Efeitos das cardiopatias congénitas no desenvolvimento neurocognitivo de crianças e jovens adultos – revisão sistemática da literatura

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Dissertação de Mestrado em Psicologia da Saúde e Neuropsicologia
Orientação: Prof. Doutora Maria Emília Areias

Gandra, Setembro de 2019
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Sónia Alexandra Silva Machado
Dissertação apresentada no Instituto Universitário de Ciências da Saúde
Instituto de Investigação e Formação Avançada em Ciências e Tecnologias da Saúde, para obtenção do grau de Mestre em Psicologia da Saúde e Neuropsicologia, sob orientação da Professora Doutora Maria Emília Areias

Gandra, Setembro de 2019
AGRADECIMENTOS

O meu sincero agradecimento a todos aqueles que amo, que fazem o favor de fazer parte da minha vida e que me apoiam e incentivam nesta aventura que é a vida.
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RESUMO

As cardiopatias congênitas (CHD) têm origem em anomalias no desenvolvimento embriológico ou fetal do coração e nos grandes vasos.¹,² A prevalência é de cerca de 8 por 1.000 nados vivos.³
As CC provocam uma circulação sanguínea fetal irregular, essencialmente no que respeita à distribuição e/ou privação de oxigénio, condição que influencia o bom desenvolvimento cerebral, que poderão ser preditores de anomalias no desenvolvimento neurocognitivo a longo prazo.
Na literatura encontramos alguns consensos e convergências, no que respeita aos domínios neurocognitivos mais afetados pela existência de cardiopatia congénita. A linguagem, as capacidades visuoespaciais, as funções executivas, a atenção, a memória e as funções sensoriomotoras são os domínios cognitivos mais representados nos estudos avaliados e selecionados para este trabalho.
Procuramos neste estudo sistematizar o estado da arte sobre a relação entre cardiopatia congénita e alterações neurocognitivas, analisando as implicações desta patologia no desenvolvimento e identificando os domínios mais afetados e as limitações associadas.
Esta dissertação consiste na realização de um artigo para submissão e publicação subordinado ao tema: Efeitos das cardiopatias congénitas no desenvolvimento neurocognitivo de crianças e jovens adultos.

Palavras-Chave: Alterações neurocognitivas; domínios neurocognitivos; cardiopatia congénita; crianças; jovens adultos.
ABSTRACT

Congenital heart diseases (CHD) have their origin in anomalies in the embryological or fetal development of the heart and great vessels.\textsuperscript{1,2} The prevalence is about 8 per 1000 neonates.\textsuperscript{3}

CHD cause an irregular blood flow in the fetus, especially in the distribution and/or oxygen privation, condition which influences the good cerebral development, which can be long term predictors of abnormalities in the neurocognitive development.

The literature is controversial regarding the neurocognitive domains most affected by the existence of congenital heart disease. In our review the selected studies report language, visuospatial capabilities, executive functions, attention, memory and sensorimotor functions as the most frequent cognitive domains in CHD.

In this study we aim to identify and understand the relationship between congenital heart disease and neurocognitive changes. With the selected studies, we were able to analyze the implications of this pathology for development and identified the most affected domains and respective limitations in the lives of patients with CHD.

This essay consists in the production of an article for submission and publishing entitled: Effects of congenital heart disease on neurocognitive development of children and young adults.

**Key-Words**: Neurocognitive effects; neurocognitive domains; congenital heart disease; children; young adults.
PARTE I

Artigo para submissão em revista: *Effects of congenital heart disease on neurocognitive development of children and young adults - a systematic review.*
Effects of congenital heart disease on neurocognitive development of children and young adults – a systematic review.

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Correspondence concerning this article should be addressed to Maria Emília Areias, Instituto Universitário de Ciências da Saúde, Rua Central de Gandra, 1317. 4585-116. Gandra (Portugal). Phone:+351-919309766. Email: metega@sapo.pt
**Introduction:** The main goal of this study was to undertake a systematic review of the literature on the characterization of the neurocognitive effects in children and young adults, with a diagnosis of congenital heart disease.

