie et al., 2014; Rueda et al., 2005a). Ici, étant donné que le PRS a été calculé à partir d'un score de FC (Trail making test) et qu'il était associé au niveau initial de stop signal, ce résultat suggère que les bases génétiques des FEs serait aussi impliquées dans la réceptivité à l'entraînement. Encore une fois, ceci est

cohérent avec les deux études qui ont montré que le polymorphisme des gènes impliqués dans les FE (DAT1 et BDNF) était lié aux gains post-entraînement. Au niveau du cerveau, nous avons pu détecter un effet du volume de base des ROIs du cerveau et des changements de volume (plasticité) sur le gain cognitif. Ces résultats sont les premiers à montrer un effet de l'anatomie cérébrale sur les bénéfices après l'entraînement, et complètent les résultats précédent qui avaient décrit un effet de l'organisation du réseau cérébral sur la réceptivité à l'entraînement (Baniqued et al., 2019; Baniqued et al., 2018; Chaddock-Heyman et al., 2020; Gallen et al., 2016).

Ces résultats se sont focalisés sur deux régions d'intérêt : l'ACC et le Putamen gauche. L'anatomie et la fonction de l'ACC ont été montrés comme liées à la performance à différentes tâches de CI comme la tâche de Stroop (Adleman et al., 2002), de Simon (Kharitonova et al., 2013) et de Go/No-Go (Pornpattananangkul et al., 2016). D'autre part, il a été démontré que l'activation du striatum, et notamment du Putamen, est liée à l'inhibition de la réponse pendant la tâche de stop signal (Vink et al., 2005), et particulièrement à la suppression de la réponse motrice (Pas et al., 2017) et à l'anticipation de l'inhibition (Pas et al., 2021; Pas et al., 2019; Zandbelt and Vink, 2010). Ainsi, alors que l'ACC est une région générale pour le CI, le putamen est plus spécifique pour la tâche de stop signal.

Chez les adolescents, les résultats étaient bien pu limités. D'autres études sont nécessaires pour déterminer s'il s'agit d'une spécificité due à cette tranche d'âge ou à un défaut de l'entraînement proposé (plateau atteint dès la 4ème séance d'entraînement).

En conclusion, cette étude ouvre la voie de la modélisation multiniveau pour étudier les résultats d'interventions. Celle-ci pourrait être utilisée pour étudier les facteurs favorisant l'apprentissage, comme dans cette étude, mais aussi, en clinique, pour comprendre l'évolution d'une pathologie, notamment suite à une intervention thérapeutique, et ainsi participer au développement d'une médecine plus précise et personnalisée.

Conclusion

Cette thèse avait des objectifs à la fois en psychologie et neurosciences, et en méthodologie.

En psychologie :

- Étudier au niveau cognitif les changements dans l'organisation des fonctions exécutives suite à l'entraînement au contrôle inhibiteur et tout au long du développement.

- Rechercher les facteurs à différents niveaux (cognitif, cérébral et génétique) influençant les différences interindividuelles dans les bénéfices directs et les effets de transfert d'un même entraînement.
- Tester l'hypothèse que l'entraînement pourrait accélérer le développement.

Cette thèse avait également des objectifs méthodologiques :

- Tester des modèles statistiques avancés (modèle d'analyse en réseau, de machine learning, SEM) pour modéliser le changement après un entraînement cognitif.
- Développer des modèles d'analyse capables de relier les différents niveaux d'observation
- Utiliser des modèles d'apprentissage automatique pour tester l'hypothèse selon laquelle l'entraînement peut modifier l'âge du cerveau.

Tout au long de cette thèse, nous avons étudié les effets de l'entraînement et du développement du contrôle inhibiteur à différents niveaux d'observation : cognitif, cérébral et génétique.

Concernant l'organisation des fonctions exécutives, nous avons pu mettre en évidence une différenciation des fonctions exécutives avec le développement, soutenant l'hypothèse d'une différenciation des processus avec l'âge et l'acquisition de ces processus (Anderson and Nelson, 2005). Nous avons également pu voir que les différentes fonctions exécutives ne jouent pas le même rôle dans cette organisation au cours du développement, au début le contrôle inhibiteur étant très central pour ensuite laisser sa place à la mise à jour de la mémoire de travail. Nous avons également pu démontrer que ces changements développementaux étaient assez similaires aux changements suivant 5 semaines d'entraînement informatisé du contrôle inhibiteur chez des enfants, soutenant l'hypothèse que l'entraînement accélère le développement (Jolles and Crone, 2012). Cependant, ces résultats n'ont pas été reproduits dans notre groupe d'adolescents. D'autres études sont nécessaires pour déterminer si ces résultats sont dus à une caractéristique du développement ou à l'entraînement proposé.

En termes de bénéfices de l'entraînement au contrôle inhibiteur, nous avons pu constater que les différences interindividuelles pouvaient être expliquées par des facteurs cognitifs, cérébraux et génétiques. Notamment, on a constaté que les participants dont les capacités inhibitrices initiales étaient plus faibles bénéficiaient davantage d'une intervention ciblant l'inhibition, ce qui soutient l'hypothèse de compensation (Karchach and Kray,

2021). En outre, les enfants qui présentaient un plus faible risque génétique pour un mauvais fonctionnement exécutif ont également montré de plus grands progrès. Ainsi, un chevauchement semble exister entre les bases génétiques des fonctions exécutives et les bases génétique de la réceptivité à l'entraînement. Un chevauchement similaire a également été observé au niveau du cerveau. D'autres études seront nécessaires pour intégrer les variables environnementales dans cette modélisation multiniveau.

Cette thèse s'inscrit également dans le contexte d'une évolution de la recherche en psychologie qui devient plus précise et interdisciplinaire, avec le développement de méthodes d'analyses telles que les modèles de réseaux, d'équations structurelles ou d'apprentissage automatique, et plus intégrative, avec l'intégration simultanée de différents niveaux d'observation. Ces développements méthodologiques permettent de répondre à des questions cruciales en psychologie du développement et de considérer les variables non plus comme des éléments isolés mais comme des éléments faisant partie d'un système intégré.