

TESIS DOCTORAL

The interplay of nature and nurture in the development of self-regulation: Genes, training and their interaction

(Desarrollo de la Autorregulación:
Factores genéticos, educativos y su interacción)

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Chapter 1

**Historical and empirical background on the study of
self-regulation in childhood**

The developmental process through which human's cognitive functions evolve from the most basic perceptive and environmentally-driven attention processes to the most complex social interactions that require the integration and manipulation of multiple sources of stimulation is greatly supported by the development of self-regulation (SR). From the field of cognitive and behavioral psychology, SR has been conceived as the capacity to voluntarily modulate one's own thoughts, emotions and actions in order to achieve goals and meet social demands. Its relevance in the development of individuals across the life span is such, that it has been defined as "the key mediator between genetic predisposition, early experience, and adult functioning" (Fonagy & Target, 2002).

In the last decades, a great deal of research has been focused on the understanding of the emotion, behavioral and cognitive aspects of SR and more recently, on the neurophysiologic mechanisms that support its development and function. Based on this knowledge, scientist in the field have been able to trace how infants develop from being dependent on external sources of regulation, usually provided by parents and caregivers during the first years of life, to the willful exercise control mechanisms in the late childhood and adolescence. The multidisciplinary approaches that have been taken within this framework of research have also shade light on the role of SR on children's social adjustment and academic competence.

A major goal of this introduction is to provide the reader with a complete review on the different approaches and more recent discoveries that have contribute to the understanding of SR. The first section of this chapter focuses on the knowledge derived from the field of temperament research where individual differences in the capacity to voluntarily regulate automatic or dominant

responses in the favor of subdominant but adaptive responses are addressed as a temperament dimension called effortful control (EC). The second part will cover the executive control of attention, a cognitive system that underlies the voluntary regulation of reactivity. This section will describe the marker tasks traditionally implemented for the scientific study of executive attention processing, the neural correlates that support it, as well as its course of development. The third section of this introduction presents a review on the social and academic implications of and adequate development of self-regulatory skills during childhood and adolescence. Finally, the introductory part of this thesis will conclude with a review on the genetic and environmental factors that influence the development of SR in childhood.

1.1. Temperament and self-regulation

From very early in life, parents can recognize patterns of emotional and behavioral reactivity in their children. While some are described as easygoing and even-tempered, others are soon label as irritable, nervous or fearful. What is more, core differences of this kind are not only found when children from different families or cultures are compared, but can also be observed among siblings who share the environmental and constitutional commonalities of the family in which they are raised.

The study of such individual differences has its roots in the ancient Greco-roman medicine that offered a description of four types of temperament (choleric, melancholic, sanguine and phlegmatic) that were thought to be determined by the four bodily fluids. Thanks to the advent of modern medical and psychological

research scientists have been able to replace this assumption with theories of temperament that are built on the basis of empirical evidence.

Two important approaches in the beginning of the 20th century laid the groundwork for that work. The first one, developed by the Russian psychologist Ivan Pavlov, was built on the objective observation of the behavior of dogs in the laboratory. Based on that work, Pavlov characterized four different types of temperament which he thought to be determined by the strength of the nervous system (Pavlov, 1935). The second approach, mainly developed in western Europe was led by the work of the British psychologists Cyril Burt and Edward Webb (Burt, 1938; Webb, 1915) who first implemented the use of self-report questionnaires and factor analysis. Their main contribution was the characterization of the first temperamental factors, which included for example, the extraversion-introversion factor, the emotional stability-instability factor or the factor “w” described by Webb as the consistency of one’s actions as a result of deliberated intention or will (Webb, 1915). Their work is known to be the basis of the factor structure of temperament, which still leads the research of personality and temperament nowadays.

Despite of the growing interest in the scientific study of temperament, most of the first approaches that took place in the beginning of the last century were focused on the description of individual differences in adults. It was not until the decade of the 1930s that the first approximations to the study of children’s temperament were made based on the pioneer work of psychologists Arnold Gesell (Kessen, 1965) and Mary Shirley (Shirley, 1973). Their profound investigation in the field provided three fundamental concepts on the understanding of development and temperament. First, temperamental differences

are the basis from which personality develops. Second, beyond the stability of temperamental traits across children, individual differences highly depend on the child's developmental changes and socialization. Third, the outcome of a given temperamental trait greatly depends on the environmental factors (education and experience) present during the child's development (Rothbart, 2011).

Based on those key concepts, during the last 30 years scientist have been investigating the early onset of temperamental traits, their development from early infancy through childhood and how they relate to the general adjustment of individuals later in life. To achieve those goals, researches in the field have developed different techniques for the assessment of temperamental traits including naturalistic observation of children in their home or at the school, structured observations in controlled settings, implementation of cognitive tasks in the laboratory and the administration of questionnaires that are either filled by parents, caregivers and teachers or by the children themselves when they are older.

One of the more important formulations, developed by Rothbart & Derryberry in the early 80's, define temperament as those "constitutionally based individual differences in reactivity and self-regulation, as seen in the emotional, motor and attention domains" (Rothbart & Derryberry, 1981). The relevance of this definition lies in the fact that it comprises the key components of the concept of temperament, as it is understood today. First, temperament –contrary to personality– entails a biological component which is highly related to the genetic endowment of the individual (Posner, Rothbart, & Sheese, 2007). Second, temperament comprises not only one's tendencies in the emotional domain but also one's disposition or capacities in the level of motor and attention reactivity.

Finally, and probably one of the most important contribution of Rothbart and collaborators, we are not helplessly driven by our temperamental traits but rather endowed with the capacity to deliberately exert regulation of our own emotions, actions and thoughts.

After decades of research, Rothbart and collaborators (Ahadi, Rothbart, & Ye, 1993; Gartstein & Rothbart, 2003; Rothbart, Derryberry, & Hershey, 2000) have proposed a model of temperament that describes three major dimensions: Surgency/Extraversion, Negative Affectivity and Effortful Control. *Surgency*, a factor that describes the tendency towards positive emotions, rewards and high activity levels, includes scales that measure approach (positive anticipation), high intensity pleasure, activity level, impulsivity and shyness (this one with a negative load). The *Negative Affectivity* factor measures tendencies towards anger/frustration, discomfort, fear, and sadness and includes a negative load on soothability. Finally, the so-called *Effortful Control* factor describes one's ability to inhibit a dominant response in order to perform a subdominant response, to detect errors and plan the course of actions (Rothbart & Rueda, 2005; Rothbart, 1989). The EC factor includes scales that measure inhibitory control, attentional focusing, perceptual sensitivity, smiling and laughter and low-intensity pleasure.

The understanding of the structure of temperament as proposed by this model entails the conceptualization of SR as a temperamental trait that serves to regulate emotional and behavioral reactivity. In principle, the two first factors (Surgency and Negative affectivity) represent the reactive elements of temperament. In other words, they describe the threshold at which one's emotions; actions and attention get aroused and elicit a response towards, away from or against a specific kind of stimulation. Individual differences contained on

these two factors reflect motor, cognitive or physiological responses that can be easily measured by their onset, intensity and duration (Rothbart, 2011). It is important to note that the reactive dimensions of temperament as described by the model already imply certain mechanisms of motivation and action that work as a self-regulatory function but they greatly depend on the emotion they serve. For example, a fearful person will deliberately avoid specific situations that signal a potential risk in the same way that a person with tendencies toward high-intensity situations would seek risky activities pursuing excitement and adventure. In contrast, EC entails a more independent self-regulatory system that serves to modulate both positive and negative reactivity on the basis of attention processing and behavioral control (Rothbart, 1989). EC allows increased control over action and adjustment to situational demands in a flexible and willful manner, including both inhibitory control of action (not eating a candy) as well as activation control (eating a fruit instead). Performance of executive attention tasks in the laboratory have been empirically linked to parents- and self-reported EC as assessed with temperament questionnaires. Children who are relatively less affected by conflict receive higher parental ratings of EC and higher scores on laboratory measures of inhibitory control (see Rueda, Posner, & Rothbart, 2011 for a review). In the following section, I present a review about the human attention system, in particular the executive aspects of attention processing, which will allow us to go one step further on the understanding of the cognitive mechanisms that underlie the exercise of SR.

1.2 Cognitive aspects of self-regulation: Attention

Historically, the human ability to focus attention has been of central interest for many great philosophers and psychologist. Already in 370 B.C., Aristotle characterized attention as the narrowing of the senses and set the path for the philosophical conceptualization of attention that centuries later gave rise to its scientific study with the advent of experimental psychology. One of the first and more influential contributions in the study of attention was provided by William James on his groundbreaking work “The principles of psychology” in which he associated attention with a variety of cognitive components that included vigilance, selectivity and control (James, 1890). Decades later, after the decay on the study of human cognition due to the height of behaviorism, a great number of researchers resumed the experimental study of attention and further developed its cognitive components. For instance, Hebb (1949) defended the existence of interrelated brain networks in the conscious processing of external stimulation. He argued that that all stimuli impact the reticular activating system to keep the cortex in a constant state of vigilance while reaching the sensory pathways to provide information about the characteristics of the stimulating event. During the following decades, particularly in the 1960’s and the 1970’s, the development of techniques for the measurement of electric signals in the brain allowed scientist in the field to identify neural correlates of attention processing. Within this framework of research, in 1971 Michel Posner and Stephen Boies provided the first characterization of attention as a compound of interrelated subsystems that are functionally and anatomically differentiated (Posner & Boies, 1971). During the past 40 years, the integration of attention paradigms to the use of neuroimaging techniques, has allowed scientist to confirm this notion based on the identification

of three neural networks that are assumed to underlie different aspects of the human attention system (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Posner & Petersen, 1990; Posner, Rueda, & Kanske, 2007). The first two of them are involved in reaching and/or maintaining the alerting state (*Alerting Network*) and orienting toward and/or selecting the source of stimulation (*Orienting Network*). The third network, so-called *Executive Attention Network* (EAN), functions to regulate thoughts, emotions and action and is the main attention mechanism engaged in the voluntarily exercise of SR. The EAN is not involved in processing information, instead it serves the function of monitoring and resolving conflict between processes carried out by other brain networks (See Table 1.1). Here, I present a brief description on the alertness and orienting components of attention while a more detailed reviewed is done on the executive attention network.

1.2.1. Alerting network

The ability to prepare and maintain a state of alertness for the processing of information is a fundamental component of human attention. Within the field of attention, a distinction has been made between tonic or intrinsic alertness and phasic alertness. Tonic alertness refers to the general level of arousal that is experienced during waking periods. This level of arousal does not remain stable during the day but rather moves within the range of sleepiness and high alert. Tonic alertness is known to be involved in the performance of tasks that demands the maintenance of attention during long periods of time and is subject top-down control of attention (Posner & Boies, 1971). Phasic alertness is task-specific and refers to the increment on the level of alertness after external stimulation is

presented. Attention paradigms in which participants are required to produce a motor respond to a particular set of stimuli have been traditionally implemented to assess the efficiency of phasic alertness. Performance of individuals (speed and accuracy) is compared under two conditions: when a warning signal precedes the presentation of the target and when no signal is presented (Posner, 2008). Early studies in the field found that the presentation of warning cues produces a cascade of physiological changes that are mediate through the action of the neurotransmitter norepinephrine, which appear to prepare the individual to give a rapid respond, oftentimes in detriment of accuracy (Posner, 1978). With the use of functional magnetic resonance (fMRI), Fan et al. (2005) demonstrated that changes in the alerting state due to the presentation of warning signals is supported by the activation of a network that includes thalamic regions, as well as frontal and parietal areas of the cortex.

Function	Structures	Modulator
Alerting	Locus coeruleus Right frontal and parietal cortex	Norepinephrine
Orienting	Superior parietal Temporal-parietal junction Frontal eye fields Superior colliculus	Acetylcholine
Executive attention	Anterior cingulate Lateral ventral prefrontal Basal ganglia	Dopamine

Table 1.1. Attention networks: Brain areas and neuromodulators
(Rueda, et al., 2011)

1.2.2. Orienting Network

An efficient performance of the everyday activities of individuals from childhood to adulthood requires the ability to ignore irrelevant stimulation from the environment by focusing only the information that is relevant for the ongoing task. This ability, known as orienting of attention, has been a focus of interest from the early experimental approaches on the study of attention. An example of this is the study carried out by Colin Cherry in 1953,) in which individuals were presented an array of auditory stimuli simultaneously to the two ears and were instructed to attend only to the stimulation presented to one of the ears. As a result, the message presented to the unattended ear was not detected and therefore, it was not processed. This kind of experimental manipulation led scientist in the field to emphasize on the attentional component of selectivity. For instance, Broadbent (1958), argued that attention acts as a filter mechanism that modulates the constant flow of sensory input and selects the information that can be sent to the limited-capacity perceptual system. Broadbent's theory was later confirmed by Hillyard (1985), through the use of event-related potentials (ERP). He demonstrated that attended stimuli trigger early ERP components that exhibit larger amplitudes compared to those triggered by unattended stimuli. This finding indicates that the orienting of attention allows the early selection of information that will further be processed.

Orienting of attention towards the source of information can be either covert (i.e. the focus of attention is shifted without any visible signal) or overt (i.e. when head or eye movements informs about the change of orientation) (Posner, 1980). Traditionally, orienting of attention has been studied through the use of paradigms in which a cue is presented to inform about the location of the

upcoming target. Reduced reaction times are observed when the cue signalizes a valid location, compared with those conditions where no cue is presented or it is presented at fixation point. In turn, neutral cues lead to reduce reaction times compared to cues that signalize the incorrect position of the target (Posner, 1980). Additionally, a distinction has been made between endogenous and exogenous orientation of attention. The endogenous orientation of attention refers to the effortful, top-down mechanism that underlies the selection of information. This kind of orientation is study by presenting cues that must be processed before the focus of attention shifts (i.e., arrows that signalize the location of the target). The exogenous orientation of attention is a bottom-up mechanism that is induced through the presentation of salient cues that automatically capture and direct attention to a particular location. These two mechanisms of orientation appear to be independent from each other and rely on different neural networks: while the top-down orientation of attention relies on the activation of areas in the intraparietal cortex and the superior frontal cortex, the bottom-up orientation system is supported by the activation of structures of the temporoparietal cortex and the inferior frontal cortex, particularly in the right hemisphere (Corbetta & Shulman, 2002). This conceptual and anatomical dissociation is of particular importance for the study of SR, as orienting of attention is considered the first mechanism of voluntary regulation shown by children in the first years of life. Integration of orienting of attention to the development of SR will be presented in subsequent sections of this introduction.

1.2.3. Executive Attention Network

During preschool period, children are challenged with an increased amount of stimulation and social interactions, which frequently demands the execution of

self-regulatory strategies. Suppose a typical situation in the school when a child takes the most beloved toy of her peer who immediately gets the impulse of throwing a tantrum to get his toy back, a normal and effective reaction at home. However, being at the school implies different rules: tantrums are not accepted and he will not get compensated for his behavior. In situations like this one, a conflict between the automatic reaction and the already internalized school rules arises. In order to produce an appropriate response, the conflicting situation needs to be detected and the inappropriate reaction must be rapidly inhibited. This is a clear example of the close and interactive relation between SR and attention. During the last decades researchers in the field have attempted to integrate these constructs. For instance, Ruff & Rothbart (1996) argued that executive attention serves as a key mechanism for the regulation of cognition, emotions and behavior. According to Botvinick, Braver, Barch, Carter, & Cohen (2001), executive attention involves the monitoring and resolution of conflict between parallel processes that take place in different areas of the brain. Early theoretical accounts in the field already stressed on the function of attention as a mechanism for the monitoring of action and the orchestrated control of different processes (Norman & Shallice, 1986; Posner & Snyder, 1975). According to them, executive attention plays a critical role for the performance of tasks that are not automatic or when automatic reactions can yield to the commission of errors. For example, when individuals face a novel or dangerous situation, when the task implies a degree of difficulty, when errors have to be corrected or when habitual responses are not appropriate or useful and need to be inhibited (Norman & Shallice, 1986). The basic mechanisms of executive attention are: monitoring, detection of conflict and inhibition of processes or responses in order to adjust to current goals (Rueda,

Posner, & Rothbart, 2005b). Functions associated with the executive attention network overlap to some extent with the more general domain of executive functions, which encompass a set of interrelated processes involved in planning and carrying out goal-directed actions, including working memory, mental-set switching or attentional flexibility, inhibitory control, and conflict monitoring (Blair & Ursache, 2011; Welch, 2001). Here, I present some of the most implemented task on the study of executive attention during the last decades.

1.3 Marker tasks for the study of executive attention

The study of executive attention and its different components have been traditionally addressed through the use of experimental tasks that are designed to resemble situations (such as those mentioned above) in which individuals are required to inhibit automatic/dominant responses in favor of subdominant responses.

Stroop task

One of the most widely used tasks in the field was developed by John Ridley Stroop (1935). In the original version of the task, individuals are presented with a series of words denoting colors, which are at the same time, written in different ink colors. Individuals are asked to respond to the color of the ink (subdominant response) while suppressing the automatic response (reading the word). This type of task is a good example of conflict between two different processes (in this case, perceptual and semantic) that are simultaneously triggered producing a delay on the response. In situations like this, the role of the executive attention is to support the effortful inhibition of the dominant response and the activation of processes needed to execute the subdominant one.

Go-NoGo task

The Go-NoGo task aims to address individual's ability to inhibit motor responses. The traditional version of the task requires individuals to produce a motor response to a target stimulus (Go-condition) while inhibiting the response to distractors (NoGo-condition). Two key aspects of the task trigger the involvement of executive attention resources: first, the target has a higher presentation frequency (75% to 80%), which requires individuals to maintain a constant level of attention in order to detect the distractors and inhibit the response. Second, trials last maximum 2000ms, which requires that participants produce fast responses. Percentage of errors in the No-Go condition and the DST sensitivity index (d') using both hits and false alarms rates are often used as an indicator of performance.

Flanker task

Another strategy to measure conflict in the laboratory is the widely used flanker task (Eriksen & Eriksen, 1974). In this task, a target stimulus is surrounded by stimulation that suggests either the same (congruent) or a different (incongruent) response than the one associated to the target. Suppressing the processing of the distracting information in the incongruent condition requires attentional control and activates the executive attention network to a greater extent than when there is no conflict between target and flankers (Jin Fan, Flombaum, McCandliss, Thomas, & Posner, 2003). The computerized version of this task allows researches to capture reaction times in the range of milliseconds. Engagement of the attention system in the incongruent condition commonly leads to an increase in the reaction time, which is measured by subtracting the averaged

reaction time in the congruent condition from that in the incongruent condition. Therefore, higher scores reflect higher interference levels and less ability to detect and resolve conflict.

1.4 The Attentional Network Task (ANT)

The ANT task (Fan, McCandliss, Sommer, Raz, & Posner, 2002) was designed to provide researchers in the field with a unique and simple experimental tool that would allow the assessment of the three attention networks (alerting, orienting and executive attention). The ANT unites previous experimental methods on the study of alertness (preparation cues); orientation (orienting cues) and executive attention (flanker task) in a single task, and provides a measure of the efficiency of each attention network. The task comprises a series of five aligned arrows ($\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow$), which appear either above or below the fixation point. Individuals are instructed to respond to the middle arrow and ignore the two distractors presented on each side. Preparation (alerting) cues informing about the upcoming presentation of the target (but not about its location) are presented either at fixation point (central cue) or above and below the fixation point (double cue). Orientation (spatial) cues informing about the possible location of the upcoming target are presented either above or below the fixation point. Together with the central cue, a control condition where no cues are presented, serve to compute the alerting and orienting effects. For the assessment of the executive attention network, distractors arrows surrounding the target can point either to the same direction as the target ($\rightarrow\rightarrow\rightarrow\rightarrow\rightarrow$ congruent condition) or to the opposite direction ($\rightarrow\rightarrow\leftarrow\rightarrow\rightarrow$ incongruent condition). The alerting score is derived by subtracting the mean reaction times of the double cue condition from that of the no

cue condition. The orienting score is calculated by subtracting the mean reaction time from the spatial cue condition from that of the central cue condition. Finally, the executive attention score is obtained by subtracting the mean reaction time of the congruent condition from that of the incongruent condition.

Given the straight-forward design of the ANT and its utility on the study of attention (Rueda et al., 2004) developed a child-friendly version, which includes all conditions and the structure of the original task (see Figure 1.1). The main change was introduced on the shape of the stimulus: instead of using arrows, this version included yellow fish, which allows researchers to introduce the task to the children in the form of a game. Thus, children are instructed to “feed” only the middle fish by pressing the key (right or left) according to the direction in which it is swimming.

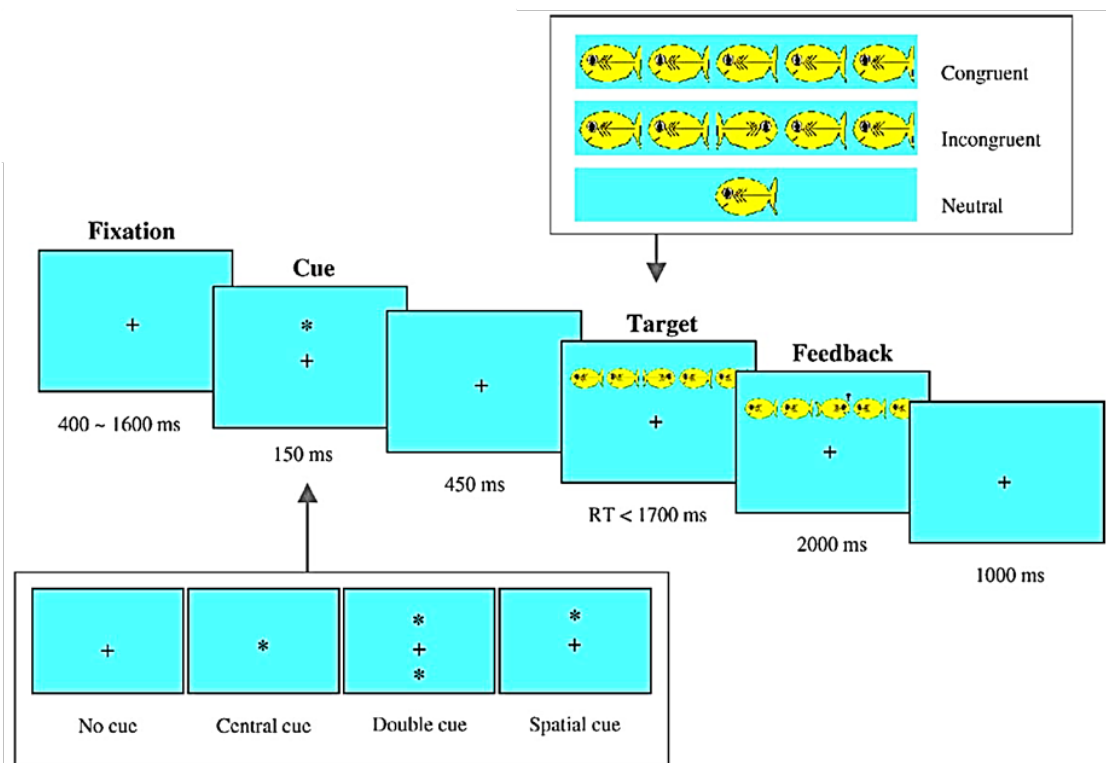


Figure 1.1 Schematic representation of the child-ANT (Rueda, et al., 2004)

The implementation of conflict tasks such as those described above has been a fundamental tool for the study of the neurobiology of the executive attention, its developmental course, individual differences and its relation to the development of SR. In the following section, I present a review on the recent discoveries regarding the neural substrates of executive attention.

1.5 Neuroanatomy of executive attention

The study of the neural areas of the brain that support executive attention has been based on the combination of marker tasks and brain imaging techniques. In the past decades, a great deal of research has revealed that attention control functions such as monitoring, resolution of conflict and inhibition of responses are not supported by the activation of a single structure in the brain, but rather by a network of structures known as the Executive Attention Network (EAN). The EAN comprises a circuitry of brain structures involving the anterior cingulate cortex (ACC) and lateral and medial prefrontal regions of the brain (Posner, Rueda, et al., 2007). These structures are target areas of the ventral tegmental dopamine system. Layer five of the cingulate contains all of the dopamine receptors and this node of the EAN is widely connected to many other cortical areas (Goldman-Rakic, 1988). Studies of functional connectivity have shown that lateral and medial frontal areas are strongly connected to parietal structures in neonates. By age 2, the ACC shows stronger connections to lateral parietal and frontal areas (Gao et al., 2009), although connectivity, particularly across more distant areas of the brain, continues to increase during childhood (Fair et al., 2009).

Imaging studies also provide some understanding of the functional role of different areas implicated in the EAN. There is evidence suggesting that the ACC is

involved in detecting the occurrence of conflict, which is then conveyed to prefrontal structures in charge of resolving the conflict (Botvinick, Cohen, & Carter, 2004; Jin Fan, Flombaum, et al., 2003). Thus, the ACC appears to be the structure involved in monitoring the need for attention control, while medial and lateral prefrontal structures may serve the function of holding in mind information relevant to the task and selecting the appropriate action by inhibiting dominant responses in favor of correct ones.

1.6 Development of the executive attention network

Developmental studies have suggested that the three attention networks follow different maturational courses. While the alerting and orienting networks appear to mature to a great extent during infancy and early childhood, the executive attention network appears to undergo a more progressive maturation, emerging at about the end of the first year of life and continuing during childhood into adolescence (Rueda, Posner, Rothbart, & Davis-Stober, 2004; Rueda & Posner, 2013). However, despite the progressive improvement throughout childhood, executive attention shows a major period of development from about the end of the first year of life up to the end of the preschool years (Rueda et al., 2005). Maturation of this function is related to structural changes in brain areas that are part of the EAN and their connectivity patterns with other brain structures. In the present section, a review on the development of the EAN and its relation to SR is presented.

One of the earliest signs of executive attention has been found in 7 months old children. Berger, Tzur, & Posner (2006) carried out an experiment to test children's ability to detect errors, a mechanism of SR that involves the activation of

the ACC. They found that at this age, children are already able to distinguish between correct and incorrect solutions to simple arithmetic problems (measured by the time children look at the screen). Moreover, they found that children and adults share the same pattern of activation when errors are detected.

Another strategy to study development of the EAN is the use of visual sequence task. On this tasks, an array of stimuli is presented at different locations following a simple and predictable pattern (A, B, C). As early as 4 months, babies are able to learn the sequence and anticipate the following location by accurately direct their looking. However, the ability to predict upcoming locations when sequences are complex (i.e., when the location is followed by two or more different locations), demands the involvement of frontal structures and it does not emerge until children are about 18-24 months of age (Clohessy, Posner, & Rothbart, 2001). Furthermore, Sheese, Rothbart, Posner, White, & Fraundorf (2008) demonstrated that at 7 months, performance of the visual sequence task is related to longer periods of inspection and slower reaching of novel toys, a measure of inhibitory control that correlates with parent-reported EC later in childhood (Rothbart, Ahadi, Hershey, & Fisher, 2001).

Conflict task has also been large implemented to study the development of the EAN. An example of this is the study carried out by Gerardi-Caulton (2000), children between 2-4 years old were presented with a task that induce conflict between location and identity. As in any other conflict task, children showed slower and less accurate responses for the incongruent conditions. At 24 months old, children performed poorly and committed more perseveration errors than older children. Increased levels of performance were already observed for children 30 months old and accuracy was above 90% for children aged 36 months.

Moreover, performance of 30 months old children on the spatial conflict task was positively correlated with children's ability to delay gratification, a measure of emotion SR.

As mentioned earlier, at a preschool age, children exhibit a mayor development of the EAN. In a recent study carried out by Abundis-Gutierrez and collaborators, two groups of children, one group of adolescents and one group of adults performed the child version of the ANT while EEG measures from the salp were being recorded. Abundis and collaborators found that compared to adults, children 4-6 years old exhibit an immature attention system, which was reflected on the delayed and more anterior distributed pattern of neural activation (Abundis-Gutiérrez, Checa, Castellanos, & Rueda, 2014). These results confirm the behavioral results previously reported by Rueda et al. (2004) who demonstrated that conflict scores, an index of efficiency of the executive attention network, exhibit a significant decreased between ages 6 and 7 years, but show little change from then on. However, the electrophysiological patterns of activation recorded by Abundis-Gutiérrez et al. (2014), do show that the executive attention system continue to develop through childhood and adolescence. Error detection, one of the executive attention functions has also been implemented to trace the development of the EAN. For instance, Checa, Castellanos, Abundis-Gutiérrez, & Rueda (2014), developed a child-friendly flanker task that allows assessing conflict interference and error detection. Three groups of children (4-6, 7-9 and 10-13) and a group of adults completed the task. Behavioral and neurophysiological measures demonstrate a developmental improvement for both conflict resolution and neural process of error monitoring. At the behavioral level, developmental changes were observed in the median reaction time, conflict interference index

and the impulsivity index (RT-correct responses – RT-incorrect responses) where younger children exhibited poorer performance compared with older children. At the brain level, ERP components of conflict resolution in younger children compared to those of 10-13 years old children and adults appear much later and are also sustained for a longer time. Moreover, the ERN, an early component of error detection was not found in children 4-6 years old, suggesting that at this age, children still depend on the affective evaluation of errors, while the more automatic mismatch that give rise to the ERN has not been yet developed. Additionally, Checa and collaborators also found that behavioral measures of SR including delay of gratification and EC are related to both behavioral and brain measures of conflict resolution and error detection. These findings validate the idea that self-regulatory abilities in the cognitive and affective domain are supported the efficiency of the executive attention system.

During the past decades, the use of neuroimaging techniques has also contributed to the study of the development of the attention control system and has corroborated the findings reported at the electrophysiological level. For instance, Casey, Tottenham, Liston, & Durston (2005) reviewed the contribution of multiple developmental neuroimaging studies, which show that during childhood, superior cognitive processing requires a widespread engagement of cortical areas. However, as children grow the activation of areas becomes more and more focalized as the system becomes more efficient. This maturational change suggests that the increasing efficiency of the executive attention system as it is observed at the behavioral level, is supported by the specialization of the different areas comprised in the EAN. An additional index of maturation of the neural system across development has been described by Fair et al. (2009). According to their

findings, cognitive functioning is supported by a number of functional networks in the brain, which exhibit local and strong connections during the first years of life. Through development, those connections become weaker while connections between distant areas of the brain become stronger. These findings suggest that the increased communication between the different areas of the brain provide the basis for a more efficient cognitive system. What is more, given that the new efficient patterns of communication are shaped by experience, individuals are better prepared to respond to the specific demands of their environment.

1.7 Social and academic implications of self-regulation

Given their role in emotion regulation and adjustment, executive attention and effortful control are considered important contributors to the socio emotional development of the child (Rueda, Checa, & Rothbart, 2010). The ability to regulate behavior in a flexible and controlled mode has proven to be central to many aspects of children development and, in fact, individual differences in efficiency of executive attention appear to play an important role in school competence and socialization (Checa, Rodríguez-Bailón, & Rueda, 2008; Eisenberg, Smith, & Spinard, 2011; Eisenberg, Valiente, & Eggum, 2010).

