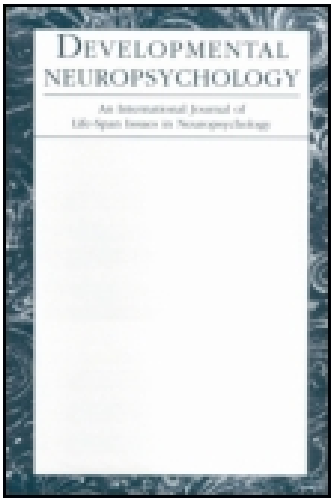

Developmental Neuropsychology
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/hdvn20

Executive Functions Development in 5- to 7-Year-Old Children With Transposition of the Great Arteries: A Longitudinal Study

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Published online: 04 Aug 2014.

To cite this article: Johanna Calderon, Isabelle Jambaqué, Damien Bonnet & Nathalie Angeard (2014) Executive Functions Development in 5- to 7-Year-Old Children With Transposition of the Great Arteries: A Longitudinal Study, Developmental Neuropsychology, 39:5, 365-384, DOI: 10.1080/87565641.2014.916709

To link to this article: http://dx.doi.org/10.1080/87565641.2014.916709

DEVELOPMENTAL NEUROPSYCHOLOGY, *39*(5), 365–384

ISSN: 8756-5641 print / 1532-6942 online
DOI: 10.1080/87565641.2014.916709

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Executive Functions Development in 5- to 7-Year-Old Children With Transposition of the Great Arteries: A Longitudinal Study

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This longitudinal study investigates executive functions (EF) in children with transposition of the great arteries (TGA) compared to typically developing children at a key age period between 5 and 7 years. We explored the presence and evolution of specific impairments on three core EF components (inhibition, working memory, and cognitive flexibility). Ninety children were evaluated for three consecutive years. Results demonstrated significant delays in inhibition and cognitive flexibility despite normal working memory. Impairments did not systematically worsen with age. EF impairments after TGA are dynamic and may affect selective components. Cyanotic congenital heart disease is associated with altered EF development.

Transposition of the great arteries (TGA) constitutes one of the most pertinent forms of congenital heart disease (CHD) to study in regards to neurodevelopmental outcomes (Miller et al., 2004). Neonates born with TGA undergo a single neonatal open-heart surgery that restores normal circulation and arterial oxygenation which limits the number of confounding variables including

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later chronic cyanosis and offers an ideal opportunity to study the impact of early neonatal brain vulnerability to hypoxic-ischemic insults on later neurocognitive development (McQuillen & Miller, 2010). Focal stroke, hypoxic-ischemic injury, diffuse disturbances in cerebral oxidative metabolism (Miller et al., 2004), delayed brain maturation, and mild to moderate white matter injury, primarily in the form of periventricular leukomalacia (PVL) (Licht et al., 2009; Petit et al., 2009), have been reported in neonates with cyanotic CHD. There is an increasing body of literature reporting long-term neurocognitive outcomes at school age and adolescence in CHD, including TGA (Bellinger et al., 2003; Bellinger & Newburger, 2010; Bellinger et al., 2011; Hövels-Gürich et al., 2002, 2007; Shillingford et al., 2008). These studies generally find normal IQ levels (Bellinger et al., 2003; Hövels-Gürich et al., 2002) but specific impairments in motor function (Hövels Gürich et al., 2002), expressive language, and visual–spatial skills (Bellinger & Newburger, 2010), social cognition (Bellinger et al., 2011; Calderon et al., 2010), and executive functions (EF) (Bellinger et al., 2003; Calderon et al., 2010). Behavioral difficulties (internalizing and externalizing problems) (Bellinger et al., 2009) as well a high prevalence of hyperactivity/impulsivity symptoms consistent with attention deficit hyperactivity disorder (ADHD) have also been reported in these children at a mean age of 8 years (Shillingford et al., 2008). There is a recent growing awareness of EF and behavioral regulation difficulties in these children (Marino et al., 2012). However, very few studies have focused on EF development in spite of their crucial influence on academic achievement (Bull, Espy, & Wiebe, 2008) and social adaptation (Hughes & Ensor, 2007) during childhood.

In a large cohort study of neurodevelopemental outcomes after TGA at age 8, children displayed weak performances in a verbal working memory (WM) test (digit span forwards and backwards) and below age expected levels on a test of vigilance and sustained attention. Based on observations conducted on the Rey-Osterrieth Complex figure test, these children seemed to get lost in the details and had difficulties structuring tasks as a whole. They had significant difficulties in organizing, implementing strategies or plans, and in modifying them as needed (Bellinger et al., 2003). These difficulties relate to problems integrating or coordinating simple skills to accomplish higher-order goals, suggesting that school-aged children with TGA may have specific deficits in EF (Bellinger & Newburger, 2010). A recent study confirmed these previous results in a group of 7-year-olds with TGA compared to typically developing same-aged peers (Calderon et al., 2010). These latter results showed significantly lower cognitive and motor inhibition scores (e.g., animal stroop test and statue test from the NEuroloPSYcological Assessment [NEPSY]) as well as lower verbal and visuospatial WM spans and scores on complex EF such as planning (e.g Tower from the NEPSY). Although these results were consistent with a previous study (Bellinger et al., 2003), they do not allow characterizing the pattern of EF impairments as consistent data are lacking concerning the status of other EF components such as cognitive flexibility. Indeed, EF organization during childhood has been commonly suggested to be characterized by three partially dissociable components (inhibition, WM and cognitive flexibility) (Diamond, 2013; Garon, Bryson, & Smith, 2008). Cognitive flexibility is thought to build upon early inhibition and WM skills (Diamond, 2013) and therefore could be particularly vulnerable after TGA. Interestingly, divergent results for this complex EF component have been observed at school age, in which children with TGA exhibited deficits on the Wisconsin Card Sorting Test but no impairment on the Trail Making test part B (Bellinger et al., 2003). No other study has explored cognitive flexibility after CHD, which prevents from drawing valid conclusions on the exact nature of its impairment.

Moreover, it is currently poorly understood how these deficits emerged in early childhood and how they evolve as children with TGA grow older. Data from 16-year-old TGA adolescents suggest that mild to moderate impairments in EF as reported by parents and teachers using the Behavior Rating Inventory of Executive Function (BRIEF) continue to be problematic in this population (Bellinger et al., 2011). These general findings may underline the existence of long-term EF vulnerabilities but they are not sufficient to understand the specific developmental trajectory of core EF subcomponents from early childhood. As suggested by Bellinger and Newburger (2010), some cognitive impairments in this population may be somehow latent early in development, only becoming evident at a later age (from the begging of formal primary education), thus being referred to as the child "growing into a deficit" (Bellinger & Newburger, 2010). Two longitudinal studies of neurodevelopmental outcomes after TGA (Bellinger et al., 2003; Hövels-Gürich et al., 2002) support this statement as the impairments detected at school-age for domains such as language, psycho-motor development, and academic achievement are twice the rate of those identified in early childhood. No longitudinal data are available concerning the online path of development for EF impairments. Thus, it is currently unknown if executive deficits at a given age may worsen as children get older or on the contrary may catch up, and if so, what exactly normalizes and what does not, taking into account the variety of executive processes.

