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Neuroimaging and executive function in dyskinetic cerebral palsy

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NEUROIMAGING AND EXECUTIVE FUNCTION IN DYSKINETIC CEREBRAL PALSY

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Roser Pueyo Benito hereby asserts that this thesis fulfills the requirements to present her defence to be awarded the title of doctor.

Signature,

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CONTENTS

FOREWORD

This thesis, presented for the degree of Doctor by the University of Barcelona, is the result of different studies carried out over a four-year period at the *Departament de Psicologia Clínica i Psicobiologia*, University of Barcelona (Barcelona, Spain) and two research visits of six and three months in the Queensland Cerebral Palsy and Rehabilitation Research Centre and the Australian e-Health Research Centre, Commonwealth Scientific and Industrial Research Organisation (Brisbane, Australia).

This thesis follows the published papers and includes three published articles (Study 1, 3 and 4) and a working paper (Study 2).

Study 1: Impact factor: 2.392 / Quartile 2 in Health Care Sciences & Services; Quartile 2 in Public, Environmental and Occupational health

Laporta-Hoyos, O., Ballester-Plané, J., Póo, P., Macaya, A., Meléndez-Plumed, M., Vázquez, E., Delgado, I., Zubiaurre-Elorza, L., Botellero, V.L., Narberhaus, A., Toro-Tamargo, E., Segarra, D., Pueyo, R. (2017). Proxy-reported quality of life in adolescents and adults with dyskinetic cerebral palsy is associated with executive functions and cortical thickness. *Quality of Life Research*, *26*, 1209-1222.

Study 2: Working paper (under review in Research in Developmental Disabilities)

Laporta-Hoyos, O., Ballester-Plané, J., Leiva, D., Ribas, T., Miralbell, J., Torroja-Nualart, C., Russi, M.E., Toro-Tamargo, E., Meléndez-Plumed, M., Gimeno, F., Macaya, A., Pueyo, R. Executive function and intellectual functioning in dyskinetic cerebral palsy: comparison with spastic cerebral palsy and typically developing controls.

Study 3: Impact factor: 3.869 / Quartile 1 in Neuroimaging

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Study 4: Impact factor: 3.869 / Quartile 1 in Neuroimaging

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GLOSSARY OF ABBREVIATIONS[1]

BRIEF: Behaviour Rating Inventory of Executive Function

CP: Cerebral palsy

CP QOL: Cerebral Palsy Quality of Life Questionnaire

CFCS: Communication Function Classification System

CT: Computed tomography

DTI: Diffusion tensor imaging

DCP: Dyskinetic cerebral palsy

FA: Fractional anisotropy

GMFCS: Gross Motor Function Classification System

HRQOL: Health-Related Quality of Life

IQ: Intelligence quotient

MRI: Magnetic resonance imaging

PVL: Periventricular leukomalacia

QOL: Quality of life

SCP: Spastic cerebral palsy

SCPE: Surveillance of Cerebral Palsy in Europe

TDC: Typically developing controls

WCST: Wisconsin Card Sorting Test

[1] Abbreviations from studies are not included

LIST OF TABLES[2]

[2] Tables from studies are not included

LIST OF FIGURES[3]

[3] Figures from studies are not included

SUMMARY (ENGLISH VERSION)

Magnetic resonance imaging has increased our understanding of cerebral palsy [1] but most studies have focused on spastic cerebral palsy, whilst neuroimaging studies of dyskinetic cerebral palsy remain scarce.

Global and specific cognitive processes may be affected in cerebral palsy, with almost 50% of the cerebral palsy population having an intellectual quotient below 70 [2]. Cognitive functions are considered one of the essential "Core Sets" in cerebral palsy [3], executive function being of particular interest because of its key role in the effective acquisition of new skills, knowledge, and the application of this knowledge in life [4]. Associations between quality of life and executive function have been described in the general population, in psychiatric conditions, and in neurological conditions other than cerebral palsy [5–9].

It is agreed that dyskinetic cerebral palsy is associated with poorer motor outcomes than other cerebral palsy types [10] but very few studies compare cognitive abilities in dyskinetic cerebral palsy with those of other cerebral palsy subtypes, particularly in groups with similar levels of motor ability. No study to date has specifically focused on executive function nor its association with brain magnetic resonance imaging characteristics in this cerebral palsy subtype. Basal ganglia and thalamus lesions are frequently described in people with dyskinetic cerebral palsy [11, 12] and fronto-striatal circuitry play a crucial role on executive functioning for typically developing people [13, 14]. However, there is a paucity of brain imaging studies focussing on executive functioning, with no studies including participants with dyskinetic cerebral palsy [15].

The overall aim of the thesis was to characterize executive functioning and general intellectual functioning and its biological bases in dyskinetic cerebral

palsy, as measured by diffusion and structural magnetic resonance imaging. Specifically, the current thesis formulated the following four aims, which were accomplished through four studies. First, to analyse the impact of executive function on quality of life in people with dyskinetic cerebral palsy (Study 1). Second, to map executive and intellectual functioning in people with dyskinetic cerebral palsy (Study 2). Third, to identify brain structure alterations in participants with dyskinetic cerebral palsy (Study 3 and Study 4). Fourth, to investigate the neural correlate of executive and general intellectual functioning in participants with dyskinetic cerebral palsy (Study 3 and Study 4).

The main findings of the studies are the following. (1) An executive function domain, cognitive flexibility, is an important driver of quality of life in people with dyskinetic cerebral palsy. (2) People with dyskinetic cerebral palsy present difficulties in both general intellectual and executive functioning but goal setting abilities are close to those in typically developing controls. Additionally, people with dyskinetic cerebral palsy display better intellectual and executive functioning than people with spastic cerebral palsy, indicating a general tendency towards a better cognitive level rather than a specific dysexecutive deficit. (3) Observable white and grey matter lesions as well as white matter integrity are involved in dyskinetic cerebral palsy. Specifically, posterior lateral thalamus and the frontal lobe lesions are the most common in our sample of people with dyskinetic cerebral palsy. In this sample, the loss in the integrity of the white matter predominantly appears outside of the frontal lobe, mainly in the parietal cortex. (4) General intellectual functioning is related to white matter integrity in several cortico-cortical and cortico-subcortical regions and with observable brain lesions particularly in the posterior thalamus. Executive functions were related with white matter microstructure in regions containing fronto-cortical and posterior cortico-subcortical pathways and with observable brain lesions particularly in the parietal lobe and the middle and posterior corpus callosum. Unexpectedly, neither in terms of white matter microstructure nor in terms of observable lesions, was there a significant relationship between executive function and the fronto-striatal pathways.

1 Introduction

1.1 Definition of cerebral palsy

During the nineteenth century, discussion regarding the definition and classification of cerebral palsy (CP) was first recorded in medical literature. The first work describing "cerebral paralysis" was written by William Little, an orthopaedic surgeon who indicated that the cause of this motor disorder was often damage to the brain during infancy, specifically associated with preterm birth and perinatal asphyxia. Little also noted that behavioural disorders and epilepsy were only occasional complications and not central to the condition. Later, Sigmund Freud advocated and recognized that the pathological findings resulted from a combination of the initial lesion and repair process and, therefore, were only partially related to the clinical manifestation. Freud statements regarding classifying CP using only clinical findings influenced research about CP during the first half of the twentieth century [16].

The most frequently cited definition of CP was published by Bax in 1964 [17]. Bax reported a definition of CP suggested by an international working group that stated that CP is "*a disorder of movement and posture due to a defect or lesion of the immature brain*". This working group also proposed to exclude from CP those disorders of posture and movement which were of short duration, due to progressive disease, or due to intellectual disability.

In 1992, Mutch et al. [18] proposed another definition resulting from several meetings held in Europe and America between 1987 and 1990: "*Cerebral palsy is an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development*".

In 2004, an international executive committee for the definition of CP organized a workshop to review the definition by Bax [17] and included some hallmarks present in Mutch et al. [18] definition. The resulting definition was as follows:

"Cerebral palsy describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that

occurred in the developing foetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behaviour, by epilepsy, and by secondary musculoskeletal problems."

This definition received mixed reviews and suggestions from different concerned fields regarding its precision, the age limits, the inclusion severity threshold, or which syndromes should be excluded. Therefore, in 2007, the group published a report in order to clarify some aspects of the definition [16]. Briefly, this report clarified that CP is a heterogeneous condition that excludes transient disorders but recognised that children and adults have changing patterns of clinical manifestations. That is, the clinical picture of CP will differ person-to-person, depending on aspects of each person's development, learning, activities, therapies, ageing, and other factors. With the term "nonprogressive disturbances", the authors aimed to clarify that mechanisms leading to CP were presumed to arise from a single event or discrete series of events which have concluded at the time of diagnosis. Thus, motor dysfunction which results from recognized progressive brain disorders was not to be considered CP. Moreover, it distinguished CP from phenotypically similar disorders in children due to lesions acquired later in life when basic motor development is relatively well established. Although there is no explicit upper age limit, the disturbance resulting in CP is presumed to occur before the affected function has developed. This means that the first two or three years of life are most important in the timing of disturbances resulting in CP [19]. In fact, a core feature of CP is that motor impairments begin to manifest very early, usually before 18 months of age, as delayed or aberrant motor progress [20]. It is also worth noting that people with neurodevelopmental disabilities that do not primarily affect movement and posture are not considered to have CP. That is, global and specific cognitive problems may be affected but a diagnosis of CP is not appropriate for child who has severely impaired cognition and no motor signs.

Resulting from the above-mentioned efforts to reach an agreement about the definition of CP, nowadays, surveillance programmes in Europe, the United

Kingdom and Australia accept any definition of CP as long as it includes five core features that fit with definitions provided by Mutch and Bax:

1. Cerebral palsy is a group of disorders i.e. it is an umbrella term,
2. It is permanent but not unchanging,
3. It involves a disorder of movement and/or posture and of motor function,
4. It is due to a non-progressive interference/lesion/abnormality,
5. This interference/lesion/abnormality arises in the developing/immature brain [21].

In 2014 a review defining the inclusion and exclusion criteria that had been adopted uniformly by surveillance programmes concluded that there was considerable agreement across programmes [21]. However, consensus is still elusive regarding 1) minimum age of survival and maximum age of postnatal brain injury, and 2) metabolic disorders with highly variable clinical courses/responses to treatment. Fortunately, age of acquisition and death is recorded which provide opportunities to pool and analyse data over time and across registers.

1.2 Classification

Cerebral palsy is a heterogeneous condition in terms of aetiology as well as in types and severity of impairments. The Reference and training manual of the Surveillance of Cerebral Palsy in Europe (SCPE) [22] highlights five characteristics which can be used to classify CP, summarised in Table 1. Which of these characteristics are useful will depend on the particular focus of the clinical or scientific endeavour at hand [23]. For the purposes of the present work, particularly relevant characteristics are the CP subtype, and symptomatic severity.

Table 1. Classification of cerebral palsy types as proposed by the Surveillance of Cerebral Palsy in Europe, 2007

1. Motor abnormalities	2. Accompanying impairments
A. NATURE AND TYPOLOGY OF THE MOTOR DISORDER: The observed tonal abnormalities assessed on examination (e.g. hypertonia, hypotonia) as well as the diagnosed movement disorders present, such as spasticity, dystonia, athetosis and ataxia. B. FUNCTIONAL MOTOR ABILITIES: The extent to which the individual is limited in his or her motor function, including oromotor and speech function.	The presence or absence of later-developing musculoskeletal problems and/or accompanying non-motor neurodevelopmental or sensory problems, such as seizures, hearing or vision impairments, or attentional, behavioural, communicative and/or cognitive deficits, and the extent to which impairments interact in individuals with CP. These impairments may have resulted from the same or similar pathophysiologic processes that led to the motor disorder, but they nonetheless require separate enumeration.
3. Anatomical and neuroimaging findings	**4. Causation and timing**
A. ANATOMIC DISTRIBUTION: The parts of the body (limbs, trunk, bulbar region, etc.) affected by motor impairments or limitations. B. NEURO-IMAGING FINDINGS: The neuroanatomic findings on CT or MRI imaging, such as ventricular enlargement, white matter loss or brain anomaly. Information is insufficient to recommend any specific classification scheme for neuroimaging findings.	Cerebral palsy may result from the interaction of multiple risk factors, and in many cases, no identifiable cause may be found. When there is a clearly identified cause, as is usually the case with postnatal CP (e.g. meningitis, head injury) or when brain malformations are present, and the presumed time frame during which the injury occurred is known, it is recommended to report it.

CP, cerebral palsy; CT, computed tomography; MRI, magnetic resonance imaging.

1.2.1 Subtypes

It is useful to categorize individuals with CP into groups in order to provide a level of detail about specific needs of individuals with CP [16].

Traditional classification schemes have focused principally on the distribution of affected limbs and the predominant type of tone or movement abnormality. Accordingly, the Reference and training manual of the SCPE divides CP into three groupings: ataxic, spastic, and dyskinetic [22].

Spastic cerebral palsy (SCP) is characterized by an increased muscle tone and pathological reflexes. Spasticity is a clinical phenomenon in which muscles overreact to rapid stretch. Accordingly, reflexes of persons with SCP can be increased e.g. hyperreflexia with pyramidal signs. This CP type is in turn classified as unilateral (hemiplegic) or bilateral (tetraplegic, diplegic).

Dyskinetic cerebral palsy (DCP) is characterized by involuntary, uncontrolled, recurring and occasionally stereotyped movements. Primitive reflex patterns predominate, muscle tone is varying and dyskinesia is differentiated into dystonia and choreoathetosis. This CP type is much less studied than SCP and can in turn be characterized as:

- ✓ Dystonic: There is a reduced activity and tone tends to be increased. Dystonia is dominated by abnormal postures that may give the impression of hypokinesia and muscle tone that is fluctuating (but with easily elicitable tone increase). Characteristics are involuntary movements, distorted voluntary movements, and abnormal postures due to sustained muscle contractions [24]. Dystonic movements are typically patterned or twisting and can be tremulous, interfering with voluntary movements. Dystonia is often initiated or worsened by voluntary action, the intention to move and non-specific stress, emotion or sensations. Characteristic features of dystonia include: co-contraction and overflow muscle activation, difficulty switching between component movements of complex tasks and reduced spinal cord and brainstem inhibition [25].

- ✓ Choreo-athetotic: Symptom presentation is dominated by hyperkinesia and tone fluctuation (but mainly decreased). While chorea includes involuntary, rapid and jerky, dance-like movements, athetosis refers to slow, writhing, or contorting movements [24, 25].

  Dystonia may coexist with chorea and athetosis often referred to collectively as dyskinetic (dystonic– choreoathetoid) CP [25].

Ataxic cerebral palsy is characterized by the **l**oss of orderly muscular coordination, so that movements are performed with abnormal force, rhythm and accuracy. Muscle tone is not varying.

It is worthy of note that the SCPE explicitly classifies SCP as unilateral or bilateral but has not explicitly described equivalent subtypes in DCP. Although the bilateral form of DCP is, by far, the most common, asymmetric patterns of DCP have been documented, with different involvement of arms, legs, mouth and eyes [26, 27]. Patients with asymmetric symptoms have also been reported in clinical studies of this condition [28–30].

Although spasticity and dystonia frequently coexist in the CP population, these two conditions have distinct pathophysiological features that require different management strategies. This can complicate treatment, because many children have mixed presentations [31].

1.2.2 Symptomatic motor severity

Functional motor abilities are commonly used to classify groups according severity levels using the Gross Motor Function Classification System (GMFCS) [32]. This scale has been widely employed internationally to group individuals with CP into one of five levels based on functional mobility or activity limitation. A parallel classification scale, the Bimanual Fine Motor Function scale [33] has been developed for assessing upper extremity function in CP. For assessing hand and arm function the Manual Ability Classification System [34] has also shown to have good interrater reliability between parents and

professionals [16]. It is worthy of note that CP subtype cannot be clearly differentiated from symptomatic severity, because DCP is particularly disabling in comparison to other forms of CP. Of persons with DCP, almost 60% use a wheelchair for ambulation and more than half suffer accompanying impairments and disabilities [10].

1.3 Epidemiology

Cerebral palsy is the most common cause of physical disability in childhood with a worldwide average prevalence of approximately 2 per 1000 live births [36]. Within Europe, between the birth years 1980 to 2003, prevalence of CP was 1.77 (1.57–1.99) per 1000 live births [37]. A posterior estimation of more recent data (birth years 2007–2010), for Sweden alone, estimated prevalence as 1.96 per 1000 live births [38].