In school, control of attention is important to adjust behavior in function of norms and goals, stay focused despite distractions, flexibly allocate attention on information (either internal or external) relevant to current tasks, and persist to complete difficult tasks even when rewards (i.e. learning, good grades, etc.) may take time to arrive. Several studies have shown that children with greater executive attention efficiency (i.e. smaller conflict scores) show higher levels of competence at school, understanding competence as a combination of school

achievement and adequate socio-emotional adjustment (Blair & Razza, 2007; Bull & Scerif, 2001; Checa et al., 2008). A good example comes from studies examining the role that attention skills play in the achievement of math tasks. Attention has emerged as a potentially robust predictor of arithmetic skills (Fuchs et al., 2005; Russell & Ginsburg, 1984). Passolunghi and collaborators have shown that children's arithmetic performance is related to the ability to control irrelevant information. In one of their studies, they selected 4th graders according to their ability to solve arithmetic tasks and followed them longitudinally for a 2-years period. Despite the fact that poor problem-solvers were able to identify relevant information, they remembered less relevant but more irrelevant information about the arithmetic questions than good problem-solvers (Passolunghi, Cornoldi, & De Liberto, 1999). This finding indicates that children exhibiting poorer arithmetic performance have greater difficulty inhibiting irrelevant information compared to better performers. Other measures tapping the EAN, such as Stroop-like interference and performance on inhibitory control tasks, have shown a consistent relationship with arithmetic competency (Blair & Razza, 2007; Bull & Scerif, 2001; Espy et al., 2004). In a recent study, Checa & Rueda (2011) showed that the brain reaction to conflict, as measured with event-related potentials (ERPs), also predict children's grades in math above and beyond general intelligence.

The role of executive attention in school performance and reasoning might also have to do with the anatomical overlap between the EAN and brain areas related to general intelligence and other cognitive demands related to the control of cognition (Duncan & Owen, 2000). Lateral frontal regions of the brain considered to be part of the EAN are activated by marker tasks of general intelligence (Duncan et al., 2000). Based on the evidence presented above, it can be

conclude that efficiency of the EAN brain network results in more successful acquisition and application of knowledge taught in the school, especially in those subjects involving complex reasoning such as mathematics.

On the other hand, individual differences in reactivity and self-regulation, as well as the interactions between them, are involved in the socialization of children and their capacity for socio-emotional regulation. When experiencing negative emotions, it is useful to use attention in order to shift thoughts away from the source of distress, to inhibit aggressive impulses and/or mask the expression of negative emotion if needed. In addition, regulation of positive emotions, as those associated with obtaining desired rewards, often require reappraising the positive value of immediate or high compensations or rewards taking into consideration that they might lead to more negative consequences in the long term (i.e. eating lots of candies or picking on friends). Flexible allocation of attentional resources facilitates fluent reasoning and helps on connecting current decisions with future consequences. These abilities clearly promote social adjustment, and several studies have supported a key role for executive attention on the use children make of them. Ellis, Rothbart, & Posner (2004) showed that both mother and self-reported low EC together with poor efficiency of executive attention predict behavior problems during adolescence. Also, other studies have shown that, during childhood, EC is negatively associated with the incidence of externalizing behavioral problems, which are characterized by high levels of aggression and impulsivity, after controlling for other cognitive and social risk factors (Olson, Sameroff, Kerr, Lopez, & Wellman, 2005; Valiente et al., 2003).

Individual differences in executive control are also related to aspects of cognition such as theory of mind (i.e., knowing that people's behavior is guided by

their mental state, which includes beliefs, desires and knowledge; Carlson, Moses, & Claxton, 2004). There is also evidence showing that EC plays an important role in the development of conscience, which involves the interplay between experiencing moral emotions (i.e., guilt/shame or discomfort following transgressions) and behaving morally, in a way that is compatible with rules and social norms (Kochanska & Aksan, 2006).

Additional evidence on the role of executive attention on socialization comes from studies looking at brain function directly. An important form of self-regulation is related to the ability to detect and correct self-made errors. Detection and monitoring of errors have been studied using event-related potentials (ERPs). A large negative deflection over midline frontal channels is often observed about 100 milliseconds after the commission of an error, called the error-related negativity (ERN; Gehring, Goss, Coles, Meyer, & Donchin, 1993). There is evidence that this post-response signal originates in the ACC (Dehaene, Posner, & Tucker, 1994; Luu, Tucker, Derryberry, Reed, & Poulsen, 2003). The ERN thus provides a means to examine the emergence of this cingulate function during infancy and childhood. In a study conducted with a flanker task and ERPs, it was shown that children who commit more errors on incongruent trials show smaller amplitudes in the error monitoring wave. This result suggests less sensitivity of the brains of these children to the commission of errors. Also, the amplitude of the ERN was predicted by individual differences in social behavior, in that children with poorer social sensitivity, as assessed by a self-report personality questionnaire, were the ones showing ERNs of smaller amplitude (Santesso, Segalowitz, & Schmidt, 2005). Moreover, empathy appears to show a positive relation with amplitude of the ERN (Santesso & Segalowitz, 2009). Children high in effortful control also appear to be

high in empathy, guilt/shame, as well as low in aggressiveness (Rothbart, Ahadi, & Hershey, 1994). Likewise, Eisenberg and her collaborators have found that 4- to 6-year old boys with good attentional control tend to deal with anger by using non-hostile verbal methods rather than overt aggressive methods (Eisenberg, Fabes, Nyman, Bernzweig, & Pinuelas, 1994). In sum, all this evidence suggests that poor efficiency of the EAN may turn on greater difficulty experiencing or appreciating the emotional significance of errors and other unfavorable outcomes leading to higher risk of maladjustment at the school and other social contexts.

1.8 The nature of Executive Attention development

In previous sections I have presented evidence establishing a connection between self-regulated behavior and the structural and functional properties of a particular network of brain areas, the executive attention network. Higher functional efficiency of this network is associated with greater self-regulatory skills. But, what makes the brain of an individual more efficient? One possible answer to this question is that neural efficiency is determined by the genetic endowment that is inherited from parents. If this was the case, then the efficiency of the network or the behavior supported by it would have to show some degree of heritability. Heritability of the attention networks was tested in a twin study conducted with the ANT. In this study, executive attention scores showed stronger concordance for monozygotic compared to dizygotic twins, indicating a significant level of heritability for this attention function (Fan, Wu, Fossella, & Posner, 2001). Genetic variation may therefore be considered as one of the factors accounting for individual differences in the efficiency of the EAN, which in turn determine the ability for attention control that we can directly observe through behavior. Brain

function may thus serve as an intermediate link (also called endophenotype) between genetic variation and behavioral differences (phenotype) in executive attention (J. A. Fossella & Casey, 2006). Tracing that link requires a thoroughly and detailed characterization of the phenotype (through the use of marker tasks and behavioral assessments) as well as the neural mechanisms (circuits and neuromodulators) subserving this function.

Given the role of the neuromodulator dopamine (DA) in the operation of the EAN, various molecular genetic studies have been carried out using behavioral and neurophysiological measures with both adults and children in order to understand the nature of the relationship between DA-related genes and executive control during development.

1.8.1 Dopamine receptor 4 (DRD4) gene

The human dopamine D4 receptor gene located at chromosome 11p15.5 contains a 48-bp variable number of tandem repeats (VNTR) polymorphism located in exon III. In humans, the most common occurrences of the sequence appear as a 2-fold repeat, as a 4-fold repeat or as a 7-fold repeat (Van Tol et al., 1992). At a functional level, presence of the 7 repeat (7r) allele has been related to a decreased expression of D4 receptors (Schoots & Van Tol, 2003). Moreover, D4 receptors encoded by the 7r variation appear to be less sensitive to endogenous DA (Asghari et al., 1995). Given that the D4 receptor is highly expressed in the prefrontal cortex and to a lesser extent in the striatum (Meador-Woodruff et al., 1996), a great amount of research has been conducted in order to discern the influence of the DRD4 gene variations on several aspects of SR such as temperament, cognitive functioning and neural activity.

In the temperament domain, Holmboe and collaborators (2011) found that the 7r allele of the DRD4 is related to higher levels of negative affect in infants between 4 and 9 months (Holmboe, Nemoda, Fearon, Sasvari-Szekely, & Johnson, 2011a). Likewise, the 7r allele has been related to the personality trait of novelty seeking, which is characterized by impulsive behavior and sensation seeking (see Paterson, Sunohara, & Kennedy, 1999 for a review). In the field of cognitive functioning, perhaps one of the most consistent findings there has been, shows that the 7r allele increases the risk for ADHD (Banaschewski, Becker, Scherag, Franke, & Coghill, 2010). However, Gizer & Waldman (2012) reported that in children and adolescents, such association appears to be specific for inattentive symptoms but not for impulsivity symptoms. In the field of typical development, Kegel & Bus (2013) further demonstrated that the 7r allele accounts for individual differences in the performance of executive function tasks including inhibitory control and working memory span. Finally, neuroimaging studies have demonstrated that the 7r allele is related to a diminished activation in the inferior frontal gyrus (IFG) as well as reduced connectivity strength between the IFG and the ACC when typically developing children and adolescents perform a combined stimulus-response incompatibility task (Gilsbach et al., 2012). Furthermore, the 7r allele has been related to an increased activation in the ventral striatum related to reward processing in a sample of adults. According to Gilsbach and collaborators, this association reflects the postsynaptic mediation of D4 receptors, which exert inhibitory effects via second-messenger signaling cascades. Given all this evidence, variants of the DRD4 gene represent a major focus of attention for the study of the development of SR, using executive function and reward processing as intermediate phenotypes.

1.8.2. Catechol-O-methyltransferase (COMT) gene

Studies of DA diffusion in the brain carried out with animal models have shown that the amount of DA transporter protein expressed along the axons of neurons in the prefrontal cortex (PFC) is significantly low and inconveniently distant from synaptic release sites. As a consequence, extracellular diffusion of DA in the PFC is higher compared to other regions in the brain and the mechanism to regulate it appears to rely to a greater extent on the action of catabolic enzymes such as COMT (Chen et al., 2004; Sesack, Hawrylak, Matus, Guido, & Levey, 1998).

A common functional polymorphism of the human gene encoding the COMT enzyme protein is related to a Methionine (Met) for Valine (Val) substitution in exon 4 that alters the amino acid codon at position 158 (Val158Met). The more stable Val allele encodes the enzyme with higher activity, which is associated with less synaptic DA in the PFC (Chen et al., 2004). Given the role of DA-mediated substrates of executive functions in the brain, it was expected that this polymorphism in the COMT gene would be associated to executive attention performance and EAN function. This association has been indeed found in several studies with adults (see Dickinson & Elvevåg, 2009 for a review). Individual homozygous for the Val allele show increased activity in the ACC associated with poorer performance on an attention control task compared with carriers of the Met variation (Blasi et al., 2005). Additional research has also shown signs of greater efficiency in the PFC, as well as the ACC, for carriers of the Met allele when performing attention-related tasks (Heinz & Smolka, 2006).

Studies in typically developing children also provide insights of how genetic polymorphisms that affect the availability of DA in the PFC underlie individual differences on executive attention during development. Diamond, Briand, Fossella,

& Gehlbach (2004) found that variations in the COMT enzyme selectively affect performance on a conflict task that indexes executive control but not other tasks targeting memory processes that may also depend on the function of prefrontal structures. In this study, variations in the COMT gene were associated with differences in performance on an inhibition task in a cumulative mode: children homozygous for the Met allele performed better than those carrying the Met variation in just one of the alleles which in turn performed better than children homozygous for the Val variation of the gene. Recent advances on pharmacogenetic studies have also determined that the high activity Val variation is most frequent among ADHD patients compared to healthy subjects. Interestingly, carriers of this variation appear to show better responses to treatment with methylphenidate, with Val/Val homozygous children also displaying less evidence of severe symptoms than those carrying the Met/Met genotype (Kereszturi et al., 2008).

1.8.3 Dopamine Transporter 1 (DAT1) gene

The DAT1 gene belongs to a family of neurotransmitter transporter genes. The DAT1 is located on chromosome 5p15.3 and encodes a sodium-dependent dopamine transporter (DAT), which terminates the action of DA by reuptaking it into pre-synaptic terminals. A common polymorphism of the gene consists of a variation in the number of tandem repeats (VNTR) at the 3' untranslated region that goes from 3 to 11 copies (David J Vandenberg et al., 1992), being the 9 and 10 repeat the most frequent variations in humans. Studies of the in vivo availability of striatal DA-transporter in humans have found allele-dependent differences in the density of DA transporter. Individuals carrying the 10-repeat

variation show higher DA-transporter availability and thus less synaptic DA than carriers of the 9-repeat (Heinz et al., 2000). Given the role of DAT for modulation of DA neurotransmission within the EAN, variations of this gene are also expected to affect the efficiency of this network.

Using the ANT task, Fossella et al. (2002) found that presence of the 10-repeat allele in adults is associated with larger flanker interference scores, indicating poorer performance of executive attention. Regarding the performance of typically developing children using the child version of the ANT, Rueda, Rothbart, McCandliss, Saccomanno, & Posner (2005), found higher flanker interference scores for homozygous of the 10-repeat variation compared to children carrying the 9-repeat variation in at least one of the alleles. With a large sample (n=110) of children aged 5 to 13 years, Brocki and colleagues (2009) found that 10-repeat homozygotes tend to show higher conflict scores (poorer executive attention efficiency) with age than those who carried the 9-repeat, despite the fact that they showed smaller conflict scores at younger ages (Brocki, Clerkin, Guise, Fan, & Fossella, 2009). The changing pattern with age may be related to changes in sensitivity of the organism to DA in part determined by age-dependent changes in the levels of DAT1 (Volkow et al., 2001). Considering the psychopathology of attention, it has been found that presence of the 10-repeat variation is associated with higher risk of ADHD (Cook et al., 1995). Moreover, ADHD children homozygous for the 10r allele also appear to have smaller volume of the caudate nucleus (Durston et al., 2005).

In summary, genetic variation is shown to influence DA modulation of the EAN and appears to affect its efficiency across development. However, further

research is needed in order to fully understand the neurochemical mechanisms underlying such influence.

1.9 The nurture of Executive Attention development

The relevance of the biological endowment for executive attention and self-regulation reviewed above could wrongly lead to the impression that attention is not susceptible to experience and cannot be enhanced by intervention. Nevertheless, the extraordinarily plastic capacity of the human nervous system, especially during development (see Posner & Rothbart, 2007), greatly contradicts that idea. Much evidence has been provided in the past years in favor on the susceptibility of systems of SR to the influence of experience. One piece of evidence comes from studies showing vulnerability of attention to environmental aspects such as parenting and socioeconomic status (Bornstein & Bradley, 2003). Also, in the past years, an increasing number of studies have shown that a broad range of executive functions, including executive attention, working memory, shifting of attention, and reasoning, can be improved during childhood by means of training or interventions at school. Besides, there is some evidence suggesting that susceptibility to the environment might even be embedded in genetic endowment, since some genetic variations, often under positive selection, appear to make children more susceptible to environmental factors such as parenting (Sheese, Voelker, Rothbart, & Posner, 2007; Voelker, Sheese, Rothbart, & Posner, 2009). Given the focus of the present dissertation, in the following section I discuss much of the evidence available on how educational experiences can shape the development of executive attention and SR.

1.9.1 Education

Together with the increased knowledge about the constitutional factors that help on building individual differences in cognitive control, there is growing interest on investigating whether attention skills can be enhanced by educational interventions. First attempts to develop intervention programs to improve attention and test their influence on cognitive abilities were made in work with patients. For example, Sohlberg, McLaughlin, Pavese, Heidrich, & Posner (2000) used an attention training program (Attention Process Training; ATP) in patients with brain injury and showed specific improvements in executive attention. Also, Kerns, Eso, & Thomson (1999) showed improvement in a number of attention measures in ADHD children after applying an intervention program combining vigilance, selective and executive attention requirements.

To examine susceptibility of the EAN to be fostered by experience in normally developing children, Rueda, et al. (2005) developed a training program suitable for preschool children. The program comprises exercises of different categories depending on the aspect of attention being trained, and each exercise consists of trials organized in increasing levels of difficulty (see Table 1.2). Most of the exercises had 7 levels of difficulty and in order to go from one level to the next the child must complete a minimum of correctly responded trials in a row (3, in most exercises).

Using this training program, the efficacy of a very brief five-days of intervention was tested in several experiments with groups of 4 and 6-year-old children. The children were brought to the laboratory for seven days for sessions lasting about 45 minutes. Half of the children were trained using the program, while the other half were assigned to a non-trained control group. Children in the

control group were watching cartoons videos, which required occasional responses to keep the movie moving forward, for the same number of sessions as the trained group. All sessions were conducted over a two-to-three weeks period. The first and last days were used to assess the effects of the training by means of children's performance on a child-friendly flanker task, and a general test of intelligence.

Category	Exercise	Trained process	Brief Description
1	Side	Target tracking	Navigating a cartoon cat to reach areas of grass and avoid muddy areas, which get progressively bigger
	Chase	Target tracking and anticipation	Anticipating where a cartoon duck that swims across a pond in a straight line will come across in order to chasing it. In the highest levels of difficulty, the duck dives so that its trajectory remains invisible.
	Maze	Anticipation	Navigating a cartoon cat through a maze to get food.
2	Portraits	Focusing attention, perceptual discrimination and working memory	Matching-to-sample exercise with cartoon pictures. Requires clicking on the one of two pictures that looks exactly the same as the sample picture. In higher levels, the sample picture disappears before the two choices appear on the screen and the child is to keep in mind the attributes of the sample picture.
3	Numbers	Conflict monitoring and resolution	Two sets of numbers are presented and children have to click in the group composed by the larger amount of items. Trials can be congruent (larger group made up of numbers of higher value) or incongruent (larger group made up of numbers of lower value)
4	Farmer	Inhibitory control	Cartoons animals (either sheep or wolfs) appear behind a bale of hay and children are asked to quickly click only to sheep in order to bring them inside a fence.

Table 1.2. Description of the exercises included in the training program.
Developed by Rueda et al. (2005)

Results revealed greater improvement in fluid intelligence in the trained groups compared to children in the control groups (Rueda et al., 2005). Also, the effect of training on brain function was characterized with ERPs. Training produced a pattern of brain activation that was more adult-like compared to the untrained group. Brain activation was registered while children performed a child-friendly flanker task, and changes in the brain reaction to conflict was characterized in two dimensions: 1) timing of the conflict effect, which showed a shorter latency after training, and 2) topography of the conflict effect, which moved to posterior leads in the frontal midline with training. In adults, the conflict-related N2 effect has a mid fronto-parietal distribution, which has been associated with a source of activation in the ACC (Van Veen & Carter, 2002). Reduction of the latency and duration of the conflict effect is a sign of increased efficiency of the underlying brain system, as similar changes happen with maturation (Jonkman, 2006; Rueda et al., 2004; Ridderinkhof & Molen, 1995). Altogether, training studies suggest that the efficiency of the EAN can be enhanced through educational intervention and that other cognitive skills, such as fluid intelligence and regulation of motivation, may also benefit from this type of intervention.

Consistent with our results, other studies have shown beneficial effects of cognitive training on attention and other forms of executive functions during development. For instance, auditory selective attention was improved by training with a computerized program designed to promote oral language skills in both language-impaired and typically developing children (Stevens, Fanning, Coch, Sanders, & Neville, 2008). Klingberg and colleagues have shown that training can enhance working memory and that the intervention shows some degree of transfer to aspects of attention (Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg,

2009). This group has also shown evidence that training produce changes at various levels of brain function, such as activation (Olesen, Westerberg, & Klingberg, 2004a), and in the density of dopamine receptors (McNab et al., 2009) of areas of the cerebral cortex involved in the trained function.

There is also some evidence that curricular interventions carried out in the classroom can lead to improvements in children's cognitive control. Diamond et al. (2007) tested the influence of a specific curriculum on preschoolers' control abilities, and found beneficial effects as measured by various conflict tasks (Diamond, Barnett, Thomas, & Munro, 2007a). A somewhat indirect but probably not less beneficial form of fostering attention in school could be provided by multi-lingual education. There is growing evidence indicating that bilingual individuals perform better on executive attention tasks than monolinguals (Bialystok, 1999). The idea is that using multiple languages on a regular basis might train executive attention because of the need to suppress one language while using the other. It has been shown that growing in a bilingual context leads to advantages in executive attention in young children, an effect that appears to transcend that of culture (Yang, Yang, & Lust, 2011).

Although all this evidence shows promising results about the effectiveness of interventions and particular educational methods to promote attention control, questions on various aspects of training remain to be answered. Further research is needed to examine whether more extended and systematic interventions would lead to sustained changes in attention skills and other abilities that are thought to rely on attention control, and whether benefits would extend to academic competence. Additionally, it will be important to address questions such as whether genetic variation and other constitutionally based variables influence the

extent to which the executive attention network can be modified by experience, and whether there are limits to the ages at which training can be effective.

1.10 Genes x Experience interactions

The development of a complex cognitive system such as executive attention is unlikely explained by the influence of a single factor such as education, temperament or genetic variation. Most likely all these factors interact in many ways to determine the efficiency with which an individual develop his cognitive capacities. In consonance with this remark, it has been suggested that proficiency of children at resolving conflict or inhibiting automatic responses is better explained by the interaction between genetic and environmental factors (Belsky, Bakermans-kranenburg, & Van Ijzendoorn, 2007). Kochanska and colleagues recently provided an example of the Genes x Experience interaction on the development of executive attention. In a study with children as young as 25, 38 and 52 months of age, Kochanska, Philibert, & Barry (2009) found that variation of the serotonin transporter (5HTT_{PR}) gene interact with early mother-child attachment in predicting later development of regulatory skills. Among children who carried the short variation of the gene, associated with risk for poor regulatory control, only those who were insecurely attached developed poor regulatory abilities. The serotonin transporter gene is related to functional and structural differences in brain areas that are part of the EAN (Canli et al., 2005) and the short allele has been linked to diminished dopamine re-uptake compared with children homozygous for the long allele.

Among DA-related genes, variations on the DRD4 gene have been shown to moderate the association between environmental factors such as parenting style

and behavioral outcomes. For instance, it has been reported that carriers of the 7-repeat variation in at least one allele show to be more susceptible to adverse conditions during early life (Bakermans-Kranenburg & van Ijzendoorn, 2006). Also, it has been found that the 7-repeat allele of the DRD4 gene interacts with the quality of parenting to influence such temperamental variables in the child as activity level, sensation seeking and impulsivity (Sheese et al., 2007). More recently, a similar gene x parenting interaction has been observed with the COMT gene for 2-year-old children's performance of a visual sequence task thought to involve attention (Voelker et al., 2009).

Chapter 2

Research Questions, Goals and Hypothesis

A great deal of research within the field of developmental psychology have pointed to the crucial role of Self Regulation (SR) on the emotional, social, and academic/professional adjustment of individuals not only during childhood and adolescence but also later in life. During the past decades, with the advent of modern neuroimaging techniques and the sequencing of the whole human genome, scientist in the field have been able to broaden the knowledge concerning the development of SR as well as the neural and molecular mechanisms that underlie it. Within this field of study, SR has been conceived as an array of cognitive control mechanisms that are supported by the interaction of specific brain networks and neuromodulators, allowing individuals to modulate reactivity in a goal-directed way. During the past decades, researchers in the field have reported that environmental (educational) and constitutional (genetic) factors as well as their interaction can explain at least in part individual differences in the ability to voluntarily modulate cognition, behavior and emotions. Inspired by the work of our predecessors, we conducted a series of experiments that aimed to answer key questions regarding the influence of each of those factors on the development of children's self-regulatory skills during preschool period. In this chapter, I present a description of the research questions that motivated our studies, their goals and hypothesis as well as the methodology implemented.

2.1 Study I: Enhanced efficiency of the executive attention network after training in preschool children: Immediate and after two months effects

Research Question I: *Does attention control training improve the efficiency of the executive attention network at the level of behavior and brain function?*

Research Question II: *Do attention control training effects in preschoolers show stable and lasting effects?*

Research Question III: *Do training effects transfer to untrained abilities related to the regulation of affect and intellectual functioning?*

The past decade has seen an increasing amount of research that aimed to prove the beneficial effects of cognitive training programs in children and adults (Jolles & Crone, 2012). However, results have been contradictory and the mechanisms that underlie cognitive improvement are still not well understood (Owen et al., 2010). With this motivation in mind, we extended a computer-based training program that was originally designed by Rueda, et al. (2005). The program implemented in this study consisted on a total of 11 child-friendly exercises (three of which were new tasks designed in our lab) that were carried out over the period of five weeks. The training exercises were divided in 5 categories: tracking/anticipatory; attention focusing/discrimination; conflict resolution; inhibitory control and sustained attention. All children in the trained and control groups underwent three assessment sessions: one prior to the intervention (PRE), one after the training (or control) sessions were completed (POST1), and one follow-up session (POST2) that was conducted two months after completion of session POST1. The battery of tasks implemented in the assessment sessions included: delay of gratification task, children gambling task, general intelligence test (KBIT-2) and a computer-based flanker task (Child-ANT). In order to assess training effects at the level of brain function, electrophysiological measures from the scalp were also recorded while children performed the Child-ANT task, using a high-density array of 128 Ag/AgCl electrodes.

The main goal of this study was to examine whether training of executive attention functions in preschoolers improves efficiency of the executive attention network (as measured with the Child-ANT) at the behavioral and brain activity level. At the behavioral level, we hypothesized that after training children would show a reduction in the conflict scores (incongruent vs. congruent), which would reflect an increased ability to focus attention while ignoring irrelevant information. At the brain level, our hypothesis were based on the results previously reported by Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, (2002) and Jonkman, (2006) regarding the neural substrates of an efficient executive attention system. We hypothesized that the effects of executive attention training would lead to a more mature pattern of activation within the executive attention network, which would be characterized by a short latency, amplitude and duration of the brain reaction to conflict as well as a more focalized frontal activation.

Our second main goal was to examine the stability of the training effects in preschoolers. For this purpose we included a follow-up session two months after the POST- assessment session was completed. Here, we did not have specific hypothesis.

Finally, we included measures of affective regulation and intelligence in order to test if training effects would transfer to untrained abilities. In this regard, we hypothesized that the increased efficiency of the executive attention network after training would also be reflected in children's ability to exert effortful regulation of their reactivity in motivationally significant contexts. This hypothesis is based on the results of a number of neuroimaging studies that point to the role of the anterior cingulate cortex, a major node of the executive attention network, in the processing of cognitive control and affect (Bush, Luu, & Posner, 2000). In the

same way, given the overlapping activation between areas of the executive attention network and those that support general intelligence (Duncan et al., 2000), we expected that the training effect would also strengthen children's intellectual functioning.

2.2 Study II: Influence of the SLC6A3-DAT1 gene on multifaceted measures of self-regulation in preschool children

Research Question I: *Do variations of the SLC6A3-DAT1 gene, known to affect the efficiency of the striatal dopaminergic system, explain individual differences of preschoolers' self-regulatory skills?*

Dopamine transporters (DAT) are the main mechanism for the modulation of extracellular dopamine levels in the striatum and a key mechanism with regard to the efficiency of the dopaminergic pathways that connect subcortical structures with areas of the prefrontal cortex (Giros, Jaber, Jones, Wightman, & Caron, 1996). In humans, the SLC6A3-DAT1 gene carries out the synthesis of the DAT protein (Vandenbergh et al., 1992). A large number of association studies have found a relation between variants of the DAT1 gene and ADHD, which has pointed to the functional role of the DAT1 gene concerning the efficiency of the brain areas that support executive attention processes. However, the evidence for this relationship is inconclusive. Most studies in the field have only used decontextualized tasks to measure the cognitive mechanisms that underlie a self-regulated behavior. Therefore, in this study we aimed to evaluate the influence of DAT1 variations on children's capacity to implement those mechanisms in contexts that impose particular demands of regulatory control such as the school or at home. To answer this question, we selected an array of multifaceted measures that were designed to

assess children's self-regulatory skills from different perspectives. These measures included: teacher-reported schooling skills, parent-reported effortful control and emotion regulation as well children's performance on the delay of gratification task, working memory, Go-NoGo, flanker task and general intelligence. Given that these measures constitute different levels of analysis of the construct of SR, we expected adults-reported measures of SR to be related to one another and to show a positive correlation with children's performance on the battery of cognitive tasks. With regard to the role of the DAT1 gene on children's SR, we expected that children carrying at least one copy of the 10r allele would exhibit poorer self-regulatory skills compared with children homozygous for the 9r allele. This hypothesis is based on previous evidence in the field which show that: 1) the corticostriatal circuit that connect the striatum with structures of the EAN is implicated in the regulation of reactivity. 2) Dopamine transporters (DAT) are the main mechanisms for the regulation of dopamine levels in the basal ganglia, particularly in the striatum (Ciliax et al., 1999). 3) The 10r allele of the DAT1 gene has been associated to a decreased expression of DAT, particularly in the striatum (Hersch, Yi, Heilman, Edwards, & Levey, 1997a).

2.3 Study III: Genetic modulation of cognitive gains following executive attention training in children

Research Question I: Does the genetic endowment of children modulate the effects of a cognitive training program?

Professionals in the area of education and clinical psychology have long known that the efficiency of educational strategies greatly varies from one child to the next one. Over the past decades, a considerable amount of literature has been

focused on how temperamental differences contribute to the susceptibility of children to both adverse and positive rearing environments during childhood (see Belsky et al., 2007 for a review). In recent years, researchers in the field have suggested that genetic variations may provide the biological basis for such susceptibility. Therefore, in this last study we aimed to examine if genetic variations associated to the efficiency of the dopaminergic system in the brain modulate individual differences in the extent to which children can benefit from an executive attention training program. A total of 107 typically developing children from different schools in the urban area of Granada participated in the study. Three genes known to affect the amount of dopamine availability in the brain DA (i.e., DAT1, DRD4, and COMT) were included in the study. Measures of general intelligence, inhibitory control and working memory were implemented before and after the training program was completed in order to examine the training effects. Based on previous evidence, we hypothesized that carriers of the 7r allele of the DRD4 gene and the 9r allele of the DAT1 gene, would exhibit greater susceptibility to training. Regarding variations of the COMT haplotype, we did not have a clear hypothesis. However, given that the MPS haplotype has been associated to higher DA availability in areas of the brain that support the cognitive processes, we speculated that carriers of this variation would show larger gains after training.

Chapter 3

Enhanced efficiency of the executive attention network after training in preschool children: Immediate and after two months effects

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3.2 Introduction

One of the major changes that takes place over the course of human development occurs in the domain of executive control. With age, children go from external regulation of their behavior, often provided by caregivers and/or changes in stimulation, to an increased ability to self-regulate emotions and actions. Mechanisms of attention have been implicated in action-regulation from early theoretical models (James, 1890; Norman & Shallice, 1986). According to Posner's neurocognitive model, attention is related to the function of three brain networks involved in 1) reaching and/or maintaining the alerting state, 2) orienting attention and selecting the source of stimulation, and 3) regulating thoughts, emotions and action. The third function is carried out by the so-called executive attention network, which involves the anterior cingulate cortex (ACC) and prefrontal regions of the brain (Posner & Petersen, 1990; Posner, Rueda, et al., 2007). Functions associated with the executive attention network overlap to some extent with the more general domain of executive functions (EFs), which encompass a set of interrelated processes involved in planning and carrying out goal-directed actions, including working memory (WM), mental-set switching or attentional flexibility, inhibitory control, and conflict monitoring (Blair & Ursache, 2011; Welch, 2001; Welsh & Pennington, 1988). These cognitive abilities are required when it is necessary to hold information in mind, manage and integrate information and resolve conflict between sources of stimulation or response options.

Developmental studies have suggested that the three attention networks considered in Posner's model follow different maturational courses (Rueda et al.,

2004a; Rueda & Posner, 2013). The alerting and orienting networks appear to mature largely during infancy and early childhood, although both networks continue developing up to late childhood, showing improvements in the endogenous control of processes related to preparation and selectivity. The executive attention network appears to undergo a more progressive maturation, emerging at about the end of the first year of life and continuing during childhood into adolescence. However, despite the progressive improvement throughout childhood, executive attention shows a major period of development from about the end of the first year of life up to about 7 years of age (Rueda et al., 2004a; Rueda, Posner, & Rothbart, 2005). Maturation of this function is likely related to structural changes in brain areas that are part of the executive attention network and their connectivity patterns with other brain structures, in particular, the emergence of greater fronto-parietal functional connectivity over development (Power, Fair, Schlaggar, & Petersen, 2010).