In typical development, EF undergo crucial improvements in early and middle childhood, paralleling the progressive maturation of prefrontal structures (Moriguchi & Hiraki, 2011). Competing models regarding the structure of EF during early childhood have been reported, some of them supporting an unitary EF factor in the first years of life (Lee, Bull, & Ho, 2013) and others supporting an earlier multicomponent structure (Diamond et al., 2013; Huizinga, Dolan, & van der Molen, 2006). Despite these divergent theoretical backgrounds, a wealth of empirical data has demonstrated that progressions in core EF components are not linear and their developmental timetable may not be synchronous (Diamond, 2013; Garon et al., 2008; Huizinga et al., 2006). Motor inhibition emerges in infancy and undergoes large improvements between the ages of 3 to 5 years (Simpson & Riggs, 2005) where children can control more efficiently prepotent responses. Cognitive inhibition, which pertains to more complex inhibitory control, involves holding a rule in mind, responding according to that rule and inhibiting a dominant response (Garon et al., 2008). Rapid improvements in early childhood have been reported in tasks such as Day/Night (Gerstadt, Hong & Diamond, 1994) or other stroop-like tests applicable from the preschool years such as the Animal Stroop task (Wright, Waterman, Prescott, & Murdoch-Eaton, 2003). In these tasks, striking gains in performance are typically observed during the preschool years until around the age of 6 (Gerstadt et al., 1994) followed by slower and smaller progressions in later childhood, particularly in terms of reaction times (RT) (Best & Miller, 2010; Wright et al., 2003). WM refers to the ability to store and manipulate a certain amount of information (verbal or visuospatial) during a limited time (Baddeley, 2012). Contrary to inhibitory skills, WM does not undergo crucial improvements early in the preschool years; instead, this EF component is reported to increase gradually across childhood with a relative steep acceleration between 6 to 11 years (Gathercole, Pickering, Ambridge, & Wearing, 2004). Finally, cognitive flexibility has been described as the most complex and late developing EF component that undergoes a critical period of progression in late preschool to middle childhood (Diamond, 2013). Set-shifting tasks involve not only switching from one mental representation to another but also require applying inhibition (i.e., suppress attention to the no longer pertinent representation) and updating to actively maintain the

rules related to the upcoming task (Chevalier et al., 2012; Diamond, 2013; Garon et al., 2008). Children aged 4 to 5 typically succeed at shifting from one rule to another within a simple set (e.g., "sort by color then by shape") as measured for example with the standard Dimensional Change Card Sort (DCCS) (Zelazo, 2006). However, performances on more advanced tasks such as the DCCS including mixed trials (trials in which a shift is needed or not according to external abstract cues) and imposing to mentally set a goal to achieve while continually re-setting rules undergo key important progressions from 6 to 9 years (Davidson, Amso, Anderson, & Diamond, 2006; Diamond, 2013).

Data from children born very preterm, who share some of the neonatal neurologic vulnerabilities (white matter injuries and cerebral immaturity) with children born at term with cyanotic CHD, have demonstrated that the developmental timetable of EF components may play a role in the deficits observable at a given age (Ritter, Nelle, Perrig, Steinlin, & Everts, 2012). Children born very preterm display an early variety of EF deficits but seem to catch up with peers on the earliest developing EF component (inhibition) at a mean age of 8 (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2012). The literature on typical and atypical developmental trajectories suggest that deficits in EF components may not manifest themselves synchronously as the progressions of these abilities follow distinct developmental timetables. A follow-up study of core EF components in children with TGA should allow us to determine if they are indeed "growing into a deficit" or instead if a maturational lag is evident in early development and how it evolves with time in the same individuals.

AIMS OF THIS STUDY

The first aim of this 3-year follow-up study was twofold. We first sought to determine the extent and nature of developmental progressions in all EF components at a key transitional period (between the mean ages of 5 to 7 years) in children with TGA compared to typically developing children. Our objective was not only to describe specific EF impairments in the group with TGA but also to determine the potential aggravation or normalization of these problems with age. Based on previous studies in typical development, we hypothesized significant general improvements in all EF components at the within-group level. Children with TGA would progress in all components even though their developmental changes are predicted to be smaller, thus characterizing a general delay. Further, we hypothesized that children with TGA would present significantly lower performances in all EF components. However, based on the typical developmental trajectory of EF where inhibition skills emerge and mature earlier in development (Diamond, 2013), we predicted that inhibition impairments would tend to decrease in severity with time (possible delay catch-up). Conversely, WM and cognitive flexibility impairments would tend to increase with time, as these abilities become more efficient and developmental gaps become more apparent.

Given that early inhibition and WM have been suggested to be main precursors of cognitive flexibility, our second aim was to examine the contributions of these EF components in each group and to identify differences in these predictors as possible markers of atypical development of complex EF in children with TGA. We predicted that cognitive flexibility at Time 3 (at a mean age of 7 years) would be predicted by initial performances in inhibition and WM measures at Time 1 and 2 (at mean age of 5 years and 6 years respectively) for both groups.

METHOD

Participants

This is a single center follow-up study of neurocognitive outcomes in children born between 2003 and 2005 with TGA. Inclusion criteria was a diagnosis of TGA requiring a single neonatal open-heart surgery (arterial switch operation) under cardiopulmonary bypass (CPB) support with no requirements for deep hypothermic circulatory arrest (mean age at operation = 7 days, mean CPB duration = 131.7 min; *SD* = 21.9 min). Exclusion criteria were birth-weight less than 2,500 g, the presence of genetic syndromes, complex associated cardiovascular anomalies or extra-cardiac pathologies, as well as additional surgical procedures. All exclusion criteria information was extracted from medical records, among children who met one or more of these criteria, two were excluded due to presence of a 22q11 deletion. Genetic screening was conducted if clinical concerns were reported. In addition, normal cardiac condition, age at the first cognitive evaluation (4 years old to 6 years, 11 months), parent's consent to participation and geographic location were also taken into account for patients' enrollment in the study. The research was approved by the local hospital ethics committee. Sixty eligible children were identified in the database. Parents of six children declined participation in the study and two children were excluded due to developmental disorders not previously identified (autism spectrum disorder and severe language disability). Six families could not be contacted due to a change of address and one child refused to cooperate with the administration of the tests.