The overall trends in the CP prevalence for the last 40 years of the twentieth century were relatively stable [39, 40] but a significant decrease in the CP prevalence in Europe has been reported for the years 1980 to 2003 [37]. Cerebral palsy prevalence may have been affected by the critical developments implemented in neonatal care. Specifically, the substantial increase in very low birth weight infants and their increased survival seem to be product of improved newborn intensive care. Moreover, brain or body cooling equipment for full-term infants with hypoxic ischaemic encephalopathy has conclusively shown during the last years its potential in to reducing the CP prevalence [41]. It should be noted that although hypothermia is promising, adverse events during transport need to be taken into account in order to provide closer clinical surveillance [42]. Other important changes include the introduction of surfactant, and improvement in the management of nosocomial infections [37].

Although the epidemiology of CP by CP types is not known in detail [25], SCP is by far the most common type of CP. Dyskinetic CP is the second largest group and the rarest form of CP is ataxic CP. Dyskinetic CP comprises about 7% of CP cases and it is more common among children born at term and among

children with normal birth weight [26,10,43,44; Table 2]. Bilateral spastic CP rates appear to have decreased since 1980 in children with normal or moderately-normal birthweight [37]. By contrast, the percentage of DCP cases has increased among those with normal birth weight in the same period, although this trend is not statistically significant.

Table 2. Cases of dyskinetic cerebral palsy for different birthweight between 1980 and 2003 according to Sellier et al., 2016 [37].

Birthweight	1980 to 1987 n (%)	1988 to 1995 n (%)	1996 to 2003 n (%)
<1000g (ELBW)	4 (3.4)	8 (3.9)	13 (3.5)
1000 to 1499g (VLBW)	25 (5.6)	19 (4.2)	27 (4.3)
1500 to 2499g (MLBW)	34 (4.7)	41 (5.6)	46 (4.8)
≥2500g (NBW)	121 (8.4)	147 (8.9)	264 (10.8)

ELBW, extremely low birthweight; MLBW, moderately low birthweight; NBW, normal birthweight; VLBW, very low birthweight.

In 2007, Krägeloh-Mann wrote in a commentary in the journal *Developmental Medicine & Child Neurology* that the unchanging prevalence of DCP could mean that some of the pathogenetic factors behind DCP are more difficult to be influenced [45]. She pointed out that, despite of the decreasing role of kernicterus (a form of brain damage due to high levels of bilirubin), children who suffer severe perinatal adverse events that lead to brain lesions and subsequent DCP are more likely to survive as a result of better neonatal care.

1.4 Aetiology

Cerebral palsy is a clinical entity very heterogeneous in terms of aetiology [25]. Clear-cut categorization by cause is, therefore, not currently possible as recording adverse events in the prenatal, perinatal and postnatal life of a child with CP would be necessary to achieve this goal. Even so, such observations would still be insufficient to perform an etiologic classification that implies these events were the cause of CP in a single affected individual [16].

1.4.1 General causes

Epidemiological studies suggest that the origins of most CP cases occur prior to labor, particularly during earlier pregnancy. As reviewed by Maclennan et al. [46], preterm delivery is seen in 35% of all CP cases and the risk of CP increases with progressively lower viable gestational age. These authors also write that the neuropathological aetiology of CP may differ from term babies and that it is likely that associated risk factors such as infection, genetic variations, and growth restriction contribute [46]. Recent studies suggest that many cases of CP are associated with genetic alterations and, accordingly, congenital anomalies (maldevelopment) in people with CP are much higher than in the general population [47]. This includes both cerebral (such as schizencephaly and hydrocephaly) and noncerebral malformations. Altered fetal inflammatory or thrombophilic responses in the fetus and the neonate are often observed too [48]. Moreover, damage acquired following perinatal bacterial or viral intrauterine infection seems to be one of the causes of white matter antenatal damage [49]. Other epidemiologic and genetic risk factors for CP include fetal growth restriction, higher-order pregnancy, tight nuchal umbilical cord, prolonged shoulder dystocia, placental pathology (such as chorioamnionitis, funisitis and villitis) or inborn errors of metabolism. Acute hypoxia beginning in labour or chronic hypoxia (i.e., long-standing compromise in pregnancy beginning before labour) can also be a cause of CP [47].

1.4.2 By subtypes

The probable causes of CP appear to be reported at different frequencies, according to CP subtype. Hemiplegic CP sometimes represents the effects of a perinatal ischaemic stroke and can also occur in premature infants who have unilateral porencephalic cavities following white matter damage. Spastic diplegia, which is usually accompanied by periventricular leukomalacia, is linked to both preterm birth and foetal growth retardation at term [25, 50–52]. The combination of spastic tetraplegia with dyskinesia in term infants has been associated with severe birth asphyxia [25].

Dyskinetic CP cases have frequently been reported to be linked to perinatal adverse events. These occur mostly in near-term or term-born children with a birth weight ≥2500 g causing an injury in the basal ganglia by various mechanisms, including asphyxia, trauma, perinatal strokes, and kernicterus [25, 53]. As for hypoxia–ischemia, at term, the vulnerability to a deficit in oxygen supply is higher than earlier in development. The grey matter tissues have the highest metabolic requirements, particularly in the basal ganglia, the thalamus and parts of the cerebral cortex [25]. As for hyperbilirubinemia, a perinatal infection, it can cause DCP at any gestational age but is now very rare in developed countries as a result of preventive interventions. However, it remains a major risk factor for CP in developing countries [25]. The fact that the bilateral form of DCP is the most common is due to the underlying aetiology. Dyskinesia accompanied by sensorineural hearing loss is the form of CP most often seen with kernicterus. Magnetic resonance imaging findings in kernicterus are characterized by bilateral damage in the globus pallidus especially on the posteromedial border [54]. That is, hyperbilirubinemia and hypoxic–ischaemic encephalopathy usually leads to bilateral brain injury and thus to a pattern of bilateral motor involvement. However, one cannot rule out the existence of other perinatal or postnatal aetiologies that can cause unilateral brain affections such as perinatal stroke, infection, or traumatic brain injury [28, 29].

Finally, ataxic CP has often been associated with the presence of a cerebellar malformation [25].

1.5 Comorbidities

The disabling condition in CP is permanent throughout the individual's life and makes heavy and constant demands on health, educational, and social services which are partly due to accompanying impairments. Many of these impairments produce even greater activity limitation than the motor impairments, interfere with the ability to function in daily life and are the main drivers of reduced Quality of Life (QOL) [55, 56].

These comorbidities include seizure disorders, sensation impairments, cognitive deficits, emotional and behavioural issues, and later-developing musculoskeletal problems [16]. The percentage with learning disability, epilepsy, or sensation impairments, increases with the severity of the motor impairment [10].

Regarding epilepsy, every seizure type and many epileptic syndromes may be seen in people with CP [2]. The 35% of children with CP have epilepsy at some point of their life and about 24% have active epilepsy. As for sensation impairments, 10% of people with CP are blind and 4% are deaf [2].

Expressive and/or receptive communication is impaired in 25% of all CP cases [2] which influences QOL [57]. A study including 152 Icelandic children with CP, aged 4 to 6 years, reported that 84% of such children with CP communicated verbally, whereas 16% were nonverbal. Among verbal participants, 80% had normal speech or mild dysarthria whereas 20% had severe dysarthria. Nonverbal status and severe dysarthria are associated with intellectual status, gross motor function and the tetraplegic and dyskinetic subtypes [58]. In children and adolescents with CP, communication abilities are important: better communicative abilities are associated with higher Health-Related Quality of Life (HRQOL) for both physical [55, 59] and also psychosocial domains [57, 59, 60].

However, research has yet to analyse the relationship between QOL and a classification system such as the Communication Function Classification System (CFCS) [61] which categorizes communication at the activity/participation level of the International Classification of Functioning, Disability and Health in a similar vein to the GMFCS and the Manual Ability Classification System.

As for psychiatric or behavioural problems, autistic spectrum, sleep, mood and anxiety disorders may be present. The prevalence of mental health symptoms is high in children with CP, ranging from 57% (when psychiatric interview was performed) to 28% (using the Child Behaviour Checklist). The estimated prevalence using the Strengths and Difficulties Questionnaire has been reported to be 30% [62]. Behavioural problems seem to occur in 25% of CP cases and sleep disturbances are present in 20% of cases [2]. Prevalence of autism spectrum disorders in children with CP is higher than in the general population [63–67]. Additionally, some studies report associations between several domains of QOL and general prosocial behaviour and psychopathology in adolescents [57] and depression, dysphoria, anxiety, inefficacy and insufficient control in adults [68] with CP.

Furthermore, people with CP may develop a variety of secondary musculoskeletal problems, such as muscle/tendon contractures, bony torsion or hip displacement (1 in 3 people). Additionally, 1 in 4 children have bladder control problems, 1 in 5 dribble, and 1 in 15 are in tube fed. Many of these problems develop throughout life and are related to physical growth, muscle spasticity, ageing and other factors [2].

Finally, comorbidities about cognitive functioning will be addressed in detail in the following sections as they are the main outcome considered in this thesis.

1.6 Neuroimaging

Cerebral palsy is diagnosed by clinical descriptive criteria rather than cerebral pathology or aetiological diagnoses. Therefore, normal magnetic resonance

imaging (MRI) is not a prerequisite, nor does it not exclude the diagnosis of CP [69]. Nevertheless, the role of MRI in the understanding of CP pathogenesis, has increased during the last fifteen years and there is a consensus that MRI may help to reveal the pathologic basis of CP and its correlates with clinical findings [11]. This may be useful in helping parents, clinicians, and others involved in the care of children with CP to better understand their condition and to predict their needs in the future [11, 69].

It is well accepted that MRI findings tend to differ between CP types [70] but in recent years, knowledge of this area has still been considered insufficient for the development of specific CP classification schemes based solely on neuroimaging findings [16]. Ideally, longitudinal studies exploring long term consequences of early brain injury in different CP types would likely drive discovery of novel early intervention strategies [71]. Unfortunately, studies of this nature are highly costly to conduct, and can take years before imaging can be compared with developmental outcomes. Given that CP disturbances in the brain are not progressive, a cross-sectional study exploring the association between brain lesions and concurrent clinical outcomes in older children or adults may more easily shed light to this issue.

White-matter damage of immaturity (including periventricular leukomalacia, PVL) is the most common neuroimaging finding in CP (42.5-56%), followed by basal ganglia lesions (12.8-18%), cortical/subcortical lesions (9.4%), malformations (9-9.1%), focal infarcts (7.4%), and miscellaneous lesions (7.1%). Systematic reviews have shown that 14 to 17% of children with functional impairment have no abnormality on T1- and T2- weighted MRI [72, 73].

The patterns of abnormalities found depend on the stage of brain development at the time of insult. During the third trimester, the white matter is particularly susceptible to injury. The major neuropathologies potentially damaging the motor tracts during this period include PVL or complications of intraventricular haemorrhage [69, 74]. White-matter damage of immaturity is common in children with spastic diplegia, hemiplegia and tetraplegia. This type of damage is thought

to mainly occur before about 34 weeks of gestation including, but not limited to, trauma suffered during preterm labour and delivery. When the location of the white matter loss is investigated, those with posterior only, or posterior and middle, white-matter damage tend to have spastic diplegia. The spastic tetraplegia group, however, mostly seems to have damage across all areas [11].

Basal ganglia and thalamic damage are mainly associated with dystonic CP, but are also seen in children with spastic tetraplegia and diplegia. Focal cortical infarcts, however, seem to be almost exclusively related to a clinical diagnosis of hemiplegia. Cortical/subcortical damage seems to be present in all CP types but ataxia [11].

Malformations are more common among term than preterm-born patients [73] and have been reported to be more common in both hemiplegia group [11] and ataxic CP [75] but can be found across all clinical subtypes [11, 73, 75]. In some instances, these may be due to disturbances of cortical neurogenesis, which takes place predominantly during the first and second trimesters. Such disturbances can result in maldevelopments such as lissencephaly, pachygyria, or polymicrogyria and cause CP. Some of these disorders may be of genetic origin, especially when symmetrical in distribution [76].

Miscellaneous MRI patterns and normal MRI findings are distributed across all clinical CP subtypes [11]. Specifically, up to 50% of those with DCP, have normal structural-MRI brain scans [25]. Interestingly, a study found that the majority of patients with DCP in their cohort had normal MRI findings and that normal-appearing MRI were significantly more prevalent in DCP than other CP types [77]. These authors suggest the possibility that conventional MRI sequences might not be as sensitive as diffusion tensor imaging (DTI) in identifying the widespread abnormalities seen in this CP subtype, and that more refined imaging techniques may be needed to evaluate patients with normal-appearing structural MRI findings [77]. It is therefore necessary to carry out studies not only that describe observable lesions, but also that apply more

advanced imaging techniques able to objectively quantify microstructural integrity of the brain.

According to several quantitative neuroimaging studies MRI findings also appear to differ by clinical CP subtype. Briefly, in children with spastic diplegic CP, white matter structure has been reported to be damaged in the corona radiata, anterior limb of internal capsule, posterior limb of internal capsule, midbrain, pons, medulla, genu and splenium of corpus callosum, and occipital white matter [78]. Moreover, a reduction in total white matter connectivity throughout the brain has been reported in severe versus moderate bilateral spastic CP, including but not limited to regions associated with the sensorimotor system [79]. In unilateral SCP, the assessment of the structural brain network identified alterations in ipsilesional projections (connecting the brain stem and thalamus with precentral and paracentral gyrus) and association pathways (such as, for example, those connecting the precuneus with the medial orbito-frontal cortex, caudal anterio-cingulate gyrus and the superior frontal cortex) microstructure [80]. As for DCP, however, very few studies have utilized advanced neuroimaging analyses and samples are small. As DCP is a particular focus of work presented in this thesis, in the following section, neuroimaging findings in this CP type are presented.

1.6.1 Neuroimaging in dyskinetic cerebral palsy

Most of neuroimaging studies of DCP have utilised qualitative categorical descriptions of computed tomography (CT) and MRI and very few have utilized advanced neuroimaging analyses. Studies reporting categorical descriptions indicate that the most frequent brain abnormality observed in DCP is in the basal ganglia and thalamus, often found in persons who suffered brief, profound hypoxic insults as term-born or near-term-born infants. White matter involvement has also been reported in dyskinetic cases, although some patients present without any apparent brain injury. There is no agreement, however, among studies about percentages of each neuroimaging finding [70, 81–83]. Table 3 summarizes the radiological findings in DCP in qualitative neuroimaging studies reporting categorical descriptions.