A widely used strategy to study executive attention in cognitive research is to utilize conflict tasks (Posner & DiGirolamo, 1998). These involve suppressing either processing or responding to information that elicits an incorrect or inappropriate response. One of these is the flanker task (Eriksen & Eriksen, 1974). In this task, a target stimulus is surrounded by stimulation that suggests either the same (congruent) or a different (incongruent) response than the one associated to the target. Suppressing the processing of the distracting information in the incongruent condition requires attentional control and activates the executive attention network to a greater extent than when there is no conflict between target and flankers (Fan et al., 2003).

The ability to regulate behavior in a flexible and controlled mode has proven to be central to many aspects of children development. Individual differences in efficiency of executive attention appear to play an important role in school competence and socialization (Checa et al., 2008; Nancy Eisenberg et al., 2011, 2010; Rueda et al., 2010). Several studies have shown that children with greater executive attention efficiency (i.e. smaller conflict scores) show higher levels of competence at school, understanding competence as a combination of school achievement and adequate socio-emotional adjustment in the classroom (Blair & Razza, 2007; Bull & Scerif, 2001; Checa et al., 2008; Rueda et al., 2010). Recently, we have shown that the brain reaction to conflict, as measured with event-related potentials, also predict children's grades in math above and beyond general intelligence (Checa & Rueda, 2011). Moreover, higher level of attentional and effortful control helps on the prevention of developing psychopathologies, such as externalizing behavioral problems and ADHD (Nancy Eisenberg et al., 2005; Rothbart & Posner, 2006). All these data show the prospect for a potential benefit of promoting children's attention regulation skills through educational interventions.

In recent years, several studies have reported positive effects of training different aspects of attention in children. Most of the studies have used computer-based tasks or sets of exercises targeting particular abilities. Kerns, Eso, & Thomson (1999) showed improvement in a number of attention measures in ADHD children after applying an intervention program combining vigilance, selective and executive attention requirements. Also, normally developing preschool children have been shown to benefit from a training program targeting executive attention (Rueda, Rothbart, et al., 2005). Other studies have also shown

improvements in attentional flexibility after task-switching training in both children and adults (Karbach & Kray, 2009; Minear & Shah, 2008). Besides, an increasing number of studies have examined susceptibility of other EFs components to be enhanced by training. Training of WM has proven to have beneficial effects on WM abilities in normally developing children (Thorell et al., 2009), children with ADHD (Klingberg et al., 2005), and adults (Jaeggi, Buschkuhl, Jonides, & Perrig, 2008).

Interestingly, most of the studies described above have also reported transfer effects of training to fluid intelligence. For instance, gains in reasoning skills have been found after training of WM (Jaeggi et al., 2008; Klingberg et al., 2005), task-switching (Karbach & Kray, 2009), and executive attention (Rueda, et al., 2005). This evidence speaks against the idea of fluid intelligence as a fixed trait (Horn & Cattell, 1966). Instead, it suggests that fluid intelligence skills can be changed, although it could be the case that reasoning skills are less subject to education than crystallized intelligence. Transfer to intelligence after training of executive functions is relatively unsurprising given the interrelated nature of EFs processes and the fact that many common regions of the frontal lobe are recruited by cognitive demands involved in general intelligence and the various processes under the umbrella of EFs (Duncan & Owen, 2000; Duncan et al., 2000).

Several studies have also examined the effect of training on brain function. Information on the neural effects of attention training mostly comes from research using rehabilitation programs with patients. Sustained attention training with neglect patients was found to produce increased activation in the superior parietal cortex, right and left frontal areas and ACC, areas known to be associated with all

three attention networks (Sturm, Thimm, Küst, Karbe, & Fink, 2006; Thimm, Fink, Küst, Karbe, & Sturm, 2006). Evidence is also available for other EFs components. For instance, using fMRI, Olesen, Westerberg, & Klingberg (2004) reported increased activation in areas involved in WM processing (i.e. the superior and inferior parietal cortices as well as in the middle frontal gyrus) after WM training in adults. Moreover, changes in brain mechanisms affecting dopamine neurotransmission have also been reported after WM training in normal adults (McNab et al., 2009).

More limited evidence is available on the effect that EFs training produces in children's brain function. In a study carried by our group (Rueda et al., 2005), the effect of training attention was characterized with event-related potentials. We found that 5 sessions of attention training in preschool children produced a pattern of brain activation that was more adult-like compared to the untrained group. Brain activation was registered while children performed a child-friendly flanker task, and changes in the brain reaction to conflict was characterized in two dimensions: 1) timing of the conflict effect, which showed a shorter latency after training, and 2) topography of the conflict effect, which moved to posterior leads in the frontal midline with training, the distribution that the flanker conflict effect shows in adults and that has been associated with a source of activation in the ACC (Van Veen & Carter, 2002). Also, using ERPs with a selective attention paradigm, Stevens, Fanning, Coch, Sanders, & Neville, (2008) reported an increased differentiation between attended and unattended processing in the brain signal (i.e. greater ability to filter-out irrelevant information) of children who underwent an intensive training program designed to improve language skills.

The aim of the present study was to further examine the effect of training attention on brain function in a group of preschool-aged children. Training focused on executive attention, although also included exercises targeting sustained and selective attention. To examine brain function, a high-density electroencephalogram system was used while children performed a flanker task before and after training. Moreover, in order to study durability of the training effect, a short-range follow-up session was carried out two months after completion of the training program. Finally, we were interested on examining possible transfer effects to untrained abilities that have been related to individual differences on executive attention efficiency. In particular, we assessed children's performance on tasks involving regulation of affect and intelligence in all sessions (PRE, POST1 and POST2).

Training was expected to result in increased executive attention efficiency both in performance of the conflict task and the underpinning brain activation. In terms of brain activation, increases in efficiency due to maturation appear to result in a reduction of the latency and duration of the conflict effect (Jonkman, 2006; Ridderinkhof & Molen, 1995). Also, prior imaging studies have shown that brain activations related to executive control become more focused and refined with maturation (Bunge et al., 2002; Casey et al., 1997). Therefore we expected that training would result in shortening the latency, amplitude and duration of the brain reaction to conflict. Besides, we predicted that the source of activations related to the ERPs effects would also show more focused frontal activation after training.

Given previous evidence on the transfer of training EFs abilities to reasoning, we also expected our training to increase fluid intelligence. Finally, we hypothesized that increasing executive attention efficiency would generalize to tasks requiring regulation of responses involving rejection of immediate rewards in exchange for delayed but more favorable consequences. This hypothesis was based on evidence coming from both developmental and imaging studies. Developmental studies have pointed to the idea that children who show better attention control (i.e. smaller conflict interference in the flanker task) appear to be more able to regulate affect (Simonds, Kieras, Rueda, & Rothbart, 2007). In addition, imaging studies have provided evidence for a role of the ACC, a major node of the executive attention network, in the regulation of affect (Bush, Luu, & Posner, 2000; Ochsner & Gross, 2007; Ochsner, Bunge, Gross, & Gabrieli, 2002).

3.3 Method

3.3.1. Participants and procedures

A total of 37 children (20 males; mean age: 64.7 months; SD: 3.2) recruited at an urban Primary School in Granada (Spain) participated in the study. Caregivers of all the children gave written consent to be involved in the study after being informed of its general purpose. All participants were Caucasian/European and had a similar social background. Prerequisites for participation were having normal or corrected-to-normal sensory capacities and no history of chronic illness and/or psychopathologies.

All participants carried out a first assessment session (PRE) at the Cognitive Neuroscience Lab of the Psychology Dept., University of Granada. During this

session children were administered a set of pen and paper tasks including the Delay of Gratification and Children Gambling tasks and the Kaufman Brief Intelligence Test (K-BIT). After conclusion of these tasks, children were fitted with the 128-channels Geodesic Sensor Net (www.egi.com) and were asked to perform the child version of the Attention Network Task (ANT) while EEG was recorded. The duration of the session was 1 hour approximately, including time for instructions and breaks between tasks. During this session, parents were also asked to fill out a temperament questionnaire.

After completion of the first session, children were pseudo-randomly assigned to either the experimental (to-be-trained) or the control (untrained) group. The assignment was made so children in each group would be matched by gender, average intelligence and flanker interference in the ANT. A total of 19 children (10 males; mean age: 65.1; SD: 3.73) were assigned to the experimental group, and 18 (10 males; mean age: 64.3; SD: 2.56) to the control group. Participants in the two groups did not differ in age ($F > 1$) or parental educational level, and they all attended the same school. Also, there were not significant differences (all $t < 1$; except $t(35) = 1.7$; $p = .09$ for orienting and $t(35) = -1.12$; $p = .26$ overall commission errors) between the groups in the scores of the assessment tasks obtained in the PRE session.

Children in the trained group went through intervention with a set of computerized exercises for a total of ten 45-minute sessions that were carried out over a period of 5 weeks (2 sessions per week). Those sessions were conducted individually for each participant in a quiet room at the school. Participants assigned to the control group underwent the same number of sessions in similar

conditions (individually with the experimenter and in a quiet room at school) but watched cartoon videos instead.

Once the intervention period was completed, children in both groups were invited to the lab in two more occasions. The first post-intervention (POST1) session was carried out within a period of one week after completion of the intervention. The second post-intervention (POST2) session was conducted two months after completion of the POST1 session. The tasks completed in these sessions and the procedure followed was identical to that of the PRE session.

3.3.2 Materials

Assessment Tasks

Delay of Gratification (DoG). The DoG task administered in this study was a modified version of the task designed by Thompson, Barresi, & Moore (1997). Children were instructed to choose between getting a prize immediately or waiting until the end of the task in order to a) get two prizes instead of one (DoG_{self}), or b) have someone else (the experimenter) get a prize too (DoG_{other}). Three different types of reward were used: stickers, 5-cents of euro coins, and candies. An example of a DoG_{self} trial is "You can choose between having one sticker right now or getting two of them when we finish the game". An example of the DoG_{other} trial is "You can choose between having one coin for you right now or having one for you and one for me at the end of the game". Two practice trials were used to explain the task. Experimental trials began only when it was clear that the child understood the instructions. Then, each participant completed 12 trials, 6 of each condition (DoG_{self} / DoG_{other}), four with each type of reward. The immediate-choice was presented in the first part of the statement in half of the trials and the delay-choice

was presented first in the other half. The experimenter provided no feedback other than supplying the rewards immediately or putting them in an envelope that the child would get at completion of the task, depending on the child's choice. Percentage of delay choices in each condition was the dependent measure in this task.

Children Gambling Task. The gambling task administered in this study was a simplified version of the Iowa Gambling Task by Kerr and Zelazo (2004). Children had to pick one card at a time from one of two sets of cards in order to win candies. Each card could have smiling and sad faces printed on it. Children were told and shown that happy faces on the cards indicate the number of candies won, whereas sad faces indicate the number of candies lost. One of the sets provided a constant reward of one smiling face and either no sad faces or only one (Advantageous Set; ADV), consisting of a low-immediate-reward/low-win rate in the long run. The other set (Disadvantageous Set; DIS) provided a constant reward of two smiling faces and could have either zero, two, four or six sad faces, consisting of a high-immediate-reward/high-lost rate in the long run. The two sets of cards were placed in front of the child facing down so the child would have to figure the contingencies of each deck out progressively. In the beginning of the task, children were given a stake of 10 candies in order to start playing. There were 4 demonstration trials in which the experimenter sampled two cards from each deck. When a card was turned over, only the happy faces were visible while the sad faces were covered with a note. After the number of won candies was revealed to the child and the candies were supplied, the note was removed revealing the number of candies lost. Rewards were deposited into, and removed from (according to the number of happy and sad faces obtained in each trial), a

transparent container situated in front of the child at an equal distance from each of the two decks. A total of 50 trials were administered. The dependent variable was the number of picks from the ADV set minus the number of picks from the DIS set made in the last 40 trials. The location of the two decks and the design at the back of the decks were counterbalanced across participants.

K-BIT. The Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990) was used to measure general intelligence. The test provides a measure of crystallized (Verbal) intelligence and a measure of fluid reasoning (Matrices) as well as a composite intelligence (IQ) score. Administration of the test takes approximately 15 minutes with children aged 4 to 5 years.

Child ANT. We used the children version of the ANT task (Rueda et al., 2004a) to measure attention. In each trial of this task a row of five fish appearing either above or below a fixation point is presented. Children are told to press either the right or the left key on a panel depending on the direction in which the fish in the middle is pointing while ignoring the flanker fish, which point in either the same (congruent) or opposite (incongruent) direction as to the middle fish. Before the fish appear, visual signals are presented that inform either about the upcoming of the target (alerting cue) only or about the upcoming of the target as well as its location (orienting cue). Completion of the task allows calculation of three scores related to the efficiency of the attention networks by means of measuring how response times are influenced by alerting cues, orienting cues and congruency of the flankers. The alerting score is obtained by subtracting mean (or median) RT of trials with alerting signal from that of trials with no cue. The orienting score is obtained by subtracting RT from trials with orienting cue from

trials in which the visual cue was presented at the location of the fixation point. Finally, the executive attention score is calculated by subtracting RT from trials with congruent flankers from that of trials with incongruent flankers. This is considered an index of the interference experienced by the participant when incongruous information is presented in the display along with the target. Larger interference scores indicate less efficiency of executive attention.

3.3.3 EEG Recording and Data Processing.

EEG was recorded using a high-density array of 128 Ag/AgCl electrodes arranged into a net (Geodesic Sensor Net, EGI Inc., Eugene, OR) while children performed the Child ANT during the pre- and post-training evaluation sessions. All 37 participants agreed to wear the sensor net. Impedances for each channel remained at or below 80 k Ω during testing. During acquisition, EEG recording was vertex-referenced and the signal was digitalized at 250 Hz. A time constant value of 0.01 Hz was used. Off-line data were filtered using a 0.3 to 12 Hz finite impulse response (FIR) band-pass filter and segmented into 200 ms pre-target and 1200 ms post-target epochs. Segmented files were scanned for eye and/or movement artifacts. One child (belonging to the control group) who had less than 12 clean segments per congruency condition was excluded from further processing. Segments were averaged across congruency conditions and re-referenced to the averaged (across channels) activation.

3.3.4 Training Program

The training program was the same as the one used by Rueda, Posner, et al., (2005; also described in Rueda, Rothbart, Saccomanno, & Posner, 2007). The

program consists of several computerized exercises divided in 4 categories: 1) Tracking/Anticipatory; 2) Attention Focusing/Discrimination; 3) Conflict Resolution; and 4) Inhibitory Control Exercises. In the current study the program was extended with three more exercises, one in the category of Attention Focusing/Discrimination, one in the Conflict Resolution category and another in a new category of Sustained Attention. Therefore, the new program consisted of a total of 11 exercises divided in 5 general categories. The exercises were programmed to be child-friendly and involved playing with a joystick or a mouse. All exercises required completion of a number of trials organized in increasing levels of difficulty. Most of the exercises had 7 levels of difficulty and in order to go from one level to the next the child must complete a minimum of correctly responded trials in a row (3, in most exercises).

Exercises in the Tracking/Anticipation category were designed to teach the children to track a cartoon cat on the computer screen by using the mouse, and monitor the position of other cartoons in the screen. In the *Side* exercise the child is asked to take the cat to the grass while avoiding going into the mud. As the child achieves higher levels, the mud area gets progressively bigger and the grass area gets smaller, increasing the difficulty to control the movement of the cat. In the *Maze* exercise, children help the cat to get food by navigating it through a maze to where the food is. Finally, in the *Chase* exercise children must anticipate the location where a duck that swims across a pond in a straight line will come across in order to chasing it. In a second version of the exercise (*Chase Invisible*), the duck becomes invisible when it goes into the pond, as if diving, so that its trajectory remains invisible.

The exercises in the Focusing/Discrimination category are of two types. The first type consists on matching-to-sample games, in which children have to click on the one of two pictures that looked exactly the same as a sample picture. Similarities between the two options increased progressively, requiring the child to pay closer attention. There are two versions of the exercise. In this first version (*Portraits*), the sample picture remains on the screen while the child selects the matching item. In the second version (*Portraits Delay*), the sample picture disappears forcing the child to keep in mind the attributes of the sample picture. The second type of exercise (*Shapes*) consists of the presentation of a number of overlapping figures and the child is to determine which are the ones presented by clicking on the appropriate buttons displayed on the sides of the screen. Difficulty is augmented in successive levels by increasing the number of overlapping shapes and the complexity of the patterns.

The Conflict exercises consisted on Stroop-like games with numbers. In the first one (*Number of Numbers*), children are presented with two sets of items. Their job is to click in the group composed by the larger amount of items. In the firsts levels of the exercise, sets consist of pictures of fruits and the number of items in each group differs by a large amount (e.g., two compared to eight). As the difficulty levels increase, the two sets are made of digits, and therefore trials can be congruent (when the larger set of digits is formed by digits of higher value, for example four numbers 8 vs. two numbers 1) or incongruent (when the larger set of digits is formed by digits of smaller value, for example six numbers 2 vs. four numbers 9). The second Stroop-like exercise (*Value-Not-Size*) also involves numbers, but in this case the conflicting dimensions are value and size. In successive trials, various numbers (either two, three or four), which differ in size,

are presented and children are asked to click on the number of higher value disregarding the size. Again, there can be congruent (the larger number is the one with higher value) or incongruent (the larger number is not the one with higher value) trials. To go on from one difficulty level to the next children must correctly perform three incongruent trials in a row. Before performing these exercises, children completed another exercise in which their knowledge of Arabic digits was practiced.

The exercise (*Farmer*) included in the Inhibitory Control category consist in a Go/No-Go game in which the child's job is to help a farmer taking sheep inside a fence. The picture of a bale of hay is displayed in the middle of the computer screen. Children click on the bale of hay to find out whether the animal behind it is a sheep or a wolf. If the animal is a sheep the child is to click as quick as possible to make it go inside the fence, whereas the response must be hold to the wolf. In advanced levels, the wolf dresses-up as a sheep and only after a short interval it losses its mask and reveals its identity, making the response inhibition more challenging.

Finally, a category of Sustained Attention was included. This consists of one exercise (*Frog*) in which children are asked to help a frog catch flies that come out of a bottle at a particular time rate. The child must press a key as fast as possible in order to unroll the frog's tongue and catch the fly. In some trials, the fly makes a noise before coming out of the bottle. The requirement to sustain attention is increased across blocks of trials by enlarging the interval of time between flies.

3.4 Results

3.4.1 Effects on behavioral measures

To assess the effect of training on the various behavioral tasks included in the study we conducted a set of repeated measures ANOVAs with Session (PRE, POST1 and POST2) and Group (Untrained vs. Trained) as factors and each of the tasks scores as dependent measure. Then, changes in the PRE vs. POST sessions (PRE vs. POST1 and PRE vs. POST2) scores were examined with planned comparisons given that changes were predicted after intervention. For the measures that showed significant differences between groups at PRE test (i.e. orienting scores and % of commission errors in the ANT), pre scores were included as covariates in the ANOVAs. Results on the Group x Session interaction and planned contrast for each measure and group are summarized in Table 3.1.

Child ANT. Attention network scores for Alerting, Orienting and Executive Attention were obtained. Also, general performance indexes such as overall RT and percentage of commission and omission errors were examined. Alerting scores were calculated by subtracting median RT to Double-Cue trials from median RT to No-Cue trials. The Orienting score was calculated by subtracting median RT in Spatial-Cue trials from median RT in Central-Cue trials. Finally, Executive Attention scores (flanker interference effect) were calculated by subtracting median RT for congruent trials from median RT for incongruent trials for each participant and session (see Table 3.1).

ANOVAs contrasting sessions PRE and POST1 revealed a significant main effect of Session for overall RT ($F(1,35)= 13.34; p<.001$) and for overall percentage of commission errors ($F(1,35)= 4.97; p<.05$). Planned contrasts showed a

reduction in overall RT for both trained ($F(1,35)= 9.9$; $p<.001$) and control ($F(1,35)= 4.1$; $p<.05$) groups at POST1 compared to PRE. Also, we found a reduction between session PRE and POST1 in overall commission errors for the control group ($F(1,35)= 4.17$; $p<.05$) which was not present for the trained group ($F(1,35)= 1.2$; $p=.27$). No other contrast showed significant results.

The PRE vs. POST2 ANOVAs revealed a significant main effect of Session for overall RT ($F(1,35)= 67$; $p<.001$), overall percentage of commission errors ($F(1,35)= 10.68$; $p<.01$), and alerting scores ($F(1,35)= 5.9$; $p<.05$). No significant Group x Session interactions were obtained for any of the scores. However, contrasts showed significant reductions at POST2 compared to PRE for overall RT for both trained ($F(1,35)= 33.5$; $p<.001$) and untrained ($F(1,35)= 33.5$; $p<.001$) children. Also, the reduction in overall commission errors at session POST2 was significant for the control group ($F(1,35)= 8.3$; $p<.01$) and marginal for the trained group ($F(1,35)= 2.94$; $p=.09$). Finally, a marginal increase in alerting was observed for the trained group ($F(1,35)= 3.4$; $p=.07$).

TASK	DV	GROUP	PRE	POST 1	POST 2	Group x Session Interaction F value	Planned Contrasts	
			Mean (SD)	Mean (SD)	Mean (SD)		Pre vs. Post1	Pre vs. Post2
IQ	Matrices	Trained	104 (9.6)	110 (10.45)	109 (11.6)	<1	4.9*	2.8#
		Control	107 (10.6)	112 (12.47)	107 (10.8)		2.5 ^{ns}	<1
	Vocabulary	Trained	110 (10.8)	110 (12.9)	110 (10.7)	<1	<1	<1
		Control	107 (10.2)	108.5 (11.1)	106 (11.6)		<1	<1

Gambling	V-D last 40 trials	Trained	6.9 (20.2)	12.7 (18.2)	16 (18.9)	<1	<1	4.2*
		Control	5.11 (18.5)	5.4 (22.8)	3 (18.2)		<1	<1
DoG	Self	Trained	77.2 (33.9)	82.5 (32.1)	84.2 (29.6)	2.5 #	1.1 ^{ns}	1.9 ^{ns}
		Control	70.6 (30.5)	60.2 (39.2)	68.5 (41.1)		4.22*	<1
	Other	Trained	63.1 (33.1)	61.4 (42.3)	61.4 (44.1)	<1	<1	<1
		Control	59.3 (33.4)	43.5 (40.1)	50.9 (44.4)		4.43*	1.15 ^{ns}
Child ANT	Overall RT	Trained	1071.4 (241.6)	934.5 (195.8)	823.8 (129.6)	<1	9.9**	33**
		Control	1064.1 (233)	973.2 (303)	809.47 (227)		4.1*	33**
	Overall % commission errors	Trained	5.9 (4.84)	4.6 (5.8)	3.6 (2.7)	<1	1.2 ^{ns}	2.9 [#]
		Control	9 (10.8)	6.4 (10.9)	4.9 (4.9)		4.2*	8.3**
	Overall % omission errors	Trained	4.11 (4.87)	3.54 (6.16)	4.11 (4.8)	<1	<1	<1
		Control	4.36 (6.57)	3.9 (5.74)	4.28 (6.57)		<1	2.05 ^{ns}
	Alerting	Trained	12.8 (148.5)	56.5 (111.8)	63.3 (56.03)	<1	1.2	3.4 [#]
		Control	14.3 (95.6)	17.9 (111.8)	59.5 (54.9)		<1	2.5 ^{ns}
	Orienting	Trained	24.2 (125.5)	-21.6 (95.7)	9.9 (105.7)	2 ^{ns}	1.3 ^{ns}	1.1 ^{ns}
		Control	-61.4 (179)	-20.0 (130)	6.5 (82.01)		<1	1.5 ^{ns}
Executive	Trained	66.5 (168.6)	53.5 (154.1)	51.4 (63.3)	<1	<1	<1	
	Control	84.5 (161.5)	72.1 (183.6)	80.1 (178.6)		<1	<1	

Table 3.1. Means and standard deviations (SD) of all the dependent variables (DV) included in the study for each group at session PRE, POST1, and POST2. The columns on the right show results of Group x Session interactions and planned contrasts performed between PRE vs. POST1 and PRE vs. POST2 scores for each group. Significance level: **p<.01; *p<.05; #p<.10; ns: p>.10.

K-BIT. When including Matrices scores as DV, only the main effect of Session for PRE vs. POST1 was significant ($F(1,35)=7.4$; $p<.01$). No significant effects for PRE vs. POST2 were found. Despite the non-significant Group x Session interactions, planned contrasts showed a significant increase in the Matrices score following intervention only for the trained group ($F(1,35)=4.9$; $p<.05$; $F(1,35)=2.6$; $p=.12$ for the untrained group). The increase in Matrices was marginal for the trained group when comparing PRE to POST2 scores ($F(1,35)=2.8$; $p=.10$) but did not approach significance ($F<1$) for the control group. For the Vocabulary subscale, no significant effects were obtained in the ANOVAs or with planned comparisons.

Gambling task. None of the main effects or the Group x Session interaction was found significant when including the PRE and POST1 data in the ANOVA. However, the Group x Session interaction was marginally significant ($F(1, 35)=3.07$; $p=.08$) in the ANOVA including PRE vs. POST2 scores. Planned contrasts showed that children in the training group selected more advantageous choices than those in the control group ($F(1, 35)=4.5$; $p<.05$), and that trained children increased the percentage of total choices from the advantageous deck between sessions PRE and POST2 ($F(1, 35)=4.17$; $p<.05$).

Delay of Gratification. ANOVAs were conducted separately for the scores (percentage of delay choices) obtained at the DoG_{self} and the DoG_{other} versions of the task. For the DoG_{self}, main effects of Session or Group were not observed in any of the ANOVAs (PRE vs. POST1 or PRE vs. POST2). For the ANOVA with PRE vs. POST1 scores, the Group x Session interaction was significant in the DoG_{self} task ($F(1, 35)=4.91$; $p<.05$). Planned contracts showed that untrained children decreased the percentage of delay choices between PRE and POST1 sessions

($F(1,35)=4.22$; $p<.05$) and that the trained group had the tendency to delay more than the control group following intervention ($F(1, 35)= 3.58$; $p=.07$). For the DoG_{other} version of the task, the pattern of results was similar. The only significant difference observed occurred between percentage of delay choices from session PRE to POST1 for children in the control group ($F(1,35)=4.43$; $p<.05$).

3.4.2 Effects on brain electrophysiology

Target-locked ERPs per congruency condition are presented in Figure 3.1 for the entire sample at session PRE and for children at the trained and non-trained groups at sessions POST1 and POST2. ERPs pertaining to the PRE intervention session showed amplitude differences between congruency conditions (i.e. larger negative amplitudes for incongruent trials) in leads situated in the frontal midline, as previously reported in the literature with the same (Rueda, Posner, et al., 2004) or similar tasks (Jonkman, 2006; Van Veen & Carter, 2002). To assess possible differences in this effect between groups at the PRE-intervention session, amplitude and latency effects of congruency at frontal midline channels in the time window ranging from 300 to 700 ms were tested with ANOVAs including Group (to be trained and control), Channel (AF, Fz, Fcz & Cz) and Condition (Congruent vs. Incongruent) for both amplitude (using both minimum amplitude within the time window and adaptive meanⁱ values) and latency measures. In any of these analyses the main effect of Group or any of its interactions with other factors approached significance ($F<1$ in all cases except for

ⁱ The adaptive mean consists of the mean amplitude of a new time window created including 10 samples (40 ms) around the peak of minimum amplitude found within the larger time window of 300 to 700 ms.

Channel x Cond x Group interaction for latency which reached a non-significant, $p=.24$, F value of 1.41). Given the absence of differences between groups the waveforms are presented for the entire sample at session PRE. The top row shows ERPs at prefrontal sites (AF/Fz) and the row at the bottom at fronto-parietal (Fcz/Cz) positions.

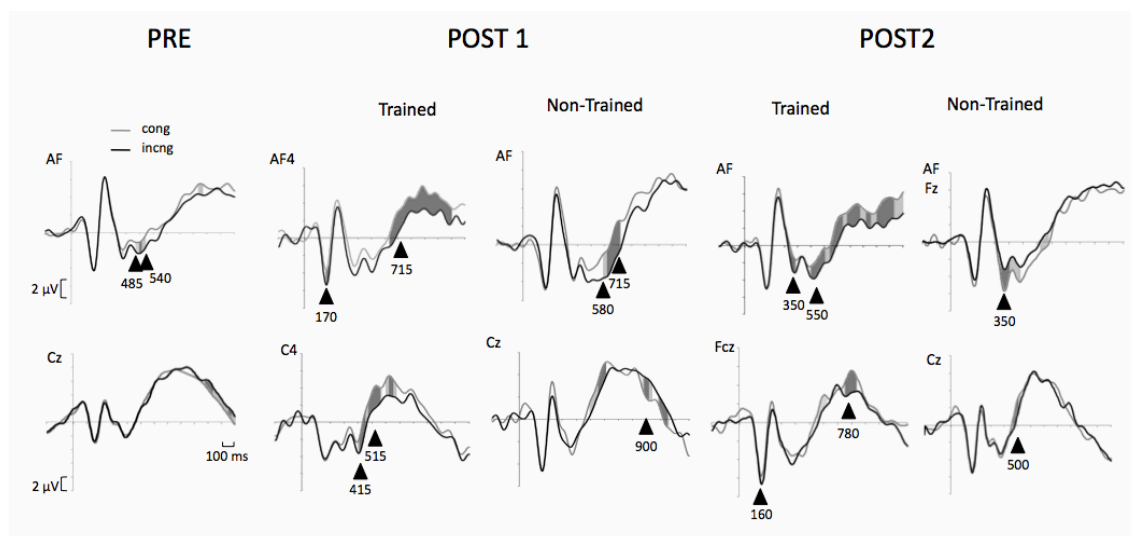


Figure 3.1. Plots of grand averaged ERPs waveforms to congruent and incongruent trials for all children at session PRE, and children assigned to the trained and non-trained groups at sessions POST1 and POST2. The top row shows ERPs at channels located in anterior frontal (AF) positions and the bottom row shows ERPs at channels in fronto-posterior (Fcz/Cz) leads. Shaded areas between conditions show areas of significant amplitude differences between congruency conditions (dark grey: $p < .01$; light grey: $p < .05$). Arrow heads point to post-target times (in ms) for which topographic maps of t -tests differences were created (shown in Figures 3.2 and 3.3).

Dependent-samples t tests of the differences in amplitude between congruent and incongruent conditions were carried out (using the t -test tool incorporated in the Net Station software, EGI, Eugene, OR) for each sample along the entire ERP segment. Areas of significant differences among conditions are shadowed in the waveforms presented at Figure 3.1. Only differences in amplitude that were found significant in at least 10 consecutive samples (40 ms) were marked as significant in the waveforms. Also, topographic maps of the scalp

distribution of significant incongruent vs. congruent differences at particular post-target times are shown in Figure 3.2 (session POST1) and 3.3 (session POST2). At session POST1, trained children show the expected N2 effect (i.e. larger negative amplitude for incongruent compared to congruent trials) from around 400 ms after presentation of the target, whereas untrained children show the effect around 580 ms post-target. Also, the effect is observed in more posterior sites (around Fcz) for trained compared to non-trained children, who show the effect in the same sites (around Fz) as was observed in the PRE intervention session. This difference between trained and untrained children in the timing of the conflict effect is still present in data obtained at session POST2, where trained children show the expected N2 effect around 360 ms post-target, and children in the control group show the effect at about 500 ms after presentation of the target. We also found an early negative deflection around 170 ms after stimulus presentation that was significantly more negative for the incongruent condition at frontal sites in POST1 only in the trained group. This early effect was also evident at POST2 although its topography moved to more posterior channels (see waveforms in Figure 3.1 and topo maps in Figures 3.2 and 3.3).