Forty-five eligible children (75%) participated in the study (15 female, 30 male). No significant differences were found between participants ($n = 45$) and non participants ($n = 15$) for all medical-related variables ($p > .05$) including time of diagnosis of the cardiac malformation, gestational age, birth weight, duration of CPB, presence of preoperative metabolic acidosis and Intensive Care Unit (ICU) stay. Same-aged comparison children were recruited in public kindergartens and elementary schools in the same geographic area of children with TGA over the same time period. One or two classrooms per school were randomly chosen and exclusion criteria given to teachers were a known developmental or physical impairment, confirmed or suspected learning disabilities and/or mother language other than French. Parents of all children meeting the inclusion criteria received a letter of information and a consent form. A rational of 1:3 males was applied to match TGA sex ratio by means of simple randomization among girls in each classroom. Of eligible families, 80% gave consent for participation. Forty-five typically developing children were included and the group comprised 17 females and 28 males. Families of all comparison children included in this study provided information on children's health status, medical antecedents and demographic variables. No abnormal data were reported for any child in the comparison group. All children underwent a neuropsychological evaluation once a year for a 3-year period. The flow chart of participants in the study from intake (Time 1) to follow-up at Time 3 is presented in Figure 1. All evaluations were individual and were conducted in a single session (with regular breaks). Evaluations at time 1 (T1) lasted approximately 2 hours. Evaluations at Time 2 (T2) and Time 3 (T3) took approximately 3 hours with regular and fixed pauses for both groups. Parental educational level and socioeconomic status were recorded for all children. No significant differences were found between patients and comparisons in any of these variables ($p > .05$).

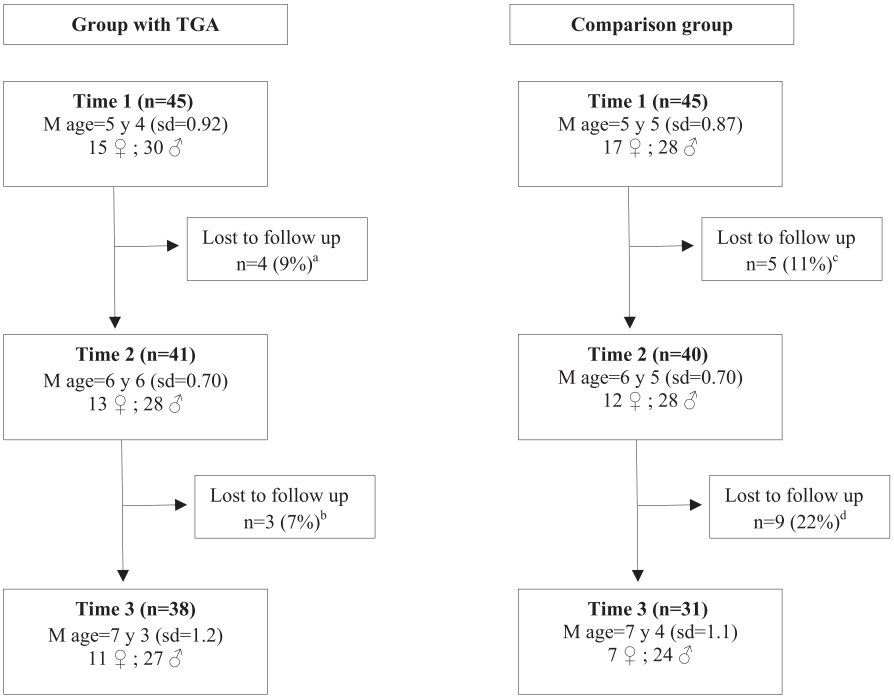

FIGURE 1 Flow chart of participants in the study from intake (Time 1) to follow-up at Time 3. Longitudinal gaps between Time 1 and 2 have a mean of 14 months and between Time 2 and Time 3 a mean of 13 months for both groups. [a]Three children with transposition of the great arteries (TGA) were lost to follow-up due to family change of residence area and 1 due to parental refusal to continue participation. [b]Three children with TGA were lost to follow-up due to lost contact with family. [c]Five comparison children were lost to follow-up due to change of school in the transition between kindergarden and primary school ($n = 4$) and 1 child due to parental refusal to give written consent for continuing participation. [d]Four children were lost to follow-up due to a family change of area or children change of school, 3 due to parental refusal to continue participation, 1 child refused to complete the tests, and 1 child had repeated absence to school during the examination schedule.

Procedure and Measures

Children were individually scheduled for assessment as soon as written informed consent was obtained from the parent(s). Every year, children with TGA were evaluated at our cardiology unit and comparison children at their schools. All children completed a general evaluation of IQ using the Columbia Mental Maturity test (Burgemeister, Blum, & Lorge, 1972) at Time 1 and Time 3 as well as an assessment of receptive language using "the comprehension of instructions" subtest from the NEPSY (Korkman, Kirk, & Kemps, 1998) at Time 1, 2, and 3. In this subtest, children are asked to execute oral instructions (pointing to a series of animals or geometrical shapes)

of increasing syntactic complexity. A measure of verbal and visuospatial short-term memory was also proposed using the Digit Span Forwards (extracted from the Wechsler Intelligence Scale–Fourth Edition [WISC–IV]; Wechsler, 2003) and the Visuo-Spatial Span Forwards (Berch, Krikorian, & Huha, 1998). In these measures, children are asked to repeat the numbers (Digit Span Forwards) and to show the squares (Visuo-Spatial Span Forwards) in the same order they were stated/pointed by the experimenter. All children were also assessed by a comprehensive battery of EF measures (motor and cognitive inhibition, verbal and visuospatial WM, cognitive flexibility).

This battery was administered by a neurodevelopmental psychologist who was not blind to children's group membership but who did not review children's medical or demographic information during the time of evaluations. The order of presentation of tests was randomly counterbalanced.

Motor Inhibition Measures

The Hand Game (Hughes, 1998) comprised two conditions (a control and a conflict condition). In the control condition, the experimenter shows hand shapes (either making a fist or pointing a finger) to the child and asks him to do exactly as shown. Once the child made six consecutive correct responses, the conflict condition was introduced. In this condition the experimenter asked the child to do the opposite hand shape as shown. A total of 15 trials were administered and children were awarded a point if they produced the correct hand action immediately (or if they self-corrected their action without feedback immediately). Score ranges between 0 and 15. As this test was specifically designed for preschoolers (with reported ceiling effects beyond 6–7 years), it was only presented at Time 1.