Table 3. Radiological findings in dyskinetic cerebral palsy

Reference	n	Age range	Radiological findings	n (%)
Kerrigan et al., 1991 [84]	5	1y-6y	**Thalamus and lentiform nuclei**	**2 (50%)**
			Thalamus and putamen	**2 (50%)**
Yokochi et al., 1991 [85]	22	3y-12y	**Thalamus and/or putamen**	**9 (41%)**
			No apparent abnormality	7 (31%)
			Thalamus and putamen and white matter	3 (14%)
			White matter	3 (14%)
Rutherford et al., 1992 [86]	3	1y-2y	**Basal ganglia**	**3 (100%)**
			Thalamus	**3 (100%)**
			Putamen	2 (67%)
			White matter	2 (67%)
			Subthalamic	0 (0%)
Menkes et al., 1994 [87]	6	1y-19y	**Posterior putamen and ventrolateral or posterior thalamus nuclei**	**6 (100%)**
			Caudate	2 (33%)
			Globus pallidus	0 (0%)
			Internal capsule	0 (0%)
Yokochi et al., 1996 [85]	21	3y-20y*	**Thalamus and putamen**	**9 (43%)**
			Thalamus and putamen and perirolandic area	4 (19%)
			Thalamus or putamen	7 (33%)
			Peritrigonal area	1 (5%)
Hoon et al., 1997 [88]	1	3y	**Posterior putamen and ventrolateral thalamus nuclei**	**1 (100%)**
			Lentiform nuclei	
Lee et al., 1998 [89]	2	6m-6y:11m*	**Thalamus**	**2 (100%)**
			Basal ganglia	**2 (100%)**
			Temporal lobe	1 (50%)
			Cerebellum	0 (0%)
			Extratemporal cortex	0 (0%)

Continuation

Reference	n	Age range	Radiological findings	n (%)
Krägeloh-Mann et al., 2002 [90]	4 purely DCP	2w-3y:6m	*Purely DCP* **Lentiform and ventro-lateral thalamus nuclei**	**4 (100%)**
	6 dyskinetic –spastic	16d-15y	*Dyskinetic–spastic CP* Lentiform and ventro-lateral thalamus nuclei only	2 (33%)
			Lentiform, ventro-lateral thalamus nuclei and pericentral region	2 (33%)
			Lentiform nuclei, entire thalamus, pericentral region, and hippocampus	2 (33%)
Bax et al., 2006 [91]	34	1m-87m	Among 62 participants with basal ganglia and thalamic damage 75.6% (n=34) had DCP	
Himmelmann et al., 2007 [26]	43	mean age CT: 7m mean age MRI: 3y	**Basal ganglia, thalamus, and cortico-subcortical lesion**	**25 (58%)**
			Basal ganglia/thalamus/cortico-subcortical lesion and white matter lesion	8 (19%)
			No apparent abnormality	5 (12%)
			White matter lesion only	3 (7%)
			Maldevelopment	2 (4%)
Griffiths et al., 2010 [92]	20 (vs 20 SCP)	1y-16y	Subthalamic nucleus injury more frequent in DCP than SCP	
			Subthalamic nucleus	**15 (75%)**
			Globus pallidus	2 (10%)
			Caudate	2 (10%)
Prasad et al., 2011 [93]	6	0.5y-15y	**Diffuse encephalopathy**	**5 (83%)**
			No apparent abnormality	1 (17%)
			Periventricular white matter	0 (0%)
			Malformations / Miscellaneous/ Unclassifiable	0 (0%)
			Focal ischemic or haemorrhagic lesions	0 (0%)

Continuation

Reference	n	Age range	Radiological findings	n (%)
Yoshida et al., 2011 [94]	19	10m-12y	**Basal ganglia and/or thalamus hyperintensity**	**10 (53%)**
			Rolandic-type injury	5 (26%)
			Volume loss of myelinated white matter	5 (26%)
			Periventricular leukomalacia	4 (21%)
			Parasagittal cerebral injury	2 (11%)
			No apparent abnormality	2 (11%)
			Thinning of corpus callosum	1 (5%)
Yoshida et al., 2013 [95]	7	2y–12y	**Rolandic type injury**	**2 (29%)**
			Parasagittal cerebral injury	**2 (29%)**
			Periventricular leukomalacia	**2 (29%)**
			White matter	1 (13%)
Himmelmann et al., 2014 [38]	32	Year of birth: 2003-2006	**Basal ganglia/thalamus lesions**	**16 (50%)**
			White matter	2 (6%)
			Cortical/subcortical	6 (19%)
			Maldevelopment	6 (19%)
			Other abnormalities	0 (0%)
			No apparent abnormality	2 (6%)
Park et al., 2014 [96]	23	16y–50y	**No apparent abnormality**	**12 (52%)**
			Thalamus and/or putamen	7 (31%)
			Thalamus, putamen and white matter	4 (17%)
Reid et al., 2014 [75]†	Sweden: 30/ Quebec: 15/ Victoria: 33	Years of birth: 1995-2002/1999-2006/1999-2002	**Grey matter injury**	**23 (77%) / 2 (13%) / 9 (27%)**
			Miscellaneous	- / 8 (53%) / 3 (9%)
			White matter	2 (7%) / 1 (7%) / 13 (39%)
			No apparent abnormality	2 (7%) / 4 (27%) / 7 (21%)
			Focal vascular insult	3 (10%) / 0 (0%) / 1 (3%)
			Malformations	0 (0%) / 0 (0%) / 0 (0%)

Continuation

Reference	n	Age range	Radiological findings	n (%)
Reid et al., 2015 [97]	7	Year of birth: 1999-2008	**Thalamus and/or basal ganglia involvement**	**7 (100%)**
			Cortical-subcortical	
			Central sulcus/Hyppocampus	4 (57%)
			White matter	4 (57%)
			None/Focal/Parasagital	3 (43%)
Monbaliu et al., 2015 [27]	42	1m-17y:3m	**Thalamus and/or basal ganglia**	**30 (71%)**
			Periventricular white matter	17 (40%)
			Cortical	10 (23%)
			Maldevelopments	5 (12%)
			No apparent abnormality	5 (12%)

*Age range corresponds to the hole sample of participants and not only those with DCP; †Review article including five population-based studies of three geographic regions: Sweden [44, 82, 98], Quebec [81], and Victoria [99]. Percentages are shown in this order: Sweden/Quebec/Victoria; CP, cerebral palsy; CT, computed tomography; d, days; DCP, dyskinetic cerebral palsy; m, months; MRI, magnetic resonance imaging; SCP, spastic cerebral palsy; w, weeks; y, years. Bold indicates most frequent finding in each study.

Only five studies have performed quantitative neuroimaging analyses in DCP. Specifically, Yoshida et al. [94, 95] concluded that subjects with DCP have more severe and diffuse alterations in white matter and deep grey matter microstructure than subjects with SCP. Harlaar et al. [100] found smaller tract sizes and/or lower fractional anisotropy (FA) values in participants with DCP than in controls in the arcuate fasciculus and the extreme capsule. Finally, Park et al. [96] found a FA reduction in areas adjacent to pyramidal tract. These studies have begun the important work of identifying the potential involvement of white matter in DCP, beyond observable lesions. However, presently there are two limitations that make it difficult to draw firm conclusions about the whole-brain injury pattern in DCP. Firstly, these results are limited by the use of a priori selected regions of interest that are normally related to sensorimotor function, leaving prefrontal, temporal and occipital white matter areas poorly assessed [101]. Only one study applied a whole-brain approach [95] but an atlas-

based analysis in 205 predefined structures was used. Secondly, the number of participants with DCP is very small. These and additional details of these five studies are available in Table 4.

Table 4. Findings of quantitative neuroimaging studies in dyskinetic cerebral palsy

Reference	n	Age range	Methods	Findings
Iwasaki et al., 1997 [102]	9	2y-13y	Measured volume of five cadaver brains with two methods: real volume using water displacement and axial T1	Hemispheric volumes 2SD below TDC 44% (n=4) Basal ganglia, thalamus and internal capsule 2SD below TDC 22% (n=2) Volume of myelinated white matter 2SD below TDC 33% (n=3)
Yoshida et al., 2011 [94]	19	10m-12y	FA and MD were measured with ROIs of bilateral deep grey and white matter structures, including projection fibres, association fibres, and commissural fibres	FA values in the athetotic CP group were significantly lower than those in the TDC and SCP groups for multiple structures, including deep gray and white matter. These differences were also associated with increasing MD
Yoshida et al., 2013 [95]	7	2y-12y	Atlas-based anatomical analysis of the entire brain. For 205 parcellated brain areas, the volume, FA, and MD were measured. Principal component analysis was performed for the Z scores of these parameters	Abnormalities more severe and widespread in DCP than in SCP

Continuation

Reference	N	Age range	Methods	Findings
Harlaar et al., 2013 [100]	4*	5y-23y	Tractography was performed using FSL. Eight regions of interest were used as masks for tractography	Both language (arcuate fasciculus and extreme capsule) and pyramidal tracts were smaller in CP than in TDC
Park et al., 2014 [96]	23	16y–50y	Gray matter was assessed using VBM The CST and the SLF were analysed by DTT	VBM showed reduced volume of the hippocampus and parahippocampal gyrus In DTT, no abnormality was observed in CST, but in SLF

*Analyses were performed with the whole sample of people with CP (n=5) including one participant with spastic cerebral palsy. CP, cerebral palsy; CST, corticospinal tract; DCP, dyskinetic cerebral palsy; DTT, diffusion tensor tractography; FA, fractional anisotropy; m: months; MD, mean diffusivity; ROI, region of interest; SCP, spastic cerebral palsy; SD, standard deviation; SLF, superior longitudinal fasciculus; TDC, typically developing controls; VBM, voxel-based morphometry; y: years.

As mentioned above, quantitative neuroimaging studies in DCP are necessary to shed light on the pathogenesis of DCP. However, its translatability to routine clinical settings is limited. In part, this is because such studies have relied heavily on specialised high-quality images that are free of motion artefacts and require specialised processing. Ideally, quantitative neuroimaging findings would be best translated into clinical practice in a manner that utilises tools and imaging that clinicians are already familiar with. Fot example, the semi-quantitative scale for classification of structural brain MRI (sqMRI) [103, 104] that has been tested for reliability [104] and construct validity in unilateral CP [103], can be robustly scored despite some motion artefacts that are highly likely to occur in DCP. This system, which has not been used yet in DCP, scores the brain injury in CP semi-quantitatively. The scoring considers both the extent of the lesion/s (the

higher the score, the more extensive the lesion) and the anatomical location of this/these lesion/s.

1.7 Cognitive functioning

Global and specific cognitive processes may be affected in CP both as a function of the primary disturbance to which CP is attributed and as a secondary consequence of activity limitations [16]. Cognitive functions are a key outcome in CP as they are determinant to gain access to different medical, educational and social resources. Identifying cognitive problems and strengths is also important for the initiation of support that can enable a positive course of development. Accordingly, the SCPE recommends collecting information on intellectual function [24] and the International Classification of Functioning, Disability and Health considers intellectual function as one of the essential "Core Sets" for children and youth with CP [3]. In the following sections, knowledge about cognitive functioning in CP is presented, paying special attention to DCP and executive function.

1.7.1 General intellectual functioning

Almost 50% of the CP population have an intellectual quotient below 70 [2] and children with CP and intellectual disability have a higher risk of mental health symptoms [105]. Although children with CP have an increased risk of both general and specific cognitive impairments, there are also children with CP who have no cognitive impairments and some that show signs of giftedness [106, 107]. This variability in general intellectual ability could be explained by variability brain lesion types, severity of motor impairments, and presence of epilepsy [106].

As for general intellectual functioning, no differences have been found between level of verbal comprehension and level of perceptual reasoning but when an uneven cognitive profile is observed, scores tend to be higher on verbal

comprehension than on perceptual reasoning [106]. Accordingly, a better performance has been reported in verbal than performance intelligence quotient (IQ) in preterm-born children with spastic diplegia due to PVL [51] and other CP types including DCP [108].

Motor ability has been shown to be strongly correlated with intellectual level in CP [109]. Similarly, verbal comprehension, perceptual reasoning, and nonverbal reasoning have also been shown to be statistically different between GMFCS groups [106]. Two complementary explanations exist for these relationships between gross motor function and cognitive abilities. Firstly, cognitive impairments and motor disabilities may be being commonly caused by the same primary disturbance. Secondly, the amount of stimulation received from the environment may differ depending on motor ability and, thus, affect the person's general intellectual functioning.

It is agreed that DCP is associated with poorer motor outcomes than other CP types [10] but there are few studies which have compared cognitive abilities in DCP with those of other CP subtypes, particularly in groups with similar levels of motor ability. Results from existing studies have been mixed; details are available in Table 5. For example, some studies have reported that people with DCP present higher rates of cognitive difficulties than those with bilateral SCP [10] and that people with DCP have a lower IQ than people with other CP types [108]. Verbal IQ has also been reported to be significantly higher among children with spastic diplegia and hemiplegia than in DCP [58]. Other studies, however, did not find such differences. For example, Pueyo et al. [110] did not find differences between bilateral DCP, mixed CP, and SCP in nonverbal reasoning using the same measure in all participants. In fact, some studies have reported higher cognitive performance in DCP. Strauss et al. [111] found that in a sample of people with tetraplegic CP with severe motor dysfunction, 95% of those with SCP had an IQ<50 and only 2% had no intellectual disability. Among the participants with DCP, however, only 40% had an IQ<50, and 20% had an IQ≥70 or higher. Indeed, another study [112] found that the percentage of learning disability was higher (100%) in people with spastic tetraplegia

(GMFCS IV n=2, V n=21) than in DCP (42%; GMFCS I n=2, II n=4, III n=5, IV n=15, V n=26). Along this line, a recent study has found that cognitive quotient in tetraplegic SCP was significantly lower than in other CP types including DCP [106]. Finally, another study found that the lowest IQ level was more frequent in spastic tetraplegia than in DCP. Specifically, in this study hypotonic, spastic tetraplegic, and hemiplegic but not dyskinetic patients had the highest odds to assign higher ratings in impaired IQ [109].

Overall, these studies might suggest that when people with DCP are comparable to other CP types in terms of motor severity, they might not present poorer cognitive performance. However, this hypothesis needs still to be tested as results vary depending on whether the participants with DCP are compared with participants with severe or moderate forms of SCP. Moreover, measures used to assess intellectual level often differ between participants and the reliability of some tests is unknown. Finally, the number of participants with DCP in some studies is small and the motor severity by CP type is not always reported.

In conclusion, no study to date has compared general intellectual functioning between a relatively large sample of people with DCP and a group of participants with SCP who have similar motor severity and prematurity. To truly understand the cognitive correlates of different CP types, the field requires comparative neuropsychological studies of cognition that control for variables known to play a role in cognition, such as prematurity [113, 114]. The results would help to guide the design of more appropriate interventions and follow-up programs focused on DCP.

Table 5. Studies comparing/reporting percentages of general intellectual functioning in dyskinetic and spastic cerebral palsy

	n	Age range	Motor assessment/ Motor severity by CP type	CP type (n)	IQ assessment	Results
Stadskleiv et al., 2018 [106]	70	5y:1m-17y:7m	GMFCS / - (GMFCS range of the whole sample I-V)	DCP (8) SCP tetraplegia (9) SCP hemiplegia (35) SCP diplegia (18)	Cognitive quotient measured by one of the following options: 1) Cognitive Ability Quotient: *Verbal comprehension* Test for Reception of grammar Vocabulary score (British Picture Vocabulary Scale and/or Receptive Vocabulary) *Perceptual reasoning* WPPSI-III/WISC-IV (substituting Block Design with Picture Completion for children with severe fine motor impairments) 2) Developmental Quotient BSID-III/Receptive Vocabulary	Significantly lower cognitive quotient in the tetraplegic SCP group **DCP** 75% IQ≥85 **SCP tetraplegia** 33% IQ≥85 **SCP hemiplegia** 86% IQ≥85 **SCP diplegia** 78% IQ≥85 **Mixed CP** 76% IQ≥85

Continuation

	n	Age range	Motor assessment/ Motor severity by CP type	CP type (n)	IQ assessment	Results
Dalvand et al., 2012 [109]	662	3y-14y	GMFCS	DCP (53) SCP tetraplegia (218) SCP hemiplegia (57) SCP diplegia (223) Mixed CP (63) Ataxic CP (18) Hypotonic (30)	WPPSI, WISC-R	**DCP** 26% IQ≥85; 9% IQ 71–84; 19% IQ 50–70; 45% IQ<50 **SCP tetraplegia** 8% IQ≥85; 5% IQ 71–84; 10% IQ 50–70; 77% IQ<50 **SCP hemiplegia** 25% IQ≥85; 21% IQ 71–84; 28% IQ 50–70; 26% IQ<50 **SCP diplegia** 24% IQ≥85; 18% IQ 71–84; 22% IQ 50–70; 35% IQ<50 **Mixed CP** 33% IQ≥85; 21% IQ 71–84; 13% IQ 50–70; 33% IQ<50

Continuation

	n	Age range	Motor assessment/ Motor severity by CP type	CP type (n)	IQ assessment	Results
Sigurdardottir et al., 2011 [58]	111	4y:6y	GMFCS / - (GMFCS range of the whole sample I-V)	DCP (11) SCP tetraplegia (10) SCP hemiplegia (35) SCP diplegia (49) Ataxic CP (6)	n=29 BSID-II n=4 Reynell Zinkin Developmental Scales n=9 Columbia Mental Maturity Scale n=4 The Leiter International Performance Scale	Verbal IQ was lower in DCP than SCP
Himmelmann et al., 2009 [10]	5220	Years of birth 1991-1996	Severe: needing a wheelchair Moderate: ambulation with aids Mild: ambulation without aids / DCP: 16% mild, 24% moderate, 59% severe SCP bilateral: 36% mild, 2% severe	DCP (474) SCP bilateral (4746)	Measure not specified Categorized into IQ above / below 50	**DCP** 52% IQ<50 **SCP bilateral** 33% IQ<50

Continuation

	n	Age range	Motor assessment/ Motor severity by CP type	CP type (n)	IQ assessment	Results
Sigurdardottir et al., 2008 [108]	118	4y-6y: 6m	GMFCS / - (GMFCS range of the whole sample I-V)	DCP (14) SCP tetraplegia (28) SCP hemiplegia (31) SCP diplegia (45)	50% WPPSI 26% WPPSI in combination with the other developmental scales 12% BSID-II 10% BSID-II in combination with other developmental scales n=4 Reynell Zinkin Scales n=5 Columbia Mental Maturity Scale n=1 Leiter International Performance Scale-Revised in combination with TONI-2	Median IQ was lower in DCP than SCP **DCP** 29% IQ/DQ ≥85; 14% IQ/DQ 70 to 84; 21% IQ/DQ 50 to 69; 36% IQ/DQ <50 **SCP tetraplegia** 50% IQ/DQ ≥85; 14% IQ/DQ 70 to 84; 21% IQ/DQ 50 to 69; 14% IQ/DQ <50 **SCP hemiplegia** 61% IQ/DQ ≥85; 19% IQ/DQ 70 to 84; 13% IQ/DQ 50 to 69; 6% IQ/DQ <50 **SCP diplegia** 53% IQ/DQ ≥85; 18% IQ/DQ 70 to 84; 22% IQ/DQ 50 to 69; 7% IQ/DQ <50

Continuation

	n	Age range	Motor assessment/ Motor severity by CP type	CP type (n)	IQ assessment	Results
Himmelmann et al., 2006 [112]	70	4y-8y	GMFCS / DCP (GMFCS I n=2, II n=4, III n=5, IV n=15, V n=26) SCP (GMFCS IV n=2, V n=21)	DCP (50) SCP tetraplegia (20)	WPPSI-R, WISC-III, Griffith scales or estimated from clinical observation	**DCP** 40% IQ≥70; 18% IQ 50-70; 42% IQ<50 **SCP tetraplegia** 100% IQ<50
Strauss et al., 2005 [111]	446	-	Severe: tetraplegia with no functional hand use and inability to crawl, creep, scoot, or walk / All participants with severe motor dysfunction	DCP (20) SCP (426)	Measure not specified	**DCP** 20% IQ≥70; 40% IQ<50 (profound mental retardation)+ **SCP** 2% IQ≥70; 95% IQ<50 severe mental retardation (75% profound)

Continuation

	n	Age range	Motor assessment/ Motor severity by CP type	CP type (n)	IQ assessment	Results
Pueyo et al., 2003 [110]	19	16y-38y	- / All bilateral	DCP tetraplegia (2) DCP diplegia (2) DCP triplegia (2) SCP tetraplegia (5) SCP diplegia (6) SCP triplegia (2)	RCPM	No statistically significant differences between DCP and SCP

-, data not provided; + The term used is the same that authors use; CP: cerebral palsy; BSID, Bayley Scales of Infant Development; DCP: dyskinetic cerebral palsy; DQ: developmental quotient; GMFCS: Gross Motor Function Classification System; ICD10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; IQ: intelligence quotient; m, months, RCPM: Raven's coloured progressive matrices; SCP: spastic cerebral palsy; TONI-2: Test of Nonverbal Intelligence, 2nd Edition; WIPPSI: Wechsler Preschool and Primary Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; y, years.