**Methods:** Research was done in Pubmed and Cinahl’s data base aiming to identify random and controlled studies that tackled this connection. For that effect, there were used the following English keywords: *neurocognitive development; psychological adjustment; congenital heart disease; children and young adults*. A descriptive sum-up was made as well as the quality of all the selected studies for analysis was assessed.

**Results:** 10 publications were identified with randomized and controlled studies that were related to the objective of this work. The neurocognitive domains of the executive functions of memory and attention are the most mentioned aspects, by the investigators, as well as it was assessed the deficient areas in children, adolescents and young adults, conditions that affect their personal and social development.

**Discussion and Conclusion:** We can conclude that patients with congenital heart disease, especially those who have severe forms of disease and those that have been submitted to surgical procedures in childhood, present alterations in several cognitive domains, showing worse cognitive performance when compared with healthy children and adolescents. These modifications tend to affect psycho-social development, school performance as well as the growth and social integration. Therefore, future studies should examine if the limitations are sustained in adulthood and if they affect significantly the quality of life of this population.

**Key-words:** Neurocognitive effects; neurocognitive domains; congenital heart disease; children and young adults.
INTRODUCTION

Congenital heart diseases (CHD) have their origin in anomalies in the embryological or fetal development of the heart and great vessels. The prevalence is about 8 per 1000 neonates. CHD can be classified, according to their severity, in mild, moderate and complex. Mild CHD do not cause major restrictions in the patient’s life, in most cases they are asymptomatic and do not require any surgical procedures. Most cases of moderate CHD, patients are symptomatic and may require surgical procedures in order to provide better life expectations and improve life quality. Complex CHD demand frequent medical monitoring and vigilance since these patients suffer major limitations in their everyday life, needing one or multiple surgical procedures. Clinically, CHD can also be classified as cyanotic and acyanotic. Cyanotic CHD are characterized by low oxygen saturation in the blood. Examples of cyanotic CHD are Tetralogy of Fallot (TOF) and Transposition of the Great Arteries (d-TGA). A surgical procedure after birth is mandatory in d-TGA and in TOF, increasing the chances of survival if it is performed during the first year of life.

In Acyanotic CHD, on the other hand, there is a normal saturation of oxygen in arterial blood. Examples of acyanotic CHD are Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), Persistence of Ductus Arteriosus (PDA), Aortic Stenosis (AS), Pulmonary Stenosis (PS) and Coartation of the Aorta (CoA).

Congenital Heart disease and Neuropsychological development

Congenital heart diseases may cause abnormal foetal blood flow, resulting in deprivation of oxygen and nutrients to the brain. This condition may influence cerebral growth, predicting abnormalities in the neurocognitive development, in the long run. There is general agreement in literature about which are the cognitive domains that are most affected in congenital heart disease. Most of the selected studies highlight language, spatial-visual abilities, attention, memory, executive and sensory-motor functions as the affected cognitive domains. Most investigations concerning the effects of congenital heart disease on neurocognitive development have been carried out at school or preschool age, as it is difficult to assess
children at an earlier age with structured methodologies, particularly in cognitive domains with later maturation, being an example the executive functions. Several studies refer the presence of global cognitive deficits (attention, executive functions, visuospatial and visual motor abilities, learning disabilities, among others) in patients with CHD, with surgical intervention in early childhood. According to the authors, these disorders lead to school failure, poor social and general adjustment and neurocognitive vulnerabilities in adulthood. Bearing in mind the premise that CHD are complex pathologies associated with neurocognitive changes, a holistic and multidimensional view of health (physical, mental and social well-being) should increasingly be considered. Thus, this systematic review aimed to present the current state of scientific knowledge about the most prevalent neurocognitive disorders in children, adolescents and young adults with congenital heart diseases.
METHODS

We conducted this systematic review according to Preferred Reporting Items for Systematic Review and Meta-Analysis’ declaration, and accordingly it is not an update of a previous review.

The research was performed using the PubMed and Cinahl’s databases, and the following key-words: neurocognitive development* AND psychological adjustment* AND congenital heart disease* AND children* OR young* OR adult*.

We considered the following inclusion criteria: controlled and randomized studies that studied neurocognitive changes in children and young adults with a diagnosis of CHD, considered only full-text studies, dated 2005 onwards and written in Portuguese, Spanish or English.