Hearts and Flowers incongruent condition (Diamond, Barnett, Thomas, & Munro, 2007). This was a computerized test, adapted from Davidson et al. (2006), originally named "the Dots task." It requires the inhibition of a behavioral tendency to press on the same side where a stimulus appears. It comprises three conditions (a congruent, an incongruent and a mixed condition). In all conditions of the Hearts and Flowers task, a red heart or flower appears on the right or left side of the computer screen. The presentation time for each stimulus for children aged 7 years or younger was 1,500 msec and 750 msec for older children. In the congruent condition, the rule was to press the button on the same side as the heart. The incongruent condition also required remembering a rule ("press the button on the side opposite the flower") but in addition it required inhibiting the spatial compatibility effect. All conditions were presented after a practice session where children could get feedback (from two to six trials). The congruent and incongruent conditions included 12 trials each. Two dependent measures were analyzed: Number of correct responses /12 (accuracy) and mean reaction times (RT) for each condition (speed, in msec). Responses faster than 200 msec were excluded from the analyses (anticipatory responses, too fast to be related to the stimulus). No feedback was given during test trials. This test was administered at Time 2 and 3.

Cognitive Inhibition Measures

Day and Night (Gerstadt et al., 1994). Children were presented with a white card with a yellow sun and a black card with a white moon and stars on it. Children were told that in this

game they had to say "night" for the sun card and "day" for the moon/stars card. After a brief warm-up, there were 15 test trials with each card presented in a pseudorandom order. Accuracy (number of correct responses out of 15) was recorded. This task was presented at Time 1.

Animal stroop test (Wright et al., 2003). It consists of a pictorial version of the Stroop task that does not require reading abilities. Visual stimuli (four exemplar images of farm animals: a cow, a sheep, a duck, a pig) are congruent in the first condition, neutral in the second condition, and then incongruent in the third condition, where each animal's head is substituted with another animal's head. Children are required to name the animal's body and then inhibit a preferred response based on the identification of the animal's head. Scores are given in terms of RT (in seconds) as well as the number of errors committed in the incongruent condition (scores for the number of errors can range between 0 to 24). This task was presented at all three times of evaluation.

WM Measures

Digit span backwards (Wechsler, 2003). It measures the ability to store and manipulate verbal information for a short time. Children are required to repeat a series of numbers of increasing length in the reverse order (scores range from 0 to 16). This test included results from children aged 5 and older.

Spatial span backwards task (Berch et al., 1998). This test is analogous to the verbal WM task; the stimuli are a set of small squares randomly positioned. Children reproduce a sequence of squares locations of increasing length in the reverse order as they saw it. Scores range from 0 to 12 for each condition. This test included results from children aged 5 and older.

All measures of WM were presented at all three times of evaluation.

Cognitive Flexibility Measures

Dimensional change card sorting test (DCCS) standard level 1 version and advanced border level 2 version (Zelazo, 2006). All children received level 1 version in which they were required to sort a series of bidimensional cards (depicting a red rabbit or a blue boat) into two trays (depicting a blue rabbit or a red boat), first, in a pre-switch phase, according to one dimension (e.g., shape, *"If it's a boat, put it here"*), then in a post-switch phase, according to the other dimension (e.g., color *"if it's blue, put it here"*). Scores for level 1 go from 0 to 6 (post-switch phase). Children who obtained a score higher than 4 (passing criteria) were given immediately after a more difficult border level 2 version. Children were first shown two test cards like those used in the standard version as well as two new test cards that had additionally black borders. Children were then told that the black borders indicated that they must play a new game (e.g., "If there's a black border, you have to play the shape game; if there is no black border, you have to play the color game"). No feedback was provided. The score for the advanced border version (level 2) ranges between 0 and 12. Finally, this test was presented at all three times of evaluation.

Hearts and Flowers Mixed condition (Diamond et al., 2007). This condition was presented after the incongruent condition and consisted of incongruent and congruent trials that were

intermixed. The rules were unchanged for each stimulus but needed to be alternated between trials ("if you see a heart, press on the same side" and "if you see a flower, press on the opposite side"). The presentation time for each stimulus for children aged 7 years or younger was 1,500 msec and 750 msec for older children. Two dependent measures were analyzed: Number of correct responses /33 (accuracy) and mean reaction times for each condition (speed, in msec). Responses faster than 200 msec were excluded from the analyses (anticipatory responses, too fast to be related to the stimulus). No feedback was given during test trials. This test was presented at Time 2 and 3.

Data Analysis

ANOVAs repeated-measures and non parametric X^2 tests were respectively used for numerical (age, IQ, language, and short-term memory scores) and categorical variables (socioeconomic status [SES] and Parental Educational Level [PEL]). In order to determine significant differences in performances between children with TGA and comparisons at all time points, repeated measures ANOVA for each EF task was performed with group (TGA *versus* comparison) as the between-subject factor and time point (T1, T2, T3) as the within-subject factor. Planned comparisons at each time point were conducted when significant differences between groups were observed. When a datum was missing, a case-wise deletion method was used. Effect sizes were also estimated for each measure by means of partial eta squared (η_p^2). Conventionally, large effects correspond to ($\eta_p^2 \geq 0.14$); moderate effects to ($\eta_p^2 \geq 0.06$ and $\eta_p^2 < 0.14$) and weak effects to ($\eta_p^2 < 0.06$) (Cohen, 1992). Moreover, in order to characterize the degree of impairment and its extent for children with TGA when compared to typical values from the comparison group, effect sizes for significant differences in terms of standardized mean differences (SMD) were calculated. The SMD refer to the differences between the two groups means divided by an estimate of the within group standard deviation. Effect sizes of 0.2, 0.5, and 0.8 refer to small, medium, and large effects, respectively. These latter analyses provide information regarding potential longitudinal aggravation or normalization of significant impairments that may be detected. Finally, a series of stepwise regression analyses were conducted to determine the potential early predictors of later set-shifting tasks such as DCCS 2 and HF mixed at T3. One model was conducted with variables at the first time point and another model was calculated with variables at T2. All measures of inhibition, WM and short-term memory as well as language were included in the models. Tests were considered significant when p value $< .05$. Statistical analyses were performed with Statistica software (version 9.1; Stat Soft Inc.).

RESULTS

As shown in Table 1, children with TGA did not significantly differ from comparison children in age and non-verbal IQ at all time points. However, receptive language scores ("comprehension of instructions" NEPSY subtest) and verbal short-term memory scores (Digit Span Forwards) were significantly lower at T2 and T3. Finally, visuospatial short-term memory scores did not significantly differ between the groups.