The topographic distribution of significant differences between flanker conditions changes differentially for trained and non-trained group in sessions POST1 and POST2. As shown in Figure 3.2, the larger negativity associated with the incongruent condition moves from anterior sites in session PRE to a more posterior and right lateralized localization in sessions POST1 and POST2 for the trained group. However, this pattern of activation is not observed for children in the non-trained group who showed the conflict effect later in time and with a more

anterior and left lateralized distribution in POST1, similar to the one observed in session PRE, and a more distributed effect in session POST2 (see Figures 3.2 and 3.3).

3.4.3 Source localization analyses

Grand averaged (across subjects) ERPs data for each group were used to compute the most likely cortical generators of the pattern of electrical fields registered on the scalp with a source localization software (GeoSource, EGI, Eugene, OR). A Finite Difference Model (FDM) was used for inverse modelingⁱⁱ, in which the Minimum Norm Least Squares (MNLS) algorithm is used with a set of 2,447 dipoles triples (comprising dipoles in the x, y, and z orientations) sampling the cerebral cortex. The Sun-Stok 4-Shell Sphere was used as a forward head model. Weighting was placed equally across locations with regularization carried out via TSVD (1×10^{-4}) using LAURA (Local Auto-Regressive Average; (Grave de Peralta Menendez, Murray, Michel, Martuzzi, & Gonzalez Andino, 2004) as a constraint. The Radius of influence was set to 12.2 mm with an exponent equal to 3.

Data corresponding to the entire sample at session PRE, and subsequently with trained and untrained groups at sessions POST1 & 2, were source analyzed at the post-target times in which significant differences between congruency conditions

ⁱⁱ The Finite Difference Model (FDM) that is used by GeoSource is based on the Montreal Neurological Institute (MNI) database for estimating its geometrical constraints. The MNI brain model is based on adults. By using GeoSource to isolate neural sources in preschool children we recognize that the source models may be subject to some error as brain size and level of maturation for cortical structures in children will differ from those of adults. Nevertheless, in our study the source modeling error derived from using an adult brain model remains constant for both the within group comparison as well as across groups, given the fact that children in the two groups were matched in age and gender.

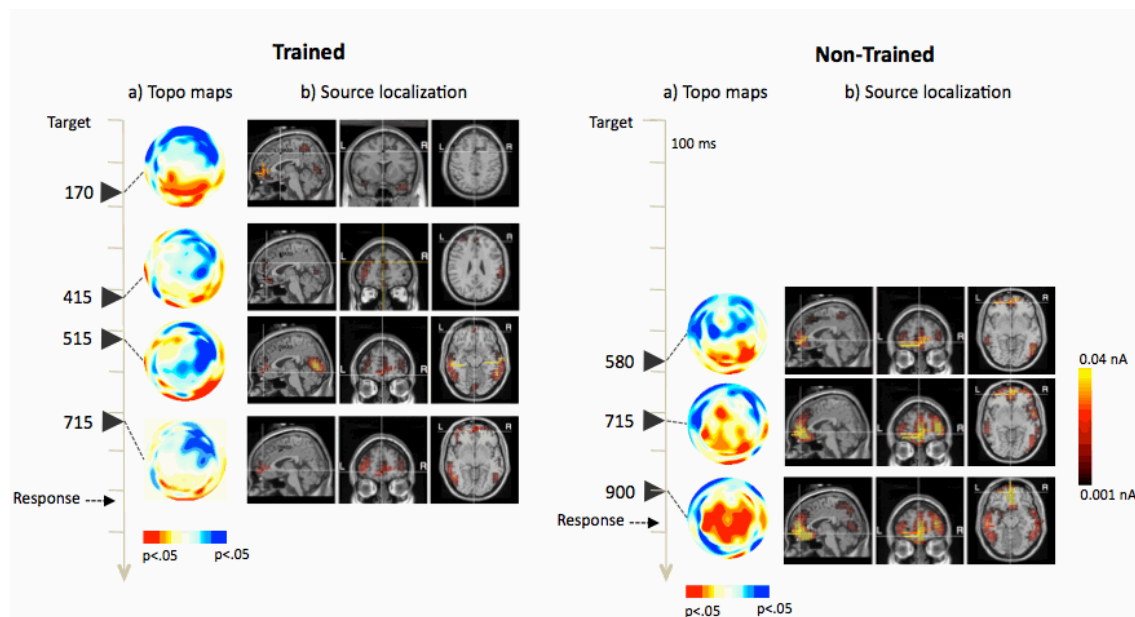


Figure 3.2. Topographic maps of significant amplitude differences between congruency conditions (a) and corresponding source solutions (b) for each group at session POST1. Arrowheads show the particular time points (in ms) between the presentation of the target and the averaged time of the response to which each topo map corresponds. Dark blue areas in the topographic maps indicate sites in which amplitude of the ERPs was significantly more negative for incongruent, compared to congruent, trials. The top part of the topo maps corresponds to the front of the head.

were found. With the PRE session data, the main sources were obtained at bilateral medial frontal gyrus (r and lMFG; BA10), medial inferior frontal gyrus (mIFG; BA11), bilateral medial temporal gyrus (lMTG & rMTG; BA21), and a weak source at dorsal ACC (BA32). A ROI montage was then created with these areas with a radius of 7 mm around the dipole of maximum activation, in order to trace changes in the intensity assigned to these dipoles in function of training at the POST sessions. Sources obtained at these ROIs (and additional areas) for trained and untrained groups are presented in Figure 3.2 (session POST1) and 3.3 (session POST2).

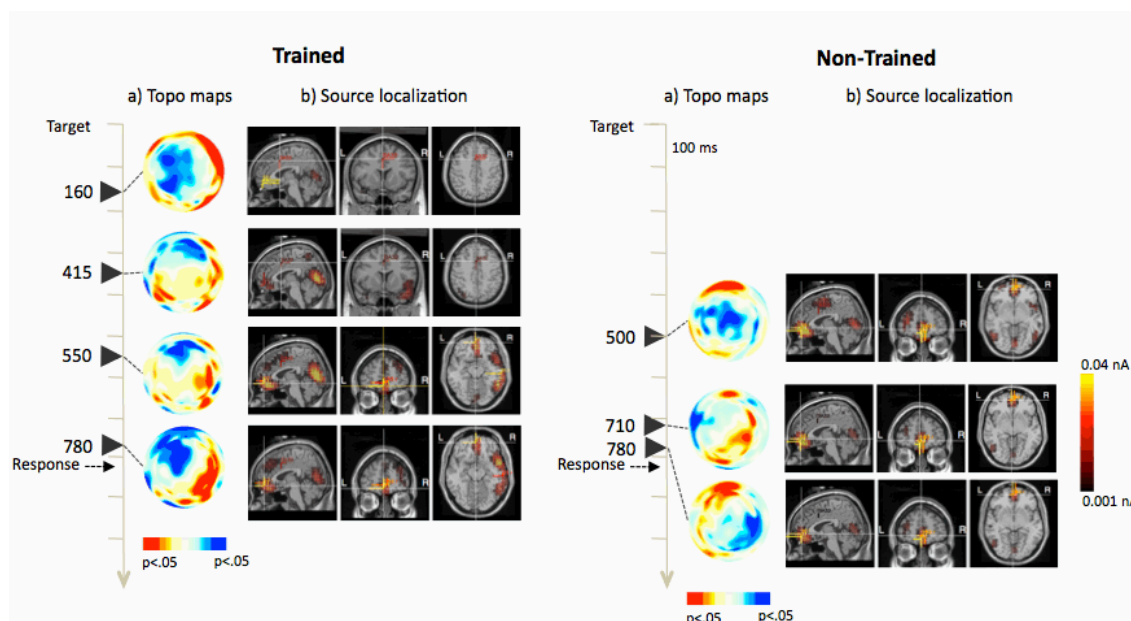


Figure 3.3. Topographic maps of significant amplitude differences between congruency conditions (a) and corresponding source solutions (b) for each group at session POST2. Arrowheads show the particular time points (in ms) between the presentation of the target and the averaged time of the response to which each topo map corresponds. Dark blue areas in the topographic maps indicate sites in which amplitude of the ERPs was significantly more negative for incongruent, compared to congruent, trials. The top part of the topo maps corresponds to the front of the head

3.5 Discussion

In this study, we extended the training program applied by Rueda et al., (2005) with several new exercises, and increased from 5 to 10 the number of sessions used to train attention with a group of preschoolers. The study aimed to replicate and extend prior results on the effect of training attention on the efficiency of the executive attention network and related abilities. The specific goal was to investigate whether applying the extended training program has an effect on the efficiency of executive attention and the underlying brain mechanisms and to test durability of the effect in a short-term follow-up two months after completion of the training. We also aimed at examining whether training attention

produces transfer effects to untrained abilities, although related to attention, such as intelligence and regulation of affect.

3.5.1 Effects of training on the performance of the Child ANT

As revealed by the analyses, training had no significant effect on the behavioral performance of the ANT. Overall RT and percentage of errors data clearly show that children in both groups become more proficient performing the task in post sessions. Also, attention network scores, particularly the executive attention and alerting scores, show some evidence of increased efficiency. However, the fact that the pattern of change is very similar for trained and untrained groups indicates that repetition of the task itself is responsible for the improvement. Mean interference scores showed some evidence of a reduction of the conflict effect, indicating gains in efficiency of executive attention skills, for both the trained and untrained groups at session POST1. However, none of the observed reductions in conflict interference reached statistical significance. A similar pattern was observed for the Alerting score. The trained group exhibits an increase in alerting after training, which is marginally significant when comparing the PRE vs. POST2 scores. Mean scores of the untrained group also show an increase at session POST2, indicating that the mere repetition of the task is at least partially responsible for the effect. The increase in alerting scores would indicate that children become more able to prepare from the presence of warning cues, making faster responses when this happens. Nevertheless, despite showing changes in the network scores in the expected direction, those changes did not reach statistical significance. This is likely due to the high variability that children of the age included in the study show in reaction time when performing this task (large SDs,

see Table 3.1). It is also probable that children reach a ceiling level of performance when carrying out the task in repeated occasions because the network scores obtained by the participants (particularly those in the trained group) in post-sessions are similar to the ones shown by adults (Conflict score: 61 ms; Alerting score: 30 ms) when performing the same task (Rueda et al., 2004a).

3.5.2 Transfer of training to fluid intelligence

Transfer of training to fluid intelligence was highly expected given prior results described in the literature. Both trained and untrained children showed an increase in the matrices subscale score at session POST1 as indicated by the significant main effect of Session. However, planned contrasts showed that only observed gains for trained children reached the significance level. This result replicates previous findings that training of executive attention improves non-trained reasoning abilities. The effect of training is specific for fluid intelligence and does not have an impact in the verbal scale related to learning-dependent or crystallized intelligence. Interestingly, we found some evidence (as indicated by a marginally significant PRE vs. POST2 contrast) suggesting that the generalization of training to fluid intelligence is still observed two months later without further training, whereas the matrices score returned to the initial level ($F < 1$ for the PRE vs POST2 contrast) for the untrained group. Transfer to fluid intelligence skills was expected because it has been shown that there is an extended overlap between the brain structures implicated in general intelligence and those of the executive attention network (Duncan et al., 2000). Our data add on to evidence provided by other studies indicating that fluid intelligence can be improved with intervention (Bergman Nutley et al., 2011; Jaeggi et al., 2008; Rueda, et al., 2005b). The modest

effect observed in our study could be due to the fact that more extended interventions are required to change cognitive abilities such as reasoning that appear to be heritable to an important extent (Cattell, 1987; Gray & Thompson, 2004). However, data of this sort challenge the idea that fluid intelligence is not subject to the influence of education and socialization.

3.5.3 Transfer of training to regulation of affect

Another question that was addressed in this study was whether training of attention would generalize to tasks that are thought to rely on attention control skills. In our study, we included two tasks, Children's Gambling and Delay of Gratification (DoG), to examine transfer of training to regulation of affect and motivation (also known as "hot" executive function; Hongwanishkul, Happaney, Lee, & Zelazo, 2005). Regulation of motivational tendencies can be observed in situations in which inhibition of immediate rewards is required in the face of a higher price in the long term. We found that children trained with our program increased the number of advantageous choices in the Gambling Task when comparing performance at sessions PRE vs. POST2, whereas untrained children performed similarly in all three sessions (PRE, POST1 and POST2). In this task, it is necessary to reappraise the motivational significance of immediate rewards in order to learn to choose advantageously. Our results indicate that trained children became more able to control their choices according to the wins/loses contingencies of each deck, being more able to inhibit choosing from the dominant high-reward deck but subject to higher potential loses.

For the DoG task the pattern was somewhat different. In the two versions of the task used in our study (DoG_{self} and DoG_{other}), untrained children showed a

significant decrease in the number of delay choices the second time they played the task (session POST1 compared to PRE). Trained children, however, did not show a decrease in the percentage of delay choices. A plausible explanation for the drop in the percentage of delay choices shown by children in the control group at the POST1 session is that the second time children perform the task they know how long the delay period is, because they experienced it at the PRE session, which may discourage them from choosing the delay option. This circumstance is also true for the trained group. However, in this case, training may have helped children to be more able to control dominant, yet unfavorable, responses, therefore preventing them from showing a decline in the percentage of delay choices in post-intervention sessions.

3.5.4 Effects of training on brain function

A major goal of our study was to advance understanding of the neural mechanisms of training and to examine whether the effect of the intervention on brain function shows signs of stability over time in a relatively short follow-up two months later. Brain electrical activity was recorded with a high-density electroencephalography system while children performed a child-friendly flanker task. As expected, the congruency of flankers modulated a negative component of the ERPs that was frontally distributed (often referred to as the N2). This component showed larger amplitude in trials involving conflict (i.e. with incongruent flankers). Prior studies had reported that preschool children show modulation of the frontal negativity sometime later than adults and at more anterior channels (Rueda, et al., 2004b). In the current study, we observed modulation of the frontal negativity starting around 500 ms post-target at session

PRE (see Figure 3.1). Additionally, our results replicate previous findings that training affect both timing and topographic distribution of ERPs related to conflict monitoring (Rueda, et al., 2005b). The effect of flankers on the amplitude of the ERPs at frontal leads is shown earlier and in more posterior channels for trained children compared to children in the control group (Figure 3.1). Moreover, the pattern appears to be maintained two months later, as trained children show the expected larger negativity for incongruent trials earlier (from 360 ms post-target on) than non-trained children (see also topo maps of significant congruency effects in Figures 3.2 & 3.3). In adults, the conflict N2 effect has been associated with a source of activation in the ACC (van Veen & Carter, 2002). There is evidence suggesting that the ACC is involved in detecting the occurrence of conflict, which is then conveyed to prefrontal structures in charge of resolving the conflict (Botvinick et al., 2004; Walsh, Buonocore, Carter, & Mangun, 2011). Thus, a delayed frontal negativity may be indicative of poorer efficiency of the executive attention network related to a slower detection of conflict in children compared to adults. Data from our study suggest that one of the processes by which training may influence the executive attention network is by hastening the neural mechanisms supporting the detection and signaling of conflict from the ACC to prefrontal structures.

Data from source localization analyses are also consistent with the idea of a more efficient activation of the executive attention network in trained children. Modeled images of electrophysiology data identified the more likely neural generators of the effects observed in the ERPs. Figures 3.2 and 3.3 show the sources of activation modeled from the topographic maps of the incongruent minus congruent difference in electrical recordings at times in which significant

differences in amplitude between those two conditions were observed. Overall, generators were localized at medial inferior frontal (BA11), medial-lateral PFC (mlPFC), medial frontal gyrus (BA10), and dorsal ACC (BA24/32). The pattern of activation is consistent with the one observed with similar tasks in somewhat older children using fMRI (Bunge et al., 2002; Konrad et al., 2005). Besides, source modeling data demonstrate that children in the trained group show earlier engagement of dorsal ACC than the untrained controls, who only show a clear ACC generator the third time they perform the task (session POST2). In addition, sources of activation in mlPFC become more lateralized to the right hemisphere as children gain experience with the task (POST2 compared to POST1). However, this lateralization to the right is only observed for the trained group. Imaging studies of interference suppression have reported activation in ventro-lateral PFC that is left lateralized in children but right lateralized in adults (Bunge et al., 2002; Konrad et al., 2005). Moreover, the right vlPFC activation in adults correlates positively with the ability to suppress interference (Bunge, et al., 2002). These data suggest that children in the trained group may be showing a more adult-like pattern of brain activation while performing the task than children in the control group. However, comparison of source modeled ERPs data in children and fMRI data obtained with adults must be done with caution (see Note 2) and this interpretation should be subject to replication using more comparable brain imaging techniques.

A final remarkable result of the source localization data is related to the strength of activation and focalization of the modeled sources. Overall, children in the non-trained group show broader and stronger activations than children in the trained group. The idea that cortical function becomes less diffuse and more focal with maturation is well documented in recent neuroscience research (Casey et al.,

2005; Durston & Casey, 2006). Moreover, tuning of activations appears to be dependent of the functional significance of the circuitry of brain structures, displaying attenuated activations in areas relatively less involved in a particular function and more focal activation of areas related to that function (Durston et al., 2006; Fair et al., 2007). Our source modeling results show more focused activation for trained children in nodes of the executive attention network, which suggests that activation of this network becomes more fine-tuned after training.

3.5.5 Limitations of the study

In our study, a video-watching non-active control group was used to examine the effect of training. The video-watching control may not be optimal for disentangling effects that are specific to the attention training aspects of the computerized program. However, the video-watching situation shares several aspects with the training experience, in that it involves interacting with a computer screen in the presence of the experimenter for a period of time. Also, prior studies reported no differences between active and passive control groups in training studies conducted with preschoolers (Rueda, et al., 2005b; Thorell et al., 2009). In future studies, it may be more appropriate to include an active control group. The active control could either carry out a training program designed to improve a cognitive ability that is non-specific for attention or just perform the most basic levels of the exercises included in the training program.

To our knowledge, our study is the first to examine durability of training effects on cognitive and brain function in children. However, the amount of training in the current study was only moderate both in terms of number of sessions (a total of 10) and time (a maximum of 500 minutes in total over a period

of 5 weeks). In spite of this, we found some evidence of lasting effects of training two months later on some of the measures used in the study, which were more clearly observed in brain function. We believe that producing a larger impact on cognition would require more extended interventions. As a matter of fact, there is evidence showing that curricular interventions based on Vygotsky's theory of development involving teacher-students exchanges or interactions between peers result in increased performance of conflict tasks and hence better executive attention efficiency (Diamond, Barnett, Thomas, & Munro, 2007b). Similarly, experiences that are likely to be more extended in time, such as being exposed to more than one language during development, appear to have a positive impact in attention control skills as measured by the ANT (Yang et al., 2011).

In our study, we did not find a clear effect of training on performance of the ANT. One question that emerges from the pattern of behavioral results in our study is why, despite not obtaining significant training effects on the task targeting the closest cognitive skills (the child ANT), significant effects were observed for intelligence and moderately for emotion regulation. Standard deviations of scores for each task presented at Table 3.1 suggest that differences in performance variability between the ANT task and the rest of behavioral measures included in the study could explain the fact that the effect of intervention is observed in the paper and pencil tasks and not in the ANT. Additionally, improvements observed for the control group in the ANT task at post sessions suggest that practicing may be another form of useful training. Also, the fact that scores obtained at post intervention sessions for both trained and untrained children reached adults levels of performance suggests the issue of a possible ceiling effect. For future studies it

may be useful to include additional behavioral tasks designed to examine executive attention that are more challenging and sensitive to changes in efficiency for preschool-aged children.

3.5.6 Conclusions

Our results show that the brain circuitry involved in executive attention is activated faster and more efficiently after training. Training appears to accelerate mechanisms associated with monitoring of conflict supported by the dorsal division of the ACC, an effect that is still apparent two months after completion of training. More efficient engagement of the ACC is likely to be responsible of transfer of training to regulation of affect. The dorsal division of the ACC appears to be involved in reappraising the emotional value of events (Etkin, Egner, & Kalisch, 2011). Affect regulation in our tasks require reappraising the positive value of immediate or high compensations or rewards taking into consideration that they lead to more negative consequences in the long term. Flexible allocation of attentional resources facilitates fluent reasoning and helps on connecting current decisions with future consequences. A major conclusion of our study is that efficiency of the executive attention network can be enhanced by means of an educational intervention and that other cognitive skills that rely on attention control or are associated with it may also benefit from this type of intervention.

3.5.7 Implications for education

Interventions of the type carried out in our study might be useful to help children get ready for school. They also have the potential to prevent children with poor attention skills from school failure, and even to help on the prevention of

developing attention-related pathologies and conduct problems. It was discussed at the introduction that executive attention is important for a wide range of aspects in children's lives, including socialization and emotion regulation. In school, control of attention is important to adjust behavior in function of norms and goals, stay focused despite distractions, flexibly allocate attention on relevant information (either internal or external), and persist to complete difficult tasks even when rewards (i.e. learning, good grades, etc.) may take time to arrive. We think that showing evidence of the susceptibility of the executive attention network to be enhanced by training is only the start point, but that data of this sort will provide an opportunity for curricular improvement. Results of the current study point out the potential to produce larger and more durable impact in children's attention skills and related domains with more extended interventions.

Chapter 4

**Influence of the SLC6A3-DAT1 gene on multifaceted
measures of self-regulation in preschool children**

4.1 Introduction

During the first years of life, children undergo rapid and continuous processes of cognitive development that are crucial to their adjustment later in life. One of the major changes is observed in their capacity to voluntarily modulate thoughts, emotions, and actions in order to achieve goals and meet social demands. This capacity, known as self-regulation (SR) has been found to positively influence social adjustment as well as cognitive and academic performance of individuals from early childhood to adolescence (Checa, Rodríguez-Bailón, & Rueda, 2008; Checa & Rueda, 2011; Eisenberg, Smith, & Spinard, 2011).

A great deal of studies in the field of developmental cognitive neuroscience have shown that the progressive emergence of self-regulatory skills during childhood is strongly related to the development of the executive attention network (EAN), a neural system that comprises frontal and subcortical structures such as the anterior cingulate cortex (ACC), the dorsolateral prefrontal cortex and the basal ganglia (Posner & Rothbart, 2009; Rueda, Posner, & Rothbart, 2011). Activation of the EAN is mainly mediated by the action of dopamine neurotransmission and has been related to the performance of tasks that entail attention control such as error detection, inhibition of dominant responses, conflict processing, and performance monitoring (Botvinick et al., 2001; Jin Fan, Flombaum, et al., 2003). Moreover, activation of the ACC has been found to be crucial on the processing of affective information and the regulation of emotional reactivity (Bush et al., 2000).

The development of executive attention skills follow a progressive course that starts in the early childhood; exhibit a major growth spurt between the 4th and

the 7th year of life (Rueda, Fan, et al., 2004; Rueda, Posner, et al., 2005b) and continue to develop until the adolescence (Pozuelos, Paz-Alonso, Castillo, Fuentes, & Rueda, 2014). Electrophysiological and neuroimaging studies have shown that structural and activity changes in the brain support this development. With age, children show a faster and more efficient engagement of the EAN while performing tasks involving attention control (Abundis-Gutiérrez et al., 2014). Also, activation of brain regions evolves from diffuse to focal (Durstun & Casey, 2006), and long connectivity patterns emerge linking distant areas of the brain while local short-range connections appear to weaken (Fair et al., 2009; Power et al., 2010).

The attention control processes associated with the EAN greatly overlap with the efficiency of the executive functions (EFs), an array of interrelated cognitive mechanisms that serve to organize and execute complex behavior when automatic responses are not appropriate or useful (Diamond, 2013). Several cognitive mechanisms fall under the umbrella of EFs including working memory, inhibitory control, cognitive flexibility as well as the organization and integration of information for planning, problem solving and reasoning (Collins & Koechlin, 2012). Furthermore, a number of studies have found that the performance of executive attention and superior EFs tasks is highly correlated with measures of general intelligence (See Kane & Engle, 2002 for a review) and exhibit overlapping patterns of activation in the dorsolateral prefrontal cortex (Duncan & Owen, 2000). It has been suggested that a reciprocal interaction between the brain areas that support the lower-level executive control of attention and those underlying the higher-level executive functions provides the neural support for the implementation of self-regulatory strategies (Alvarez & Emory, 2006; Blair & Ursache, 2011).

From the field of temperament, individual differences in the ability to modulate emotion and behavioral reactivity have been characterized under the construct of effortful control (EC), a temperamental factor that describes the capacity to plan, detect errors and inhibit dominant but inappropriate responses (Rothbart, Ellis, Rueda, & Posner, 2003). Several studies have reported that performance on tasks that engage the activation of the EAN correlates with scores on caregiver's or self-report measures of EC in children and adolescents (see Rueda & Posner, 2013 for a review). Moreover, individual differences on the efficiency of SR at the cognitive (executive attention) and temperamental (EC) levels have been related to children's social adjustment and academic performance during preschool (Dennis, Brotman, Huang, & Gouley, 2007); late childhood (Checa et al., 2008) and adolescence (Ellis et al., 2004).

One major advantage of approaching the study of SR as interplay of cognitive processes that are supported by the interaction of specific brain networks and neuromodulators is that it allows us to understand the neurological basis of individual differences. In the forebrain, dopamine (DA) neurotransmission plays a central role in the modulation of basal ganglia structures and its integration with areas in the cerebral cortex. This integrative action is critical for the modulation of processes that underlie the voluntary exercise of regulation including motor reactivity, attention, learning, motivation, reward processing and higher-order executive functions (Nieoullon & Coquerel, 2003; Nieoullon, 2002). On this base, dopamine neurotransmission has been considered a key endophenotype for the study of genetic-based individual differences in the development of the executive mechanisms that underlie SR.

The action of dopamine transporters (DAT) plays a central role on the regulation of DA levels in the brain through the rapid re-uptake of the neurotransmitter in the presynaptic neuron. Several studies have localized the highest density of DAT in the basal ganglia, particularly in the striatum while a more widespread localization was observed in the cerebral cortex (Ciliax et al., 1999; Hersch, Yi, Heilman, Edwards, & Levey, 1997b). Studies have shown that changes in the expression of DAT causes severe changes in DA pathways. For instance, Giros, Jaber, Jones, Wightman, & Caron (1996) found that inactivation of DAT produces spontaneous hyperactivity and disinhibition in knockout mice, a phenotype that was accompanied by a diminished action of D₁ and D₂ receptors and decreased levels of the tyrosine hydroxylase enzyme that synthesizes DA. Thus, in the absence of DAT, diffusion would be the only mechanism left for the clearance of DA.

In humans, the SLC6A3/DAT1 gene carries out the synthesis of the DAT protein. A 40-bp variable number of tandem repeats (VNTR) in the 3' untranslated region of the gene has been related to differences in the expression of gene (D J Vandenberg et al., 1992). In particular, the 10-repeat allele has been associated to an enhanced expression of the gene compared to the 9-repeat allele (Fuke et al., 2001; Heinz et al., 2000), a relation that appears to be positively related to the number (either none, one, or two) of 10r alleles (Mill, Asherson, Browes, D'Souza, & Craig, 2002). On the question of how variations on the VNTR polymorphism affect levels of DA in the brain, VanNess, Owens, & Kilts (2005) found that the density of the DAT binding site is about 50% higher for individuals carrying the 10r allele compared to carriers of the 9r allele, a phenotype that functionally

translates into less availability of DA in the synaptic space and the hypoactivity of the DA pathways (Yang et al., 2007).

Extensive research has been conducted to discern the relation between variations of the DAT1 gene and the cognitive functioning that underlies SR, however much uncertainty still exists as studies have yielded contradictory results. For instance, a large number of clinical studies have reported an association between the 10r allele and symptoms of ADHD that are related to attention and behavioral control (Brookes et al., 2008; Cook et al., 1995; Curran et al., 2001; Mill et al., 2005). However, various studies have failed to replicate this finding and others have reported contrary results where the possession of the 9r allele is associated to ADHD (see Rommelse et al., 2008, for a review). Similar inconsistencies have been reported in the field of typical development. Using neuropsychological and neurophysiological measures of attention control, some authors have found an association between poorer performance and homozygosity for the 10r allele (Cornish et al., 2005) while others reported no differences between homozygous for the 10r allele and carriers of the 9r allele (Meyer et al., 2012).

Despite of all these significant contributions, it is still unclear how variations of the DAT1 gene influence children's SR. Most of the studies in the field have approach this question through the controlled assessment of attention control processes and EFs in laboratory settings. Therefore, little is known about the impact that variations of the DAT1 gene may have on children's capacity to implement those mechanisms of regulation in contexts that impose particular demands of regulatory control such as the school or home. In this study, we attempt to contribute the next step by assessing preschoolers' SR from a

multifaceted perspective and examining whether variations of the DAT1 gene, specifically presence of the 10r allele, accounts for individual differences in children's performance. To achieve this goal we have included a variety of tools that allow evaluating cognitive, temperamental and socio-emotional aspects of children's SR from different angles: teacher-reported of schooling skills, parent-reported of EC and emotional regulation, as well as children's performance on a battery of executive control tasks that included delay of gratification, working memory, Go-NoGo and flanker tasks, as well as an intelligence test.

The array of measures included in this study are known to constitute different levels of analysis of the construct of SR (see Eisenberg, Valiente, & Eggum, 2010 for a review). Therefore, we expected adults-reported measures of SR to be related to one another and to show a positive correlation with children's performance on the battery of cognitive tasks. Concerning the genetic-based individual differences of self-regulatory skills, we hypothesized that children carrying one or two copies of the 10r allele would exhibit significantly poorer self-regulatory skills. Three pieces of information support this hypothesis: 1) DA circuits connecting the structures of the EAN, in particular the basal ganglia and the prefrontal cortex have been found to be crucial for the regulation of attention, actions and emotions (Nieoullon & Coquerel, 2003). 2) Regulation of DA levels in the basal ganglia (particularly in the striatum) and to a lesser extent, in the prefrontal cortex, is carried out by the action of DAT (Ciliax et al., 1999). 3) Presence of the 10r allele of the DAT1 gene has been related to a diminished functioning of the dopaminergic transmission system, particularly in the basal ganglia (VanNess et al., 2005).

4.2 Method

4.2.1 Participants

A total of 127 children (55 girls; mean age: 63.9 months; SD: 6.5) whose parents gave written consent participated in the study (Table 4.1). Recruitment was conducted at several preschools and nursery schools of an urban area of southern Spain. Participants had normal or corrected-to-normal sensory capacities, no history of chronic illness and/or psychopathologies and were not under pharmacological treatment of any kind.

Valid <i>n</i>	Gender		Mean Age (months)	SD
	Girls	Boys		
127	55	72	63.9	6.48

Table 4.1. Descriptive information of the sample

4.2.2 Procedure

Data for this study was collected during two school years. Children were assessed in two different sessions by the same experimenter. The first session took place at the school where children underwent a cognitive assessment that included delay of gratification, working memory, and intelligence tests. This session lasted approximately 30 to 45 minutes including short breaks after each task. The second session took place in our laboratory where children completed a Flanker and a Go-NoGo task, and the saliva sample for DNA analysis was collected. While children were carrying out the tasks, their parents were asked to complete the temperament questionnaire CBQ and the Emotion Regulation Rating Scale (S. M.

Carlson & Wang, 2007). Additionally, teachers received a modified version of the Student-report version of the Health Resources Inventory (HRI; Juvonen & Keogh, 1992) and were instructed to complete it separately for each participant.