1.7.1.1 General intellectual functioning and neuroimaging

General intellectual functioning is considered a reflection of the state of the brain and advances in MRI techniques have allowed extending this study to specific brain regions. In 2012, a review about diffusion MRI findings in CP concluded that networks associated with cognition had been scarcely studied and that the existing limited literature was conflicting [101]. One potential source of conflicting results was the heterogeneity within cohorts in existing studies.

As for studies reporting lesion patterns by intellectual level, Himmelmann et al. [82] found that IQ<50 was most common in children with brain maldevelopment together with cortical/subcortical lesions. Severity of the MRI lesion pattern also correlated significantly with cognitive development. Specifically, when neuroimaging findings where circumscribed to the ventro-lateral thalamus and the lentiform nucleus, cognitive development was normal or only mild delayed. When the pericentral region was further involved, both severe and mild cognitive delays were reported. Finally, when hippocampus and thalamus were involved together with the above mention areas, all participants presented severe cognitive delay [90]. Partly contrary to these results, a study in in spastic diplegia showed that the frequency of patients with severe motor dysfunction and intellectual disability was not different between those with normal and abnormal MRI findings [107].

The majority of the above mentioned findings agree with Riva et al. [115] who found that lesions of the thalamus and basal ganglia as well as features of lesions such as lesion type (PVL vs arterial ischemic stroke) and lesion severity were associated with the severity of cognitive impairment in spastic CP. This aligns with the fact that when global thalamus is involved cognitive delay is more severe [90] and with the fact that IQ<70 is frequently found among participants with cortico-subcortical involvement [82].

The above mentioned correlates between general cognitive function and brain structure are, however, often based in the pattern and extent of brain injury and

the frequency of intellectual disability [82, 90, 107, 115] rather than quantitative neuroimaging analyses. To date, studies that have tested the intelligence-brain relationship with quantitative neuroimaging analyses in this population are scarce. One of these works includes the one of Rai et al. [78], who found a significant positive correlation between IQ and FA of the corona radiata, anterior limb of internal capsule, posterior limb of internal capsule, midbrain, pons, medulla, genu and splenium of the corpus callosum, periventricular white matter, and occipital white matter in children with spastic diplegia. Additionally, significantly decreased FA values in temporal white matter and occipital white matter regions were observed in participants with low verbal IQ in comparison to those with a verbal IQ within the average range [78]. Most studies available, however, have focused on spastic CP [78, 115, 116]. Himmelmann et al. [82] included thirty participants with DCP but they do not report IQ and neuroimaging findings for participants with DCP independently.

1.7.2 Specific cognitive functioning

Visual-perceptual abilities are the most commonly impaired cognitive domain in CP. As reviewed by Ego et al. in 2015 [117] such impairments occur among 40% to 50% of children with CP, with a mean visual perception quotient ranging from 70 to 90. This review also notes that visual–perceptual abilities do not seem to be influenced by IQ level, side of motor impairment, neuro-ophthalmological outcomes or seizures. Although the influence of prematurity is controversial (lower gestational age is more often associated with lower visual motor skills than with decreased visual–perceptual abilities) deficits in visuo-perceptual skills have been very frequently identified in children with PVL [51, 118]. No study have reported any influence of CP subtype on visual–perceptual abilities but specific investigations into this relationship have so far only reported on no more than six participants with DCP [117]. Finally, the severity of neuroradiological lesions seem to be associated with visual–perceptual abilities [117]. Specifically, visuo-perceptual impairment has been reported to be related to PVL which has been interpreted as a reflection of malfunctioning of the occipitoparietal pathway, the

so-called "dorsal stream" [119]. Moreover, spatial memory span in both manual (table Corsi task) and locomotor space (magic carpet task) has been found to correlate with the extent of right hemispheric injury [120].

Receptive and expressive language impairments are also common (61%) in CP. Isolated impairments of this type are rare in CP; rather, generalized language deficits are often seen, which are associated with general cognitive abilities [121]. As for reading ability, children with CP with intellectual disabilities seem to have a disadvantage in acquiring phonological awareness, especially when their speech abilities are also impaired [122]. Phonological awareness is a key process involved in reading acquisition [123]. Although general cognitive functioning and speech ability are important facilitators of emergent phonological awareness in children with CP, other foundation measures have also shown to play a role [122]. As for DCP, a study of six participants found no impairment in receptive grammatical abilities when compared to population-based norms, but all participants exhibited poor vocabulary [124]. Another study reported that people with DCP performed better than SCP participants in language comprehension despite a comparable level of gross motor function (GMFCS IV and V) and expressive communication (non-speaking) [125].

Moreover, arithmetic development also shows signs of stagnating development in children with CP who do not show severe intellectual impairment [126]. Developmental of arithmetic performance seems to be, in turn, dependent of non-verbal intelligence and working memory in children with CP [127, 128].

Studies focused on long-term memory in CP are scarce but difficulties on short-term memory have been reported [129]. Working memory, however, has been by far better studied which will be broadly discussed in the next section. As for the neuroanatomical correlate of memory in CP, it was found that adults with hypoxic-ischaemic prenatal spastic diplegic CP present low levels of short-term memory [129]. Furthermore, memory span has been reported to correlate with FA in corona radiata, anterior limb of internal capsule, posterior limb of internal

capsule, midbrain, pons, medulla, corpus callosum (genu and splenium) and occipital white matter in children with spastic diplegic CP [78].

Finally, difficulties related to theory of mind and irony comprehension have been observed in children with CP [130] which has suggested to be related with executive function deficits [131]. These difficulties align with the prevalence of autism spectrum disorders in children with CP [63-67].

The vast majority of the above described studies are focused on unilateral CP, and their results may not be generalized to bilateral cases. This is, in part, because greater severity of motor impairments in DCP can cause difficulties when conducting neuropsychological assessments. Most neuropsychological tests can hardly be used with people with severe motor, cognitive and speech impairments so it is necessary to do adjustments in the testing procedure. This fact, together with the lower frequency of DCP, could explain why DCP has been barely studied so far. This has led to a lack of knowledge about DCP's distinctive features and, consequently, a lack of follow-up programs and interventions adapted to their needs [132].

Interestingly, a systematic review focused on cognition in childhood dystonia has been recently published [133]. Although this work not is not specifically focused on secondary dystonia due to CP, it indicates that people with DCP often have mild deficit in memory, impairments of visuospatial functions, information processing speed, and social cognition. This review stresses that available data is very limited and that there is a strong need for case-control studies assessing cognition and using standardized neuropsychological tests, with particular emphasis on attention and executive functioning skills among others. It is further encouraged to assess control groups consisting of patients with other movement disorders [133].

1.7.3 Executive function

1.7.3.1 General view

Executive function is a psychological construct composed of multiple interrelated high-level cognitive skills. Several definitions for executive function have been proposed due to the construct multiplicity but common themes are clearly present in all of them. Specifically, there is agreement in the fact that the key elements of executive function include [134]:

a) Anticipation and deployment of attention
b) Impulse control and self-regulation
c) Initiation of activity
d) Working memory
e) Mental flexibility and utilization feedback
f) Planning ability and organization
g) Selection of efficient problem-solving strategies

In the present thesis, the executive control system described by Anderson [134] has been used to drive tests selection and executive function components. This model is a conceptual framework derived from the developmental neuropsychology literature which makes it especially suitable in the study of CP taking into account that it can be considered a neurodevelopmental disorder. Noteworthily, this model has been largely influenced by factor analytic and developmental studies.

Anderson [134] conceptualizes executive function as a control system which comprises four distinct domains: attentional control, cognitive flexibility, goal setting and information processing. These domains are known to exhibit different developmental trajectories but must interact and have bidirectional relationships. Therefore, although they are treated as "independent", these functions work as an overall control system. Each domain includes highly integrated cognitive processes and receive stimuli from various sources including subcortical, motor and posterior brain regions.

Attentional control includes the capacity to selectively attend specific stimuli and the ability to focus attention for a prolonged period. Vitally, it also involves the regulation and monitoring of actions, including impulse control, such as the capacity to delay gratification.

Cognitive flexibility includes the ability to shift between response sets, learn from mistakes or devise alternative strategies, divide attention and process multiple sources of information currently. Working memory is an integral component of this domain.

Goal setting is the ability to plan, organize and think strategically. It includes the capacity to initiate or to start an activity and devise a plan to complete the activity. It also comprises the ability to planning to formulate a goal and devising the sequence of steps or actions that will achieve the goal.

Information processing is more general and involves fluency of responses as well as efficiency and speed of output. It is generally reflected in the time component of executive function measures or in the volume of output generated under a particular time constraint.

Additionally, as Anderson [134] reviews, executive function is characterized in emotional responses and behavioural actions, so it has been recently proposed that the processes that constitute executive function could be dichotomized as "cool" and "hot" executive processes [135]. While "cool" executive processes are considered purely cognitive and tapped during abstract, decontextualized problems, "hot" executive processes refer to affective aspects of executive functioning and are required when a situation is meaningful and involves the regulation of affect and motivation. Therefore, when studying executive function, it is also important to take "hot" executive function paradigms into account, as they have an affective, motivational or incentive/reward component, and are associated with behaviour problems [134].

Interestingly, several studies have reported an association between specific executive function domains and intelligence. The fact that some individuals with

significant executive deficits, however, score within normal ranges on tests of intelligence has been used to evidence that executive functioning is an independent entity different from general intelligence [136].

1.7.3.2 Impact of executive function

Executive function is of particular interest in CP because of its key role in the effective acquisition of new skills, knowledge, and the application of this knowledge in daily life [4]. Moreover, it is related with other cognitive abilities. For example, working memory has shown to be a precursor of the development of early numeracy [137] and working memory deficits increase the risk for arithmetic difficulties after controlling for general intellectual functioning [138]. Furthermore, working memory and inhibitory control, seem to be particularly relevant for figurative language and false-belief understanding [130]. Inhibition and updating impairments have been also reported to be related to false belief and faux pas [131].

Importantly, executive function appears to be linked to QOL. Quality of life is defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns" [139]. Health-related quality of life is a subset of QOL [140] focused on the health-related components of life satisfaction such as self-care, mobility and communication [141] and it is also an important outcome in CP [56] related conceptually with QOL. Associations between QOL and executive function have been described in the general population and in other neurological and psychiatric conditions [5–9]. In CP, however, only the influence of IQ on QOL has been studied, results differing between studies due to different choices of QOL questionnaires and IQ measures [55, 57, 59, 60, 142]. Although specific cognitive functions other than IQ, such as executive function, have been found to be impaired in CP, they have not been considered as possible determinants of QOL.

1.7.3.3 Executive function in cerebral palsy

The study of executive function in CP has grown in popularity during the last ten years. Available studies, however, greatly differ between measures used to assess executive function, CP type assessed, and inclusion criteria used.

If we focus on studies that directly assessed executive function in CP using tests, most reported executive function deficits and were primarily focused on attentional control and cognitive flexibility domains. Results from these studies are presented in Table 6, where they have been classified according to the executive function domains previously presented and proposed by Anderson [134]. It must be noted, however, that most of the tasks used to assess executive functioning involve different executive function domains. Here, for the sake of clarity, we have made an effort to classify the tasks accordingly to the main cognitive ability required. This classification is based in our criteria and, thus, other classifications are possible.

Regarding attentional control, selective attention and inhibition capacity are by far the most studied components. According to the majority of studies, both selective attention and inhibition seem to be impaired in CP in all or some tasks assessed [131, 138, 143–153]. Studies limiting inclusion criteria according to cognitive level, however, report within average performance in some [138, 146, 149, 152] or all tasks assessed [130, 154]. Additionally, two studies not limiting inclusion criteria according to cognitive level report attentional control performance within average. Specifically, Bodimeade et al. [150] reported no significantly different performance in two of six measures of attentional control, whilst Piovesana et al. [155] reported attentional control ability within average. Only Pirila et al. [151] specifically assessed sustained attention by the Conners Continuous Performance Test, finding that 88% of participants performed significantly below average.

Cognitive flexibility has mainly been studied in terms of working memory and divided attention. Other subcomponents of cognitive flexibility, such as learning from mistakes or devising alternative strategies, have been scarcely studied. Overall, studies report poor cognitive flexibility in people with CP in all or some

tasks assessed [130, 138, 144, 146, 148, 150, 152, 156, 157]. Preserved cognitive flexibility, however, has been reported to be within average under two conditions: (1) when only participants with a minimum general cognitive functioning are included [130, 138, 146, 152, 154] and (2) when participants have unilateral CP or are at less severe GMFCS levels (I-III) [150, 155, 158]. However, not acomplishin any of these conditions, White et al. [143] found that perseverative errors in the California Verbal Learning Test were not more common in CP than in controls.

Goal setting has been assessed in five studies. On one hand, Piovesana et al. [154] report that people with CP attending mainstream school have a normal goal setting ability according to normative data, and Di Lieto et al. [146] did not find significant differences between children with spastic diplegia (with a verbal IQ>80) and typically developing controls (TDC) in the clocks task of the NEPSY-II. On the other hand, the three other studies found that performance was significantly poorer than TDC [149, 150, 156].

Information processing has scarcely been studied in CP. This may be due to the inherent difficulty in assessing this component in participants with motor impairment. This is indicated by the fact that three of the four studies exploring information processing only include participants with unilateral CP and GMFCS I-II [150, 154, 155]. Of these three studies, only one reported difficulties in information processing [150]. The fourth study carried out by Di Lieto et al. [146], however, included participants with spastic diplegia with a GMFCS I-IV and MACS I-III and found difficulties in this executive function domain.

Only three studies have explored all executive function domains [146, 150, 154]. Taken together, studies using direct measures of executive function are mainly focused on unilateral CP populations in which more-severe CP types have been insufficiently represented. Only one of these studies included participants with DCP, enrolling four such cases [131]. As for differences of executive functioning between CP types, knowledge is scarce. Pueyo et al. [110] found that executive function was the only function in which people with DCP seem to perform worse

than people with SCP. However, the difference was not statistically significant, the sample was small, not all domains of executive function were assessed, and other variables that influence executive function such as gestational age and motor severity were uncontrolled. Although there may be different executive function capacities depending on the CP type and the measures used to assess executive function, firm conclusions cannot yet be drawn. Thus, a study comparing cognitive function performance between CP types and controlling these variables would likely be able to identify profiles of executive functioning by CP type.