TABLE 1
Descriptive Statistics for Age, Language Comprehension, Short-Term Memory, and Non-Verbal IQ for Children With Transposition of the Great Arteries (TGA) ($n = 45$) and Comparison Children ($n = 45$) at Three Time Points

	Group with TGA	*Comparison Group*	
Variable	*M (SD)*	*M (SD)*	*p value*
Age			
Time 1	5 y 4 mo (0.92)	5y 5 mo (0.87)	*ns*
Time 2	6 y 6 mo (0.77)	6y 5 mo (0.72)	*ns*
Time 3	7 y 3 mo (1.21)	7y 4 mo (1.13)	*ns*
Language[a]			
Time 1	12,54 (0,81)	12, 4 (0, 81)	*ns*
Time 2	19,92 (2,55)	21, 51 (2, 62)	0,008
Time 3	21 (1,87)	22,88 (2,6)	0,008
Verbal Short-Term Memory[b]			
Time 1	5,46 (1,77)	6, 11 (1, 80)	*ns*
Time 2	6,85 (1,86)	7, 74 (1, 83)	0,05
Time 3	7,45 (1,65)	8, 61 (1, 47)	0,05
Spatial Short-Term Memory[c]			
Time 1	4,46 (1,34)	5, 04 (1, 26)	*ns*
Time 2	6,12 (1,36)	6, 15 (1, 60)	*ns*
Time 3	6,27 (1,59)	6, 29 (1, 29)	*ns*
Non-Verbal IQ[d]			
Time 1	113 (8,3)	116 (8,8)	*ns*
Time 3	112 (8,4)	115 (9,6)	*ns*

Note. Values are mean (*SD*). *p* values were calculated by using ANOVA-repeated measures for comparisons between the groups across time points.
[a]"Comprehension of instructions" subtest from the NEuroloPSYcological Assessment (NEPSY). At Time 1, scores range from 0 to 13 and at Time 2 and 3, score range between 0 and 28. [b]Verbal short-term memory was assessed with the Digit Span Forwards subtest from the Wechsler Intelligence Scale–Fourth Edition (WISC–IV), scores range between 0 and 16. [c]Visuospatial short-term memory was evaluated using the Visuo-spatial Span Forwards from the Batterie d'Evaluation Mnésique (BEM)-144 (Memory Battery), scores range between 0 and 16. [d]Columbia Mental Maturity Scale (CMMS) ($M = 100$; $SD = 15$).

Executive Functions

Children's performances on all EF measures are shown in Table 2.

Inhibitory control measures. Results on elementary motor and cognitive inhibition (Hand Game and Day/Night) demonstrated that at a mean age of 5, children with TGA had significantly lower performances than comparison group on both tests [$t(88) = 2.7$; $p < .01$ and $t(88) = 2.68$; $p < .01$, respectively].

In the Hearts and Flowers test *incongruent condition*, neither the number of correct responses nor the RT were significantly different between the groups at any time point [$F(1, 63) = 2.54$; $p = .1$, $\eta 2 = 0.03$; $F(1,63) = 0.19$; $p = .66$, $\eta 2 = 0.003$, respectively]. There was a significant increase for both groups in the number of correct responses from T2 to T3 [$F(1, 63) = 4.26$; $p = .04$, $\eta 2 = 0.06$] and a significant decrease in RT [$F(1, 63) = 50.53$; $p = .00001$, $\eta 2 = 0.44$].

TABLE 2
Mean Executive Function (EF) Scores for Children With Transposition of the Great Arteries (TGA) and the Comparison Group at T1, T2, and T3

		Group With TGA			*Comparison Group*		
		M (SD)			*M (SD)*		
EF	*Variable, Range*	*T1 (5, 4 y) n = 45*	*T2 (6, 6 y) n = 41*	*T3 (7, 3 y) n = 38*	*T1 (5, 5 y) n = 45*	*T2 (6, 5 y) n = 40*	*T3 (7, 4 y) n = 31*
Motor Inhibition	***Hand Game***						
	Number Correct (0–15)	12.73 (1.95)§	—	—	13.68 (1.32)	—	—
	Hearts and Flowers						
	Incongruent Correct (0–12)	—	9,72 (2,9)	10,4 (1,48)	—	10,36 (1,58)	10,9 (1,06)
	Incongruent RT, msec	—	699,64 (190,79)	597,9 (117,54)	—	724,54 (207,86)	551,4 (116,7)
Cognitive Inhibition	***Day/Night***						
	Number Correct (0–15)	13.24 (2.36)§	—	—	14.26 (0.96)	—	—
	Animal Stroop						
	RT	82,42 (31,61)*	60,30 (31,75)*	42,45 (18,14)*	61,03 (20,54)	45,15 (18,56)	33,36 (9,55)
	Number of Errors	3,08 (2,77)*	1,56 (1,2)	1,10 (1,17)	1,42 (1,48)	1,37 (1,51)	1,16 (1,55)
Working Memory	***Digit Span*** (0–16)						
	Backwards	4.17 (1,98)	5,19 (1,58)	6,02 (1,31)	4,67 (2,10)	5,42 (1,05)	6,45 (1,17)
	Spatial Span (0–12)						
	Backwards	4,14 (1,53)	5,02 (1,47)	5,27 (1,57)	4,8 (1,62)	5,34 (1,4)	5,51 (1,31)
Cognitive Flexibility	***DCCS***						
	Level 1 (0–6)	5,64 (1,03)	5,54 (1,21)		5,9 (0,2)	5,85 (0,5)	
	Level 2 (0–12)	7,28 (2,86)*	8,62 (2,63)*	9,45 (2,21)*	8,6 (2,09)	10,3 (1,94)	10,6 (1,27)
	Hearts and Flowers						
	Mixed Correct (0–33)	—	22,4 (4,39)	24,2 (6,03)*	—	24,5 (3,7)	25,9 (4,8)
	Mixed RT, msec	—	947,86 (200,25)	718,2 (135,59)	—	977,2 (213,82)	711,79 (113,52)

Note. DCCS = Dimensional Change Card Sort; RT = Reaction Time.
§$p < .5$ for comparisons between groups in independent t-tests. *$p < .05$ for comparisons between groups in ANOVA repeated measures specific comparisons.

No interactions between group and time point were observed for either measure [$F(1,63) = 0.34$; $p = .55$, $\eta 2 = 0.005$ for number of correct responses and $F(1, 63) = 2.26$; $p = .13$, $\eta 2 = 0.03$ for RT].

In the Animal stroop test RT, results showed a significant main effect of group [$F(1, 66) = 9.49$; $p < .001$, $\eta 2 = 0.12$] as well as a significant effect of time of evaluation [$F(2,132) = 83.67$; $p < .001$, $\eta 2 = 0.55$] but no significant interaction [$F(2,132) = 2.48$; $p = .08$, $\eta 2 = 0.03$)]. Planned comparisons revealed that children with TGA had significantly longer RT than comparisons at all time points [$F(1, 66) = 10.58$; $p < .001$] in T1; $F(1, 66) = 5.32$; $p < .05$] in T2 and [$F(1, 66) = 6.29$; $p < .01$ in T3]. The number of errors significantly decreased across time points for both groups [$F(2,132) = 6.26$; $p < .01$, $\eta 2 = 0.08$]. A significant interaction between group and time point was observed [$F(2,132) = 3.37$; $p < .05$, $\eta 2 = 0.08$] and planned comparisons demonstrated that children with TGA produced significantly more errors than comparisons only in T1 [$F(1, 66) = 5.33$; $p < .05$].