Differences among the valid sample size for the dependent variables are mainly due to the inclusion of new measures in the second year of the study (working memory span, emotion regulation rating scale, Go-NoGo task and the HRI). Also, some parents and teachers did not complete all the questionnaires.

4.2.3 Genotyping procedure

DNA was isolated from saliva samples using Oragene collection kits (DNA Genotek Inc., Ontario, Canada) according to the manufacturer's instructions. Approximately 10-40 ng of template was included in each PCR amplification, reactions contained 0.2 mM each deoxynucleotide, 0.2 μ M each oligonucleotide, 0.05 U/ μ l recombinant Taq DNA polymerase with its 1x reaction buffer $(\text{NH}_4)_2\text{SO}_4$ (Thermo Fisher Scientific, Pittsburg, PA), and 8% DAT1QuickExtract buffer V1.0 (Epicentre Biotechnologies, Madison, WI) in addition to PCR-specific optimizations. The DAT1 amplification contained 1.5 mM MgCl_2 , 0.6 M betaine, and the oligonucleotides DAT1F 5'-TGTGGTGTAGGGAACGGCCTGAG and DAT1R 5'-CTTCCTGGAGGTCACGGCTCAAGG (Shinohara et al., 2004). Amplification conditions were the following: 95°C 4min; 35x 94°C 30 sec, 65°C 1 min, 72°C 30 sec; 72°C 3 min. Amplified products were size separated on a 2% agarose gel (GenePure LE, BioExpress, Kaysville, UT) and visualized using ethidium bromide. Genotype was grouped by 10-repeat carriers (a 480 bp product) and 10-repeat absent (homozygous for the 440 bp 9-repeat product). Three participants were

excluded from the analysis because they carried rare variants of the DAT1 gene. Numbers and frequencies of alleles and genotypes are presented in Table 4.2.

		DAT1 gene						
	Total	Alleles		10r Allele		Genotype		
		10	9	Pr	Ab	10-10	10-9	9-9
Valid N	127	169	85	110	17	59	51	17
Frequency		0.67	0.33	0.87	0.13	0.47	0.40	0.13

Table 4.2. Genetic distribution of the sample

4.2.4 Materials

Teachers' Report

Schooling skills (Health Resources Inventory; HRI; Juvonen and Keogh, 1992). A modified version of the HRI was used in this study. Here, the number of items included in each scale was reduced to five in order to facilitate the involvement of teachers in the study. Besides, a scale designed to assess children's assertiveness in the school context was included in order to emphasize on children's self-regulatory competences in the socioemotional domain. The assertiveness scale replaced the student-role understanding scale, which was not included in this study. In total, the questionnaire includes 20 items that assess teacher's perceptions about children's school competences in four dimensions: assertiveness (Cronbach's $\alpha = .84$), sociability ($\alpha = .82$), rule following ($\alpha = .62$) and tolerance to frustration ($\alpha = .70$). The mean score for each scale as well as the averaged mean of all of them (*Schooling Skills* $\alpha = .84$) were calculated and included in the analysis. Teachers were asked to answer the questionnaire

separately for each child. Response options were presented on a 5-point Likert scale ranging from never to always (see Appendix I).

Parents' Report

Children's Behavior Questionnaire (CBQ - Putnam & Rothbart, 2006). The CBQ is a reliable instrument designed to assess temperament features in children 4 to 8 years of age based on parents or caregivers' report. In this study we implemented the Spanish short version of the original questionnaire designed by (Rothbart, Ahadi, Hershey, & Fisher, 2001). Parents were instructed to rate their child on each item using a 7-point liker scale ranging from "extremely untrue for your child" to "extremely true for your child". An extra response option "not applicable" was also available. Parents were asked to choose this option if their children never experienced the situation described in the questionnaire. The 94 items included in the CBQ are grouped in 15 scales that load on one of the three broad temperament factors. For this study we focused on the effortful control factor, which measures children's capacity to modulate their own reactions through five scales: inhibitory control ($\alpha = .60$), attentional focusing ($\alpha = .67$), low intensity pleasure ($\alpha = .64$), perceptual sensitivity ($\alpha = .67$) and smiling and laughter ($\alpha = .59$). The internal consistency of the EC factor was found to be appropriate ($\alpha = .79$).

Emotion Regulation Rating Scale (S. M. Carlson & Wang, 2007). It is a brief questionnaire in which caregivers are asked to answer 6 questions to assess children's capacity to modulate their own behavior in situations that elicit emotion reactivity. The response scale was adapted to the one used in the CBQ in order to make it easier for parents to answer all questionnaires. In this study, the internal consistency of the scale ($\alpha = .46$) was low (see Appendix II).

Cognitive control assessment

Delay of Gratification (DoG). The DoG task administered in this study was a modified version of the task designed by Thompson, Barresi, & Moore (1997). Children were instructed to choose between getting one prize immediately or waiting until the end of the task in order to (a) get two prizes instead of one (delay for oneself) or (b) get one prize for themselves and let the experimenter get a prize too (social delay). The overall percentage of delay responses was calculated and included in the analysis.

Working Memory Span Subtest of the WISC (Wechsler, 1991). It provides scores in two conditions. The forward condition (WM-f) measures maintenance of information in WM and the backwards condition (WM-b) grasps processes of maintenance and manipulation of information. Children are instructed to listen and repeat series of digits in the same (forward) or reverse (backward) order of presentation. The number of correct trials (series of digits correctly remembered) was registered for each condition and included as dependent variable.

Go-NoGo Task. For this task, children were sited in front of a computer screen where a traffic light was presented. Participants were instructed to press a button as fast as possible every time the green light was on (Go-signal), but hold the response when the light was red (NoGo-signal). As depicted in Figure 4.1, trials consisted of a 500 ms fixation point, followed by presentation of the stimulus, followed by 500 ms inter-trial. Target presentation was terminated once the response was made or after 1000 ms. The task included 160 trials (75% Go-trials), that were divided in two blocks. Performance was measured with the DST sensitivity index (d') using both hits and false alarms rates.

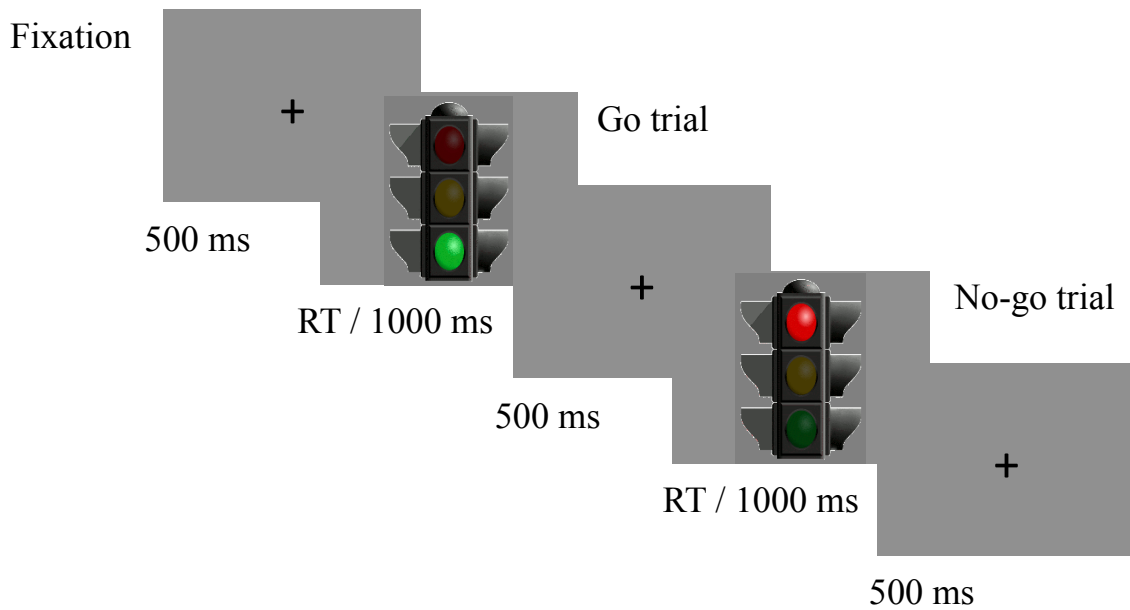


Figure 4.1. Schematic representation of the Go-NoGo task

Flanker Task. A child-friendly flanker task with shapes (see Checa, Castellanos, Abundis-Gutiérrez, & Rueda, 2014) was used. A cartoon picture with a row of five robots was presented at the center of the screen either above or below the fixation point. Participants were asked to indicate the shape of the robot in the middle (either round or square) by pressing the corresponding key. Flanking robots could be of the same (congruent) or different (incongruent) shape as that of the middle robot. Flanking robots were congruent in half of the trials, and the congruency condition was randomly selected for each trial. The response could be made during presentation of the target or up to 800 ms after it disappeared. In order to adjust the difficulty of the task to the participant's performance level, the duration of the target was adjusted in each trial according to the participant's performance in the previous trial. Following the response, a 600 ms-lasting feedback was provided. The feedback consisted of a visual animation of the central figure plus an auditory word ("yes" for correct response, "no" for incorrect

response, and “late” for omission or off-time responses). Participants completed 144 trials divided into six blocks with small breaks between them (Figure 4.2). A flanker interference conflict score was calculated for the reaction time (Conflict-RT) and percentage of errors (Conflict-Err) by subtracting performance at the congruent condition from the incongruent condition. An index of interference suppression was calculated by averaging the Z scores for the two measures.

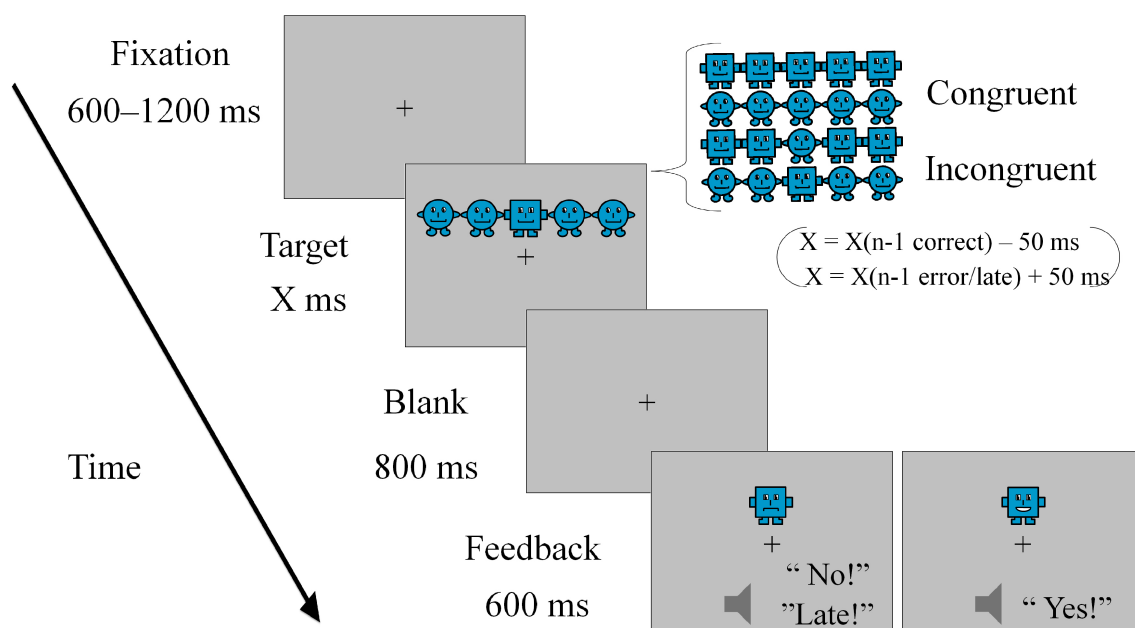


Figure 4.2. Schematic representation of the Flanker task

Intelligence Test

Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990). This test provides standardized scores for two subscales: Crystallized (Verbal) and Fluid (Matrices) Intelligence (IQ-v and IQ-f respectively).

4.3 Results

Unilateral Pearson's correlations among the variables considered in the study are presented on Table 4.3.

Teachers-reported schooling skills correlate positively with parent-reported measures of EC and children's percentage of delay of gratification choices in the DoG task. Also, a negative correlation was observed between schooling skills and the conflict-processing index obtained in the flanker task, which indicates that higher scores on schooling skills are associated with greater executive attention efficiency (i.e. lower interference costs). Furthermore, parent-reported measures of children's EC and emotion regulation are positively correlated with each other. In relation to the executive function assessment and the intelligence test, EC showed to be positively correlated with children's performance on the *backwards* condition of the working memory task, the Go-NoGo task, and also with the fluid intelligence score.

Finally, children's performance on the working memory *forward* condition is positively correlated with their score on the verbal intelligence test, while performance on the *backwards* condition correlates with the Go-NoGo sensitivity index d' . The conflict-processing index correlates negatively with the two intelligence indexes (verbal and fluid): higher IQ scores were related to lower conflict-interference costs.

4.3.1 DAT1 modulation

A series of independent-samples t-test were conducted to compare the performance of children in relation to the presence or absence of the 10r allele.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Teachers' Report																			
1. Schooling Skills	-																		
2. Assertiveness	0.58	-																	
3. Sociability	0.81	0.29	-																
4. Rule Following	0.77	-	0.61	-															
5. Frustration Tolerance	0.66	-	0.43	0.52	-														
Parents' Report																			
6. Effortful Control	0.27	0.26	0.25	-	-	-													
7. IC	0.37	-	0.29	0.37	-	0.68	-												
8. AF	0.28	0.22	0.25	0.28	-	0.75	0.52	-											
9. LIP	-	-	-	-	-	0.66	0.26	0.37	-										
10. PS	-	-	-	-	-	0.62	0.22	0.25	0.31	-									
11. S&L	-	-	-	-	-	0.63	0.19	0.27	0.38	0.34	-								
12. Emotion Regulation	-	-	0.27	-	-	0.39	0.48	0.29	-	0.22	-	-							
Cognitive Control Assessment																			
13. %Delay Choices	0.23	-	0.27	-	0.28	-	-	-	-	-	-	-	-						
14. WM-f	-	-	-	-	-	-	-	0.27	0.21	-	-	-	-	-					
15. WM-b	-	-	-	-	-	0.21	-	0.23	-	-	-	-	-	0.54	-				
16. d'	-	-	-	-	-	0.27	-	0.23	-	-	0.24	-	-	-	0.26	-			
Cognitive Control Assessment																			
17. Conflict z-index	-0.23	-0.25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Intelligence																			
18. Verbal	-	-	-	-	-	-	-	-	-	-	-	-	-	0.20	-	-	-0.24	-	-
19. Fluid	-	0.24	-	-	-	0.26	-	0.31	-	-	-	-	-	-	-	-	-0.22	0.35	-

Table 4.3. Statistically significant results from correlation analysis among the variables considered in the study.

Scores calculated for the tasks and questionnaires were included as dependent variables and the genetic variation was included as the independent variable (10r-Pr vs. 10r-Ab). As a matter of caution given the small sample sizes, we assumed unequal variances on the test. Additionally, we calculated the effect size (ES) of the

between-group differences for all dependent variables using the pooled standard deviation of the groups ($\text{Mean}_{Pr} - \text{Mean}_{Ab} / \text{Pooled SD}_{Pr\&Ab}$) (see Figure 4.3). Finally, we carried out a series of one-way ANOVA and linear contrasts analyses to test for the presence of a gene-dosage effect that would further describe the genotype x phenotype relationship. In this case, children' scores were again included as dependent variables while the three genotypes of the DAT1 gene were included as factors (10/10, 10/9, 9/9). A summary of the results including size of the sample on each task, means, SD and p -values for all dependent variables is presented in Table 4.4.

4.3.2 Teachers' Report

Schooling Skills. Children carrying one or two copies of the 10r allele were given statistically significant lower rates on the schooling skills composite $t(18.4) = -2.18, p = .04$; $ES = .64$, the sociability scale $t(20) = -2.42, p = .03$; $ES = .66$ and marginally significant on the rule following scale $t(20.2) = -1.89, p = .07$; $ES = .51$ compared with those homozygous for the 9r allele. No statistically significant differences ($p > .05$) were found for the frustration tolerance or the assertiveness scales (see Figure 4.3). One-way ANOVAS and linear contrasts revealed a statistically significant allele-dosage effect for the schooling skills composite (ANOVA: $F(2,77) = 4.30, p = 0.02$; linear contrast: $F(1,77) = 7.77, p = 0.007$); the sociability scale (ANOVA: $F(2,77) = 3.45, p = 0.04$; linear contrast: $F(1,77) = 6.75, p = 0.01$) and the frustration tolerance scale (ANOVA: $F(2,77) = 3.23, p = 0.04$; linear contrast: $F(1,77) = 4.75, p = 0.03$), where children carrying two copies of the 10r allele (10/10) scored lower than those carrying only one copy (10/9) who in turn

Questionnaire /Task	DV	Mean (SD)		t-test Prvs.Ab	Mean (SD)			One-Way ANOVA	Linear Contrast	
		10r-Pr	10r-Ab		10/10	10/9	9/9			
Teachers' Report	Schooling Skills	N	66	14		38	28	14		
		Schooling Skills	3.6 (0.42)	3.9 (0.45)	-2.20*	3.5 (0.37)	3.7 (0.47)	3.9 (0.45)	4.30*	7.77**
		Assertiveness	3.7 (0.71)	3.9 (0.86)	-0.65	3.7 (0.74)	3.8 (0.67)	3.9 (0.86)	<1	1.01
		Sociability	3.7 (0.61)	4.1 (0.56)	-2.42*	3.6 (0.53)	3.8 (0.70)	4.1 (0.56)	3.45*	6.75*
		Rule Following	3.5 (0.58)	3.8 (0.53)	-1.89#	3.4 (0.51)	3.6 (0.67)	3.8 (0.53)	2.21	4.13*
		Frustration Tolerance	3.3 (0.58)	3.5 (0.58)	-1.57	3.2 (0.56)	3.4 (0.57)	3.5 (0.58)	3.21*	4.74*
Parents' Report	Temperament	N	103	17		55	48	17		
		Effortful Control	5.2 (0.57)	5.4 (0.45)	-1.35	5.2 (0.55)	5.2 (0.60)	5.4 (0.45)	<1	<1
		Inhibitory Control	4.8 (0.88)	4.8 (0.93)	-0.21	4.7 (0.87)	4.9 (0.89)	4.8 (0.93)	1.06	<1
		Attentional Focusing	4.5 (1.03)	5.0 (0.80)	-2.30*	4.4 (0.98)	4.5 (1.09)	5.0 (0.80)	1.99	3.97*
		Low Intensity Pleasure	5.7 (0.68)	5.8 (0.58)	-0.22	5.7 (0.70)	5.7 (0.67)	5.8 (0.58)	<1	<1
		Perceptual Sensitivity	5.5 (0.85)	5.7 (0.73)	-0.93	5.6 (0.77)	5.4 (0.93)	5.7 (0.73)	1.16	<1
		Smiling & Laughter	5.4 (0.82)	5.5 (0.66)	-0.47	5.5 (0.77)	5.3 (0.86)	5.5 (0.66)	0.91	<1
Cognitive Control Assessment	DoG	N	71	15		42	29	15		
		%Delay Choices	57.2 (31.2)	69.2 (18.7)	-2.20*	56.1 (30.7)	58.6 (32.0)	69.2 (18.7)	1.26	2.53
	WM	N	77	15		46	31	15		
		WM-f	4.0 (1.21)	4.1 (1.06)	-0.31	4.0 (1.13)	4.0 (1.33)	4.1 (1.06)	<1	<1
		WM-b	2.0 (1.22)	1.7 (1.45)	0.93	2.0 (1.14)	2.1 (1.35)	1.7 (1.45)	<1	<1
Go-NoGo	N	70	15		44	26	15			
	d'	1.1 (0.63)	1.2 (0.68)	-0.51	1.2 (0.67)	0.9 (0.53)	1.2 (0.68)	1.22	<1	
Flanker	N	102	15		54	48	15			
	Conflict z-index	0.09 (0.7)	-0.25 (0.7)	1.78#	0.09 (0.7)	0.08 (0.7)	-0.25 (0.7)	1.46	2.68	
Intelligence	IQ	N	109	17		58	51	17		
		Verbal	107 (14.7)	105 (11.9)	0.70	107 (16.3)	108 (12.8)	105 (11.9)	<1	<1
	Fluid	104 (12.0)	110 (9.6)	-2.03*	105 (12.2)	104 (11.8)	110 (9.6)	1.60	2.20	

Table 4.4. Summary of results on each task and genotype used in our study.

obtained lower scores than children who carried zero copies of the allele (9/9). A similar but not significant trend was observed for the rule following scale (ANOVA: $F(2,77) = 2.17$ $p = 0.12$), however, the linear contrast analysis did show a significant linearity for this trend $F(1,77) = 4.13$, $p = 0.05$ (See Figure 4.4a). Between groups t-test significance level: * = $p < .05$; # = $p < .10$.

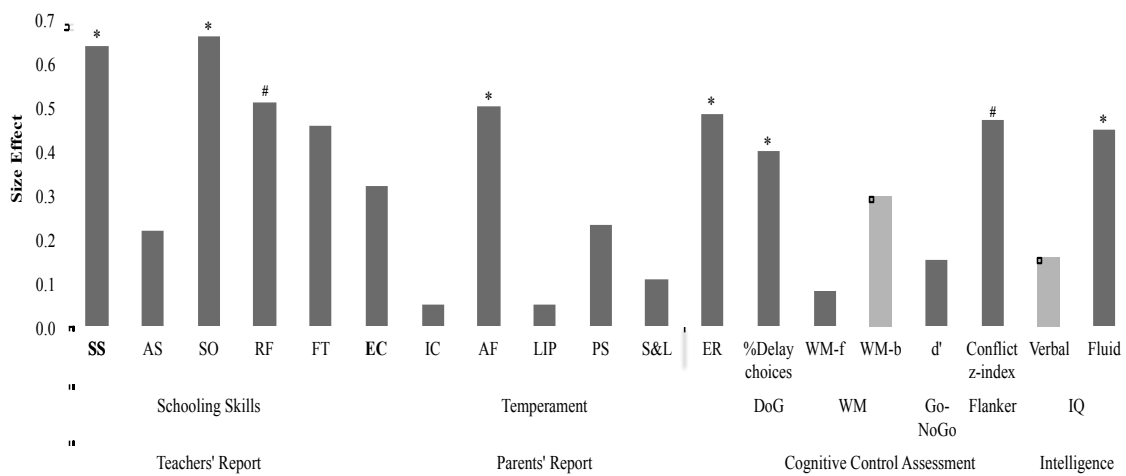


Figure 4.3. Graphical representation of the size effect of the 10r-Pr Vs. 10r-Ab comparison. Size Effect = $\text{Mean}_{Pr} - \text{Mean}_{Ab} / \text{Pooled } SD_{Pr\&Ab}$. Teachers' report. **SS**: schooling skills; AS: assertiveness; SO: socialization; RF: rule following; FT: frustration tolerance. Parents' report. **EC**: effortful control; IC: inhibitory control; AF: attentional focusing; LIP: low intensity pleasure; PS: perceptual sensitivity; S&L: smiling and laughter; ER: emotional regulation. Cognitive control assessment: DoG: Delay of Gratification Task; WM-f: working memory span forward; WM-b: backwards. Conflict z-index: $\text{Mean Z scores} = \text{Reaction Time}_{\text{ConflictEffect}} + \% \text{ Errors}_{\text{ConflictEffect}}$ (Conflict effect: Incongruent – Congruent).

4.3.3. Parents' Report

Children's Behavior Questionnaire. Statistically significant differences were observed on parent's reported measures of EC. Specifically, children in the 10r-Pr group received lower scores on the attentional focusing scale compared to those in the 10r-Ab group $t(25.6) = -2.30$, $p = .03$; $ES = .50$. No significant differences were

found for the remaining scales (for all comparisons $p > .05$). Moreover, children's scores on the attentional focusing scale also showed a tendency towards an allele-dosage effect (see Figure 4.4b) with a statistically significant linear contrast ($F(1,117) = 3.97, p = 0.05$), however the one-way ANOVA did not reach significance levels ($F(2,117) = 1.99, p = 0.14$).

Emotion Regulation Rating Scale. Children's emotion regulation skills, as reported by parents, were statistically different between the two groups: carriers of at least one copy of the 10r allele (10r-Pr) scored less compared with those in the 10r-Ab group $t(36.9) = -2.50, p = .02; ES = .48$.

4.3.4. cognitive control assessment

Delay of Gratification Task. Children in the 10r-Pr group showed a lower percent of delay of gratification responses compared to those in the 10r-Ab group $t(31.8) = -2.20, p = .04; ES = .40$.

Working Memory Span. No statistically significant differences were observed between the 10r-Pr and the 10r-Ab groups on the forward condition ($p = .76$) or the backwards condition ($p = .36$) of the task.

Go-NoGo. No statistically significant genetic-based differences were observed on children's performance of the task ($p = .62$).

Flanker Task. A marginally significant difference was found for the conflict-processing index. Children in the 10r-Pr group showed larger interference costs compared with those in the 10r-Ab group $t(18.9) = 1.78, p = .09; ES = .47$.

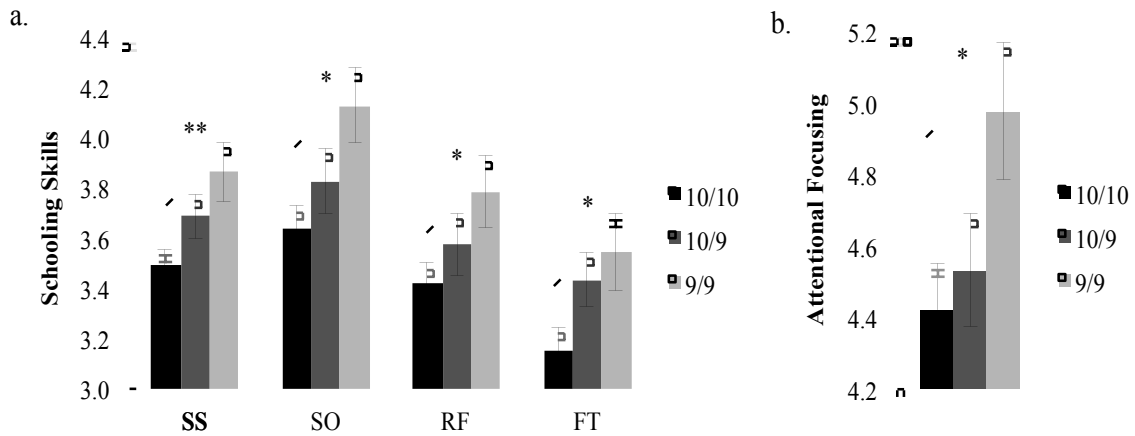


Figure 4.4. Allele-dosage effect. a) Teachers' report. **SS:** Schooling Skills; **SO:** socialization; **RF:** rule following; **FT:** frustration tolerance. b) Attentional focusing scale. Asterisks represent significance of the linear contrast. ** $p < .01$; * = $p < .05$.

4.3.5. Intelligence

KBIT. Comparison of children's intelligence scores on the fluid-IQ scale revealed a statistically significant difference between the two groups. Children homozygous for the 9r allele (10r-Ab group) outperformed those who carried one or two copies of the 10r allele $t(24.4) = -2.03, p = .05$; $ES = .45$. No significant differences were found between the 10r-Pr and the 10r-Ab groups on the, verbal IQ. For all comparisons $p > .05$

4.4. Discussion

The main goal of the present study was to determine whether presence of the 10r allele accounts for individual differences on children's capacity to modulate their own reactivity. The assessment of children included in this study was designed to evaluate SR from a multifaceted perspective by including parents' and teachers' reports, a battery of cognitive control tasks as well as an intelligence test.

4.4.1. Correlations among measures

In line with our hypothesis, correlation analysis revealed that school, home, and lab observations of SR are interrelated. First, teacher-reported schooling skills are positively related with parent-reported measures of EC and emotion regulation skills. The relation between children's schooling skills and EC has been previously reported by Checa et al. (2008) with 12 years old children. Also, Liew and collaborators demonstrated that at a preschool age, EC and emotional regulation are related to the social adjustment of children in the school as rated by parents, teachers and peers (Liew, Eisenberg, & Reiser, 2004). These correlations demonstrate that a temperamental disposition towards an adequate exercise of self-regulatory mechanisms helps on moderating reactivity in contexts that often elicit emotional activation. In this way, a child with high EC is better able to control the expression of negative emotions when facing frustration or disappointment and is therefore more likely to be accepted by the peer group.

On the question of how adult-reported measures of SR correlate with children's performance on the battery of cognitive control tasks, we found that teacher-reported schooling skills, particularly the sociability and the frustration tolerance scales are positively related with children's capacity to delay gratification in laboratory settings. This correlation indicates that the ability to regulate reactivity in situations that involve highly rewarding motivational states contribute to the adjustment of children in the school. Several studies in the field have reported data in the same direction (see Mischel, Shoda, & Rodriguez, 1989 for a review) showing that the ability to delay gratification at a preschool age has a highly predictive validity for later outcomes in the social, cognitive and health domains (Mischel et al., 2011). Moreover, we found that children who perform

better on the conflict-monitoring flanker task are perceived by teachers as being better adjusted in the school and also exhibit higher scores on the verbal and fluid intelligence test. This result is consistent with those reported by Checa et al. (2008) and confirms that at preschool age executive attention skills play a central role on the social and academic adjustment of children in the school.

Furthermore, we found that one aspect of parent-reported EC, in particular the attentional focusing scale, is related to children's working memory, inhibitory control and intellectual functioning. It has been proposed that the EAN serves as the neural substrate for the development of EC (see Rueda, 2012 for a review). The association between EC and cognitive functions supported by this brain network found in our study supports this idea. Previous studies have already reported the association between intellectual functioning and preschoolers' EC (Kochanska, Aksan, Penney, & Doobay, 2007). It is important to note that the construct of fluid intelligence comprises higher-level EFs such as problem solving and reasoning skills, which rely to a large extent on the efficiency of executive attention processing and basic EFs such as inhibitory control, cognitive flexibility and working memory (Diamond, 2013). Also, previous studies have demonstrated that the neural activation underlying intellectual functioning overlaps largely with the EAN (Duncan et al., 2000).

4.4.2. Genetic-based individual differences in SR

In accordance with the proposed hypothesis, results in the current study show that presence of the 10r allele of the DAT1-SLC6A modulates children's ability to exert voluntary regulation of their reactivity. In particular, comparisons between the two groups (10r-Pr vs. 10r-Ab) indicate that children carrying at least one copy of the 10r allele exhibit poorer self-regulatory skills mostly (although

maybe not exclusively) on the socioemotional domain (schooling skills, emotion regulation, and delay of gratification task). These instruments assess children's ability to regulate responses in situations where both reactivity and the modulation of it involve affective and motivational states that are highly influenced by social and appetitive rewards. An example of this are the scales included in the teacher-reported schooling skills. During the preschool period, children deal with an increased amount and complexity of social interactions, which constantly trigger both positive and negative emotions. In such context, the ability to efficiently manage frustration or to adapt to common rules is influenced by social rewards often provided by teachers and peers. Not surprisingly, children who show higher self-regulatory skills are also better accepted by the peer group and exhibit greater social and academic adjustment in the school (Checa et al., 2008; Nancy Eisenberg et al., 2011).

The findings of the current study are consistent with the idea of separate frontal systems underlying SR in neutral vs. motivational/emotional-relevant contexts (Zelazo & Cunningham, 2007). While the so-called "cool" or purely cognitive processes appear to be mostly supported by the activation of dorsolateral and medial structures of the prefrontal cortex, regulation of appetitive/motivated reactivity relies on the activation of a ventromedial network that comprises orbitofrontal structures of the prefrontal cortex (Dennis, 2010; Perlman & Pelphrey, 2011; Zelazo & Cunningham, 2007). Other researchers have also argued for a similar cognitive/neutral vs. emotional division within the ACC (Bush et al., 2000).