We considered the following exclusion criteria: studies that do not conform to respect inclusion criteria, studies with animals and those that involve systematic reviews or meta-analyses.

The researchers reviewed all the titles and abstracts with the intent of erasing the duplicates and assess their relevancy, taking into consideration the defined criteria of inclusion and exclusion. A third reviewer was consulted whenever ambiguity was found, to decide on dissident cases in the selection of articles, as recommended of Crochrane Collaboration’s recommendations. Data were collected, verified and analyzed for their relevance, using a pre-developed table (Table 1), with extraction of the baseline characteristics of the studies in order to form descriptive summaries.
RESULTS

Based on this research strategy, we identified 43 articles, and performed a descriptive summary to assess their quality for inclusion in the analysis. Then, 24 articles were considered for reading and 14 were excluded (8, 25,26,27,28,29,30,31,32 because they were not related to the objective of this study, 5, 33,34,35,36,37 because the type of study was not consistent to the inclusion criteria and 1,38 because the article is written in Italian). Finally, 10,19,21,39,40,41,42,43,44,45,46 were selected.
Throughout the research, we decided to include two other articles47,48 because we consider their analysis important to the interpretation of previous results, despite not stemming from the search with the keywords.
Then, 10 controlled and randomized studies, published between 2006 and 2018, were analysed. The details of the research are summarized in the flow diagram (Fig. 1).

<Figure 1>

The characteristics of the studies are shown in tables 1, 2 and 3. We did not perform a quantitative analysis of the data, as we considered that they were not sufficiently homogeneous.
In respect to the samples’ characteristics, the majority of the studies present similar contexts, concerning age, gender, family-social situation and parent’s academic studies. In six of the selected studies, the sample includes patients, whose ages vary from 9 to 16 years old. In the remaining studies, the sample includes children whose ages vary from 4 to 6 years old.

<Table 1>

Regarding the instruments, all studies (n = 10) used intelligence assessment batteries for children and young adults (either subscales of Wechsler Intelligence Scale for Children or subscales of Wechsler Adult Intelligence Scale) to assess the language, memory and attention domains; five evaluated the domains of attention, language and executive functions using a battery of tests devised for this purpose (Developmental Neuropsychological Assessment); five used the Trail Making Test and Stroop Test to evaluate executive functions, more specifically attention and inhibitory control and to evaluate the domains of memory and executive functions, four of the studies used the
Rey-Osterrieth Complex Figure Test. In addition to neurocognitive changes, behavioral assessments were found in three studies using a specific scale for this purpose, the Child Behavior Checklist.

**<Table 2>**

Analyzing the results of all studies, we can find some consensus regarding the prevailing deficits in cognitive functioning of CHD patients. In seven studies, authors refer changes in attention abilities, that even though sometimes involve mild deficits, may negatively influence school performance, giving rise to a need for special education.\(^{42}\) In eight of the studies, changes in memory were found. A study by Latal et al. showed that CHD patients undergoing cardiopulmonary bypass, compared to healthy children with similar sociodemographic characteristics, show a 10% reduction in hippocampal volume. In an attempt to understand the importance of this brain structure in the functioning of memory and in general intellectual performance, these authors verify a positive and significant association between intellectual performance and the areas of verbal comprehension and working memory, and these deficits tend to endure during adolescence, leading to limitations in adulthood.\(^{45,47,48}\)

The largest consensus is on changes in executive functioning (\(n = 10\)). There are several studies reporting that changes in these abilities seem to condition school performance and social development of these children.\(^{40}\) In addition, some researchers warn to the likelihood of these children to show behavior problems, aggressiveness, hyperactivity and impulsivity. This condition thus limits future life options.\(^{44}\) Difficulties in motor skills, speech, language and social cognition that may be related to neonatal and psychological adjustment variables, are also mentioned in some studies.\(^{46}\)

**<Table 3>**
DISCUSSION AND CONCLUSION

Congenital heart diseases have a prevalence of 8 per 1000 to 1 per cent of neonates, and have been studied for long. The increased rate of survival in last decades rendered possible the follow-up of these patients from childhood to adult life, extending the scope of scientific research to understanding the impact of sequelae on different biopsychosocial dimensions.