Table 6. Studies exploring executive function in cerebral palsy by using direct assessment

Reference	n	Age Range	GMFCS (n)	CP type (n)	Executive function measure	TDC (n; matching or age information) or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Di Lieto et al., 2017 [146]	19	5y:1m-13y:5m	I (2), II (10), III (3), IV (4)	BSCP	NEPSY-II	TDC and ND	**AC + IP** Auditory Attention Inhibition naming-speed Inhibition naming-accuracy Inhibition inhibition-speed Visual Attention **CF** Inhibition switching-speed **IP** Design Fluency	**AC** Response Set **CF** Inhibition switching-accuracy **GS** Clocks	Verbal IQ >80 (WISC-III, WISC-IV, WPPSI-III)
Piovesana et al., 2017 [154]	51+ 50	8y-18y	I (20), II (31) + I (25), II (25)	UCP	D-KEFS, WISC-IV	ND		51 participants/50 participants (reported separately) **AC** Color-word interference inhibition condition **CF** Digit span backwards TMT **GS** Tower test **IP** Symbol search	Mainstream school attendance

Continuation

Reference	N	Age Range	GMFCS (n)	CP type (n)	Executive function measure	TDC (n; matching or age information) or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Scheck et al., 2015 [147]	52	5y-17y*	I (38), II (14)	UCP	Flanker task A	TDC (n=17; age 10.6 ± 0.5, 10 female)	**AC** Significantly longer time to get a correct answer with the incongruent condition		Mainstream school attendance
Belmonti et al., 2015 [148]	22	5y-14y	I (15), II (7)	USCP (14) BSCP (8)	Magnetic carpet and Corsi block	TDC (n=22; age and sex matched)	**AC + CF** CP children performed much worse than controls on the Corsi block while only a little worse on the Magnetic carpet		
Piovesana et al., 2015 [155]	44	8y-17y	I (22), II (22)	UCP	WISC-IV	ND		**AC + CF + IP** Digit span backwards Digit span forwards Digit span total Coding Symbol search	
Stadskleiv et al., 2014 [149]	29+	6y:7m-15y:11 m	I (1), III (2), IV (9), V (17)	-	BAC Construction and BAC Description without naming	TDC (type of neighbourhood age and sex matched)	**AC + GS** BAC construction (Items correctly solved, planning, objects, attributes and specificity of utterance) BAC description (Items correctly solved and impulsivity)	**AC** BAC construction (Monitoring)	Not considered intellectually impaired by teacher

Continuation

Reference	N	Age Range	GMFCS (n)	CP type (n)	Executive function measure	TDC (n; matching or age information) or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Li et al., 2014 [131]	42	7y-12y	-	USCP (18) BSCP (13) spastic-ataxic CP (2) spastic-dyskinetic CP (1) spastic-hypotonic CP (1) DCP (4) ataxic CP (3)	Inhibition day–night task Information updating Morris & Jones's Running Memory Paradigm Attention shifting Plus–minus task	TDC (n=42; matched by age, sex and school grade level)	**AC + CF** Inhibition Information updating Attention shifting		Verbal IQ of at least 70 as measured by verbal subtests of WISC

Continuation

Reference	N	Age Range	GMFCS (n)	CP type (n)	Executive function measure	TDC (n; matching or age information) or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Bodimeade et al., 2013 [150]	46	8y-16y*	I (35), II (11)	UCP	D-KEFS, WISC-IV, TEA-Ch	TDC (n=20; age and sex matched)	~**Poor executive function in the total aggregate** **AC** Code transmission total correct raw score Inhibition total time Inhibitionswitching total errors raw score Number sequencing total time **CF** Digit span backward Trail making test (number–letter switching total time) **GS** Letter fluency number of words Category fluency number correct Rey copy trial accuracy Rey organizational strategy Tower test (achievement) Tower test (rule violations) **IP** Symbol search Cancellation	**AC** Verbal fluency repetition errors raw score Inhibition total errors raw score **CF** Verbal fluency: total set-loss errors Inhibition/witching total time	

Continuation

Reference	N	Age Range	GMFCS (n)	CP type (n)	Executive function measure	TDC (n; matching or age information) or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Dourado et al., 2013 [156]	76	7y-12y*	I (48), II (8), III (11), IV (2), V (7)	SCP	Digit span Corsi block Rey complex figure	TDC (n=89; age range 7-12)	**CF + GS** Significantly poorer performance in all tasks		
Hakkarainen et al., 2013 [158]	11	9y-18y	I (7), II (3), III (1)	SCP	Stimulus recognition task	TDC (n=12; no age differences with CP group)		**CF** Intact error detection and performance adjustment after error making. This is, in both groups responses became faster after an error in both groups: the group effect	
Caillies et al., 2012 [130]	10	7y:6m–11y:6m	-	5 BSCP 4 USCP 1 ataxic CP	Working memory tasks of WISC-IV Inhibitory control Stroop Test adapted for children NEPSY	TDC (n=10; age, sex, school grade level, and verbal comprehension matched)	**CF** Letter–Number Sequencing task	**AC** Stroop Knock–Tap **CF** Digit Span	IQ>85

Continuation

Reference	N	Age Range	GMFCS (n)	CP type (n)	Executive function measure	TDC (n; matching or age information) or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Hakkarainen et al., 2012 [157]	13	9y-18y	I (7), II (2), III (4)	SCP	Stimulus recognition task originally developed by Sternberg	TDC (n=14; no age differences with CP group)	**CF** Mean reaction time Number of errors		
Pirila et al., 2011 [151]	17	8y-17y	I (12), II (1), III, (4)	SCP	Conners Continuous Performance Test	ND	**AC** *In brackets n of participants with executive function deficit (SD≥2/SD≥4)* Attention problem only (n=2/2) Attention problem + impulsivity (n=3/1) Attention problem + poor vigilance (n=2/2) Attention problem + poor vigilance + impulsivity (n=2/1)		
Pueyo et al., 2009 [124]	40	6y-38y	-	DCP (6) SCP (14) Mixed CP (18) Unknown (2)	Digit span WISC-IV, WAIS-III WCST	ND	**CF** *In brackets % of cases presenting an impairment* Verbal working memory (57.5%) Visual working memory (21.2%) Perseverative errors (57.9%)		

Continuation

Reference	N	Age Range	GMFCS (n)	CP type (n)	Executive function measure	TDC (n; matching or age information) or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Bottcher et al., 2009 [152]	33	9y:1m-1y:7m	I (22), II (3), III, (6) IV (2)	USCP (15) BSCP (18)	TEA-Ch CNT	ND	**AC** TEA-Ch (Sky Search C&G, score!, and sky dual task) CNT (Tials 1 and 2) **CF** CNT (Tiral 3)	**AC** TEA-Ch (Sky Search B) **CF** CNT (Trial 4)	Cognitive function within or above the normal range
Jenks et al., 2009 [138]	57	mean 7y	mean GMFCS: Special school 2.51 Mainstre em school 1.63Δ	USCP (22) BSCP (32) Ataxic CP (3)	Shifting and inhibition: Adapted from tasks van de Sluis, de Jong, and van der Leij (2004). Updating: Backward Digits (WMTB-C) Visuospatial sketchpad: Knox Blocks (Snijders-Oomen Non-Verbal Intelligence Test) Phonological loop Digit/Word Reca (WMTB-C)	TDC (n=16)	**AC** Shifting **CF** Updating Visuospatial sketchpad \ Phonological loop digits	**AC** Inhibition **CF** Phonological loop words	Verbal IQ (PPVT) ≥70

Continuation

Reference	N	Age Range	GMFCS (n)	CP type (n)	Executive function measure	TDC (n; matching or age information) or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Korkman et al., 2008 [153]	12	Mean 5.2y	-	BSCP	Statue and Auditory Attention and Response Set subtest, part A (NEPSY)	n=56; extremely low birth weight controls not differing on age, sex or social class	**AC** NEPSY subtests		
White et al., 2005 [143]	16	6y-18y	-	BSCP	California Verbal Learning Test–Children's Version	TDC (n=19; age and sex matched)	**AC** Intrusion errors	**CF** Perseverative errors	
Christ et al., 2003 [144]	13	6y-18y	-	BSCP	Stroop Task	TDC (n=20; no age differences)	**AC + CF + IP** Word, color and processing speed in incongruent condition		

Continuation

Reference	N	Age Range	GMFCS (n)	CP type (n)	Executive function measure	TDC (n; matching or age information) or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Kolk et al., 2000 [145]	37	4y-9y	-	USCP	Orientation, Inhibition and Control Sustained Concentration (NEPSY)	TDC (n=13; age and sex matched)	**AC** NEPSY (all subtests)		Cognitive function within average determined by clinical examination related to the age norms of the Developmental Scale Battery

This table has partly been extracted from my master thesis entitled "Executive functioning in cerebral palsy: systematic review" (Máster universitario en intervención psicológica en el desarrollo y la educación in UNED). Studies included are those available in PubMed and PsycInfo (last search 24th March, 2018) and accomplishing the following key terms: cerebral palsy [Title/Abstract]) AND executive function [Text Word]. In the present table, two additional studies not fulfilling the search strategy were included.

When impairment is based on standardised scores level, poor executive function column includes standardized scores 1.5 SD below the mean. AC, attentional control; CF, cognitive flexibility; BAC; Becoming an aided Communicator; BSCP, bilateral spastic cerebral palsy; CNT, Contingency Naming Test; D-KEFS, Delis-Kaplan Executive Function System; GMFCS, Gross motor function classifications system; GS, goal setting; IP; information processing; IQ, intelligence quotient; m, months; NEPSY, Neuropsychological Assessment, ND, normative data; SCP, spastic cerebral palsy; TDC, typically developing controls; TEA-Ch, Test of Everyday Attention for Children; TMT, Trail Making Test; UCP, unilateral cerebral palsy; USCP, unilateral spastic cerebral palsy; WCST, Wisconsin Card Sorting Test; WISC, Wechsler Intelligence Test for Children; WMTB-C Working Memory Test Battery for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence 3rd edition; y, years. *age range for inclusion criteria; +results reported refer to 29 children using aided communication (27 diagnosed of CP); -data not reported. ~ The classification of tasks by executive domain is based on the author's criteria. ▵ Only mean values of GMFCS are reported.

As for studies that assessed executive function by using proxy reported questionnaires, all but one used the Behaviour Rating Inventory of Executive Function (BRIEF; Table 7) and none included participants with DCP. Three of these studies reported that BRIEF scores were not clinically significant or only mildly high [154, 155, 159]. Muriel et al. [160] also reported that scores were not clinically significant or mildly high for the majority of domains assessed, but global executive composite, metacognition index and two specific scales were potentially clinically significant when the questionnaire was completed by teachers. Finally, the remaining three studies found executive function difficulties in all [161, 162] and almost all [152] domains assessed.

Table 7. Studies exploring executive function in cerebral palsy by using proxy reported questionnaires

Reference	n	Age Range	GMFCS (n)	CP type (n)	Questionnaire	TDC or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Piovesana et al.,, 2017 [154]	101 (51+50)	8y-18y	I (20), II (31) + I (25), II (25)	UCP	BRIEF Parents	ND		**GEC** **BRI** **MI**	Mainstream school attendance
Forsman at al., 2016 [161]	46	6y-15y	-	-	Five to Fifteen parent and teacher questionnaire	ND	Clinically relevant problems (percentile of the norm group) n=10 (90–95th); n=2 (95th)		
Garcia-Molina at al., 2015 [160]	46	7y-15y	I (16), II (3), III (11), IV (10), V (4), missing (2)	Spastic hemiplegia (8), spastic diplegia (17), spastic tetraplegia (21)	BRIEF Parents/teacher	ND	GEC Teacher MI Teacher Initiate teacher Working memory teacher	**GEC** **BRI** **MI** Inhibit Emotional Control Shift Initiate Working Memory Plan/Organize Org. of Materials Monitor	
Piovesana, et al., 2015 [155]	44	8y-17y	I (22), II (22)	UCP	BRIEF parents	ND		**GEC** **BRI** **MI** Inhibit Emotional Control Shift Initiate Working memory Plan/Organize Org. of Materials Monitor	

Continuation

Reference	N	Age Range	GMFCS (n)	CP type (n)	Questionnaire	TDC or ND	Poor executive function	Within average executive function	IQ inclusion criteria
Sørensen et al., 2014 [159]	14	2y:2m-4y:9m	I-III	USCP (7) BSCP (7)	BRIEF-P Mother/father /teacher	ND		**GEC** Inhibitory self-control Flexibility Index Emergent Metacognition Index	
Whittingham et al., 2014 [162]	46	8y-16y*	I (35), II (11)	UCP	BRIEF Parents/teacher	TDC	**BRI** **MI**		
Bottcher et al., 2009 [152]	33	9y:1m-1y:7m	I (22), II (3), III (6), IV (2)	USCP (15) BSCP (18)	BRIEF Teacher	ND+	**GEC** **BRI** **MI** Inhibit Shift Emotional control Initiate Working memory Plan/organise Monitor	Org. of Materials	Cognitive function within or above the normal range

Within average column includes BRIEF scoring 0-59 (not clinically significant) and 60-64 (mildly high). Poor executive function column includes BRIEF scoring 65-69 (potentially clinically significant) and ≥70 (clinically significant). BRI, Behavioural Regulation Index; BRIEF, Behavior Rating Inventory of Executive Function: CP, cerebral palsy; BSCP, bilateral spastic cerebral palsy; GMFCS, Gross Motor Function Classifications System; GEC, Global Executive Composite; IQ, intelligence quotient; m, months; MI, Metacognition Index; ND, normative data; Org, organization; SCP, spastic cerebral palsy; TDC, typically developing controls; UCP, unilateral cerebral palsy; USCP, unilateral spastic cerebral palsy; y, years. *age range for inclusion criteria.

1.7.3.4 Executive function and neuroimaging

Executive function depends on the integrity of the entire brain, but it is mainly mediated by the frontal lobes and its connections with posterior and subcortical brain regions [134]. In fact, dysexecutive behaviour has been associated with frontal lobe lesions for more than a century. Such lesions are widely accepted to impair different domains of executive function depending on the cortical area in which they reside. Furthermore, because the cortex of the frontal lobe is exceptionally well connected with other brain structures [163], it should not be surprising that dysexecutive behaviour has been reported in patients with lesions outside the frontal lobe. The lesions of the basal ganglia and the thalamus, for example, have been linked to such deficits [13, 14], highlighting the role of the frontal-subcortical loop between these structures. Among the series of parallel segregated frontal-subcortical circuits, some circuits in the basal ganglia originate in the prefrontal and limbic regions of the cortex and are known to be involved in executive function [164]. Specifically, there are three behaviourally relevant circuits with origins in the prefrontal cortex: the dorsolateral (linked to cognitive processes), the medial (known to be involved in motivational mechanisms) and the orbitofrontal circuit (partly involved in inhibition and control of impulsivity in social behaviour) [165]. Distinct and identical dysexecutive behaviour has been reported in patients who had lesions in different frontal-subcortical loops which does not support a clear functional segregation of these circuits in humans [133].

A review published in 2013 concluded that there was a paucity of brain imaging studies focused on executive function in CP with no studies including participants with DCP [15]. Briefly, the fiew available studies report that parieto-occipital periventricular haemorrhagic infarction, intraventricular haemorrhage of grade IV, ventricular dilatation or white matter reduction were found to be related to poorer performance on specific executive function domains. Bilateral lesions, indeed, were associated with poorer executive function performance compared to unilateral lesions. It was further shown that children with right sided lesions experienced more severe executive function problems than

children with left sided lesions. Overall, the review concludes that different types of brain abnormalities influence executive function performance but that no specific brain areas were associated with executive function performance across included studies [15]. Moreover, a posterior study exploring DTI correlates of cognition in children with spastic diplegic CP found that attention and working memory were related with white matter integrity in the anterior limb of internal capsule, midbrain, medulla, genu of the corpus callosum, posterior white matter, occipital white matter, corona radiata and pons [78]. Later on, Scheck et al. [147] found that connectivity to the anterior cingulate cortex was altered due to periventricular white matter lesions. This connectivity was associated with impaired executive function in children with unilateral CP. Finally, in 2017, Di Lieto et al. [146] explored the association between executive function and lesion characteristics as measured with the reliable sqMRI scale [103, 104]. These authors found a significant negative correlation between the corpus callosum score and executive functioning and poorer performance in children with involvement of anterior portions of the corpus callosum than in those without such involvement.