WM measures. The digit span backwards data showed a significant effect of time point [$F(2, 90) = 33.8$; $p < .001$, $\eta 2 = 0.42$] but no significant effect of group [$F(1,45) = 0.47$; $p = 0.49$, $\eta 2 = 0.01$] and no significant interaction [$F(2,90) = 0.10$; $p = 0.89$, $\eta 2 = 0.002$].

The spatial span backwards, there was a significant effect of time [$F(2,86) = 15.42$; $p < .001$, $\eta 2 = 0.26$], no significant effect of group [$F(1,43) = 0.12$; $p = .72$, $\eta 2 = 0.002$] and no significant interaction [$F(2,86) = 0.13$; $p = 0.87$, $\eta 2 = 0.003$].

Cognitive flexibility measures. In the Hearts and Flowers mixed condition, for the number of correct responses (accuracy), analyses revealed a significant main effect of group [$F(1, 63) = 4.26$; $p < .05$, $\eta 2 = 0.07$] and time point [$F(1, 63) = 7.43$; $p < .01$, $\eta 2 = 0.10$] but no significant interactions [$F(1, 63) = 0.005$; $p = 0.94$, $\eta 2 = 0.0006$]. Planned comparisons revealed that children with TGA's accuracy was significantly lower than controls' only in T3 [$F(1,63) = 4.11$; $p < .05$]. RT in this condition did not significantly differ between groups [$F(1, 63) = 0.03$; $p = .85$, $\eta 2 = 0.0005$]; however, they significantly decreased from T2 to T3 for all children [$F(1, 63) = 122.18$; $p < .001$, $\eta 2 = 0.66$]. No significant interaction was observed for this measure [$F(1, 63) = 0.18$; $p = .66$, $\eta 2 = 0.002$ for RT].

Analyses on the DCCS 2 revealed a significant effect of group [$F(1,56) = 11.21$; $p < .001$, $\eta 2$=0.16] and time point [$F(2,112) = 20.75$; $p < .001$, $\eta 2 = 0.27$] but no significant interaction between group and time [$F(2,112) = 0.67$; $p = .51$, $\eta 2 = 0.01$]. Planned comparisons demonstrated that children with TGA had significantly lower scores at all time points [T1 ($F(1,56) = 5.56$; $p < .05$), T2 ($F(1,56) = 8.62$; $p < .01$) and T3 ($F(1,56) = 4.54$; $p < .05$), respectively].

Degree of EF Impairments Across Measures

In order to clinically characterize the degree of EF dysfunction and its extent in children with TGA (e.g., are there some EF measures more severely affected than others?) and how it evolves with time (aggravation or catch-up of impairments), we compared their scores at tasks found to be significantly impaired to an SMD. We used this measure in order to have the same scale of comparison across EF tasks. Effect sizes of 0.2, 0.5 and 0.8 refer to small, medium and large effects respectively. Results are shown in Figure 2.

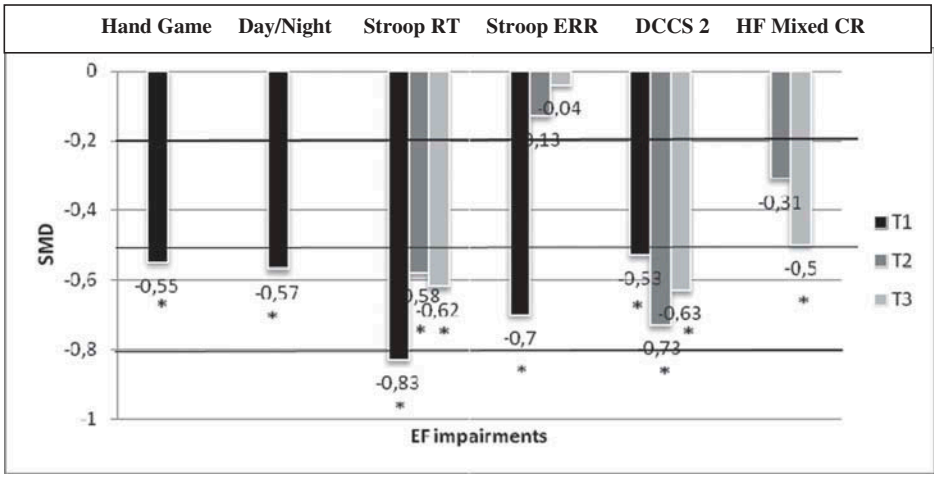

FIGURE 2 Profile of executive function (EF) dysfunctions in children with transposition of the great arteries (TGA) as expressed by standardized mean difference (SMD) score, with the comparison group as the reference group (SMD = 0.0). SMD range from small (0.2), medium (0.5) to large (0.8). Stroop RT = Reaction Times; Stroop ERR = Number of errors; DCCS 2 = Dimensional Card Sorting Test level 2; HF Mixed CR = Correct responses.

At T1, results show that impairments in motor and cognitive inhibition as well as in cognitive flexibility (DCCS 2) are clinically important as they have medium to large effect sizes (> .5; >.8 for Stroop RT). At T2, the degree of cognitive inhibition impairment tend to decrease as children with TGA present medium effects sizes for Stroop RT and no longer effects difference for Stroop Errors. However, the severity of impairments in cognitive flexibility (DCCS 2) increased. At T3, the severity of impairments in cognitive inhibition (Stroop RT) and cognitive flexibility (DCCS 2) remained relatively stable (from T2 to T3) whereas impairments in cognitive flexibility under a motor format tend to increase to a medium size.

Early Predictors of Cognitive Flexibility

In these analyses we sought to identify the early predictors (inhibition and WM scores at T1 and T2) of later complex EF performances (cognitive flexibility scores at T3) for both groups independently. We carried out stepwise multiple regressions analyses with the cognitive flexibility measure as the dependent variable. One model was conducted with variables at T1 and another model was calculated with variables at T2. In all models all EF, short-term memory measures (digit and spatial spans forwards) as well as language scores were included. In the group with TGA, performances at the DCCS 2 at T3 were significantly predicted by spatial span forwards scores at T1 (Bêta = 0.51; $p = .01$) (Multiple R = .73; $R^2 = .53$; adjusted $R^2 = .40$) and HF incongruent RT (Bêta = –0.46; $p = .02$) (Multiple R = .62; $R^2 = .39$; adjusted $R^2 = .18$). For the

comparison group, only scores at the digit span backwards at T1 significantly predicted scores at the DCCS 2 at T3 (Bêta = 0.79; $p = .02$) (Multiple R = .73; $R^2 = .54$; adjusted $R^2 = .22$).