Therefore, the authors of this study found relevant, at this stage, to perform a systematic review of the literature, in order to gather scientific evidences on neurocognitive changes in CHD, and how they affect development and quality of life of patients.

The literature points to evidence of neurological alterations and cognitive deficits, affecting attention, memory and executive functions, visuo-constructive and visuo-spatial abilities. Some studies show also retardation in expressive language and learning disabilities

There is wide consensus on the literature in considering that deficits in executive functioning are good predictors of later neurocognitive development, school performance, social adjustment and quality of life of patients. These factors, altogether with parental overprotection and less exposure to physical activity, limit the potential for development of these children.

Some authors report that prenatal diagnosis of CHD is associated with better outcomes in neuropsychological tests, as it allows early intervention and stimulation, and that a late diagnosis may be considered a risk factor to poor performance in executive function and social cognition, therefore stressing the importance of early diagnosis of CHD to reduce general sequelae of illness later on.

Several studies point out that the individual outcomes of illness are influenced by some neonatal variables and the psychological adjustment of patients.

In conclusion, the importance of this systematic revision was to enable a wide perspective on scientific evidence about the effects of CHD on neurocognitive performance, and how the later affects development and adjustment of patients along the life cycle.

Despite this main contribution, we must stress that in future it should be considered as a main objective to broaden the scope of the selected data, enabling a meta-analytic study, with deeper understanding of the consequences of these changes on the lives of patients with CHD.
Finally, we believe that future studies should focus on aspects that are relevant for clinicians that deal with the limitations of patients.
REFERENCES

1. Popelová J, Oechslin E, Kaemmerer H et al. Congenital Heart Disease in Adults (1ª Ed.) United Kingdom: Informa Health Care, Ltd.2008


Figure 1 – Flux diagram

Registry found in data bases (n=43)

PubMed – 24
Cinahl - 19

Analysed and selected articles, after the reading of titles and abstracts. (n=24)

Excluded articles according to inclusion and exclusion criteria. (n=14)
Reason for exclusion:
Outcomes: 8
Study design: 5
Article written in another language: 1