Despite basal ganglia and thalamus lesions being frequently described in people with DCP [11, 12], no study to date has focused on exploring the association executive function and brain structure in this CP subtype. Dyskinetic CP might be characterized by a poorer executive functioning than SCP but this hypothesis has still to be tested. This hypothesis is consistent with the lesions of the basal ganglia and thalamic systems which are frequently described in people with DCP [12]. Finally, when aiming to specifically identify the association between spasticity/dyskinesia and cognition alone, influential variables other than CP type such as motor severity and prematurity should be taken into account, because they may prompt additional cognitive impairments [166].

Considering the studies above described, there are critical gaps in the literature that are necessary to be studied to increase our understanding of executive function in CP and, specifically, in DCP. Studies tend to focus only on specific executive function subdomains such as attention or working memory and there

is a paucity of studies broadly assessing executive function. Furthermore, research is mainly focused on studying participants with mild CP, being participants with severe levels of GMFCS scarcely studied. Importantly, there is no work specifically studying executive function in DCP.

2 Aims

The overall aim of the thesis was to characterize executive functioning and general intellectual functioning and its biological bases in DCP, as measured by diffusion and structural MRI. To that end, the following specific goals were formulated:

I) To analyse the impact of executive function on QOL in people with DCP taking into account other variables that have been demonstrated to affect QOL in CP and other populations (Study 1).

Hypothesis: executive function is expected to predict QOL given its role on the successful completion of everyday, novel, goal-directed and complex activities and the associations found in the general population and in other neurological and psychiatric conditions [5–9].

II) To map executive and general intellectual functioning in people with DCP by comparing their performance with: 1) TDC matched for age and sex, and 2) participants with SCP matched for age, sex, gestational age and motor severity (Study 2).

Hypothesis: Given the basal ganglia and thalamus lesions frequently described in people with DCP [25, 53], we expect executive function to be impaired in this CP subtype in comparison to TDC and to be poorer than people with SCP. Considering previous research, we further expect people with DCP not to present poorer general intellectual functioning than people with SCP comparable in terms of motor severity and gestational age [106, 109-112] (see Table 5).

III) To identify brain structure alterations in participants with DCP in terms of both a) white matter microstructure and b) observable brain lesion severity as measured by a semi-quantitative lesion scoring system (Study 3 and Study 4).

Hypothesis: We expect to find alterations in deep grey matter microstructure [26, 27, 38, 85] (Table 3). We are further expected to confirm the presence of severe widespread alterations in white matter microstructure [94–96, 100] (Table 4).

IV) To investigate the neural correlate of executive and general intellectual functioning in participants with DCP in terms of both a) white matter microstructure and b) observable brain lesion severity as measured by a semi-quantitative lesion scoring system (Study 3 and Study 4).

Hypothesis: Taking into account that DCP is characterized by basal ganglia and thalamus injury and the crucial role of fronto-striatal circuitry on executive functioning for typically developing people [13, 14], we expect executive function to be related with white matter microstructure in regions known to contain fronto-striatal pathways and to observable lesions in the basal ganglia and thalamus. As for general intellectual functioning, we expect it to be associated with white matter integrity in all cerebral lobes [169, 170, 78] as well as pericentral white matter lesions [90] and cortical and subcortical [82, 90, 171–173] observable lesions.

3 Results

3.1 Study 1

Reference

Laporta-Hoyos, O., Ballester-Plané, J., Póo, P., Macaya, A., Meléndez-Plumed, M., Vázquez, E., Delgado, I., Zubiaurre-Elorza, L., Botellero, V.L., Narberhaus, A., Toro-Tamargo, E., Segarra, D., Pueyo, R. (2017). Proxy-reported quality of life in adolescents and adults with dyskinetic cerebral palsy is associated with executive functions and cortical thickness. *Quality of Life Research, 26*, 1209-1222.

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Proxy-reported quality of life in adolescents and adults with dyskinetic cerebral palsy is associated with executive functions and cortical thickness

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Abstract

Purpose Quality of life (QOL) is a key outcome for people with cerebral palsy (CP), and executive functioning is an important predictor of QOL in other health-related conditions. Little is known about this association in CP or about its neural substrate. We aim to analyze the influence of executive functioning (including cognitive flexibility) as well as that of other psychological, motor, communication and socioeconomic variables on QOL and to identify neuroanatomical areas related to QOL in adolescents and adults with CP.

Methods Fifty subjects diagnosed with dyskinetic CP (mean age 25.96 years) were recruited. Their caregivers completed the primary caregiver proxy report version of the CP QOL-Teen questionnaire. Motor status, communication, IQ, four executive function domains, anxiety/depression and socioeconomic status were evaluated. Correlations and multiple linear regression models were used to relate CP QOL domains and total score to these variables. Thirty-six participants underwent an MRI assessment. Correlations were examined between cortical thickness and CP QOL total score and between cortical thickness and variables that might predict the CP QOL total score.

Results Executive functions predict scores in four domains of CP QOL (General well-being and participation, Communication and physical health, Family health and Feelings about functioning) in the regression model. Among the cognitive domains that comprise executive function, only cognitive flexibility measured in terms of performance on the Wisconsin card sorting test (WCST) predicts the CP QOL total score. Monthly income, fine motor functioning and communication ability predict scores on the domains Access to services and Family Health, Feelings about functioning and School well-being, respectively. The clusters resulting from the correlation between cortical thickness and both CP QOL total score and WCST performance overlapped in the posterior cingulate and precuneus cortices.

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Conclusions Cognitive flexibility predicts proxy report CP QOL-Teen total score in dyskinetic CP. This relationship has its anatomical correlate in the posterior cingulate and precuneus cortices.

Keywords Cerebral palsy · Cortical thickness · Executive functions · Magnetic resonance imaging · Quality of life

Abbreviations

ABCL	Adult behavior checklist
ASEBA	Achenbach system of empirically based assessment
ASR	Adult self-report
BART-Y	Balloon analogue risk task-youth
BFMF	Bimanual fine motor function
CBCL	Child behavior checklist
CFCS	Communication function classification system
CP QOL	Cerebral palsy quality of life questionnaire
CP	Cerebral palsy
GMFCS	Gross motor function classification system
HRQOL	Health-related quality of life
IQ	Intelligence quotient
MACS	Manual ability classification system
MRI	Magnetic resonance imaging
PPVT-III	Peabody picture vocabulary test-3rd
QOL	Quality of life
RCPM	Raven's colored progressive matrices
SOC	Stockings of Cambridge
WAIS	Wechsler adult intelligence scale
WCST	Wisconsin card sorting test
WISC	Wechsler intelligence scale for children

Introduction

Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain [1]. Motor disorders in CP are often accompanied by other deficits such as disturbances of communication, of cognition [2] and psychological problems [3] that might have an impact on quality of life (QOL). One type of CP is dyskinetic CP, which tends to present an injury pattern mainly affecting the basal ganglia and thalamus [4, 5], structures that have been related to executive functions [6].

Because CP is a permanent disorder, current treatment programs are aimed at improving QOL defined as "an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns" [7]. Health-related quality of life (HRQOL) that is a subset of QOL [8] focused on the health-related components of life satisfaction such as self-care, mobility and communication [9] is also an important outcome in CP [11] related conceptually with QOL. However, measuring the whole QOL is better if we want to assess perceived holistic well-being. The Cerebral palsy quality of life questionnaire (CP QOL) fits the World Health Organization's definition of QOL and embraces well-being and how an individual feels, rather than simply what they can do [10]. The CP QOL is an appropriate condition-specific instrument that is more sensitive than generic instruments and assesses QOL as it covers the issues that people face across their whole life, not just health.

Given the relevance of QOL in this population [11], it is essential to identify which aspects are determinant of QOL in CP. To date, most studies have focused on motor functioning and have found no clear and consistent associations with global QOL, indicating that the relationship between gross motor functioning and the psychosocial domains of QOL tends to be weak or not significant [12–18]. However, this association has rarely been studied in people over 18 years old. Interestingly, recent studies have shown that there is increased deterioration in mobility and health-related quality of life (HRQOL) in adults with CP [19, 20]. Thus, it is important to clarify how motor problems affect QOL in adults with CP.

Other comorbidities which affect QOL in this population such as communication abilities [15, 21–23], cognition [15, 21, 22], psychological problems [22, 38] and socioeconomic status [12, 21, 25] have been also reported. Regarding communication abilities, some studies have found that the better they are, the higher is the HRQOL of different physical [21, 26] and also psychosocial [15, 21, 22] domains in children and adolescents with CP. However, research has yet to analyze the relationship between QOL and a classification system such as the Communication function classification system (CFCS).

Among cognitive functions, only the influence of intelligence quotient (IQ) on QOL has been studied [21–23, 27, 28] and the results differ depending on which QOL questionnaire and IQ measures are used. Although cognitive functions other than IQ have been found to be impaired in CP [29], these cognitive functions such as verbal, visual–spatial and perceptual skills, memory and executive functioning have so far not been considered as possible determinants of QOL. Executive functions, however, might have clear repercussions for daily functioning because such functions are necessary for the successful completion of everyday, novel, goal-directed and complex activities [30]. Associations between QOL and executive functions have been described in the general population and in other neurological and psychiatric conditions

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[31–36]. Thus, it is important to take these functions into account when studying QOL in CP. Executive function is a collection of interrelated functions which are responsible for goal-directed or future-oriented behavior, and has been referred to as the conductor which controls, organizes and directs cognitive activity, emotional responses and behavior [37].

Thus, executive function is not exclusive to cognitive (cool) processes, but is also characterized in emotional responses and behavioral actions (hot processes) [38]. Cool executive processes are considered purely cognitive and tapped during abstract, decontextualized problems. In contrast, hot executive processes refer to affective aspects of executive functioning and are required when a situation is meaningful and involves the regulation of affect and motivation [39]. Therefore, when studying executive functions it is also important to take hot executive functions paradigms into account such as decision-making under conditions of risk, as they have an affective, motivational or incentive/reward component [40], and are associated with behavior problems [41, 42] which might affect QOL. Dyskinetic CP is the most suitable CP type for studying this association because it may be characterized by a dysfunction in executive functions [43].

Regarding other variables that have been associated with QOL in CP, previous studies report associations between several domains of QOL and general prosocial behavior and psychopathology in adolescents [22] and depression, dysphoria, anxiety, inefficacy and insufficient control in adults [24] with CP. In addition, environmental factors such as socioeconomic status have been reported to be related to some physical and psychosocial domains of QOL in children with CP [12, 21, 25].

The neural substrate underlying QOL has only been examined in psychiatric disorders [36–38], and none of the corresponding reports has considered cortical thickness. A study that focuses on cortical measures might therefore strengthen the scientific and conceptual basis of QOL. More specifically, a study of this kind focused on CP would increase our knowledge about QOL in this disorder. Although QOL has been related to some clinical outcomes in CP, research has yet to examine the neural substrate underlying QOL in CP. Dyskinetic CP is a specially suitable context for a study of this kind, since it is characterized by a homogeneous brain injury pattern among affected individuals. In sum, studying the nature of the interrelationship between QOL, symptoms and brain structure in CP is necessary in order to enhance our understanding of QOL and its biological basis in CP.

The aims of this study are (1) to analyze the impact of different variables (gross and fine motor status, communication, IQ, executive functions, anxiety and depressive symptoms and socioeconomic status) on QOL in adolescents and adults with CP and (2) to identify neuroanatomical areas related to the CP QOL total score in adolescents and adults with CP.

Methods

Participants

The inclusion criteria were (1) clinical diagnosis of CP with predominant dyskinetic features, (2) age 12 years or over and (3) for the neuropsychological assessment, being able to understand instructions, as evaluated by the Spanish Grammar Screening Test (receptive part) [44]. Exclusion criteria were (1) presence of severe visual or auditory disability that precludes neuropsychological assessment and (2) lack of an intelligible yes/no response system.

Participants were mainly recruited from the Hospital Vall d'Hebron and the Hospital Sant Joan de Déu in Barcelona, Spain. The total sample comprised 50 subjects. Perinatal information was obtained from medical reports and complemented with information provided by participants and/or their relatives. According to this information, the main perinatal antecedents were: signs of perinatal asphyxia in 35 cases, signs of vascular events in five cases, congenital brain malformations in two cases and signs of infection in two cases. In six subjects, the perinatal antecedents were unknown. In order to undertake the cortical thickness analysis, all participants were asked to undergo a brain magnetic resonance imaging (MRI). Two refused to participate in this procedure, two could not be scanned because they had metal devices implanted, five did not complete scans due to anxiety and three presented movement artifacts. A further two subjects were not included in the MRI analysis because they did not complete the executive functions assessment. Thus, a total of 36 participants are included in the neuroimaging analysis. Demographic and clinical data of both the total and the neuroimaging sample are summarized in Table 1.

Measures

QOL

QOL was evaluated using the parent-proxy version of the CP QOL-Teen [45], an instrument comprising the following seven domains: General well-being and participation, Communication and physical health, School well-being, Social well-being, Access to services, Family health and Feelings about functioning. Scores were calculated transforming items into a scale with a possible range of 0–100 and then computing the algebraic mean for the items included in each domain. Total score was also calculated.

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Cronbach's alphas for the scales range from 0.81 to 0.96 indicating an acceptable internal consistency. Test–retest reliability ranges from 0.29 to 0.83, and there are moderate correlations with other generic- and condition-specific measures of QOL indicating adequate construct validity. Moreover, this questionnaire conforms to the consensus that QOL domains should be based on qualitative research [45]. The proxy version was used because some participants, despite having a basic understanding of grammar, were unable to complete the self-report version due to difficulties in complex verbal comprehension and abstract reasoning. Given that there is not an adult version of this questionnaire, the teen version was also used to assess QOL in adult participants.

Fourteen of the 84 questions on the CP QOL-Teen are not relevant to adult life, and so they were adapted to typical habits of adults. Most of these questions form part of the School well-being domain and were adapted by asking adult respondents to think about the institutions they currently attended (occupational therapy center, care facility or place of work, as applicable).

Motor status

Severity of gross motor function was determined based on the Gross motor function classification system (GMFCS) [46]. Distinctions between levels are based on functional abilities, the need for assistive technology, including hand-held mobility devices or wheeled mobility, and to a much lesser extent, quality of movement. The fine motor function was assessed using the Manual ability classification system (MACS) [47] and the Bimanual fine motor function (BFMF) [48]. In all three cases, higher scores indicate lower levels of motor functioning and the range is from I to V.

Communication

The CFCS ranged from I to V describes everyday communication performance and was used to categorize communication [49]. Higher scores indicate lower levels of communication ability in terms of effectiveness and velocity of the communication. This scale categorizes communication according to the activity/participation level of the World Health Organization's International Classification of Functioning, Disability and Health [49].

Cognitive assessment

Verbal IQ was assessed using the Peabody Picture Vocabulary Test-3rd (PPVT-III) [50]. Nonverbal IQ was computed by means of Raven's colored progressive matrices (RCPM) [51]. The raw scores were converted into IQ scores in order to correct for age. These tests are widely used and recommended for people with physical disabilities because neither verbalization nor skilled manipulative ability is required [52].

Three main subdomains comprising executive functions [39] were assessed. Attentional control was assessed using the forward digit span from either the Wechsler intelligence scale for children (WISC) or the Wechsler adult intelligence scale (WAIS) [53, 54]; goal setting was evaluated by means of the Stockings of Cambridge (SOC) test form the Cambridge neuropsychological test automated battery [55]; and cognitive flexibility was assessed using the 64-item computerized version of the Wisconsin card sorting test (WCST) [56]. In order to assess risk taking, participants also completed the youth version of the Balloon analogue risk task (BART-Y) [57], on which higher scores indicate higher risk-taking propensity. All raw scores were converted into age-corrected z scores. The neuropsychological battery used is well suited to people with CP because most of the tests are computerized and allow for assistive technology.

Anxiety and depressive symptoms

Achenbach system of empirically based assessment (ASEBA) was used to assess anxiety and depression. Specifically, the anxious/depressed scale of the Child behavior checklist (CBCL) was used in children, the Adult self-report (ASR) in adults who could self-report and the

Table 1 Demographic and clinical data in a sample of adolescents and adults with dyskinetic CP; data correspond to the general sample and the neuroimaging sample

	General sample ($N = 50$)	Neuroimaging sample ($N = 36$)
Age in years mean (SD)/range	25.96 (12.41)/12–62	27.81 (13.42)/12–62
Gender (male/female)	27/23	20/16
Preterm/term	9/41	6/30
Motor distribution	Tetraplegia (42), hemiplegia (7), monoplegia (1)	Tetraplegia (30), hemiplegia (5), monoplegia (1)

SD standard deviation

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Adult behavior checklist (ABCL) in those adults that were not able to self-report (in this case a familiar or caregiver answered the questionnaire). All raw scores were converted into age- and gender-corrected T scores.