At the level of neural functioning, the observed influence of the 10r allele on children's self-regulatory skills may be explained by the patterns of connectivity

between the dorsolateral and ventromedial networks and other regions of the brain. On the one hand, the dorsolateral prefrontal cortex is strategically connected with a widespread number of structures including the thalamus, the basal ganglia (particularly the dorsal caudate nucleus), the hippocampus, as well as primary and secondary association areas of the neocortex that comprise posterior temporal, parietal and occipital areas (Fuster, 1989). On the other hand, the functional role of the orbitofrontal cortex on the regulation of affective responses is based on its direct reciprocal connections with subcortical structures that process the motivational salience of stimuli and produce reward-dependent behaviors such as the ventral (limbic) compartment of the striatum as well as other areas associated to the limbic system such as the amygdala and the ventral anterior cingulate cortex (Kringelbach, 2005; Lehericy et al., 2004). Previous neuroimaging studies have provided the evidence for the role of this corticostriatal circuit on the regulation of affective and motivational responses. An example of this is the fMRI study carried out by Urry et al. (2006) using a voluntary emotional regulation task. They found that the ventromedial prefrontal cortex, including the ventral anterior cingulate cortex is reciprocally connected with the amygdala when individuals regulate affective responses to negative picture stimuli.

Integrating our data in the line of this knowledge, we suggest that the less efficient striatal dopaminergic system associated to the presence of the 10r allele impacts the adequate functioning of the corticostriatal circuit, influencing children's ability to regulate themselves in motivationally significant situations. This finding is in agreement with those previously reported by Dreher, Kohn, Kolachana, Weinberger, & Berman (2009) and Forbes et al. (2009) who found that carriers of two copies of the 10r allele exhibit a decreased reward-related activity

in the ventral striatum. Furthermore, there is evidence of a relation between striatal dopamine availability and neural activity in frontal structures of the ventromedial network in healthy individuals (Siessmeier et al., 2006). The findings reported in present study, while preliminary, shed light on the neurobiological basis of SR in typically developing children. However, further neuroimaging studies need to be undertaken in order to understand how the decreased striatal dopamine levels linked to the presence of the 10r allele influences the actual functioning of the corticostriatal circuit when regulation takes place in motivationally salient contexts.

In our study, presence of the 10r allele was also related to lower scores on the parent-reported attentional focusing scale of the CBQ. This result agrees with findings of other studies that have pointed to a central role of attention control on the regulation of motivational/appetitive reactivity (see Metcalfe & Mischel, 1999 for a review), a function that appears to be mediated by the action of the anterior cingulate cortex (Bush et al., 2000). Decreased levels of striatal dopamine on carriers of the 10r allele may influence the activity of the anterior cingulate cortex via dopamine neurons connecting these structures.

Our results reported in the current study provide a new insight on the neurobiological mechanisms that may underlie SR in childhood, which has not been reported before. However, it is important to note that the model tested in this study differs from that tested in previous studies. Due to the low incidence of individuals homozygous for the 9r allele, most of the previous studies in the field have compared the performance of individuals with the 10/10 homozygous genotype with that of individuals with the 10/9 heterozygous genotype, which assumes dominance of the less frequent 9r allele for example as a protective factor for the diagnosis of ADHD.

However, as mentioned in the introduction, no conclusive results in favor of such model have been reported and studies with healthy individuals have also led to contradictory results (see Rommelse et al., 2008 for a review). In contrast, the current study tests how presence of the 10r allele, a variation that is associated to less efficient DA pathways (Mill et al., 2002; VanNess et al., 2005), influences children's SR. In detail, we tested a model where the less frequent 9r allele is recessive and two copies of it are necessary to build up an efficient mechanism of DA re-uptake in the basal ganglia, which in turn impacts the whole dopaminergic system through the different DA pathways.

Based on the findings reported by Mill et al. (2002), we further explored if the influence of the 10r allele exhibits an allele dosage effect. This quantitative effect of the 10r allele was found significant on the measures of socialization, rule following, frustration tolerance and attentional focusing. The same tendency, albeit being not significant was observed in the emotional regulation and the delay of gratification tasks. Results show that carriers of two copies of the 9r allele perform better than those who carry only one copy of the allele, who in turn over perform those who are homozygous for the 10r allele. However, given a small sample size, we have to be cautious drawing conclusions. To investigate the influence of the DAT1 gene on SR is an important avenue for further research with an extended sample size and a fair balance of individuals from each genotype in each group.

The current study provides additional evidence regarding the influence of the DAT1 gene on SR during preschool period. In particular, we found that presence of the 10r allele influences preschooler's self-regulatory skills, especially those needed to modulate affective/motivational reactivity in social contexts. Compared to previous studies, the assessment of SR implemented here adopted a multifaceted approach including a whole range of measures that allow evaluating children's capacity to

regulate themselves from different perspectives and in different contexts. The results we report gathered with this multi-angular experimental design support the idea of Green and collaborators (2008) who suggest that the study of the genetic basis of cognitive processes require the precise definition of phenotypes. Therefore, to confirm the association reported here and identify the neural endophenotype that links DAT1 variations with the observable self-regulatory abilities, future work in this direction will likely combine measures of affective regulation with neuroimaging techniques as well as measures that assess children's self-regulatory abilities in their daily contexts.

Chapter 5

Genetic modulation of cognitive gains following executive attention training in children

5.2. Introduction

Executive attention refers to a set of processes involved in the conscious control of cognition and action, and is a core mechanism of self-regulation (Rueda et al., 2011). Regulation of behavior is needed in order to meet social demands and achieve goals, and individual differences in this ability are an important predictor of children's academic outcomes and socio-emotional adjustment (Checa et al., 2008; Nancy Eisenberg et al., 2010; Rueda et al., 2010). Much evidence suggests that the development of self-regulation is supported by maturation of a network of frontal structures, involving the anterior cingulate (ACC) and lateral prefrontal cortices, which is referred to as the executive attention network (Michael I Posner & Rothbart, 2009). Mechanisms of the executive attention network include conscious detection of targets and errors, monitoring of conflict among responses, and inhibition of dominant but inappropriate responses (Rueda, Posner, et al., 2005b).

Executive attention shows a protracted developmental course throughout childhood and adolescence (Rueda, 2013) that is common to typically developing individuals, however children greatly differ in their ability to regulate thoughts and behavior. Compelling evidence has been provided that environmental (e.g., parenting, education, nutrition, etc.) as well as constitutional (e.g., temperament, genes) factors account for these remarkable individual differences (Rueda & Cómbita, 2013). Nonetheless, much less is known about how these factors may interact with each other. The main goal of the current study is to examine interactions between genetic variation and experience during an early period of development of executive attention.

Mounting evidence is showing that children's executive skills can be enhanced at different stages of development by means of cognitive training. Beneficial effects of training have been reported using a variety of programs on measures of fluid intelligence (Rueda, Rothbart, et al., 2005), working memory (Thorell et al., 2009) and cognitive control (Diamond et al., 2007b) in children of different ages (Diamond & Lee, 2011), as well as in adulthood (Jaeggi et al., 2008) and elderly (Dorbath, Hasselhorn, & Titz, 2011; Karbach & Kray, 2009). Besides, electrophysiological data indicate that both children (Rueda, Checa, & C3mbita, 2012; Rueda, Rothbart, et al., 2005) and adults (Millner, Jaroszewski, Chamarthi, & Pizzagalli, 2012) show faster and more efficient brain reactions while engaged in attention tasks after training. Moreover, training-related gains in performance are accompanied by increased activation in brain areas that are largely modulated by DA neurotransmission, such as prefrontal (Buschkuohl, Jaeggi, & Jonides, 2012; Jolles, Grol, Van Buchem, Rombouts, & Crone, 2010; Olesen et al., 2004b), and striatal (Dahlin, Neely, Larsson, B3ckman, & Nyberg, 2008) structures, as well as changes in the binding potential of particular DA receptors (B3ckman et al., 2011; McNab et al., 2009). Despite the accumulating evidence showing beneficial effects of training, sometimes the effect is shown to be weak and/or limited to particular measures (Rueda et al., 2012; Thorell et al., 2009), and may be determined to a larger extent by individual differences in training performance (Jaeggi, Buschkuohl, Jonides, & Shah, 2011). The question of why some individuals show improvements with training while others do not remains unknown. In the current study, we aimed at testing whether susceptibility to executive attention training depends, at least in part, on genetic variability in DA-related genes.

Compelling evidence indicates that genetic factors also play an important role in executive skills. Twin studies have provided evidence that executive attention shows a significant level of heritability (Fan et al., 2001). The influence of variation in DA-related genes has primarily been examined given the modulatory role of this neurotransmitter in the prefrontal cortex (Diamond, 2001) and specifically within the circuitry of the executive attention network (Fan, Fossella, Sommer, Wu, & Posner, 2003; Fossella et al., 2002).

One of the mechanisms of DA regulation in the brain is provided by the action of dopamine transporters (DAT). *In vivo* studies have shown that the action of DAT represents the main mechanism for DA reuptake in the human striatum (Garris & Wightman, 1994). Expression of DAT is regulated by a variable number of tandem repeat (VNTR) polymorphism in the SCL6A3/DAT1 gene. Genetic evidence reveals that individuals homozygous for the 10-repeat allele (10/10 genotype) show a higher expression of the gene, a feature that functionally translates into less availability of extra-synaptic DA (Heinz et al., 2000; Mill et al., 2002; VanNess et al., 2005). In healthy children, homozygosity for the 10r allele is associated with poorer performance on measures of spatial attention, response inhibition and selective attention, but not on measures of WM (Bellgrove et al., 2007; Cornish et al., 2005).

Dopamine D4 receptors, encoded by the Dopamine Receptor D4 (DRD4) gene, are also an essential mechanism for DA transmission in the human prefrontal cortex. A variable number tandem repeat (VNTR) polymorphism in exon III of the gene, specifically the 7-repeat (7r) allele, alters the primary structure of the protein and has been related to a diminished DA response. Association studies with typically developing children have shown that carriers of this variant appear

to be more distractible (Laucht, Becker, & Schmidt, 2006); show higher levels of negative affect (Holmboe, Nemoda, Fearon, Sasvari-Szekely, & Johnson, 2011b); exhibit preference for novel stimulation during infancy (Auerbach, Benjamin, Faroy, Geller, & Ebstein, 2001), and perform worse in measures of executive attention (C. a T. Kegel & Bus, 2013; Schmidt, Fox, Perez-Edgar, Hu, & Hamer, 2001) and spatial WM (Froehlich et al., 2007).

Finally, mechanisms of DA degradation have also been studied in relation to individual differences in executive control. Action of the catechol-*O*-methyltransferase enzyme represents the main mechanism of DA degradation within the prefrontal cortex (Tunbridge et al., 2007). Its activity level is regulated by variations of the COMT gene, particularly the Val¹⁵⁸Met polymorphism, which affects COMT stability, and thus, function. COMT genotype can be assessed by looking at combinations of different variations within the gene (i.e., haplotypes). It has been suggested that a haplotype containing 4 single nucleotide polymorphisms (including the Val¹⁵⁸Met variation) is related to the regulation of pain sensitivity in humans and accounts for COMT expression level as well as activity (Diatchenko et al., 2005; Nackley et al., 2006). The proposed categorization, i.e., Low, Average and High pain sensitivity (LPS; APS and HPS respectively), has recently being used in the field, proving to be a more precise measure of the regulation of DA availability by COMT within the prefrontal cortex. The LPS haplotype is associated to higher COMT enzymatic activity (therefore less DA levels), compared to the APS and the HPS haplotypes. In a study carried by (Voelker et al., 2009), the Val¹⁵⁸Met polymorphism was tested in comparison to the COMT haplotype in relation to attentional function in toddlers. The latter classification was found to be a stronger predictor of performance, with children in the *Low pain sensitivity* (LPS) group

showing better performance compared with infants in the *Moderate pain sensitivity* (MPS) group.

A further question is whether DA function also influences the extent that experience affects brain plasticity. Stroemer and colleagues (1998) reported that the administration of an amphetamine-based treatment that stimulates DA release in presynaptic terminals to rats with lesions produces a significant increment in the expression of proteins that contribute to neurite growth and synaptogenesis. The induced DA release was also related to both behavioral and cognitive recovery. Moreover, pharmacoinaging evidence with animals indicates that DA levels influence changes in the BOLD signal in the striatum through the action of D1 receptors (Knutson & Gibbs, 2007). In humans, it has been examined whether the effect of different environmental factors on cognitive development is modulated by variation in DA-related genes. There is evidence that carriers of the DAT1 10r/10r variation show poorer self-regulated behavior compared to carriers of at least one copy of the 9r allele when subject to negative situations such as prenatal smoke exposure (Becker, El-Faddagh, Schmidt, Esser, & Laucht, 2008; Kahn, Khoury, Nichols, & Lanphear, 2003) or low birth weight (Langley et al., 2008). Conversely, carriers of the 9r polymorphism appear to benefit more from favorable familial and educational factors than carriers of the 10r allele (Lahey et al., 2011; Sonuga-Barke et al., 2009; van den Hoofdakker et al., 2012). Also, children carrying at least one copy of the 7r allele of the DRD4 gene appear to be more susceptible to environmental variables such as parenting (Bakermans-Kranenburg & van IJzendoorn, 2006, 2011; Knafo, Israel, & Ebstein, 2011; Sheese, Rothbart, Voelker, & Posner, 2012; Sheese et al., 2007) and literacy instruction (Kegel, Bus, & van IJzendoorn, 2011) when compared to 4r homozygous peers. Regarding the COMT

haplotype, Voelker et al. (2009) found that infants' ability to predict the location of upcoming targets in a visual sequence learning task was affected by the quality of parenting but only for infants in the LPS group.

For the present research, we aimed at improving children's inhibitory control and WM skills by means of a computer-based intervention (Rueda et al., 2012; Rueda, Rothbart, et al., 2005). To test for genetic modulation of training effects, the children's DNA was extracted from saliva samples and genotyped for several DA-related genes. We expected that susceptibility to training would be enhanced for carriers of the 7r of the DRD4 gene and the 9r of the DAT1 gene, whereas the prediction was somewhat less clear for variations of the COMT haplotype. We speculated that carriers of the COMT haplotype associated to a moderate pain sensitivity (MPS), might show larger gains after training, attributable to their higher DA availability in areas of the brain that support the cognitive processes being trained.

5.3. Method

5.3.1. Participants

Preschool-aged children (n=107; 58 males; mean age: 60.1 months; SD: 7.3) from an urban area of southern Spain whose parents gave written consent participated in the study. They had normal or corrected-to-normal sensory capacities, no history of chronic illness and/or psychopathologies and were not under pharmacological treatment of any kind. Children received presents (e.g. toys and a lab t-shirt) in appreciation for their participation. A total of 5 families did not consent to the part of the study involving genetic analysis. Children who did not

complete the pre and post evaluation sessions ($n=10$) were excluded from the analysis. Descriptive data of the final sample are presented in Table 5.1.

Group	N	Gender (girls)	Age in months (SD)	DAT1		DRD4		COMT		
				9r Pr	9r Ab	7r Pr	7r Ab	LPS	MPS	HPS
Trained	64	27	63.5 (7.5)	26	31	17	43	35	16	7
Control	33	13	63.7 (6.6)	19	13	7	25	16	10	4

Table 5.1. Sample description

5.4. Procedure

Experimental sessions were carried out before (PRE) and after (POST) intervention by experimenters who were blind to the experimental condition of the participant. During these sessions, participants completed a set of pen and paper tasks aimed at measuring intelligence, inhibitory control, and working memory. Each session lasted approximately 45 minutes including small breaks between tasks. After the pre-intervention session, participants were pseudo-randomly assigned to either the training group or the active control group. Individuals in the two groups were matched in age, gender and IQ. Children in the Trained Group carried out eight 45-min sessions during a period of 3 weeks (2-3 sessions a week) in which they played different computer exercises of increasing levels of difficulty. Training sessions were run individually for each participant in a quiet room at the school, and were guided by trained experimenters. Participants assigned to the untrained control group underwent similar conditions but performed only the initial levels of the exercises in the training program and

completed the session time when needed by watching popular cartoon videos. Session POST was completed within one week after the completion of the intervention period.

5.4.1. Genotyping procedure

DNA was isolated from saliva samples using Oragene collection kits (DNA Genotek Inc., Ontario, Canada) according to the manufacturer's instructions. Approximately 10-40 ng of template was included in each PCR amplification, reactions contained 0.2 mM each deoxynucleotide, 0.2 μ M each oligonucleotide, 0.05 U/ μ l recombinant Taq DNA polymerase with its 1x reaction buffer $(\text{NH}_4)_2\text{SO}_4$ (Thermo Fisher Scientific, Pittsburg, PA), and 8% (COMT, DAT1)-20%(DRD₄) QuickExtract buffer V1.0 (Epicentre Biotechnologies, Madison, WI) in addition to PCR-specific optimizations. The DAT1 amplification contained 1.5 mM MgCl_2 , 0.6 M betaine, and the oligonucleotides DAT1F 5'-TGTGGTGTAGGGAACGGCCTGAG and DAT1R 5'-CTTCCTGGAGGTCACGGCTCAAGG (Shinohara et al., 2004). Amplification conditions were the following: 95°C 4min; 35x 94°C 30 sec, 65°C 1 min, 72°C 30 sec; 72°C 3 min. Amplified products were size separated on a 2% agarose gel (GenePure LE, BioExpress, Kaysville, UT) and visualized using ethidium bromide. Genotype was grouped by 9-repeat carriers (a 440 bp product) and 9-repeat absent (homozygous for the 480 bp 10-repeat product). The COMT haplotype was amplified and identified as in Voelker et al. (2009). Three different groups were constituted. The *low pain sensitivity* (LPS) group comprised children homozygous for the LPS allele as well as carriers of the LPS/APS genotype; average pain individuals included in the *moderate sensitivity pain* (MSP) group were either homozygous for the APS allele or carriers of the HPS/LPS. Finally, children

homozygous for the HPS and carriers of the APS/HPS genotype were included in the *high pain sensitivity* group (HPS). The DRD4 genotype was determined as previously published (Sheese et al., 2012). Individuals were grouped by the presence or absence of the 7-repeat allele (619 bp).

5.5. Materials

Assessment tasks

Fluid and verbal intelligence were measured with the Kaufman Brief Intelligence Test (K-BIT; Kaufman & Kaufman, 1990). Inhibitory control was measured by means of the Simon Says task (Strommen, 2009), which requires inhibiting a predominant motor response when a verbal cue is missing. Working memory (WM) span was assessed with the forward and backward subtests of the WISC (Wechsler, 1991). The *forward* condition measures maintenance of information in WM, whereas the *backward* condition grasps processes of maintenance and manipulation of information.

Training program

The training program consisted of a set of computer-based exercises designed to train attention and executive control. Exercises within the program are divided in 5 categories: 1) Tracking/Anticipation, 2) Attention Focusing/Perceptual Discrimination, 3) Conflict Resolution/Attentional flexibility, 4) Inhibitory control, and 5) Sustained Attention. Exercises within each category are described in Table 5.2. All exercises comprised several levels of difficulty, and completion of a minimum number of correct trials in a row (3, in most exercises) is required in order to pass from one level to the next.

Category	Exercise	Trained process	Brief Description
1	Side	Target tracking	Navigating a cartoon cat to reach areas of grass and avoid muddy areas, which get progressively bigger
	Chase	Target tracking and anticipation	Anticipating where a cartoon duck that swims across a pond in a straight line will come across in order to chasing it. In the highest levels of difficulty, the duck dives so that its trajectory remains invisible.
	Maze	Anticipation	Navigating a cartoon cat through a maze to get food.
2	Portraits	Focusing attention, perceptual discrimination and working memory	Matching-to-sample exercise with cartoon pictures. Requires clicking on the one of two pictures that looks exactly the same as the sample picture. In higher levels, the sample picture disappears before the two choices appear and the child is to keep in mind the attributes of the sample picture.
	Shapes	Focusing attention, perceptual discrimination and working memory	A number of overlapping figures are presented and the child has to determine which are the ones presented by clicking on the appropriate buttons displayed on the sides of the screen.
3	Numbers	Conflict monitoring and resolution	Two sets of numbers are presented and children have to click in the group composed by the larger amount of items. Trials can be congruent (larger group made up of numbers of higher value) or incongruent (larger group made up of numbers of lower value)
	Value-not-size	Conflict monitoring and resolution	Various numbers differing in size are presented on the screen. Children are asked to click on the number of higher value disregarding the size. Size and value can be congruent (the higher number is the larger in size) or incongruent (the higher number is the smaller in size).
	Teacher	Attentional flexibility	The child is to classify items according to the rule presented by a teacher. Objects are to be classified according to dimensions of shape, color and size. The rule changes at different rates throughout the exercise.
4	Farmer	Inhibitory control	Cartoons animals (either sheep or wolfs) appear behind a bale of hay and children are asked to quickly click only to sheep in order to bring them inside a fence.
	Robots	Inhibitory control	Children are to feed robots with metal pieces according to their shape and color in a fast pace. They must avoid feeding each particular robot with pieces of non-corresponding shape/color.
5	Frog	Sustained attention and preparation	The child must press a key as fast as possible in order to help a frog catching flies that come out of a bottle. The requirement to sustain attention is increased by enlarging the interval of time between targets, and presence/absence of warning signals.

Table 5.2 Description of the exercises included in the training program

5.6. Results

5.6.1. Training effects

Using the scores of the various measures taken in the evaluation sessions as dependent variables, we conducted a number of ANOVAs including Session (pre vs. post) and Intervention Group (trained vs. control) as independent factors. Planned contrasts were conducted to assess pre vs. post changes in every score given *a priori* predictions. Additionally, we calculated the effect size (ES) of the intervention using the formula described by Carlson & Schmidt (1999): $ES = [(Trained_{Post} - Trained_{Pre}) - (Control_{Post} - Control_{Pre})] / Pooled\ SD_{Pre}$. Mean and SDs of the pre- and post-intervention scores as well as ES for each measure are presented in Table 5.3.

K-BIT. A significant main effect of Session was found for the fluid intelligence (fIQ) subscale score [$F(1, 93) = 4.00; p < .05$], which was qualified by a Intervention Group x Session interaction [$F(1, 93) = 7.99; p < .01$]. Planned contrasts revealed that only children in the trained group showed a significant increase after intervention [$F(1,93) = 16.76; p < .001$], contrary to children in the control group whose scores did not change from session pre to post ($F < 1$). For the verbal intelligence (vIQ) subscale score, neither the main effect of session ($F < 1$) nor the Intervention Group x Session interaction was significant ($F < 1$).

Inhibitory control. Children who showed difficulties for understanding the instructions and/or committed above 80% of errors in either session were excluded from the analysis ($n=31$). The percentage of inhibition errors was used as a measure of Inhibitory Control (IC). A significant main effect of Session was found [$F(1, 59) = 8.10; p < .01$]. The Intervention Group x Session interaction was not

DV	Group	n	PRE		POST		Post-Pre gain	Pre vs. Post contrast	ES
			Mean	(SD)	Mean	(SD)			
flQ	T	62	104.3	(11.9)	110.5	(10.0)	6.19	16.76***	0.59
	AC	33	106.7	(12.4)	105.7	(12.2)	-1.06	<1	
vIQ	T	62	108.6	(15.0)	110.1	(12.8)	1.50	1.27 ^{ns}	0.11
	AC	33	106.5	(16.3)	106.3	(15.8)	-0.15	<1	
IC	T	44	30.5	(19.4)	19.3	(17.1)	11.14	12.45***	0.26
	AC	17	30.6	(21.4)	24.7	(20.4)	5.88	1.34 ^{ns}	
WMf	T	64	4.2	(1.2)	4.5	(1.2)	0.34	4.92*	0.11
	AC	33	3.9	(1.5)	4.1	(1.2)	0.21	<1	
WMb	T	64	2.1	(1.4)	2.4	(1.2)	0.27	4.40*	0.19
	AC	33	1.8	(1.2)	1.9	(1.3)	0.03	<1	

Table 5.3. Training results. Means and Standard Deviations (SD) for each dependent variable (DV) included in the study and each group (T: Trained; AC: Active Control) in sessions PRE and POST. flQ: fluid intelligence; vIQ: verbal intelligence; IC: Percentage of inhibition errors in the Simon Says task; WMf: WM span in the *forward* condition; WMb: WM span in the *backward* condition. Direct pre-to-post-training gain was calculated by subtracting post-pre scores. Statistical results (F value) for the planned contrast and effect sizes (ES) are shown in the last two columns. Significance level: *** = $p < .001$; * = $p < .05$; ns = $p > .10$

statistically significant ($F < 1$). However, planned contrasts revealed a significant decrease on the percentage of inhibition errors in the trained group [$F(1, 59) = 12.45$; $p < .001$], which did not reach significance in the untrained group [$F(1, 59) = 1.34$; $p = .25$].

WM Span. A main effect of Session was found for the forward digit span score [$F(1, 95) = 4.37$; $p < .05$] but did not reach significance for the backwards digit span score [$F(1, 95) = 1.85$; $p = .18$]. The Intervention Group x Session interaction did not reach significance with neither the forward ($F < 1$) nor the backwards score [$F(1, 95) = 1.17$; $p = .28$]. However, planned contrast showed that increments on WM scores were significant only for the trained group on both the

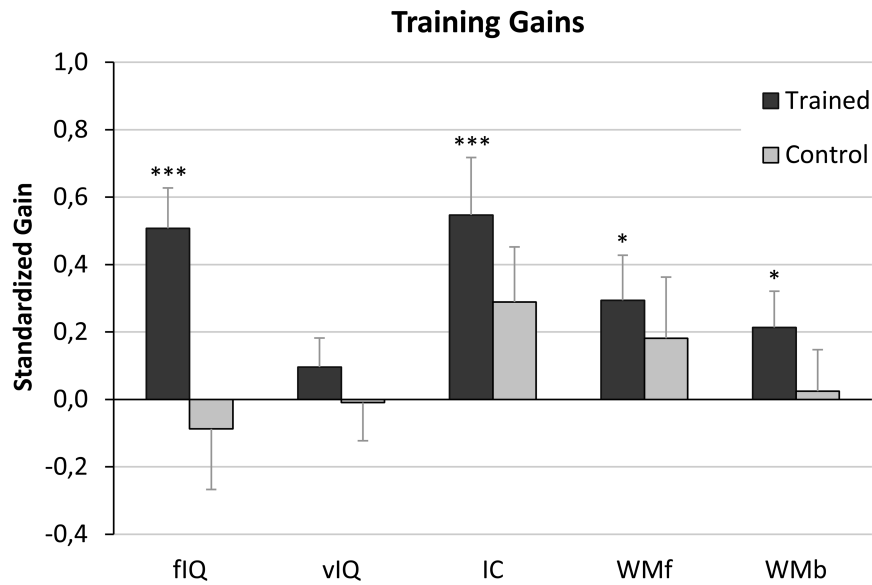


Figure 5.1. Graph representing the standardized gain (SDgain) for the trained and control groups in the different scores included in the study. Error bars represent standard errors. Asterisks depict the dependant variables were there was a statistically significant pre- to post-training gain. $SDgain = ((M_{Post} - M_{Pre}) / SD_{Pooled\ Pre})$. Significance level: ** = $p < .01$; * = $p < .05$; $\approx = p < .10$

forward [$F(1, 95) = 4.92$; $p < .05$] and backwards score [$F(1, 95) = 4.40$; $p < .05$]; all $F < 1$ for the same comparisons in the control group.

To illustrate the pre- to post-training gains standardized pre- to post-training gains were estimated for the Trained and Control groups using the pooled standard deviation of both groups in the Pre- training session ($SDgain = (M_{Post} - M_{Pre}) / SD_{Pooled\ Pre}$). SD gains are depicted in Figure 5.1.

5.6.2. Gene x Training interactions

The number of children in the High pain sensitivity group (HPS) in our sample was very low ($n = 11$; see Table 5.1), therefore children with this variation were not considered in the analysis. No statistically significant differences (all $p > .05$) in performance at pretest were found between children carrying the

variations of interest in each gene (DAT1: 9r-Ab vs. 9r-Pr; DRD4: 7r-Ab vs. 7r-Pr; COMT: Low Pain vs. Moderate Pain) in any of the dependent variables examined in the study. Homogeneity of variance was tested using the Levene's test and no significant differences were found between any of the groups (all $p > .05$). Mean and SDs of the pre- and post-intervention scores on intelligence, inhibitory control and WM for groups with genetic variations of interest are presented in Table 5.4. Also, pre-to-post-training SD gains on each measure and each genetic variation are depicted in Figure 5.2.

Analyses of variance were performed with each dependent variable including Genetic Variation and Session as independent factors. Additionally, gains following intervention were examined for each group with planned contrasts given the a priori predictions regarding differences in susceptibility to intervention.

TASK	DV	Gene Variation	n	PRE		POST		Post-pre Gain	Contrast Pre vs. Post	Effect Size
				Mean	(SD)	Mean	(SD)			
<i>DAT1 Gene</i>										
K-BIT	flQ	9rPR	26	103.8	(13.7)	109.5	(9.4)	5.73	6.73*	0.08
		9rAB	29	103.2	(10.6)	109.9	(8.9)	6.72	10.34**	
	vlQ	9rPR	26	105.5	(15.4)	108.7	(13.1)	3.19	ns	0.15
		9rAB	29	108.0	(14.0)	108.9	(12.8)	0.93	<1	
Inhibitory control	% Errors	9rPR	20	32.5	(21.5)	24	(19.3)	-8.5	ns	0.21
		9rAB	19	27.4	(17.3)	14.7	(15.0)	-12.7	5.71*	
Working Memory span	WMf	9rPR	26	4.0	(1.2)	4.6	(1.2)	0.58	5.59*	0.21
		9rAB	31	4.1	(1.2)	4.4	(1.3)	0.32	ns	
	WMb	9rPR	26	1.9	(1.5)	2.5	(1.4)	0.54	6.36*	0.33
		9rAB	31	2.1	(1.2)	2.2	(1.1)	0.10	<1	

<i>DRD4 Gene</i>										
K-BIT	fIQ	7rPR	17	103.9	(11.5)	110.7	(10.0)	6.8	6.21*	0.10
		7rAB	41	104	(12.7)	110	(9.4)	5.7	10.30**	
	vIQ	7rPR	17	106.9	(12.3)	108.1	(12.9)	1.2	<1	0.04
		7rAB	41	107.8	(15.9)	109.6	(12.6)	1.8	ns	
Inhibitory control	% Errors	7rPR	13	32.3	(20.9)	18.5	(16.7)	-13.8	4.75*	0.29
		7rAB	27	28.1	(19.0)	20	(18.2)	-8.1	3.42 \approx	
Working Memory span	WMf	7rPR	17	4.1	(1.0)	4.5	(1.3)	0.5	ns	0.15
		7rAB	43	4.2	(1.3)	4.5	(1.2)	0.3	ns	
	WMb	7rPR	17	2.1	(1.3)	2.4	(1.6)	0.3	ns	0.03
		7rAB	43	2.1	(1.4)	2.4	(1.1)	0.3	ns	
<i>COMT Haplotype</i>										
K-BIT	fIQ	LPS	34	104	(12.2)	109.7	(9.3)	5.9	8.82**	0.10
		MPS	16	105.6	(13.2)	112.8	(10.0)	7.3	6.24*	
	vIQ	LPS	34	106	(15.6)	108.3	(12.8)	2.4	ns	0.17
		MPS	16	110.1	(13.6)	109.9	(12.7)	-0.2	<1	
Inhibitory control	% Errors	LPS	24	23.3	(18.6)	18.8	(15.4)	-4.6	ns	0.57
		MPS	8	41.3	(22.3)	25	(16.9)	-16.3	5.11*	
Working Memory span	WMf	LPS	35	4.2	(1.2)	4.5	(1.2)	0.3	ns	0.02
		MPS	16	4.3	(1.3)	4.6	(1.4)	0.3	<1	
	WMb	LPS	35	2.1	(1.3)	2.2	(1.4)	0.1	<1	0.38
		MPS	16	2.2	(1.5)	2.8	(1.0)	0.6	5.83*	

Table 5.4. Gene x Training interactions. Means and Standard Deviations (SD) for each Genetic Variation group in the pre and post training sessions in several dependent variables (DV). Direct pre- to post-training gain was calculated by subtracting post-pre scores. Statistical results (F value) for the planned contrast and effect sizes (ES) are shown in the last two columns. Significance level: ** = $p < .01$; * = $p < .05$; \approx = $p < .10$; ns = $p > .10$

Presence vs. Absence of the 9r allele at the DAT1 gene. The Genetic Variation x Session interaction was not significant for any of the scores included in the study (fIQ, vIQ, IC, and WMf: $F < 1$; WMb: $F = 2.33$, $p = .13$). Planned contrasts revealed that differences in fIQ score from the pre- to the post-training session were significant

regardless of genotype of the DAT1 [9r-Ab group: $F(1, 53) = 10.34$; $p = .002$; 9r-Pr group: $F(1, 53) = 6.73$; $p = .01$] whereas no significant pre-to-post change was observed for the vIQ score in any of the groups ($F < 1$, and $F(1, 53) = 2.32$; $p = .13$ respectively for the 9r-Ab and 9r-Pr groups). Also, results revealed that the decrease in percentage of inhibition errors after training was significant for children in the DAT1 9r-Ab group [$F(1, 37) = 5.71$; $p = .02$], but only marginal for children in the 9r-Pr group [$F(1, 37) = 2.72$; $p = .10$]. Finally, only children carrying the 9r allele showed significant improvements after training on the forward [$F(1, 55) = 5.59$; $p < .05$] and backwards scores [$F(1, 55) = 6.36$; $p < .05$] whereas pre- to post-training changes were not significant for homozygous for the 10r on the forward [$F(1, 55) = 2.08$; $p = .15$] and backward scores ($F < 1$).