Articles included in the study (n=10)
<table>
<thead>
<tr>
<th>Author(s)/ Year</th>
<th>Country</th>
<th>Population/ Sample</th>
<th>Sample selection criteria</th>
<th>Type of study</th>
<th>Total (n)</th>
<th>Instruments</th>
<th>Neurocognitive Shifts</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCuster 2006</td>
<td>UK</td>
<td>Children diagnosed with heart disease, divided into 4 groups according to their clinical condition: 1 - 34 Closed acyanotic; 2 - 25 Open acyanotic; 3 - 19 Cyanotic-corrected condition; 4 - 12 Cyanotic-complex condition; Control groups: 1 - 19 Condition of mild and self-correcting heart defect in childhood; 2 - 34 Acyanotic-closed; Children 4 years old, attending school and undergoing at least 1 invasive surgical procedure, with corrective or palliative purpose;</td>
<td>Cross-sectional</td>
<td>90</td>
<td>NEPSY&lt;sup&gt;d&lt;/sup&gt; WPPSI&lt;sup&gt;‡&lt;/sup&gt; CBCL&lt;sup&gt;c&lt;/sup&gt; Maternal Worry Scale Parenting Focus Control Scale Family Environment Scale Significant Others Scale</td>
<td>All neurocognitive domains.</td>
<td>Patients with congenital heart disease, who undertook heart surgery, present a bigger risk of deficits in their neuropsychological development; have lower outcomes in all neurocognitive domains and alterations in their motor sensorial capacity, that may be connected to social and environmental factors, due to parental overprotection and minor exposure to situations involving physical activity.</td>
<td></td>
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<tr>
<td>Miatton 2007</td>
<td>Belgium</td>
<td>Children with congenital heart disease (21-F; 22-M), divided into 2 groups: 1 - 26 Cyanotic condition; 2 - 17 Acyanotic condition; Control group with healthy children Ghent University Hospital patients between 1995 and 1999, with birth weight greater than 2000g, no history of prenatal pathology, no other noncardiac malformations or genetic pathology, and who had undergone open heart surgery.</td>
<td>Cross-sectional</td>
<td>43</td>
<td>WISC&lt;sup&gt;i&lt;/sup&gt; NEPSY&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Attention Sensorimotor domain Language Memory Executive Functions</td>
<td>Patients with congenital heart disease present a deficient neuropsychological profile marked by limitations in motor sensorial and language areas. Studies point out that 25% of children with congenital heart disease show a lower performance, than expected, in motor tasks. The FE and attention domains are also affected, but in a less expressive way.</td>
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<td>Author(s)</td>
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<td>Calderon 2010</td>
<td>40</td>
<td>France</td>
<td>School age children (14-M; 7-F); Control group 21 children (12-M; 9-F) in the same age group.</td>
<td>Children undergoing corrective heart surgery in the neonatal period between January 2001 and April 2002 at the Necker Pediatric Hospital in Paris, patients diagnosed with intact ventricular septum or ventricular septal defect and who have undergone cardiac surgery using a single life support method, weighing = ≧ 2.5 Kg at birth and not carrying other genetic pathologies and other heart problems.</td>
<td>Cross-sectional (single-center trial)</td>
<td>21</td>
<td>WISC&lt;sup&gt;3&lt;/sup&gt; NEPSY&lt;sup&gt;d&lt;/sup&gt; Stroop Task Columbia Mental Maturity Scale Corsi block Tapping Task</td>
<td>Sustained Attention Visuospatial capabilities Language Psychomotor development</td>
</tr>
<tr>
<td>Calderon 2012</td>
<td>41</td>
<td>France</td>
<td>Children with congenital heart disease (67% M; 33% F); Control group: 45 healthy children with similar sociodemographic characteristics.</td>
<td>Children born between 2003 and 2005 in a pediatric hospital in Paris, diagnosed with intact ventricular septum or ventricular septal defect and who underwent cardiac surgery using a single life support method, with birth weight = or&gt; a 2.5kg, not with genetic disorders or other heart problems. Children aged between 4 and 6 at the time of the assessment and whose mother tongue was French.</td>
<td>Prospective (single-center prospective study)</td>
<td>45</td>
<td>WISC&lt;sup&gt;3&lt;/sup&gt; NEPSY&lt;sup&gt;d&lt;/sup&gt; Columbia Mental Maturity Scale</td>
<td>Language Visuospatial capabilities Executive Functions</td>
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Table 1. (Continued)