Socioeconomic status

Participants or caregivers indicated their monthly family income from among six categories, ranging from less than €300 (level I) to more than €2700 (level VI).

Magnetic resonance imaging acquisition

36 participants underwent an MRI assessment (Siemens MAGNETOM Trio 3T scanner). T1-weighted images were acquired in the sagittal plane with a MPRAGE sequence (TR/TE 1900/2.46 ms; TI 900 ms; flip angle 9°; 320 × 307 matrix and voxel size 0.7 mm × 0.7 mm × 1 mm). FreeSurfer v5.1.0 (http://surfer.nmr.mgh.harvard.edu) was used to process the MRI data. In this procedure, a cortical surface 3D model of cortical thickness is created using intensity and continuity information [58]. The initial processing of T1 high-resolution images includes several steps, which are performed independently for each subject and each time point: removal of nonbrain tissue [59], automated Talairach transformation, intensity normalization [60], tessellation of the gray matter/white matter boundary, automated topology correction [61, 62] and surface deformation to optimally place the gray/white matter and gray matter/cerebrospinal fluid boundaries [58]. The result in representation of cortical thickness is calculated as the distance between tissue boundaries [58]. Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a Full width at half maximum of 15 mm.

Statistical analyses

Pearson, Spearman or Kendall bivariate correlations between CP QOL domains/total score and the variables that might be associated with it were calculated. Variables that showed significant correlations were then entered into multiple linear regression models (stepwise method) to identify the best predictive models of CP QOL. Statistical analyses were performed using IBM SPSS Statistics version 22. The results were interpreted using the resulting r for correlation and R^2 for regression as measures of effects size. Cohen's interpretative criteria were applied [63, 64] considering r/R^2 effects as small $r \geq .10$; $R^2 \geq .01$, medium $r \geq .30$; $R^2 \geq .09$ and large $r \geq .50$; $R^2 \geq .25$. Two-tailed statistics have been used.

MRI images were used to calculate the correlation between cortical thickness and both the CP QOL total score and variables that might predict the CP QOL total score (FreeSurfer software). A vertex-by-vertex one-factor general linear model was used, with age being included as a nuisance factor. Resulting locations were labeled according to the Desikan atlas [65]. Neuroimaging results are thresholded at a minimum corrected $p \leq .05$.

Results

Demographic information

There are no significant differences in the mean age between the total and neuroimaging sample, and age range of both samples is 12–62 years. There are more males than females, and the majority of subjects were born at term and presented tetraplegia (Table 1).

Table 2 shows descriptive statistics for the CP QOL and potential predictors of QOL. The sample is notably diverse with motor and communicative impairment ranging from moderate to severe, and cognitive performance from impaired to above average. Some data from nine participants in the table are missing because one participant dropped out, another did not satisfy the inclusion criteria for neuropsychological assessment, seven were unable to complete the whole neuropsychological battery and two did not want to provide this personal information. Specific reasons why seven participants were unable to complete the whole battery are: severe speech and motor impairments, complex verbal comprehension difficulties and the simplicity of the augmentative and alternative communication system used.

Correlation analysis

Table 3 shows that the total CP QOL score was positively and moderately correlated with a subdomain of executive functions, namely cognitive flexibility. Regarding CP QOL domains, measures of motor functioning correlated negatively with the two scales related to perceived physical well-being. Specifically, there is a small correlation between the MACS and Communication and physical health and a medium to almost large correlation between the three motor scales used (GMFCS, MACS and BFMF) and Feelings about functioning. Gross motor status also correlated positively with School well-being (small effect size). The CFCS was only weakly associated with School well-being and Feelings about functioning. Regarding cognitive functions, both verbal and nonverbal IQ were positively associated with a medium effect size to three domains (General well-being and participation and Communication and physical health), and only verbal IQ with a medium effect size with Feelings about functioning.

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Table 2 Descriptive statistics for CP QOL domains, motor status, communication level, IQ, executive functions, anxiety and depressive symptoms and socioeconomic status in the total sample of adolescents and adults with dyskinetic CP

	N	Mean (SD)	Range
CP QOL domains			
General well-being and participation	50	69.95 (11.93)	41.67–94.64
Communication and physical health		71.79 (10.87)	42.97–91.41
School well-being		74.59 (14.46)	29.69–100
Social well-being		83.98 (11.33)	42.86–98.21
Access to services		55.88 (17.79)	22.22–94.44
Family health		60.02 (19.47)	3.13–90.63
Feelings about functioning		48.96 (22.60)	5–92.50
CP QOL total score		68.53 (8.20)	49.46–89.64

	N	Level (*n*)	Range
Motor status			
Gross motor functioning	50		
GMFCS		I (14), II (7), III (4), IV (11), V (14)	I–V
Fine motor functioning			
MACS		I (5), II (9), III (14), IV (10), V (12)	I–V
BFMF		I (6), II (11), III (14), IV (13), V (6)	I–V
Communication			
CFCS	50	I (18), II (20), III (6), IV (5), V (1)	I–V

	N	Mean (SD)	Range
IQ			
Verbal			
PPVT-III (IQ)	49[a]	71.53 (18.59)	55–119
Nonverbal			
RCPM (IQ)	49[a]	87.04 (26.31)	26–129
Executive functions			
Attentional control			
WISC/WAIS digit span (*z*)	42[a,b,c]	−0.94 (0.92)	−2.75 to 0.77
Goal setting			
SOC total scores (*z*)	43[a,b,c]	−0.25 (1.39)	−4 to 1.91
Cognitive flexibility			
WCST completed categories (*z*)	46[a,c]	−1.48 (0.62)	−2.67 to −0.98
WCST perseverative responses (*T*)	46[a,c]	45.74 (10.48)	26–80
Risk taking			
BART-Y pumps adjusted average (*z*)	46[a,c]	−0.22 (0.95)	−2.03 to 1.70
Anxious and depressive symptoms			
ASEBA (CBCL, ASR or ABCL as applicable) (*T*)	49[d]	57.58 (6.74)	48.52–75.95
Socioeconomic status			
Monthly income	49[d]	I (0), II (6), III (11), IV (10), V (11), VI (11)	II–VI

ABCL adult behavior checklist, *ASEBA* Achenbach system of empirically based assessment, *ASR* adult self-report, *BART-Y* balloon analogue risk task-youth, *BFMF* bimanual fine motor function, *CBCL* child behavior checklist, *CFCS* communication function classification system, *CP QOL* cerebral palsy quality of life questionnaire, *GMFCS* gross motor function classification system, *IQ* intelligence quotient, *MACS* manual ability classification system, *PPVT-III* peabody picture vocabulary test-3rd, *RCPM* Raven's colored progressive matrices, *SD* standard deviation, *SOC* Stockings of Cambridge, *WAIS* Wechsler adult intelligence scale, *WCST* Wisconsin card sorting test, *WISC* Wechsler intelligence scale for children

Reasons for missing data: [a] do not satisfy the inclusion criteria for neuropsychological assessment, [b] drop out the study, [c] being not able to complete the test, [d] do not want to provide this personal information

Executive functions were the cognitive area associated with the highest number of CP QOL domains. Specifically, it correlated positively and at least moderately with General well-being and participation, Communication and physical health, Family health and Feelings about functioning. It is important to note that the strongest association was found between completed categories of the WCST and the domain Feelings about functioning (large effect size). Anxiety and depressive symptoms were not associated with CP QOL scores in our sample. Finally, monthly income was moderately correlated with the domains Access to services (negatively) and Family health (positively). Social well-being did not correlate with any variable included in the analysis.

Regression analysis

Variables that correlated with different domains and the CP QOL total score were then introduced as predictor variables into a multiple linear regression model in order to clarify which combination of variables best predicts CP QOL.

The six fitted multiple regression models identified variables that predict CP QOL (Table 4). The model with the best predictive power for the CP QOL total score comprised cognitive flexibility, as measured by perseverative responses on the WCST. Specifically, cognitive flexibility accounted for 17.9 % of the variance (medium effect size) in the CP QOL total score. In addition, the standardized beta values indicate that the CP QOL total score will change .423 standard deviations as a result of one standard deviation in T scores for perseverative responses on the WCST.

Executive function scores contribute to the prediction of CP QOL scores on all, but two of the domains included in the regression analysis. Specifically, executive function scores alone comprised the best explanatory model for the domains General well-being and participation and Communication and physical health, with a medium effect size. Concerning motor status, the GMFCS and BFMF do not to predict any CP QOL domain, although fine motor status, measured by means of the MACS, did contribute to predicting the variance in the domain Feelings about functioning. More specifically, the MACS, together with cognitive flexibility, accounted for 52.3 % of the variance in Feelings about functioning. Communication ability does predict School well-being (with an almost medium effect size). Monthly income alone predicted the variance in Access to services (medium effect size), and together with cognitive flexibility, it accounted (moderate effect size) for the variance in Family health. IQ did not feature in any predictive model of CP QOL.

Cortical thickness

The positive correlation between CP QOL total score and cortical thickness showed two significant clusters in the left hemisphere. One with a peak in the posterior cingulated extended to superior frontal gyrus, paracentral, precuneus, cuneus, isthmus and pericalcarine cortices. The other has the peak in the pars opercularis cortex extended to precentral, pars triangularis, rostral and caudal middle frontal cortices. In the right hemisphere, another cluster was found with a peak in the precuneus cortex extended to cuneus cortex, pericalcarine cortex, lingual gyrus, isthmus and posterior cingulate cortices (Table 5; Fig. 1a).

We also performed a correlation analysis between cortical thickness and the predictor variable of CP QOL total score (i.e. perseverative responses on the WCST). This correlation showed a significant cluster (Fig. 1b) in the right hemisphere, with a peak in the posterior cingulate cortex that was extended to caudal anterior cingulate, isthmus and precuneus cortices.

Figure 1c shows the overlap of the resulting clusters (from the correlations of cortical thickness with both CP QOL total score and cognitive flexibility) in the posterior cingulate and precuneus cortices.

Discussion

To our knowledge, this is the first study to investigate a group of possible predictors of QOL (including motor status, communication, IQ, executive functions, anxiety/depression and socioeconomic status) in adolescents and adults with dyskinetic CP using a condition-specific questionnaire that conforms to the World Health Organization's definition of QOL. We also explored the association between QOL and brain structure in people with CP. The main finding of our study is that cognitive flexibility is a key outcome because it contributes to predicting the QOL of people with CP. Furthermore, this association has its anatomical correlate in the posterior cingulate and precuneus cortices of the right hemisphere.

Our results showed not only that executive functioning predicts the CP QOL total score but also that executive function is the most widely represented of the variables considered in regression models of different QOL domains. Specifically, cognitive flexibility seems to predict four domains and the total CP QOL score, while risk taking predicts one domain. In line with our results, a previous study showed that executive functioning predicts social functioning in children with CP [66]. Moreover, the association between QOL and cognitive flexibility, as measured by the WCST, has previously been reported in other health-related conditions [35, 36, 67, 68].

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Table 3 Significant bivariate correlations between CP QOL domains and potential determinants of QOL (motor status, communication, IQ, executive functions and socioeconomic status) in the total sample of adolescents and adults with dyskinetic CP

CP QOL domains	$r/r_s/r^T$	*P*
General well-being and participation		
IQ		
Verbal: PPVT-III	$.35_s$	.014
Nonverbal: RCPM	$.33_s$	.021
Executive functions		
Cognitive flexibility: WCST completed categories (*z*)	$.36_s$	.013
Cognitive flexibility: WCST perseverative responses (*T*)	$.40_s$	.006
Risk taking: BART-Y (*z*)	$.31_s$	.035
Communication and physical health		
Motor status		
Fine: MACS	$-.22^T$	.045
IQ		
Verbal: PPVT-III	$.40_s$	.004
Nonverbal: RCPM	$.35_s$	.015
Executive functions		
Cognitive flexibility: WCST perseverative responses (*T*)	.36	.013
Risk taking: BART-Y (*z*)	.38	.010
School well-being		
Motor status		
Gross: GMFCS	$.22^T$	.045
Communication		
CFCS	$.24^T$	.030
Access to services		
Socioeconomic status		
Monthly income	$-.31^T$	.004
Family health		
Executive functions		
Cognitive flexibility: WCST perseverative responses (*T*)	$.31_s$	.034
Socioeconomic status		
Monthly income	$.31^T$	.004
Feelings about functioning		
Motor status		
Gross: GMFCS	$-.45^T$	<.001
Fine: MACS	$-.49^T$	<.001
Fine: BFMF	$-.41^T$	<.001
Communication		
CFCS	$-.25^T$	.024
IQ		
Verbal: PPVT-III	$.39_s$	.005
Executive functions		
Attentional control: WISC/WAIS digit span (*z*)	$.35_s$	.022
Cognitive flexibility: WCST completed categories (*z*)	$.51_s$	<.001
Cognitive flexibility: WCST perseverative responses (*T*)	.30	.043
CP QOL total score		
Executive functions		
Cognitive flexibility: WCST completed categories (*z*)	$.30_s$	.044
Cognitive flexibility: WCST perseverative responses (*T*)	.42	.003

r_s Spearman correlation, r^T Kendall correlation

BART-Y balloon analogue risk task-youth, *BFMF* bimanual fine motor function, *CFCS* communication function classification system, *GMFCS* gross motor function classification system, *CP QOL* cerebral palsy quality of life questionnaire, *MACS* manual ability classification system, *PPVT-III* peabody picture vocabulary test-3rd, *IQ* intelligence quotient, *RCPM* Raven's colored progressive matrices, *WAIS* Wechsler adult intelligence scale, *WCST* Wisconsin card sorting test, *WISC* Wechsler intelligence scale for children

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Table 4 Multiple linear regression analysis between CP QOL domains and potential determinants of QOL that correlated with CP QOL total score in the total sample of 50 adolescents and adults with dyskinetic CP

CP QOL domains	Predictors	R^2	β	t
General well-being and participation	Cognitive flexibility			
	WCST completed categories (*z*)	.119	.345	2.41*
Communication and physical health	Cognitive flexibility	.211	.295	2.100*
	WCST perseverative responses (*T*)			
	Risk taking			
	BART-Y (*z*)		.293	2.085*
School well-being	Communication			
	CFCS	.085	.291	2.105*
Access to services	Monthly income	.144	−.380	−2.816**
Family health	Cognitive flexibility	.220	.303	2.216*
	WCST perseverative responses (*T*)			
	Monthly income		.330	2.414*
Feelings about functioning	Fine motor functioning	.523	−.615	−5.430***
	MACS			
	Cognitive flexibility			
	WCST completed categories (*z*)		.272	2.406*
Total CP QOL	Cognitive flexibility	.179		
	WCST perseverative responses (*T*)		.423	3.094**

BART-Y balloon analogue risk task-youth, *CFCS* communication function classification system, *MACS* manual ability classification system, *CP QOL* cerebral palsy quality of life questionnaire, *WCST* Wisconsin card sorting test

* $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$

Table 5 Significant correlations between cortical thickness and both CP QOL total score and perseverative responses on the WCST in the neuroimaging sample of 36 adolescents and adults with dyskinetic CP

Cortical area	Cluster size (mm^2)	Talairach coordinates of the maxima			*Z* value	Clusterwise probability (*p*)
		X	*Y*	*Z*		
CP QOL total score						
LH						
Posterior cingulate cortex extended to superior frontal gyrus, paracentral, precuneus, cuneus, isthmus and pericalcarine cortices	4763.44	−13.0	−35.2	39.4	4.122	<.001
Pars opercularis cortex extended to precentral, pars triangularis, rostral and caudal middle frontal cortices	2014.27	−43.1	16.2	19.4	4.305	.014
RH						
Precuneus cortex extended to cuneus cortex, pericalcarine cortex, lingual gyrus, isthmus and posterior cingulate cortices	3877.45	9.3	−39.6	41.8	3.157	<.001
WCST						
RH						
Posterior cingulate cortex extended to caudal anterior cingulate, isthmus and precuneus cortices	1743.57	4.5	−12.0	27.6	3.336	.050

CP QOL cerebral palsy quality of life questionnaire, *LH* left hemisphere, *RH* right hemisphere, *WCST* Wisconsin card sorting test

The question raised by these results is through which mechanism executive functioning influences QOL in people with CP. It has been suggested that executive functioning deficits have a direct impact on daily activities as they hamper more complicated or more articulated activities [69]. Poor mental flexibility undermines a person's ability to function independently, especially in new situations, affecting adaptive behavior and socialization skills

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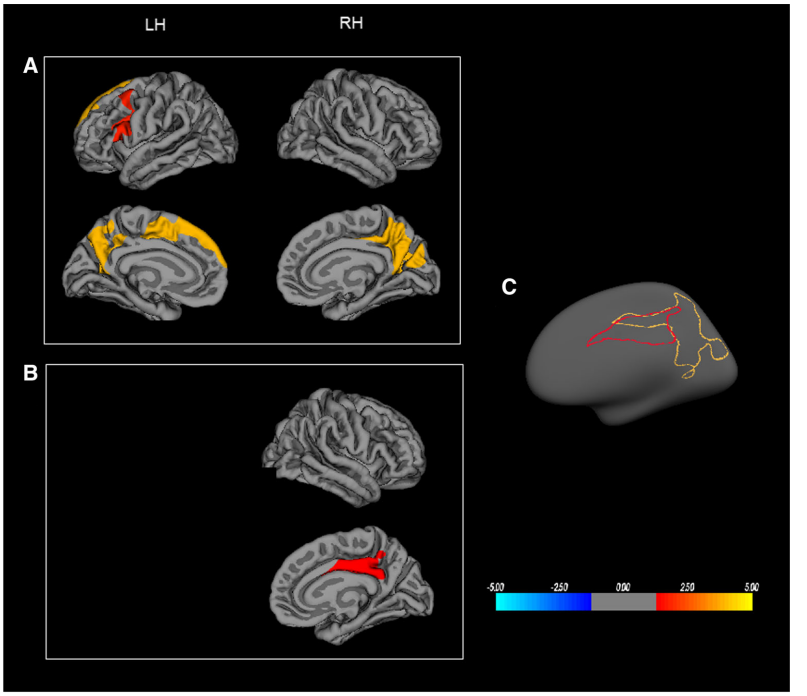

Fig. 1 Cerebral areas showing significant positive correlation with: **a** total CP QOL in LH pars opercularis and posterior cingulate and RH precuneus cortices; **b** perseverative responses of WCST in RH posterior cingulate cortex. **c** Overlapping results of both correlations (in RH precuneus and posterior cingulate cortices). Age is included in the analysis as a nuisance factor. Intensity bar indicates levels of significance. Z Monte Carlo simulation with 10,000 iterations applied to cortical thickness maps to provide clusterwise correction for multiple comparisons was used. Results were thresholded at a corrected $p \leq .05$ ($Z = 1.3$). *LH* left hemisphere, *RH* right hemisphere

[70], which ultimately reduces QOL. The results obtained with executive functions but not IQ suggest that when trying to identify determinants of QOL, it is necessary to assess specific cognitive areas and not only to measure IQ. Our results also suggest that the propensity for risk taking in CP seems to have a positive influence on the Communication and physical health domain.