Performances at the HF mixed condition RT in the group with TGA were significantly predicted by Hand game scores at T1 (Bêta = 0.54; $p = .05$) (Multiple R = .69; $R^2 = .48$; adjusted $R^2 = .16$) and HF incongruent RT at T2 (Bêta = 0.55; $p = .001$) (Multiple R = .75; $R^2 = .56$; adjusted $R^2 = .41$). In the comparison group, this task was only predicted by the HF incongruent RT at T2 (Bêta = 0.57; $p = .05$) (Multiple R = .75; $R^2 = .57$; adjusted $R^2 = .33$). Finally, performances at the HF mixed condition Number of Correct Responses in the group with TGA were significantly predicted by Hand game scores at T1 (Bêta = 0.81, $p = .01$) (Multiple R = .56; $R^2 = .31$; adjusted $R^2 = .09$) and the Digit Span backwards scores at T2 (Bêta = 0.72; $p = .02$) (Multiple R = .55; $R^2 = .31$; adjusted $R^2 = .07$). In the comparison group, this measure was significantly predicted by receptive language scores only at T1 (Bêta = 0.66; $p = .02$) (Multiple R = .77; $R^2 = .60$; adjusted $R^2 = .31$).

DISCUSSION

The present study is the first longitudinal research conducted on EF development after cyanotic CHD. Our aims were to (1) characterize the ongoing progressions of the three main EF components in children with TGA compared to a healthy same-aged group at a key transitional period between the ages of 5 to 7. We also sought to determine the degree of EF impairments in children with TGA and more importantly investigate how these deficits evolve (potential aggravation versus normalization of difficulties at this age) and (2) identify the early EF contribution to later cognitive flexibility development in both groups.

Pattern of EF Impairments in Children With TGA

The three executive components core components are dissociable and undergo heterochronous progressions during childhood (Diamond, 2013). We hypothesized that general EF impairments would be evident from an early age although they would not evolve in the same manner for children with TGA. Contrary to our hypothesis, results demonstrated that performances in verbal and visuospatial WM did not differ between groups at any time point whereas significantly lower inhibition and cognitive flexibility scores were observed during the three consecutive years. We also predicted that impairments in cognitive and motor inhibition would tend to catch up with age contrary to WM and cognitive flexibility deficits that were hypothesized to increase with time, as these abilities become more efficient and developmental gaps more apparent. Our current results partly confirmed these predictions. Indeed, children with TGA caught up on motor inhibition as the impairments observed at T1 were no longer apparent at T2 and T3. Cognitive inhibition as measured by the number of errors committed at the animal stroop task also normalized from T2. However, significantly slower RT at this task were consistently reported and ranged from severe to moderate degrees at all time points. Even if children with TGA gave a correct response, they were slower in dealing with visual interference. WM (verbal and visuospatial) were not significantly different from comparisons' scores and demonstrated normal increases throughout the time. Finally, as predicted, moderate impairments in cognitive flexibility were present from T1 (at the DCCS 2) and tended to increase as children got older for both measures of flexibility.

Motor and cognitive inhibition impairments were reported in previous cohorts of children with TGA at age 7 and 8 years (Bellinger et al., 2003; Calderon et al., 2010). Our current data demonstrates an early developmental onset of these deficits as observed in 5-year-olds with TGA. Nevertheless, motor inhibition impairments caught up at age 6 and thus differ from previous findings (Calderon et al., 2010). The tests used to assess motor inhibition in these two cohorts were not the same and differences could stem from this methodological issue. Even if this EF component may seem less vulnerable after TGA, further investigations should be conducted later in development in order to confirm this developmental catch-up.

Our current results on WM differ from previous findings. It was reported that 7-year-old children with TGA displayed significant differences in verbal and visuospatial WM (Calderon et al., 2010). Also, data from a large cohort of 8-year-old children with TGA reported significantly lower scores on the digit span task compared to normative data (Bellinger et al., 2003). However, it is worth noting that, contrary to Calderon et al. (2010) and to the present study, Bellinger et al. (2003) used the subtest score WM from the Wechsler Intelligence Scale–Third Edition (WISC–III) (combined score including passive verbal storage and verbal WM). Direct comparison to their findings can thus be limited as a combined score may either overestimate or underestimate children's difficulties with the executive component of WM. It is unclear why our group with TGA did not present significant impairments in both verbal and visuospatial WM during this developmental period (mean age of 5 to 7 years old). Differences in operative management with the Boston Circulatory Arrest Trial (the use of deep hypothermic circulatory arrest *versus* low-flow CPB in their study and full-flow CPB in our study) (Bellinger et al., 2003) or sample size (Calderon et al., 2010) could perhaps account for these divergences. Nevertheless, taking into account conflicting results in WM for these children from 7 years and beyond, special attention should be directed toward screening the long-term development of this EF component.

Regarding cognitive flexibility, our results showed that children with TGA had normal scores at DCCS level 1 at age 5 showing that they did not experience difficulties on shifting from one rule to another within a simple set. HF mixed and the DCCS 2 involve more complex set-shifting as children are not explicitly reminded of the rules during the post-switch trials and thus have to set a goal in mind to succeed (Chevalier et al., 2012; Davidson et al., 2006; Diamond et al., 2007). Moreover, shifting occurs in an unpredictable way and subjects need to guide their behavior based on external cues to decide which task is relevant on each trial (Cragg & Chevalier, 2012). Children with TGA displayed significant and persistent impairments in these advanced versions. Findings from Bellinger et al. (2003) offered divergent results on cognitive flexibility at age 8. In this later study, children with TGA exhibited significant impairments on the WCST (40% of the children attained a significantly lower number of correct categories and a third of them display perseverative errors) but normal performances on the TMT B. In regard to Cragg and Chevalier (2012), the difference in this pattern of performance could be explained by the structure of the task. Whereas the TMT B is a typical *alternating-run task* where children need to switch between rules on the basis of a predictable sequence of variables (number, letter, and so on), the WCST (as well as the DCCS 2 and the HF mixed) is an *alternating-cued task* where children switch unpredictably on the basis of external cues. Thus, the WCST would impose higher demands on goal maintenance, which is highly dependent on inner speech development and verbal WM (Cragg & Chevalier, 2012).

Are Children With TGA "Growing Into a Deficit" for EF?