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<tr>
<td>Schaefer 2013[42]</td>
<td>Switzerland</td>
<td>Teenagers with CC (34F; 25M) Control group: 40 healthy adolescents (22F; 18M) with a mean age of 13A and 18M</td>
<td>The children studied were selected after analysis of the database of the University Hospital of Zurich. Patients who underwent the first surgery between 1995 and 1998, with an average age at the time of surgery of 11 months. Parents would have to have a good command of the German language and children would be between 6 and 16 years old by the time they were tested. Children without a diagnosis of chromosomal or genetic syndrome and without congenital or acquired neurological disease.</td>
<td>Longitudinal</td>
<td>59</td>
<td>WISC⁴ Beery test of visual motor integration FCR⁵ ZNAI SDQ⁶ KIDSCREEN</td>
<td>Visual perception Neuromotor integration Working Memory Reasoning Executive Functions</td>
<td>Patients with congenital heart disease present worse neurodevelopment performances, being the areas of reasoning, work memory, motor visual integration, visual perception and EF’s the most affected, deficits that can last in time and influence academic performance and lead to the implementation of special educational measures.</td>
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<tr>
<td>Matos 2013[43]</td>
<td>Portugal</td>
<td>Children and adolescents with CHD (43M; 34F) Control Group; 16 Healthy Children and Adolescents (11M; 5F)</td>
<td>Participants in this study were selected from the Pediatric Cardiology Service at a Central Hospital in Porto. (data was collected in a single moment)</td>
<td>Cross-sectional</td>
<td>77</td>
<td>WISCj FCR⁴ Stroop TMT⁸</td>
<td>Divided and selective attention Visual and working memory Executive Functions (Appointment, planning, organization, problem solving, visual-constructive capabilities)</td>
<td>Patients with congenital heart disease present worse neuropsychological performances in all cognitive domains, with a higher prevalence in patients with cyanosis. The heart and fetal condition seems to influence the cerebral development, foretelling a cognitive dysfunction verified in adolescence, which may go on through all life time.</td>
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<td>Sarrechia 2015</td>
<td>Belgium</td>
<td>Children evaluated after cardiac surgery, divided into: 1 - 17 Children with UVH (13M; 4F); 2-46 Children with BiVH (19M; 27F). Control group: 17 Healthy children (13M; 4F).</td>
<td>The sample was selected from two centers specialized in cardiac pathology from two Belgian hospitals. Patients undergoing cardiac surgery and with two diagnoses associated with CHD: 1) UVH (HLH / TA) and BiVH (ASD-II / VSD) and aged between 6 and 12 years. Patients with severe genetic disorders, developmental syndromes or mental retardation were excluded from the UVH group. Children with evidence of perinatal problems were excluded from the group of patients with biVH, gestational age less than 37 weeks, birth weight, less than 2000g, have other cardiac malformations, genetic changes or developmental syndrome.</td>
<td>cross-sectional</td>
<td>63</td>
<td>WISC&lt;sup&gt;3&lt;/sup&gt; NEPSY&lt;sup&gt;4&lt;/sup&gt; CBCL&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Attention Fine motor skills Visuospatial Processing Sensoromotor Memory Executive Functions</td>
<td>Patients with congenital heart disease present results within the expected in the intelligence domain, few alterations in attention, motor skills, spatial-visual information processing and memory. Some investigators alert to the presence of behavioural problems, aggressiveness, hyperactivity and impulsivity. This condition predicts the future results in their academic performance and future life.</td>
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<td>Latal 2016[45,47,48]</td>
<td>Switzerland</td>
<td>Adolescents with CHD who survived cardiopulmonary bypass surgery in childhood, with a mean age of 13A and 8M (21M; 44F), 9 had brain lesions and 34 did not. Control group: 32 Healthy adolescents with similar sociodemographic characteristics.</td>
<td>Participants were selected at the Zurich Pediatric Hospital and had as an eligibility criterion that they underwent cardiopulmonary surgery in childhood, occurring between 1995 and 1998, without genetic changes, under 16 years of age at the time of the evaluation, without cochlear implants or pacemaker.</td>
<td>cross-sectional</td>
<td>48</td>
<td>WISC⁵ FCR⁴ Beery test of visual motor integration MRI⁶</td>
<td>Memory Language Executive Functions</td>
<td>Patients with previous surgical intervention and cerebral lesion have a 10% smaller and less larger hippocampus than the controlled group. This cerebral structure has significance in the functioning of memory domains and in most intellectual development, which demonstrated a positive and significant association with the results of intellectual performance in domains of verbal comprehension and work memory that according to the authors prevail through time.</td>
</tr>
<tr>
<td>Murphy 2017[41]</td>
<td>U.S.A</td>
<td>Children and young adults with CHD with a mean age of 16A (61% F; 39% M); Control group: 18 healthy children and young adults, siblings of children diagnosed with CHD, mean age 16A (56% F; 44% M)</td>
<td>Participants were identified through patient records from a Cardiology Clinic and selected when they went to the health facility for routine consultations. Inclusion criteria were: a) to have a diagnosis of d-TGA or TOF, requiring surgical intervention before 15 years of age; b) between 10 and 29 years old, without genetic, cognitive or developmental alterations. In the control group the same assumptions were considered, except for the clinical condition.</td>
<td>cross-sectional (data were collected using an online questionnaire and testing was performed in a single moment).</td>
<td>18</td>
<td>WISC⁵ WAIS⁴ CBCL⁵ ABCL⁴</td>
<td>Attention Processing speed Visuospatial Processing Reasoning Working memory Executive Functions</td>
<td>Patients with childhood diagnosis of congenital heart disease present neurocognitive alterations identified and studied in infancy, including processing velocity in reasoning and work memory. These alterations predict bad social adaptation and neurocognitive vulnerabilities in adulthood.</td>
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Table 1. (Continued)