Presence vs. Absence of the 7r allele at the DRD4 gene. The Genetic Variation x Session interaction was not significant for any of the scores included in the study ($F < 1$ for all scores). Planned contrasts revealed that differences in performance from pre- to post-training session for the fIQ score were significant regardless of genotype of the DRD4 [7r-Ab: $F(1, 56) = 10.30$; $p = .002$; 7r-Pr: $F(1, 56) = 6.21$; $p = .002$] and were not significant for the vIQ score [7r-Ab: $F(1, 56) = 1.12$; $p = .29$; 7r-Pr: $F < 1$] (see Figure 5.2b). Regarding the percentage of inhibition errors in the Simon Says task, contrasts revealed that reductions were significant for children who carried at least one copy of the DRD4 7r allele [$F(1, 38) = 4.75$; $p = .04$] and only marginal for children in the 7r-Ab group [$F(1, 38) = 3.42$; $p = .07$]. As for the WM span task, planned comparisons showed no significant changes with training for any of the genetic variation groups on any of the WM scores [WMf: 7r-Ab: $F(1,$

58) = 2.34; $p = .13$; 7r-Pr: $F(1, 58) = 2.24$; $p = .14$; WMb: 7r-Ab: $F(1, 58) = 2.34$; $p = .13$; 7r-Pr: $F(1, 58) = 1.22$; $p = .27$ ($p > .10$).

LPS vs. MPS haplotype of the COMT gene. The Genetic Variation x Session interaction was only marginally significant for the WMb score [$F(1, 49) = 2.98$; $p = .09$; $F < 1$ for the rest of measures]. Unlike training gain on WMf scores, which was not significant for any of the COMT haplotype groups ($F(1, 49) = 1.48$; $p = .23$] for the LPS group, and $F < 1$ for the MPS group), gain on the WMb score was only significant for children in the MPS group ($F(1, 49) = 5.83$; $p = .02$, $F < 1$ for children in the LPS group). Likewise, planned contrasts showed differential effects on the inhibitory control measure depending on the COMT haplotype. Children in the MPS group showed a statistically significant reduction of inhibition errors [$F(1, 30) = 5.11$; $p = .03$] following training, whereas the effect was not significant for children in the LPS group [$F(1, 30) = 1.22$; $p = .28$]. Regarding intelligence scores, we found that carriers of both haplotypes showed equivalent effects. Both groups showed a significant increase in the fIQ score with training ($F(1, 48) = 8.82$; $p = .005$ for the LPS group, and $F(1, 48) = 6.24$; $p = .02$ for the MPS group), but did not show changes in the vIQ score ($F(1, 48) = 1.53$; $p = .22$ for the LPS and $F < 1$ for the MPS group).

5.7. Discussion

Results of this study showed that inhibitory control and working memory skills can be improved with training. Unlike children in the active control group, trained children significantly improved performance in the Simon Says and WM tasks (see Table 5.2). Further, benefits of training transferred to fluid intelligence.

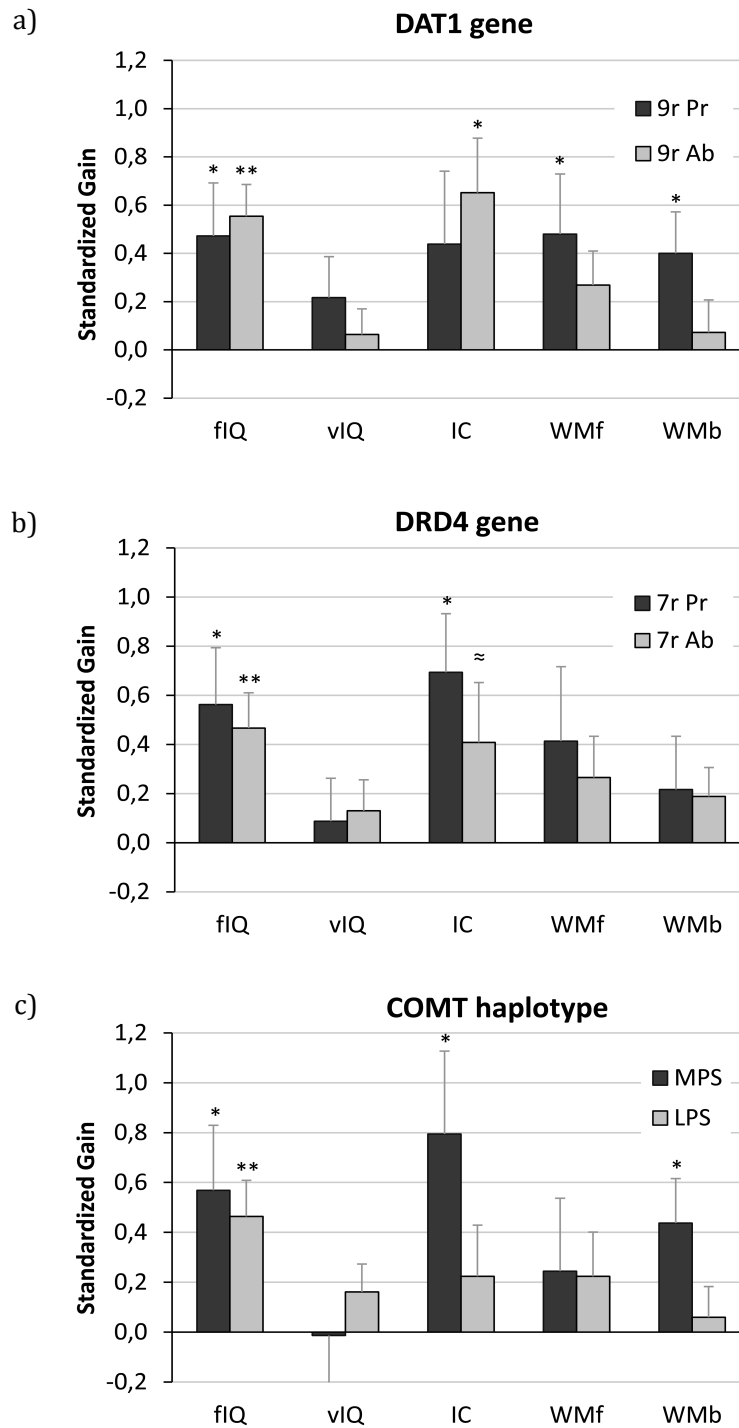


Figure 5.2. Graphical representation of the standardized training gain (SDgain) for each genetic variation group. a) DAT1 gene: (9r Pr: 9r-present; 9r Ab: 9r-absent); b) DRD4 gene (7r Pr: 7r-present; 7r Ab: 7r-absent); c) COMT haplotype (LPS: low pain sensitivity; MPS: moderate pain sensitivity). $SDgain = ((M_{Post} - M_{Pre}) / SD_{Pooled\ Pre})$. flQ: fluid IQ score; vIQ: verbal IQ score; IC: Inhibitory control score estimated by the percentage of inhibition errors in the *Simon Says* task; WM-f: Working Memory Span forward; WM-b: Working Memory Span backwards). Error bars represent standard errors. Asterisks depict the dependant variables were there was a statistically significant pre- to post-training gain. Significance level: ** = $p < .01$; * = $p < .05$; ≈ = $p < .10$

This pattern of results replicates previous data observed with our training program (Rueda et al., 2012; Rueda et al., 2005) and those obtained in other cognitive training studies with children (Bergman Nutley et al., 2011; Thorell et al., 2009).

5.7.1. Cognitive gains following training

The results presented here support a good deal of evidence showing that cognitive skills can be enhanced by means of intervention programs. Cognitive gains following training have been found with programs tapping specific executive functions such as response inhibition, working memory, task switching, monitoring and conflict resolution (Bäckman & Nyberg, 2013; Diamond & Lee, 2011). Likewise, several studies have shown that this sort of practice also enhances untrained fluid reasoning skills (Bergman Nutley et al., 2011; Jaeggi et al., 2011; Rueda et al., 2012).

A powerful argument that supports transfer from executive functions training to fluid intelligence is that both functions overlap in terms of processing components and neuroanatomical substrates. Compelling evidence from different levels of analysis point to a central role of the executive attention system in fluid intelligence (Kane & Engle, 2002). Executive attention and working memory skills are critical in actively maintaining access to stimulus representations and goals, particularly in interference-rich contexts, and these processes are basic to reasoning and problem-solving in novel situations. Additionally, there is evidence of considerable anatomical overlap between brain regions involved in executive functions and those engaged by tests of general intelligence (Duncan & Owen, 2000), and results from imaging research indicates that transfer of training only

occurs when trained and transfer tasks engage overlapping brain regions and networks (Dahlin et al., 2008).

An important question related to training and transfer is whether every person can benefit from this type of intervention. Prior results reveal the existence of important individual differences in the extent to which children benefit from training (Jaeggi et al., 2011). Like in many other studies, training effects in our study are only small-to-moderate before genetic variation is taken into consideration. Moderate and often null results cast legitimate doubts on the usefulness of training to enhance cognitive skills (Owen et al., 2010; Shipstead, Redick, & Engle, 2012). Results from our study shed light into this important question. We found that particular variations in genes involved in DA neurotransmission affect children's susceptibility to benefit from executive attention training.

5.7.2. Gene x Training interactions

Three of the most studied genes related to DA function were examined, and we found that different genes impacted training gains in distinct cognitive functions. In particular, we found that carriers of the DRD4 7r variation show larger training effects in tasks targeting IC compared to children who do not carry that variation. Likewise, only children carrying the MPS haplotype form of the COMT gene showed increased effects of training in IC and the task tapping manipulation of information in WM. Finally, the influence of the VNTR polymorphism of the DAT1 gene depended on the particular skills being tested. Concretely, gains in WM were only observed in children with presence of the 9r, whereas gain in IC was only significant for carriers of the 10r allele. These

distinctive patterns of G x T interactions are likely due to the specific DA signaling pathways associated with each gene and to the extent that each particular function taps on these different pathways.

5.7.3. DAT1 modulation

Our data revealed that DAT1 genotype modulated gains in IC and WM. The size of the modulatory effect was small-to-moderate (0.21 for IC and WM-*f*, and 0.33 for WM-*b*) and showed opposite patterns for IC and WM with putative DAT1 function. Carriers of the 9r allele exhibited the largest pre to post-intervention effect on their capacity to maintain and manipulate information in WM whereas 10/10 individuals showed the largest improvement in IC.

The DAT1 gene is predominantly expressed in the basal ganglia. Studies on the functional organization of basal ganglia-thalamocortical circuits have reported the existence of segregated pathways for motor and prefrontal regions, which involve the putamen and caudate nucleus respectively (Alexander, DeLong, & Strick, 1986). Using PET to measure DA synthesis in the brain, Landau, Lal, O'Neil, Baker, & Jagust (2009) showed a double dissociation between caudate/putamen DA signaling and WM/motor processes. DA signaling in the caudate nucleus (but not putamen) was positively related to WM maintenance, whereas putamen (but not caudate) DA was related to motor speed. Variations of the DAT1 gene modulate dopaminergic activity in the striatum that may vary in these different pathways. Carriers of the 10r allele show lower DA signaling (Heinz et al., 2000) and volume (Durstun et al., 2005) in the caudate nucleus, but higher neuronal functionality (i.e., increased amount of metabolic markers) in the left putamen (Scherk et al., 2009) compared to 9r carriers.

Recent work has shown that general WM performance and WM improvements after intervention are related to enhanced neural activity in the striatum (Dahlin et al., 2008; Wallace, Vytlačil, Nomura, Gibbs, & D'Esposito, 2011) as well as increased levels of DA release in the caudate (Bäckman et al., 2011). Further, observed increments on the striatal BOLD signal seem to be directly influenced by local DA release (Schott et al., 2008). In one of the few studies examining Gene x Training interactions prior to this one, (Brehmer et al., 2009) found that children carrying the 9r allele of the DAT1 gene showed larger gains in WM than carriers of the 10r variation following 4 weeks of training. Integrating all this evidence we can hypothesize that differential intervention-related gains in 9r and 10r carriers are associated with how training impacts the DA signaling in the distinct striatal-cortical pathways. Training-related boosts in DA release in the caudate lead to better WM performance particularly in carriers of the 9r allele, or perhaps the 9r individuals are better able to respond to training because of their level of synaptic DA in the caudate, resulting in more efficient or greater signaling. However, less information is available in the literature about how training impacts the level of DA activity in the putamen. We found that children homozygous for the 10r, who show higher neuronal activity in the putamen, show larger gains in response control compared to carriers of the 9r allele. This suggests that the training effect on inhibitory control may be related to DA transmission within the basal ganglia-cortical circuit involved in motor preparation, which includes the putamen and other cortical regions such as the supramarginal gyrus (Landau et al., 2009).

Previous heritability studies (Groot, de Sonnevile, Stins, & Boomsma, 2004) and single-gene association studies (Cornish et al., 2005) have already shown that

individual differences in children's capacity to inhibit automatic responses are related to genetic differences. However, the impact of G x E interactions on the development of inhibitory control skills has only been addressed by correlating environmental risk factors such as psychosocial adversity or prenatal exposure to different drugs with children's genetic variation on the DAT1 gene. In these studies individuals homozygous for the 10r allele appear to be more sensitive to adverse environmental conditions compared to carriers of the 9r allele (Becker et al., 2008; Kahn et al., 2003). Data from our study are informative about the neural mechanism underlying plasticity of inhibitory control. Our results indicate that the reduced striatal DA activity in individuals homozygous for the 10r allele may contribute to an efficient functioning of the frontal neurotransmission system that supports children's ability to withhold a response. However, further neuroimaging and pharmacoinaging intervention studies need to be undertaken to disentangle the role of dopaminergic transporters in the neural and behavioral plasticity of response inhibition during development.

5.7.4. DRD4 Modulation

Increasing evidence indicates that the presence of at least one copy of the 7r allele in the exon III of the DRD4 gene modulates individuals' susceptibility to environment. Most of the G x E studies carried out with this gene have focused on analyzing how environmental factors such as parenting in children and peer attitudes in adults interact with genotype to influence self-regulation skills (Bakermans-Kranenburg & van Ijzendoorn, 2011). The convergent finding from several studies is that carriers of the 7r allele are more sensitive to both positive/enriching as well as negative/stressful rearing environments (Belsky,

Bakermans-Kranenburg, & Van IJzendoorn, 2007), thus suggesting that this genetic variation makes the individual more susceptible to the experience “*for better and for worse*”. However, in these studies, children’s genetic endowment may determine at least in part parenting styles and peer relationships. Much fewer studies have examined G x E interactions with randomized designs in which children with different genotypes are randomly assigned to conditions varying in the amount of experience that they provide to train a particular skill. One of the first approaches to use this method was developed by Bakermans-Kranenburg and colleagues (2008) who observed G x E interactions by implementing an intervention program that aimed to improve maternal sensitivity and adequate discipline styles, however, their program did not involve the training of behavioral or cognitive skills for children (Bakermans-Kranenburg, Van IJzendoorn, Pijlman, Mesman, & Juffer, 2008).

5.7.5. COMT Haplotype modulation

Studies in humans and other species have shown that there is an inverted-U shape relationship between prefrontal dopaminergic function and performance of executive function tasks (Barnett et al., 2009; Williams & Goldman-Rakic, 1995). For instance, carriers of the COMT haplotype associated with moderate levels of DA signaling at the PFC perform better than those carrying the haplotypes associated with lower or higher DA levels in tasks involving WM and response control (Barnett et al., 2009). Data reported here indicate that constitutionally based individual differences in DA-signaling also interacted with training-induced changes in DA function. In our study, individuals carrying the APS/APS and the HPS/LPS haplotypes, associated with moderate levels of COMT enzymatic activity,

showed larger training-related gains in IC and WM-manipulation processes compared to those carrying the LPS/LPS and APS/LPS haplotypes in the Low Pain group. This result is in line with Brehmer et al.'s hypothesis about the relationship between optimal levels of DA signaling and response to training. They suggested that individuals who carry the genetic variation associated with greater levels of synaptic DA are constitutionally endowed with a mechanism that is better able to respond to increased levels of DA following training (Brehmer et al., 2009).

Modulation of the COMT haplotype affected gains in WM and IC tasks, which are known to activate the PFC. This part of the brain depends to a great extent on the function of the COMT enzyme to degrade the DA released by presynaptic neurons. Our results suggest that less efficient enzymatic activity at the PFC, which leads to higher synaptic DA and greater DA signaling, results in better training-related performance. Interestingly, the influence of the COMT haplotype on gains in WM was qualified by an interaction with the VNTR variation of the DAT1 gene (see Figure 5.3). Given that the sample size in our study was small to examine

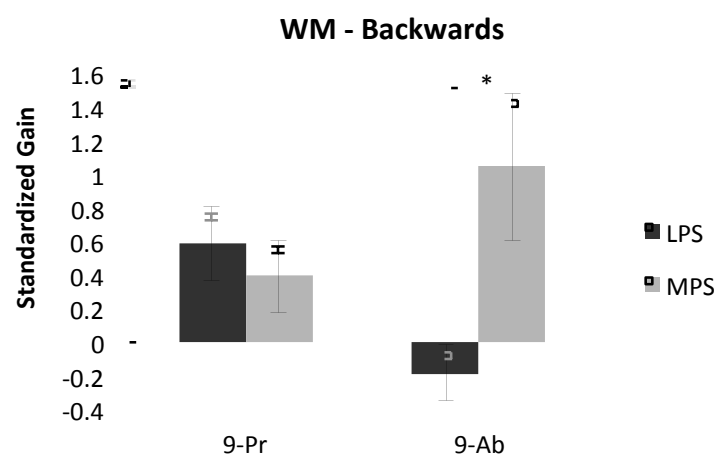


Figure 5.3. Gene x Gene interactions. Graphs depicting gene x gene interactions. DAT1 x COMT-haplotype interaction on SDgain in the WMb score. Error bars represent standard errors. Significance level: * = $p < .05$; ≈ = $p < .10$

interactions between variations in the different genes, we must consider this finding with caution. However, this result indicates that an optimal level of DA at the PFC may be necessary for children with variations associated with less synaptic DA in the striatum (i.e., greater rate of DA reuptake with 10r) to show benefits from intervention.

5.7.6. Conclusions and further directions

Previous work in the field had already highlighted the association between variation in DA-related genes and stimulating rearing environments during childhood (Lahey et al., 2011; Sonuga-Barke et al., 2009; van den Hoofdakker et al., 2012), but very little work had been done to test such interaction by introducing changes in the environment in the form of cognitive interventions.

This study presents one of the first attempts to understand how dopaminergic neurotransmission may act as the neural mechanism that moderates the influence of genetic and environmental factors on preschoolers' cognitive plasticity. The sample size of our study is modest and a replication with a bigger sample is necessary. However, based on the fact that children's performance at baseline was not significantly different between genotype groups, the reported modulations of training-related gains by genotype are likely due to the impact that such variations have on the brain systems supporting the cognitive skills being trained. As discussed above, genetic variations not only impact the efficiency of the brain to carry out particular cognitive functions, results from our study also indicate that they influence the capacity of the brain to be altered by experience.

Mounting evidence informs that cognitive skills can be boosted by intervention during development. Different training programs have shown positive effects at the cognitive and the brain function levels. Skills as the ones targeted by our training program have proven to be central to academic achievement in subjects such as reading and math (Blair & Razza, 2007; Checa et al., 2008; Checa & Rueda, 2011), as well as to other outcomes later in life (Deary, Strand, Smith, & Fernandes, 2007; Gottfredson, 1997). Further research is needed to examine in what extent these interventions can generalize to other relevant skills such as emotional regulation, planning, problem solving and creativity. Future studies will also benefit from combining techniques such as neuroimaging, pharmacoinaging and imaging genetics to further unravel the modulatory role of dopaminergic neurotransmission on cognitive plasticity.

Chapter 6

General discussion

The work presented in this dissertation was motivated by the fascinating research of our predecessors that has revealed the importance of self-regulatory skills for the adequate adjustment of individuals during childhood, adolescence and adulthood. Self-initiated behaviors that might look like simple good manners during childhood (i.e. following conduct rules of formal places like churches or hospitals, respecting turns to talk, engaging and maintaining the focus of attention in low intensity activities, etc.) are actually reliable predictors of the general wellbeing of individuals regarding their physical health, professional success, and social competence later in life (Baumeister, Heatherton, & Tice, 1994; Mischel et al., 2011, 1989).

Throughout the history of developmental psychology, scientists have attempted to identify and understand the constitutional and environmental factors that underlie individual differences in the development of SR. Early approximations in the field addressed the influence of constitutional factors from the domain of temperamental features, where self-regulatory skills were characterized under the concept of effortful control (Rothbart & Derryberry, 1981; Rothbart, 2011). At the same time, the study on the influence of environmental factors was mainly focused on the impact of both positive and adverse conditions present during the first years of life, especially related to parenting styles (Grolnick & Ryan, 1989; Karreman, van Tuijl, van Aken, & Deković, 2006) and socioeconomical background (see Blair, 2010 for a review).

For many years researchers in the field had little to contribute regarding the neural and molecular basis of SR and the processes by which environmental conditions could influence its development, especially because the technology to investigate them was yet to be discovered. Two major scientific developments

have recently provided such instruments, opening up new directions of research that have contributed to broaden the knowledge about the development of SR.

The advent of modern neuroimaging techniques allows researchers to correlate in real time cognitive functions to patterns of neural activation in distinct areas and networks of the brain (Posner & Raichle, 1998). From early theoretical accounts, SR was associated to the exercise of attention control mechanisms and basic executive functions such as error detection, inhibition of dominant responses, problem solving, and self-monitoring (Rueda et al., 2011; Ruff & Rothbart, 1996). Based on this characterization a large number of neurocognitive studies were carried out in order to identify the neural underpinnings of SR through the combination of marker tasks and brain imaging techniques. Those studies led to the identification of a network of frontal and subcortical structures in the brain, known as the executive attention network (EAN), which support attention control mechanisms through the facilitation or inhibition of the functions of other networks in the brain (Posner & Petersen, 1990; Posner & Rothbart, 2000).

The second major breakthrough was the sequencing of the human genome (Lander et al., 2001; Venter et al., 2001). With the characterization of the neural basis of SR, a great amount of research was carried out in order to determine whether genetic variations that modulate structure and efficiency of the EAN would explain individual differences in the cognitive and behavioral domain (see Posner & Rothbart, 2009 for a review). Given that structures within the EAN are target areas of the ventral tegmental dopamine system, most of the studies in the field have been focused on the study of genes that impact the dopaminergic

pathways (Brocki et al., 2009; Diamond, 2007; Greene, Braet, Johnson, & Bellgrove, 2008; Logue & Gould, 2013).

The studies presented in this dissertation take advantage of these recent technological advances to bring back the old “nature vs nurture” question to the field of attention and self-regulation development in a context of new technological development. For decades, developmental psychologists were able to move beyond the nature vs. nurture debate to make it more a “nature, nurture and their interactions factors” intent to explain human development (Johnson & De Haan, 2011). In our work, we aimed at providing new insights into the constitutional and environmental factors that shape the development of self-regulatory skills during preschool, a period of life where major cognitive growth spurts take place. The first study presented here was designed to examine whether training executive attention by means of a computer-based program can boost self-regulatory skills and the efficiency of the neural network that supports them. In the second study, we aimed to investigate how variations of the dopamine transporter gene SLC6A3-DAT1 relate to individual differences in children’s SR as assessed with an array of multifaceted measures. In the last study, we tested to what extent variations of three dopamine-related genes modulate plasticity of the executive attention network to cognitive training.

In this final chapter, I will further discuss the results of our research and its impact in the fields of Psychology and Education, the limitations of our studies and what I consider could be further directions in the field.

6.1. Nurture of Self-Regulation

The well documented influence of environmental conditions on the development of SR have led to the conclusion that self-regulatory skills are susceptible to be modified by experience. This understanding raised the interest of scientist for the possibility to improve children's self-regulatory skills through the implementation of training programs. One of the first investigations in this direction was developed by Douglas, Parry, Marton, & Garson, (1976) who designed an intervention program that aimed to enhance inhibitory control skills in hyperactive children. Besides to the observed improvement on the trained ability, Douglas and collaborators reported a transfer of the training effects to measures of general intelligence. This pioneer work, have motivated the implementation of a large number of studies in the field of cognitive neuroscience, which aimed to elucidate the effects of cognitive training programs in children, adults and elders (Diamond & Lee, 2011; Jolles & Crone, 2012; Karbach & Unger, 2014).

As with almost every complex aspect like human cognition and brain functioning, determining the effectiveness of any training program highly depends on a number of factors that must be taken into consideration before solid conclusions can be drawn. For instance, researchers in the field have found that the type (process-based or strategy-based) and length of the intervention, the period of life when the intervention takes place, or the cognitive function that is being subject to training, influence efficacy of intervention (Jolles & Crone, 2012; Rabipour & Raz, 2012). Designing programs that can improve individuals' cognitive skills and behavior is the primary goal. In this endeavor, understanding the impact of interventions at the level of neural mechanisms underlying cognitive

functions can help both understanding processes of brain plasticity and providing information useful to enhance efficiency of those interventions (Willis & Schaie, 2009).

One of the main contributions of the first study of the thesis regards plasticity of the typically developing brain and the processes by which training influences efficiency of the neural network involved in executive attention. Preschool is a period of major maturational changes concerning executive attention functioning (Rueda, Fan, et al., 2004), which suggests that cognitive training at this age may have particular beneficial effects. However, it is still not clear whether developmental changes at this age would heighten the effect of training or constrain it depending on the level of maturation of the child (Jolles & Crone, 2012). One of the first studies to address this question was carried out by Rueda, Rothbart, McCandliss, Saccomanno, & Posner (2005), who showed that at age 4 to 6 years children can benefit from a 5-session training program. In their study, significant changes in the patterns of neural activation were observed when children performed the child-ANT task. According to their findings, the brain response to conflict (measured through the significant differences in amplitude between the congruent and incongruent condition) exhibited: 1) shorter latency and 2) more posterior distribution after training.

In our study, we extended the program implemented by Rueda, et al. (2005) introducing new exercises and increasing the number of sessions up to 10. With these adjustments, we not only confirmed the findings reported by Rueda and collaborators but also provided additional evidence regarding the neural generators of the effect as well as the strength of the activation. In particular, the findings of our study show that training enhances efficiency of the EAN in two

ways: 1) accelerating the detection and signaling of conflict from the anterior cingulate cortex to the prefrontal structures and 2) producing patterns of activation that appear more focal when modeled with source localization methods. The second relevant finding reported in our study is that the observed effects of training on the efficiency of the EAN appear to remain stable two months later without further training. Finally, our data suggest that executive attention training transfer to other cognitive domains that were not subject to intervention, including fluid intelligence and the ability to regulate motivational significant responses as measured with the gambling task.

These findings have important implications in the field of Education. Our data suggest that a relatively short intervention consisting of only 10 45-minutes sessions of executive attention training already makes an impact on the efficiency of the neural system that supports SR. This effect translates at the behavioral level as an improvement of children's intellectual functioning as well as their ability to modulate their reactivity in motivationally significant situations. Both fluid intelligence and emotional regulation are two robust predictors of children's academic and social adjustment in the school (Nancy Eisenberg et al., 2011; Neisser et al., 1996). Furthermore, we found that more stable and durable effects can be produced when extended training programs are implemented, suggesting that training cognitive abilities require time and should not be approached as "once in a life time" but more as a continuous effort. The results from study I together with those of other studies in the field (Diamond, 2012; Karbach & Unger, 2014; Posner & Rothbart, 2005) provide significant information that can serve to design and implement training programs in the classroom. The inclusion of this kind of tools in the school curriculum could help children to optimize their

cognitive skills and can provide particular support for those who are at risk of developing pathologies or those who have special needs for either constitutional or environmental reasons.

6.2. Nature of Self-Regulation

The well-known influence of genetic variation on brain related signal transmission like for instance dopaminergic pathways has led to the suggestion that cognitive functions can be linked to a susceptible genetic background and thus led to a number of genome-wide association studies. Surprisingly few polymorphic sites with strong associations were detected, mostly located in genes for receptors, membrane transporters, ion channels and dopamine/serotonin metabolism (see Goldberg & Weinberger, 2004; Green et al., 2008 for reviews).

In their review about the use of genetic data in cognitive neuroscience, Green and collaborators (2008) pointed out: "...Even the most precise molecular-genetic data cannot be useful if the phenotypes are not well defined. Thus, cognitive neurogenetic studies are only as good as their ability to measure mental phenotypes validly and specifically" (p. 710). With this understanding in mind, the work presented in this dissertation has been based on the conception of SR as a combination of attention control mechanisms and executive functions that are supported by the neural activation of the well-defined executive attention network (EAN). Within this framework, we set out to study the relation between dopamine-related genetic variations and individual differences in SR at the phenotypic level during preschool, a period of development characterized by major behavioral and brain changes as well as extensive individual differences related to self-regulation

skills. The existence of such differences provided the strong effects needed to investigate genetic associations with a reasonably small amount of children.

In particular, we examined the association between variations on the DAT1 gene and children's self-regulatory skills. One important strength of our study is that it integrates the knowledge and technology from the field of molecular genetics with what has been described about SR from the fields of developmental psychology and developmental cognitive neuroscience. On the one hand, variations of the SLC6A3-DAT1 gene were selected given their well documented role on the efficiency of dopaminergic pathways (Mill et al., 2002; D J Vandenberg et al., 1992; VanNess et al., 2005) and the findings reported in previous studies that relate them with individual differences in children's inhibitory control and the ability to regulate behavior (Braet et al., 2011; Congdon, Constable, Lesch, & Canli, 2009). On the other hand, we included an array of multifaceted measures to assess children's SR, which were carefully selected based on the available empirical evidence derived from psychological and cognitive neuroscience studies in the past decades.