It has been suggested that some cognitive difficulties after TGA have a relative late emergence and tend to worsen with age (Bellinger & Newburger, 2010; Hövels-Gürich et al., 2002). Hövels-Gürich et al. (2002) demonstrated that deficits in domains such as speech, motor development, and academic skills significantly worsen between the ages of 5 and 8 years. The rate of impairment at school age (55%) was twice the rate of impairment at age 5 (26%) supporting the fact that these children may have more difficulties in certain abilities as they grow older. The results of the current longitudinal study on EF do not agree with these previous findings and show that most EF impairments have an early onset during the preschool years. Nevertheless, these impairments may not systematically worsen with age as maturational lags on motor inhibition caught up one year later in our cohort. However, impairments found at age 5 in cognitive inhibition and cognitive flexibility demonstrate that early difficulties persist and continue to have a moderate to important severity.

This pattern of EF delay after TGA is consistent with data reported in school-age children born very preterm. Indeed, these two pediatric populations present some neonatal neurological commonalities (Licht et al., 2009). Term neonates with TGA have been reported to have general mild brain immaturity (around one month difference) suggesting that altered fetal circulation may have restricted brain growth in utero (Limperopoulos et al., 2010). Both populations have a higher incidence of neonatal white matter injury and elevated risks of hypoxic-ischemic injuries (Petit et al., 2009). Interestingly, children born very preterm also display important EF difficulties but generally compensate on motor inhibition when they reach school-age (Aarnoudse-Moens et al., 2012; Ritter et al., 2012). This could suggest that neonatal brain vulnerabilities related to immaturity and/or hypoxic-ischemic injuries following cyanosis may slow down the pace of acquisitions for early developing EF skills. However, both populations exhibit WM and cognitive flexibility impairments later in the school-age years, suggesting that more complex and late-maturing EF may be at higher risk of long-term dysfunction (Aarnoudse-Moens et al., 2012). Finally, as important EF refinement occurs in late childhood and adolescence, our findings on normalization of motor inhibition skills should be considered with caution. Future studies should confirm if this "catch-up" effect is long-lasting in these patients.

Early Predictors of Later Cognitive Flexibility Development After TGA

Our second main objective was to investigate if children with TGA would present early atypical mechanisms of cognitive flexibility development as evaluated with the DCCS 2 and the HF mixed. Our multiple regression analyses showed that DCCS 2 at T3 was significantly predicted by early spatial short-term memory and motor inhibition in children with TGA and by verbal WM in comparison children. As reported in the literature, efficient memory spans and verbal WM abilities during the preschool years significantly determine later flexibility capacities in tests such as DCCS level 1 and 2 (Cragg & Chevalier, 2012). Children with TGA may not sufficiently rely on emergent verbal WM skills and they may be lacking aspects of goal maintenance to correctly reset rules, particularly in the advanced DCCS version.

Reaction Time of the HF mixed condition at T3 was significantly predicted by early motor inhibition in both groups and HF mixed accuracy measure associated with motor inhibition and

verbal WM in children with TGA and language in comparison children. It is worth noting that the language comprehension NEPSY subtest requires active verbal maintenance of sentences of increasing length. It is thus not surprising to observe that performances at this task may predict later cognitive flexibility in terms of verbal WM contributions in typical development. Similarly, in children with TGA, initial performances in verbal WM with additional contributions in motor inhibition significantly predict HF performances. In conclusion, despite some variations, our results demonstrated that children with TGA had generally similar contributions of early inhibitory skills and short term/WM to later development of cognitive flexibility. These results demonstrate that the mechanisms underlying cognitive flexibility are not atypical but instead may be significantly delayed after TGA.

CONCLUSIONS AND PERSPECTIVES

Neonatal neurological vulnerabilities as experienced by children with TGA may significantly alter the development of EF from an early age. White matter injury and global brain immaturity have commonly been reported in term neonates with TGA (Petit et al., 2009) and recently studies begin to demonstrate that infants with cyanotic CHD may be at high risk of reduced anterior cortical volumes including frontal and parietal regions (Ortinau et al., 2012). A delayed brain maturation of these structures could then compromise the long-term development of executive processes.

However, even though the diversity of EF processes may not be manifest at very early age (Lee et al., 2013), the investigation of EF impairments in late preschool/school-age children with CHD should ideally consider that executive difficulties can be heterogeneous and emerge at different developmental periods. Particularly, impairments observed in children with TGA are dynamic and suggest that not all aspects of EF might have the same degree of long-term risk. Indeed, children with TGA in our sample displayed normal performances in motor inhibition from age 6 and in WM at least until age 7. However, despite these positive aspects, children with TGA displayed persistent moderate to severe impairments in cognitive inhibition and flexibility from preschool to early school years. This may suggest that the developmental progressions underwent for these EF components are not sufficient to achieve age-expected milestones. Our data on motor inhibition suggest that some aspects of EF development may not be necessarily atypical but only delayed after TGA. Nevertheless, even if some EF delays may progressively normalize with time, we cannot exclude potential cascading effects on later development into adolescence, where an important consolidation and refinement of EF functioning take place (Diamond, 2013). In fact, it has been reported that 16-year-olds with TGA still present significant EF vulnerabilities as reported by parents and teachers on the BRIEF (Bellinger et al., 2011). Further research is required to apprehend the extent and exact nature of these later difficulties in these patients.

Our research has some limitations that should be acknowledged. Our study cannot discriminate the exact correlates of neurological neonatal risks as no brain magnetic resonance imaging (MRI) was obtained from patients. Also, we did not address impairments in processing speed as potential confounders in our data concerning EF. Motor slowness (longer times to initiate and execute movements) have been reported in school-age children with CHD (van der Rijken, Hulstijn, Hulstiojn-Dirkmaat, Daniëls, & Maassen, 2011). It is currently unknown if slow processing speed may explain, at least partially, difficulties in EF after TGA. Our study focused on a

homogenous cyanotic CHD corrected in the neonatal period that restricted the risk of prolonged cyanosis or other potential confounding variables. As a consequence of these inclusion criteria, our data cannot be generalized to all forms of cyanotic or non-cyanotic CHD as timing of neurological insult and intra-operative management may not be equivalent. However, our results are in agreement with findings reported in school-age children with tetralogy of Fallot (ToF), another cyanotic CHD corrected early in infancy (Hövels-Gürich et al., 2007).

In conclusion, EF screening in children with cyanotic CHD should constitute a priority as weaknesses in this domain could have broad repercussions in academic and social adaptation (Bull et al., 2008; Hughes & Ensor, 2007). As recommended by scientific statements from the American Heart Association (Marino et al., 2012), early identification of cognitive challenges in high-risk children with CHD should ideally include complete assessments of EF development at key age periods where significant difficulties may be emerging, such as the preschool years. Follow-up of older children is also necessary as it may offer a long-term perspective on specific developmental catch-up for some abilities and/or the potential emergence of new cumulative impairments.

ACKNOWLEDGMENTS

We are grateful to all families who participated in this study.

FUNDING

This study was supported by the Association pour la Recherche en Cardiologie du Foetus à l'Adulte (ARCFA) and by a Paris Descartes University doctoral fellowship to the first author.

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