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</tr>
</thead>
<tbody>
<tr>
<td>Areias 2018&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Portugal</td>
<td>Patients with CHD (116M; 101F) with a mean age of 15Y. Control group: 80 children and young adults (35M; 45F) with a mean age of 16 Y.</td>
<td>The sample was selected from a public hospital and considered only patients who at the time of the interview were between 12 and 30 years old, who had an educational level that would allow them to answer the questions and who had a complete clinical record. The control group was selected in several schools and universities in the city of Porto and in demographic terms would have to have similar characteristics regarding the age, gender and educational level of the parents.</td>
<td>cross-sectional (data was collected in a single moment)</td>
<td>217</td>
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<td>All neurocognitive domains.</td>
<td>Patients with congenital heart disease present lower neurocognitive performances in all neurocognitive domains when compared to their reference group. The areas of motor ability, speech, language, executive functions, social cognition and impulsive behavior are the most affected. These performances are connected with neonatal variables and psychological adjustment.</td>
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Legenda:

a) Adult Behavior Checklist  
b) Behavioural Assessment of the Dysexecutive Syndrome  
c) Child Behavior Checklist  
d) Developmental neuropsychological assessment  
e) Magnetic Resonance Imaging  
f) Rey-Osterrieth Complex Figure Test  
g) Strengths and Difficulties Questionnaire  
h) Trail Making Test  
i) Wechsler Adult Intelligence Scale  
j) Wechsler Intelligence Scale for Children  
k) Wechsler Preschool and Primary Scale of Intelligence  
l) Zurich Neuromotor Assessment
Table 2. Instruments used in the included studies

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*Instruments used only in one study: ABCL; BADS; MRI; SDQ; WPPSI; ZNA; Maternal Worry Scale; Parenting Focus Control Scale; Family Environment Scale; Significant Others Scale; Corsi Block; Tapping Task; Kidscreen.
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ANEXOS
ANEXO I

Normas para submissão na *Revista Portuguesa de Cardiologia*
Revista Portuguesa de Cardiologia

INTRODUCTION

Revista Portuguesa de Cardiologia, órgão oficial da Sociedade Portuguesa de Cardiologia, foi fundada em 1982 com o objectivo de informar e formar os cardiologistas portugueses através da publicação de artigos científicos na área da arritmologia, cirurgia cardíaca, cuidados intensivos, doença coronária, ecocardiografia, electrofisiologia, hipertensão arterial, insuficiência cardíaca, métodos de imagem entre outros. Trata-se duma revista mensal de elevada qualidade científica e gráfica, publicada em português e em inglês desde 1999 o que permitiu a sua larga projecção no estrangeiro.

Types of article

The Journal accepts the following article types:

- Original Articles reporting clinical or basic research;
- Review Articles (including systematic reviews and meta-analyses) on clinical or basic science topics;
- Case Reports;
- Editorials, which are written at the invitation of the Editor and consist of commentary on articles published in the journal or on subjects of particular importance;
- Letters to the Editor, which consist of concise opinions on recently published articles;
- Images in Cardiology;
- Snapshots;
- Guidelines; and
- Current Perspectives.

Manuscripts submitted for publication should be prepared in accordance with the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" of the International Committee of Medical Journal Editors (ICMJE). This document is available at http://www.icmje.org/recommendations/.

Review Articles and Systematic Reviews

Review Articles should have a maximum of 5000 words, with a total of up to 15 tables and/or figures, and should be structured as follows: Abstract (maximum 250 words; unstructured); 3-10 keywords; Introduction; thematic sections at the discretion of the
authors; Conclusion(s); Acknowledgements, if any; References (up to 100); and figure legends, if any.

*Systematic Reviews* should be structured as Introduction, Methods, Results, Discussion and Conclusion(s). The subject should be clearly defined. The objective of a systematic review should be to produce an evidence-based conclusion. The Methods should give a clear indication of the literature search strategy, data extraction, grading of evidence and analysis.

Systematic Reviews should not normally exceed 4000 words, with a total of up to 6 tables and/or figures and up to 100 references.