The study of the association between the DAT1 gene and cognitive function is not new but still many questions remained unsolved, as former reports have been quite controversial. To our understanding, one of the challenges has been the methodology implemented to assess SR. A review of the literature shows that most of the studies have used abstract and decontextualized tasks, which are often completed by children in laboratory settings. Without neglecting the great value of these measures, we aimed to go one step further by assessing children with a set of tasks and questionnaires that would also measure their self-regulation skills in different contexts such as school or home.

Results from the second study show an association between variations of the DAT1 gene and children's self-regulatory skills. Further, DAT1 variation appears to mostly influence self-regulation efficiency in social contexts subject to social-emotional reinforcements like school.

Variations of the DAT1 gene affect the amount of dopamine transporter in the striatum. In particular, the 10r allele has been associated to an increased number of DAT (VanNess et al., 2005) which at the functional level translates into lower dopamine levels in the extra synaptic space. Therefore, this finding suggests that presence of the 10r allele exerts stronger impact on the corticostriatal circuit that convey information between subcortical structures involved in the processing of information and reactivity in affective/motivational context and frontal areas that support the exercise of top-down control mechanisms.

Taking together, these findings represent a significant contribution to the understanding of the neurobiological basis of SR. During decades, the knowledge regarding the neural substrates of individuals' self-regulatory abilities was confined to what was inferred from neuronal diseases or brain lesions. With the avenue of molecular genetics, we are now able to describe parts of the individual genetic background that modulate the efficiency of brain function and translate into observable differences at the behavioral level in a number of abilities that can impact the social adjustment of children and adults.

6.3. The interplay of nature and nurture of Self-Regulation

In the first two studies presented here we aimed to understand the influence of factors related to the nurture and nature on the development of SR. In particular, we focused on the influence of executive attention training on the one

side and the influence of variations of the DAT1 gene on the other side. Although significant contributions were made in both studies, there were still open questions: Do all children respond in the same way to executive attention training? Or does their genetic background modulate to what extent they can benefit from it?

For both parents and educators it is clear that not all children respond in the same way to conditions in their environment. What seems to be beneficial for some children does not exert any impact on others. During the past decades a great amount of scientific studies in the field of developmental psychology have investigated how individual characteristics of children make them susceptible to the conditions of their environment. For instance, children with a temperamental disposition to manifest high levels of negative emotions exhibit stronger problematic outcomes when they face adverse conditions during the first years of life. Interestingly, these children also show greater benefits when they grow in a positive and supportive environment (see Belsky, Bakermans-kranenburg, & Van Ijzendoorn, 2007 for a review).

These observations led to the hypothesis that the genetic endowment of children could explain individual differences in their response to environmental influences. The pioneer work of Caspi and collaborators (2002) in this direction revealed that some genetic variations moderate children's vulnerability to adverse environmental conditions. Moving one step further, recent approaches have been investigating Gene x Environmental (GxE) interactions in the context of differential susceptibility, that is, how the genetic configuration of individuals mediates the impact of both stimulating and unfavorable conditions "for better and for worse" (Bakermans-Kranenburg & van Ijzendoorn, 2007; Belsky et al., 2007). Several

studies have been conducted that examine how dopamine-related genes modulate the influence of environmental factors that affect children during pregnancy and later during the first years of life (see Bakermans-Kranenburg & van Ijzendoorn, 2011 for a review). However, much less research has been carried out to test G x E interactions in the context of cognitive training.

In the last study of this dissertation, we examined whether variations of three genes that are known to modulate dopamine function (DAT1, DRD4 and COMT), can explain individual differences of children's cognitive plasticity to executive attention training. Three measures of cognitive function were implemented before and after training to measure training-related gains: 1) fluid intelligence, 2) Inhibitory control and 3) working memory. Our data suggest that training effects on inhibitory control and working memory are modulated in gene-specific ways. The observed pattern further suggests that the genetic modulation of environmental influences depend on the brain circuit affected by each gene. Genotypes leading to more optimal cortico-striatal balance in DA-signaling also promote plasticity of the system.

The findings reported here have several implications for the way we understand SR and especially, for the methodology we use to foster children's self-regulatory skills during preschool. From the experimental perspective in the field of cognitive neuroscience, and also in applied educational sciences, all children within the same age range and similar socioeconomic background are assumed to be at the same level of development. Thus both training programs and educational strategies in schools are designed and implemented to meet the needs of only one part of the population within that group while individual differences are often ignored. However, what our data indicates is that each child with her unique

genetic make-up and environmental conditions may not only differ from others in her ability to voluntarily modulate her own reactivity but also in the extent to which she can benefit from a given cognitive training. Therefore, the optimization of training programs should take into account both genetic and environmental factors to better aide children according to their specific needs.

6.4. Future directions

During the past decades, great contributions have been made to the understanding of the development of SR, the factors that influence it as well as the instruments that can be implemented to optimize and/or foster this capacity in childhood. However, many questions remain open and new questions emerge from the knowledge gained along the way.

The field of cognitive training research has great potential for further progress. In recent years, a large number of new training strategies have been proposed which have been proven useful to improve attention, SR and executive functions in both children and adults. For instance meditation techniques (Flook et al., 2010; Tang et al., 2007), reflection training (Espineta, Anderson, & Zelazo, 2013) or the combination of parenting training and attention training for children (Neville et al., 2013) to name but a few. Future studies will be required in order to elucidate 1) how different cognitive training strategies influence brain function, 2) what type of training program is more efficient to improve a specific cognitive function, 3) what length of intervention is needed to ensure lasting results, and 4) what type of training is more effective depending on the developmental stage of the individual. Moreover, based on the findings reported in this dissertation, one crucial aspect to be taken into account when designing and implementing training

programs is the influence of individual differences. An important feature of computer-based training programs is that they can be designed so that the level of difficulty of the exercises can be easily adjusted to the level of each user. Further, computer-programming technologies advance fast and provide increasingly sophisticated ways to implement training itineraries that are adjusted to individual with particular needs either of constitutional, educational or clinical origin.

One important task in the field is the translation of scientific discoveries to the applied educational context. Therefore, one important role of developmental cognitive neuroscientists will be to develop strategies for cognitive training programs that can be integrated into school curriculums.

In our study we reported that variations of the DAT1 gene influence children's skills related to attention and socio-emotional regulation. However, further research is needed to confirm this association. One challenge in this line of research is the characterization of a neural endophenotype that can help to understand how differences in the genetic make-up of individuals translate into observable differences at the behavioral level. To achieve this, we need further studies combining neuroimaging techniques with the measurement of well-defined behavioral phenotypes. This same strategy is fundamental for the understanding of G x E interactions in the context of cognitive training: once neural endophenotypes have been clearly defined between dopamine-related genes and cognitive functions, we will be able to further characterize the role of dopamine function in mediating the relation between genes and environment in the effort to understand the development of executive attention and self-regulation.

6.5. Conclusions

- Self-regulation can be fostered by means of cognitive training programs
- Cognitive training enhances the function of the executive attention network by accelerating the detection of conflict and conveying the information to frontal structures that exert control mechanisms.
- Executive attention training has the potential to enhance children's fluid reasoning skills and their ability to regulate behavior in order to obtain larger but delayed rewards.
- The effect of a reduced number of executive attention training sessions in brain function is still observable in a two months follow-up without further training. However, the effect shows to be weaker suggesting that cognitive training should, like exercise, be practiced in a regular basis.
- Children's self-regulatory abilities are modulated by variations of the dopamine transporter gene DAT1.
- Presence of the 10r allele of the DAT1 gene, known to influence dopaminergic signaling in the striatum, influences children's attention capabilities, as well as their capacity to regulate socio-emotional behavior in the classroom.
- The study of the genetic basis of behavioral and cognitive phenotypes requires the use of theoretically- and empirically-grounded methods to have more precise characterization of phenotypes.
- Dopamine-related genes appear to differentially modulate the influence of executive attention training on measures of inhibitory control and working memory, depending on the neural circuit affected by each gene.

- Genotypes associated to an optimal dopamine signaling in the cortico-striatal pathway also support plasticity of the system to cognitive training.

Chapter 7

Resumen en español

Durante los primeros años de vida, los niños experimentan un desarrollo cognitivo rápido y continuo, el cual ejercerá un papel fundamental en su futuro ajuste durante la edad adulta. Quizá uno de los cambios más importantes que se puede observar a esta edad es la aparición de la capacidad de modular de forma voluntaria sus pensamientos, emociones y acciones con el fin de conseguir sus objetivos y responder a las demandas de su entorno social. En el campo de la psicología del desarrollo, esta capacidad es conocida bajo el nombre de autorregulación. Un gran número de estudios han mostrado que una adecuada capacidad de autorregulación influye positivamente en el ajuste social, rendimiento académico y función cognitiva de niños y adolescentes (Checa, Rodríguez-Bailón, & Rueda, 2008; Checa & Rueda, 2011; Eisenberg, Smith, & Spinard, 2011).

A lo largo de la historia, los investigadores en el campo de la psicología del desarrollo han tratado de identificar y comprender los factores constitucionales y ambientales que subyacen las diferencias individuales en el desarrollo de la autorregulación. Las primeras investigaciones en el área abordaron el estudio de los factores constitucionales desde el campo del temperamento, desde el cual las habilidades de autorregulación fueron caracterizadas a través del concepto de control voluntario (Rothbart & Derryberry, 1981; Rothbart, 2011). Por su parte, el estudio de la influencia de los factores ambientales estaba principalmente enfocado al estudio del impacto tanto de condiciones favorables como de desfavorables durante los primeros años de vida, prestando especial atención al impacto del estilo de crianza de los padres (Grolnick & Ryan, 1989; Karreman et al., 2006) y el nivel socioeconómico de la familia (Blair, 2010).

Durante muchos años, los investigadores en el área de la psicología del desarrollo pudieron contribuir muy poco al estudio de las bases neurales y moleculares de la capacidad de autorregulación, así como al estudio del proceso mediante el cual las condiciones ambientales influyen en su desarrollo. Esto se debió a que no existían en aquellos días las herramientas ni la tecnología necesaria para investigarlas. Recientemente, dos grandes descubrimientos científicos han dado lugar al surgimiento de los instrumentos necesarios, abriendo nuevos campos de investigación en el área, a través de los cuales se ha podido contribuir al conocimiento que se tiene acerca del desarrollo de la autorregulación.

El primero de estos avances fue el desarrollo de las técnicas modernas de neuroimagen, las cuales permiten correlacionar, en tiempo real, funciones cognitivas con patrones de activación neural en diferentes áreas y redes de estructuras en el cerebro (Posner & Raichle, 1998). Desde las primeras aproximaciones teóricas, la capacidad de autorregulación se ha asociado con la activación de mecanismos de control atencional y de funciones ejecutivas básicas tales como detección de errores, inhibición de respuestas dominantes, solución de problemas y la capacidad de auto-monitorización (Rueda et al., 2011; Ruff & Rothbart, 1996). En base a esta caracterización, una gran cantidad de estudios en el campo de la neurociencia surgieron con el objetivo de identificar las bases neurales de la autorregulación combinando el uso de tareas experimentales y técnicas de neuroimagen. Dichos estudios llevaron a la identificación de una red de estructuras cerebrales conocida como “red de atención ejecutiva” (EAN, por sus siglas en inglés), la cual incluye estructuras de la corteza frontal y estructuras subcorticales tales como la corteza anterior del cíngulo, la corteza dorsolateral prefrontal y los ganglios basales (Posner & Rothbart, 2009; Rueda, Posner, &

Rothbart, 2011). La activación de esta red de estructuras, la cual esta mediada por la acción del neurotransmisor dopamina (DA), sirve de base a los mecanismos de control atencional a través de la facilitación o inhibición de las funciones de otras redes neurales en el cerebro (Posner & Petersen, 1990; Posner & Rothbart, 2000).

El segundo aporte científico fue la caracterización completa de la secuencia del genoma humano (Lander et al., 2001; Venter et al., 2001). Uniendo este conocimiento a la identificación de las bases neurales de la autorregulación, gran cantidad de investigaciones comenzaron con el objetivo de intentar determinar si aquellas variaciones genéticas que modulan la estructura y eficiencia de la red de atención ejecutiva podrían explicar diferencias individuales a nivel cognitivo y comportamental (Posner & Rothbart, 2009). Dado que las neuronas del sistema dopaminérgico del área tegmental ventral se proyectan hacia las estructuras que conforman la red de atención ejecutiva, la mayoría de investigaciones en el campo se han interesado en estudiar las variaciones genéticas que ejercen un impacto en las vías dopaminérgicas del cerebro (Brocki et al., 2009; Diamond, 2007; Greene et al., 2008; Logue & Gould, 2013).

Los estudios que se presentan en esta tesis doctoral se cimientan sobre la base de estos recientes avances tecnológicos, con el objetivo de aportar nuevos conocimientos acerca de los factores constitucionales y ambientales que modulan el desarrollo de la atención y de la capacidad de autorregulación durante la edad preescolar. El estudio I, fue diseñado para investigar si el entrenamiento de la atención ejecutiva en edad preescolar mejora la capacidad de autorregulación de los niños y la eficiencia de la red neural que la subyace. El objetivo del estudio II fue el de examinar de qué forma las variaciones del gen SLC6A3-DAT1, el cual juega un importante papel en la eficiencia de las vías dopaminérgicas del cerebro

(Mill, Asherson, Browes, D'Souza, & Craig, 2002) y ha sido previamente asociado con la capacidad de control voluntario (Braet et al., 2011; Congdon et al., 2009), influye en la capacidad de autorregulación de los niños. Para ello, los niños fueron evaluados con una serie de tareas y cuestionarios que permiten la evaluación de su capacidad de autorregulación desde diferentes ángulos, utilizando tanto informes de profesores, informes de padres, así como tareas de memoria de trabajo, demora de la gratificación, control inhibitorio y de resolución del conflicto. Finalmente, el objetivo del estudio III fue el de examinar si las variaciones alélicas en tres genes asociados a la eficiencia del sistema dopaminérgico en el cerebro (DAT1, DRD4 and COMT) pueden explicar diferencias individuales en la plasticidad cognitiva de los niños cuando reciben un programa de entrenamiento de atención ejecutiva.

7.1. Factores ambientales

Como mencionaba antes, muchos estudios en el campo de la psicología del desarrollo han informado de la influencia de factores ambientales en el desarrollo de la capacidad de autorregulación. Esto ha llevado a los científicos en el área a concluir que dichas habilidades son susceptibles de ser modificadas por la experiencia y que, por tanto, pueden ser mejoradas a través de la implementación de programas de entrenamiento. Uno de los primeros estudios en este campo fue desarrollado por Douglas y colaboradores (1976), quienes diseñaron un programa de intervención que tenía como objetivo mejorar la habilidad de control inhibitorio en niños hiperactivos. Sus buenos resultados motivaron el trabajo de una gran cantidad de investigadores en el campo de la neurociencia cognitiva, quienes se han embarcado en el estudio de los efectos del entrenamiento cognitivo en niños,

adultos y adultos mayores (Diamond & Lee, 2011; Jolles & Crone, 2012; Karbach & Unger, 2014).

En el marco de la neurociencia cognitiva del desarrollo, el objetivo principal de los estudios es el diseño de programas de intervención que mejoren tanto habilidades cognitivas como comportamentales. Sin embargo, comprender el impacto de este tipo de entrenamientos sobre los mecanismos neurales a la base de dichas funciones cognitivas, puede no solo contribuir a la comprensión de los procesos de plasticidad cerebral, sino que además provee información que es de gran utilidad para mejorar la eficacia de dichas intervenciones (Willis & Schaie, 2009).

Uno de los principales aportes del estudio I tiene que ver con la plasticidad del desarrollo del cerebro, así como con el proceso mediante el cual un programa de entrenamiento de la atención ejecutiva influye en la eficiencia de la red neural que la soporta. Uno de los primeros estudios en investigar esta cuestión fue desarrollado por Rueda y colaboradores (2005), quienes demostraron que a la edad de 4 a 6 años, los niños se pueden beneficiar de un programa de entrenamiento de 5 sesiones. Adicionalmente, Rueda y cols (2005), informaron sobre cambios significativos en los patrones de activación neural de los niños mientras realizaban la tarea experimental ANT. De acuerdo con sus observaciones, la respuesta neural al conflicto (medida a través de las diferencias significativas en la amplitud entre la condición congruente e incongruente) después del entrenamiento mostraba: 1) latencia más corta y 2) distribución más posterior.

En nuestro estudio, extendimos el programa de entrenamiento implementado por Rueda y cols (2005), introduciendo nuevos ejercicios e incrementando el número de sesiones a un máximo de 10. Con estas

modificaciones, no solo replicamos los resultados encontrados por Rueda y colaboradores, sino que además aportamos nuevos datos acerca de los generadores neurales del efecto, así como acerca de la fortaleza de la activación. Más específicamente, los resultados del estudio I muestran que el entrenamiento mejora la eficiencia de la red de atención ejecutiva de dos formas: 1) acelerando la detección y señalización del conflicto desde la parte anterior del cíngulo hacia estructuras prefrontales y 2) produciendo patrones de activación que parecen más focalizados cuando son modelados con métodos de localización de la fuente. El segundo aporte relevante fue que los efectos del entrenamiento en la eficiencia de la red de atención ejecutiva parecen mantenerse estables incluso dos meses después de que el entrenamiento haya finalizado. Finalmente, los resultados de este estudio sugieren que los efectos del entrenamiento de la atención ejecutiva se transfieren a otros dominios cognitivos que no han sido entrenados, tales como la inteligencia fluida y la habilidad de regular respuestas con alto contenido motivacional.

Estos resultados tienen implicaciones importantes en el campo de la educación. Lo que indica este estudio es que una intervención relativamente corta de entrenamiento de la atención ejecutiva (10 sesiones de 45 minutos), influye en la eficiencia del sistema neural que sustenta la capacidad de autorregulación. A nivel comportamental, este efecto se traduce en una mejora de la capacidad intelectual de los niños así como en su capacidad de regular su comportamiento en situaciones de alto contenido emocional. Estas dos capacidades son predictores robustos tanto del rendimiento académico de los niños como de su adaptación social en la escuela (Nancy Eisenberg et al., 2011; Neisser et al., 1996). Por otra parte, el hecho de que los efectos se muestren duraderos cuando se implementa un

programa de entrenamiento más largo, sugiere que el entrenamiento de habilidades cognitivas no debería abordarse como una intervención puntual sino más bien como una actividad de implementación continua. Los resultados que se presentan en este estudio, junto con los resultados de otros estudios (Diamond, 2012; Karbach & Unger, 2014; Posner & Rothbart, 2005) proporcionan información de gran relevancia para el diseño e implementación de programas de entrenamiento cognitivo en el aula que puedan ayudar a los niños a optimizar sus capacidades cognitivas y en especial a aquellos niños que más lo necesiten ya sea por razones temperamentales, ambientales o por que estén en riesgo de desarrollar patologías.

7.2. Factores constitucionales

Gran cantidad de estudios de genética molecular muestran cómo algunas variaciones genéticas influyen en la transmisión de señales neuronales como por ejemplo, en las vías dopaminérgicas. En base a estos hallazgos, científicos en el campo de la neurociencia cognitiva sugirieron que las funciones cognitivas podían estar relacionadas a un trasfondo genético. Esta conclusión motivó la puesta en marcha de una gran cantidad de estudios de asociación del genoma completo. Sin embargo, pocos sitios polimórficos con asociaciones fuertes se detectaron, los cuales estaban principalmente localizados en genes relacionados con receptores, transportadores de membrana, canales iónicos y el metabolismo de la dopamina y la serotonina (Goldberg & Weinberger, 2004; Green et al., 2008).

En su revisión acerca del uso de datos genéticos en la neurociencia cognitiva, Green y colaboradores (2008) afirmaron que: "...incluso los datos genéticos-moleculares más precisos no pueden ser útiles si los fenotipos no están

bien definidos. Por tanto los estudios cognitivos neuro-genéticos solo pueden ser tan buenos como su habilidad para medir fenotipos mentales de forma válida y específica” (p. 710). Con este planteamiento en mente, el trabajo que se presenta en esta tesis doctoral ha sido basado en la caracterización de la capacidad de autorregulación como una combinación de mecanismos de control atencional y de funciones ejecutivas, los cuales están relacionados con la activación de una red de estructuras neurales bien definida, como lo es la red de atención ejecutiva. Dentro de este marco de investigación nos propusimos estudiar la relación entre variaciones genéticas y diferencias individuales en la capacidad de autorregulación de los niños en edad preescolar, un periodo en el desarrollo caracterizado por cambios significativos tanto a nivel conductual como de maduración cerebral

En este estudio en particular, analizamos la relación entre variaciones en el gen DAT1 y la habilidad de autorregulación de los niños. Una fortaleza de nuestro estudio es que integra el conocimiento y tecnología provenientes del campo de la genética molecular con el conocimiento que se tiene de la capacidad de autorregulación desde el campo de la psicología del desarrollo y de la neurociencia cognitiva del desarrollo. Por una parte, las variaciones del gen SLC6A3-DAT1 fueron seleccionadas debido al impacto que ejercen en la eficiencia de las vías dopaminérgicas (Mill, Asherson, Browes, D’Souza, & Craig, 2002; VanNess, Owens, & Kilts, 2005) y porque estudios previos han encontrado que dichas variaciones se relacionan con diferencias individuales en el control inhibitorio y la capacidad de regular voluntariamente la conducta durante la niñez (Braet et al., 2011; Congdon et al., 2009). Por otra parte, para evaluar la habilidad de autorregulación se incluyeron una serie de medidas multifacéticas, las cuales fueron cuidadosamente seleccionadas en base a la evidencia empírica proporcionada por varios estudios

en el campo de la psicología del desarrollo y en el campo de la neurociencia cognitiva durante las últimas décadas.

El estudio de la relación entre el gen DAT1 y cognición no es nuevo, sin embargo muchas preguntas aún siguen sin resolver dado que los resultados de previas investigaciones han sido contradictorios. A nuestro entender, uno de los mayores retos en esta línea de investigación es la metodología implementada para evaluar la autorregulación. Una revisión de la literatura muestra que la mayoría de los trabajos que han sido publicados en este campo, han implementado tareas abstractas y descontextualizadas, las cuales son usualmente realizadas por los niños en un ambiente de laboratorio. Sin intención de ignorar o menospreciar el gran valor de dichas medidas, nuestro objetivo fue ir un paso más allá utilizando una serie de tareas y cuestionarios que evalúan la capacidad de autorregulación de los niños en contextos más ecológicos como el hogar y la escuela.

Los resultados de este segundo estudio revelan que las variaciones del gen DAT1 están relacionadas con las habilidades de autorregulación de los niños, específicamente, con su capacidad de modular voluntariamente sus reacciones en contextos sociales que están sujetos a reforzamiento emocional como es el caso de la escuela. Las variaciones del gen DAT1 afectan la cantidad de transportadores de la dopamina en el cuerpo estriado. En particular, el alelo 10r ha sido asociado a un incremento en el número de transportadores de la dopamina (VanNess et al., 2005), lo que a nivel funcional se traduce en bajos niveles de dopamina en el espacio sináptico del estriado. Este hallazgo sugiere que la presencia del alelo 10r ejerce un gran impacto en el circuito cortico-estriado el cual transfiere información entre estructuras subcorticales implicadas en el procesamiento de información y la

reactividad en contextos de afectivo/motivacionales y áreas frontales que apoyan el ejercicio de mecanismos de control arriba-abajo.

En conjunto, nuestros resultados representan una contribución significativa al entendimiento de las bases neurobiológicas de la autorregulación. Durante décadas, el conocimiento relacionado a los sustratos neurales de las habilidades de autorregulación ha sido confinado a lo que se infería de padecimientos neurológicos y lesión cerebral. Hoy en día con las técnicas de genética molecular somos capaces de describir partes de la genética de un individuo que modulan la eficiencia de funciones cerebrales, lo cual se traduce en diferencias observables a nivel comportamental en distintas habilidades que influyen en el ajuste social de niños y adultos.

7.3. La interacción de factores genéticos y educativos en el desarrollo de la autorregulación

En los dos primeros estudios presentados en esta tesis, nuestra meta fue profundizar en el entendimiento de la influencia de factores constitucionales y ambientales en el desarrollo de la autorregulación. En particular, nuestro trabajo se enfocó en dos aspectos: la influencia del entrenamiento de la atención ejecutiva y la influencia de variaciones del gen DAT1 en la habilidad de los niños para autorregularse. Mas allá de las contribuciones hechas, algunas preguntas continuaban abiertas: ¿todos los niños responden de la misma forma al entrenamiento de la atención ejecutiva? o ¿es posible que la configuración genética de un niño module hasta qué punto se puede éste beneficiar del entrenamiento?

Tanto para padres como para educadores es claro que no todos los niños responden de la misma forma a las condiciones de su entorno. Lo que parece

beneficiar a algunos niños no tiene impacto alguno en otros. Durante las últimas décadas, gran cantidad de estudios científicos en el campo de la psicología evolutiva se ha enfocado a entender cómo las características individuales de los niños están implicadas en la susceptibilidad que muestran a las condiciones de su entorno. Por ejemplo, aquellos niños que muestran una disposición temperamental a manifestar altos niveles de emociones negativas muestran mayores problemas comportamentales cuando se enfrentan a condiciones adversas durante los primeros años de vida. Sin embargo estos mismos niños muestran también mayores beneficios cuando crecen en un ambiente positivo y acogedor (ver revisión del tema en Belsky, Bakermans-kranenburg, & Van Ijzendoorn, 2007).

Estas observaciones apuntaron a la hipótesis de que la configuración genética de los niños podría explicar las diferencias individuales en la forma en la que éstos responden a las influencias del ambiente. En este sentido, el trabajo pionero de Caspi y cols. (2002) reveló que algunas variaciones genéticas modulan la vulnerabilidad de los niños a condiciones adversas del ambiente. Investigaciones recientes han ido un paso más allá mediante el estudio de la interacción Gen-Ambiente (G x A) en el contexto de susceptibilidad diferencial, esto es, cómo la configuración genética de un individuo media el impacto tanto de condiciones favorables como de condiciones desfavorables “para bien o para mal” (Bakermans-Kranenburg & van Ijzendoorn, 2007; Belsky et al., 2007). Diversas investigaciones han estudiado cómo los genes relacionados con la dopamina modulan la influencia de factores ambientales que afectan al niño durante el embarazo y durante los primeros años de vida (para revisión del tema ver Bakermans-Kranenburg & van

Ijzendoorn, 2011). Sin embargo, menos investigaciones se ha llevado a cabo para estudiar la interacción G x A en el contexto de entrenamiento cognitivo.

En el último estudio de esta tesis doctoral, examinamos si las variaciones genéticas de tres genes que han sido relacionados con distintos mecanismos de modulación de los niveles de dopamina en el cerebro (DAT1, DRD4 y COMT), pueden explicar diferencias individuales en la plasticidad cognitiva de los niños frente a un programa de entrenamiento de la atención ejecutiva. Tres medidas de la función cognitiva se implementaron antes y después del entrenamiento para medir los efectos relacionados con la intervención: 1) inteligencia fluida, 2) control inhibitorio y 3) memoria de trabajo. Nuestros datos indican que los efectos del entrenamiento en las medidas de control inhibitorio y de memoria de trabajo se ven modulados de forma diferencial por cada gen. El patrón observado, sugiere que la modulación genética a influencias del ambiente depende del circuito neuronal en el cada gen ejerce alguna influencia. De forma general, los genotipos asociados a un balance óptimo de la señal dopaminérgica en el circuito cortico-estriado también contribuyen a la plasticidad del sistema.

Los resultados encontrados en este estudio tienen varias implicaciones a la forma en la que entendemos la capacidad de autorregulación y, especialmente, a la metodología que implementamos para mejorar dicha capacidad en niños en edad preescolar. Tanto desde el campo experimental en la neurociencia cognitiva, como desde el campo de la educación, se asume que todos los niños que están en el mismo rango de edad y que comparten niveles socioeconómicos similares, también están en el mismo nivel de desarrollo cognitivo. Por esta razón, tanto los programas de entrenamiento cognitivo, como las estrategias educativas implementadas en las escuelas, se han venido diseñando para cubrir las

necesidades de una parte de la población mientras que las diferencias individuales son usualmente dejadas de lado. Lo que nuestros datos indican es que cada niño, con su configuración genética y condiciones ambientales únicas no solamente difiere de otros en su capacidad de autorregulación sino que además difiere de otros en su capacidad para beneficiarse de un entrenamiento cognitivo dado. De estos datos se puede concluir que, la optimización de los programas de entrenamiento debe tener en cuenta tanto factores de tipo genético como factores ambientales con el objetivo de brindar el apoyo que cada niño necesita de acuerdo con sus necesidades específicas.

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Appendix

Appendix II

Escala de Regulación Emocional

A rellenar por el personal:

Num. Exp. _____

Fecha de Hoy: D_____ M_____ A_____

Fecha de nacimiento del niño/a: D_____ M_____ A_____

Edad: _____ años, _____ meses. Sexo del niño/a: M_____ V_____ (Marque uno)

Relación con el niño:

Madre _____ Padre _____ Otro (por favor indicar) _____

INSTRUCCIONES: Rogamos que lea detenidamente las siguientes indicaciones antes de comenzar el presente cuestionario.

En las páginas siguientes usted podrá ver la descripción de las reacciones de los niños ante determinadas situaciones. Deseamos que usted nos indique qué reacción es la más probable de su hijo/a en estas situaciones. Sabemos que no existe una forma "correcta" de reaccionar; los niños se diferencian mucho en sus reacciones; son precisamente estas diferencias las que pretendemos captar. Por favor, lea cada descripción y decida si es verdadera o falsa en relación con la reacción de su hijo/a durante los últimos seis meses.

Utilice la siguiente escala para indicar el grado en que cada una de las afirmaciones se adecua al comportamiento de su hijo/a:

Haga un círculo alrededor del número correspondiente si la descripción es:

- | | |
|---|-----------------------|
| 1 | Falsa en extremo |
| 2 | Bastante falsa |
| 3 | Ligeramente falsa |
| 4 | Ni falsa ni verdadera |
| 5 | Ligeramente cierta |
| 6 | Bastante cierta |
| 7 | Cierta en extremo. |

Si usted no puede contestar una de estas preguntas porque nunca ha visto a su hijo/a en una situación determinada, marque con un círculo la opción NA (No Aplicable). Así por ejemplo, si le preguntan por la reacción de su hijo cuando usted canta, y usted no le ha cantado, entonces debe marcar NA.

Por favor, asegúrese de responder todas las preguntas.

1. Si recibe un regalo que no le gusta lo manifiesta
1 2 3 4 5 6 7 NA

2. No puede contener la risa si ve a alguien caerse o hacerse daño
1 2 3 4 5 6 7 NA

3. Le cuesta moderar sus reacciones, por lo que tiende a romper cosas o a agredir con facilidad cuando juega
1 2 3 4 5 6 7 NA

4. En contextos formales (ej. Iglesia, hospital) comprende la situación y se comporta adecuadamente
1 2 3 4 5 6 7 NA

5. Es capaz de guardar un secreto sobre algo emocionante (ej. No decirle a su hermano el regalo que se la ha comprado para su cumpleaños)
1 2 3 4 5 6 7 NA

6. Evita contar lo sucedido para ayudar a que no se castigue a otros niños
1 2 3 4 5 6 7 NA

MUCHAS GRACIAS POR SU COLABORACIÓN