Authors are strongly recommended to consult the PRISMA statement (http://www.prisma-statement.org/), which is intended to help improve the reporting of systematic reviews and meta-analyses.

**Current Perspective**

This type of manuscript is submitted upon invitation by the Editorial Board. It may cover a broad diversity of themes focusing on cardiology and healthcare: current or emerging problems, management and health policies, history of medicine, society issues and epidemiology, among others. An author who wishes to propose a manuscript in this section is requested to send an abstract to the Editor-in-Chief including the title and Author list for evaluation. The text should not exceed 1200 words, and up to 10 references, two tables or two figures are allowed. An abstract is not required.

**Contact details for submission**

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**Language**

This journal is published in Portuguese and in English language.

The title (and abstract and key words if applicable) must be submitted in both English and Portuguese.

Articles submitted to the Journal should be clearly written in Portuguese (from Portugal) and/or English of a reasonable standard. Text may be edited to maintain linguistic quality and to conform with standard American English.

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You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.
Ensure that the following items are present:

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  - E-mail address
  - Full postal address

All necessary files have been uploaded:

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- Include keywords
- All figures (include relevant captions)
- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided
- Indicate clearly if color should be used for any figures in print

*Graphical Abstracts / Highlights files* (where applicable)

*Supplemental files* (where applicable)

Further considerations

- Manuscript has been 'spell checked' and 'grammar checked'
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- Permission has been obtained for use of copyrighted material from other sources (including the Internet)
  - A competing interests statement is provided, even if the authors have no competing interests to declare
  - Journal policies detailed in this guide have been reviewed
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BEFORE YOU BEGIN

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In line with the position of the International Committee of Medical Journal Editors, the journal will not consider results posted in the same clinical trials registry in which primary registration resides to be prior publication if the results posted are presented in the form of a brief structured (less than 500 words) abstract or table. However, divulging results in other circumstances (e.g., investors’ meetings) is discouraged and may jeopardise consideration of the manuscript. Authors should fully disclose all posting in registries of results of the same or closely related work.

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PREPARATION

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This journal operates a rigorous single blind peer review process, in which manuscripts are sent to external reviewers selected from an extensive database. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding
acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

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It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.

To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

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Divide your article into clearly defined sections. Each subsection is given a brief heading. Each heading should appear on its own separate line. Subsections should be used as much as possible when cross-referencing text: refer to the subsection by heading as opposed to simply 'the text'. Use generic names of drugs (first letter: lowercase) whenever possible. Registered trade names (first letter: uppercase) should be marked with the superscript registration symbol ® or ™ when they are first mentioned.
The Journal recommends the guidelines for publication of the EQUATOR network (http://www.equator-network.org), including the CONSORT statement and its extensions for randomized trials (http://www.consort-statement.org/), STROBE for observational (cohort, case-control and cross-sectional) studies (http://www.strobe-statement.org/), STARD for diagnostic accuracy studies (http://www.stard-statement.org/), PRISMA for systematic reviews and meta-analyses (http://www.prisma-statement.org/), SQUIRE for quality improvement studies (http://www.squire-statement.org/) and CARE for case reports (http://www.care-statement.org/). Reporting of the statistical aspects of studies should be in accordance with the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines (http://www.equator-network.org/reporting-guidelines/saml/).

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State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods
Provide sufficient details to allow the work to be reproduced by an independent researcher. Methods that are already published should be summarized, and indicated by a reference. If quoting directly from a previously published method, use quotation marks and also cite the source. Any modifications to existing methods should also be described.

Results
Results should be clear and concise.

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This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions
The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

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Submission of an article must include a cover letter with the following information:

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2. a declaration of originality, specifying that none of the paper's contents have been published or are under consideration elsewhere;
3. a declaration that all authors have read and approved the manuscript;
4. a full disclosure of any potential conflict of interest for any of the authors;
5. and which manuscript type is being submitted for publication.

Title page must contain the following information:

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- **Word count** of the manuscript text.

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principal conclusions. It should emphasize new and important aspects of the study or observations.

Abstracts for all article types should not contain any references. Abbreviations should be avoided or kept to a minimum.

The headings will consist of: Introduction and Objectives, Methods, Results and Conclusion(s))

Keywords
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