Our study also shows that fine motor functioning predicts scores on the Feelings about functioning domain of CP QOL. Previous studies of fine motor functioning have reported inconsistent results. While some suggest that fine motor function is associated with some QOL domains [6, 15], others have found no such association [9]. Our results specifically show that the MACS is more strongly associated with the Feelings about functioning domain of CP QOL than is the BFMF. This may be due to the fact that the MACS measures a more generic use of the hands in daily life [48] it being more focused on well-being than on the specific capacity to grasp, hold and manipulate, which is what is measured by the BFMF. Our findings consistent with previous studies indicate that fine motor functioning as measured by the BFMF is not associated with QOL [15], whereas when measured by the MACS it is [12].

Regarding communication, we found that CFCS level predicts better School well-being. Specifically, having more communication difficulties was related to feeling better at currently attended institutions (school, college, occupational therapy center, care facility, place of work, etc.). Although this result might seem surprising, it may be due to the fact that people who have more communication problems attend centers that are adapted to their special needs, where they receive more supported from teachers, carers or staff, etc.

Anxiety and depressive symptoms were not associated with CP QOL scores. The discrepancy with previous studies [22, 24] could be due to the use of different measures of anxiety/depression.

Regarding socioeconomic status, our results partly agree with previous studies showing that the higher the socioeconomic status the lower the CP QOL scores in some domains [12, 21]. Chen et al. [12] found negative associations between two domains of CP QOL (Social well-being and acceptance and Functioning) and socioeconomic status, while we found that it predicts Access to services. A possible explanation for this discrepancy might be attributable to differences between children and adolescents/adults. Studies in which caregivers of children completed the QOL questionnaire have reported an association between more general domains of children's QOL and socioeconomic status because children have more social

services input and it is uncertain what the future holds for them at the social level. By contrast, reports given by caregivers of adolescents and adults are more in line with what one would expect in terms of the relationship between socioeconomic status and aspects of CP QOL that are directly related to it (such as Access to services), and this is likely because adolescents and adults are more developed as individuals and have less access to services. In our study, we also found that monthly income is a potential predictor of the Family health domain. Other studies have similarly found positive associations between income and overall QOL scores [25]. Our results are consistent with the idea that people with a higher socioeconomic level tend to have higher expectations about the services they deserve, and thus, they perceive their access to service opportunities as inadequate because they can afford better private services (i.e. they are more aware of what could be offered). However, they report better family health because they have the financial resources that enable them to obtain better medical care.

Recent robust studies [15, 22] have found that pain in childhood or adolescence, a variable not taken into account in the present study, predicts lower QOL in all domains. Unfortunately, these studies do not consider specific cognitive impairments, such as executive functions, which according to our results, seem to be associated with the majority of CP QOL domains. Future studies about QOL in adults should therefore include measures of both pain and executive functions in order to create models that explain a higher percentage of the variance in QOL.

Regarding brain structure, the CP QOL total score correlated with cortical thickness in both the right precuneus cortex (extending to the cuneus, pericalcarine, lingual, isthmus and posterior cingulate cortices) and the left posterior cingulate and pars opercularis cortices. These neighboring areas have reciprocal corticocortical connections [71]. The connectivity of the precuneus is involved in elaborating highly integrated and associative information, and it also plays a crucial role in self-processing and in the internal processes of self-consciousness [71]. Perfusion in the posterior cingulate and precuneus has been associated with well-being and HRQOL in patients with major depressive and post-traumatic stress disorders [72, 73]. However, in these patients the perfusion was negatively associated with well-being, probably due to the greater self-focus that is commonly seen in people with these mental problems. Conversely, we propose that in CP, people with more self-awareness have better QOL or, at least, are more able to externalize their well-being. If they are more aware of their inner feelings, they might be more effective in expressing themselves clearly. Hence, caregivers can capture this information and then reflect it when answering the CP QOL questionnaire. Interestingly, gray matter reductions in the superior frontal gyrus have been associated with lower scores in a domain of QOL in people with schizophrenia [74]. These findings are coherent with our results for the superior frontal gyrus and precuneus cortex, which has its principal extraparietal corticocortical connections with the frontal lobes [71]. Finally, it is important to mention that these results should not be interpreted reductively because QOL is a broad concept and its relationship with brain structure is a complex one involving several variables and cerebral areas.

Cognitive flexibility correlated with the right posterior cingulate cortex (extending to the caudal anterior cingulate, isthmus and precuneus cortices), overlapping partly with cortical thickness areas related to CP QOL. Thus, our neuroimaging findings support the key role of cognitive flexibility in the QOL of people with dyskinetic CP. Posterior cingulate involvement in cognitive flexibility has previously been described in other conditions [75]. Moreover, the precuneus–prefrontal network is involved in a wide variety of potential functions such as self-processing and attention shift. For instance, it has been reported that the precuneus cortex contributes to shifting between the first- and third-person perspective [71], which is coherent with its involvement in both cognitive flexibility and QOL.

This study has certain limitations. First, the number of statistical tests performed is large in comparison with the sample size, and caution is therefore required when interpreting of our preliminary results. Second, because there is no a condition-specific tool that can be used to measure the QOL of adults with CP, we had to use the teen version of the CP QOL. Although we adapted the questionnaire items to our sample, important domains for adults such as employment, housing and social networks are not captured by this questionnaire [76]. Third, our assessment of the participants' QOL was not based on the self-report version of the CP QOL questionnaire, which is recommended whenever possible [77] in order not to put together self- and proxy reports. Although the questionnaire has been developed for people with CP, it is not well suited to all levels of severity because it requires both complex verbal comprehension and abstract reasoning. This bias could, however, be partially corrected by some features of the CP QOL questionnaire, which can take into account the caregiver's perception of the CP individual's inner feelings. Moreover, the relationship between the self-report and caregiver proxy report versions of the CP QOL-Teen is moderate [45]. Fourth, QOL can be affected by other factors such as pain [15, 22]. Special attention should be paid in future studies to potential confounding factors not taken into account in our analysis.

In conclusion, the results suggest that fine motor status, communication, socioeconomic status and, specially, executive functions might predict QOL in dyskinetic CP.

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This exploratory study also investigated the neural substrate underlying the CP QOL total score and indicates an overlap with brain areas involved in cognitive flexibility. From a clinical point of view, our results highlight the importance of considering executive functions as part of intervention programs designed to improve the QOL of adolescents and adults with CP. Further studies combining neuroimaging, QOL questionnaires and cognitive assessments are necessary to elucidate the factors affecting QOL in people with CP.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the study were in accordance with the ethical standards of the institutional research committee (IRB 00003099) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study or their parents/legal guardian.

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3.2 Study 2

Working paper (under review in *Research in Developmental Disabilities*)

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Executive function and intellectual functioning in dyskinetic cerebral palsy: comparison with spastic cerebral palsy and typically developing controls

Abstract

Aim

To comprehensively describe intellectual and executive functioning (EF) in people with dyskinetic cerebral palsy (DCP), by comparing their performance with that of: 1) age- and sex-matched typically developing controls (TDC); and 2) participants with spastic cerebral palsy (SCP) matched for age, sex, term/preterm and gross motor function classification system (GMFCS).

Method

This cross-sectional study was conducted by the University of Barcelona in collaboration with five institutions. Participants were people with DCP (n=52; 24 females, median age 20.5y: 5mo, interquartile range [IQR]= 13.75y: 7mo; GMFCS I-V). As comparison groups, participants with SCP (n=20; 10 females, median age= 20.5y: 5.5mo, IQR= 13.75y 9mo; GMFCS I-V) and TDC (n=52; 24 females, median age= 20y: 4mo, IQR= 12y 7mo) were included. General intellectual functioning and EF were assessed using common tests in all participants.

Results

Both CP groups had lower general intellectual functioning than TDC and performed poorer in almost all EF tasks. General intellectual functioning was higher in DCP than SCP (z=-2.51, p=.01). Participants with DCP also performed significantly better in goal-setting tasks (z=2.27, p=.03) and information processing (z=-2.54, p=.01) than those with SCP.

Interpretation

People with DCP present lower general intellectual functioning and poorer EF across multiple domains than typically developing controls. When similar levels

of motor severity, people with DCP have higher intellectual functioning and better EF than people with SCP.

What this paper adds

This is the first study to compare intellectual functioning and executive function in a relatively large sample of people with DCP against samples of typically developing controls (TDC) and people with spastic cerebral palsy (SCP) who are similar in terms of age, sex, being term/preterm and motor severity. The present study contributes, therefore, to the characterization of cognitive impairments in dyskinetic cerebral palsy (DCP). Participants with DCP present poorer general intellectual functioning and executive function than TDC in terms of attentional control, cognitive flexibility, goal setting and information processing. People with DCP display stronger intellectual functioning and executive function than those with SCP. The results suggest that cognitive functions may have been underestimated and masked by motor severity in people with DCP. Observations made in SCP cannot be generalized to dyskinetic forms. It is important to properly assess general and specific cognitive functions in people with cerebral palsy even in the most severe cases.

Highlights

- General intellectual functioning is higher in DCP than in SCP.
- People with DCP display stronger executive function than those with SCP.
- People with DCP present poorer executive and intellectual functioning than controls.

KEYWORDS
Dyskinetic cerebral palsy
Spastic cerebral palsy
Executive function
General intellectual functioning
Goal setting

1. INTRODUCTION

Although cerebral palsy (CP) is primarily a disorder of movement and posture, it often involves disturbances of communication and cognition [2] which may have an impact on quality of life [57]. Dyskinetic cerebral palsy (DCP) is the second largest CP group, with high rates among children born at term and among children with normal birth weight [10]. It is agreed that DCP presents poorer motor outcomes than other CP types but there is less scientific evidence of the presence of poorer cognitive abilities in comparison with other CP types, especially when levels of motor severity are equivalent between groups [10, 58, 108, 109–112].

Some studies have reported that people with DCP present higher rates of cognitive difficulties. Specifically, a study including 555 participants with DCP (16% walked without aids, 24% with aids and 59% were confined to a wheelchair) and 4746 participants with bilateral spastic cerebral palsy (SCP) (36% walked unaided, 42% unable to walk) found learning disability to be more frequent in children with DCP (52%) than in children with bilateral SCP (33%) [10]. Similarly, another study reported that people with DCP (n=5) have a lower intelligence quotient (IQ) than people with other CP types [108]. Verbal IQ was also found to be significantly higher among children with spastic diplegia (n=49) and hemiplegia (n=35), and lower in those with DCP (n=11) [58]. Neither of those studies reported the GMFCS level separately for participants with DCP and other CP types. Only Himmelmann et al. [10] reported motor severity by CP type. While 59% of participants with DCP needed wheelchair, only 2% of participants with SCP needed it. Interestingly, Pueyo et al. [110] did not find differences between bilateral DCP, mixed CP, and SCP in nonverbal reasoning using the same measure in all participants. Strauss et al. [111] found that in a sample of people with tetraplegic CP with severe motor dysfunction (defined as tetraplegia with no functional hand use and inability to crawl, creep, scoot, or walk), 95% of those with SCP had an IQ<50 and only 2% had no intellectual disability. Among the participants with DCP, only 40% (n=8) had an IQ<50, and 20% (n=4) had an IQ≥70 or higher. However, a limitation of that study

which the authors themselves indicated was that the reliability of the cognitive assessments was untested. Indeed, another study [112] found that the percentage of learning disability was higher (100%) in people with spastic tetraplegia (GMFCS IV n=2, V n=21) than in DCP (60%; GMFCS I n=2, II n=4, III n=5, IV n=15, V n=26). Finally, a recent study has found that cognitive quotient in the tetraplegic SCP was significantly lower than other CP types including DCP [106]. Overall, these studies might suggest that when people with DCP are comparable to other CP types in terms of motor severity, they might not present poorer cognitive performance. Some aspects of these studies, however, preclude drawing firm conclusions. For example, some studies have small samples of participants with DCP, motor severity by CP type is not always reported and groups are not comparable in terms of gestational age and motor severity.

Executive function (EF) is necessary for the successful completion of everyday, novel, goal-directed activities and has been associated with quality of life in DCP [174]. Most studies of EF in CP focus on SCP or unilateral CP, and have shown that people with CP perform significantly worse than typically developing children [150] in all EF domains described by Anderson [134]. Briefly, these domains include attentional control (capacity to selectively attend to specific stimuli, to focus attention for a prolonged period, and impulse control), cognitive flexibility (ability to shift between response sets, learn from mistakes, devise alternative strategies, divide attention, apply working memory and process multiple sources of information simultaneously), goal setting (ability to initiate an activity and devise a plan to complete it) and information processing (fluency, efficiency and speed of output) [134]. Although it has been proposed that DCP may be characterized by an executive dysfunction [110], this hypothesis has still to be tested. The hypothesis is consistent with the lesions of the basal ganglia and thalamic systems which may impair focused attention and executive function [152] and are frequently described in people with DCP [12]. Executive functions depend on the integrity of the entire brain but they are mainly mediated by the frontal lobes and their connections with posterior and

subcortical brain regions. Specifically, some circuits in the basal ganglia originate in the prefrontal and limbic regions of the cortex which are known to be involved in the executive function [164]. As regards the differences between CP types, one study [110] found that EF was the only function in which mean performance was poorer in DCP participants than in participants with SCP; however, the differences were not statistically significant, the sample was small, not all domains of EF were assessed, and other variables that influence EF such as gestational age and motor severity were not controlled. When aiming to identify the association between spasticity/dyskinesia and cognition, influential variables other than CP type, such as motor severity and prematurity, should be taken into account, since they may prompt additional cognitive impairments [166].

The International Classification of Functioning, Disability and Health considers intellectual functions to be an essential Core Set for people with CP, and intellectual functions play an important role in communication [175], employment [176] and quality of life [174]. Nevertheless, few studies so far have focused on cognitive functions in DCP or have analysed the EF profile in depth, and the results they present are partly conflicting. Most of them have used different measures for assessing cognition in the participants, and the results vary depending on whether the participants with DCP are compared with participants with severe or moderate forms of SCP. No study to date has compared cognitive functioning between a relatively large sample of people with DCP and a group of participants with SCP who are similar in terms of motor severity and prematurity. To truly understand the cognitive correlates of different CP types, neuropsychological studies able to differentiate between subtypes of the condition are required [114]. The results would help to guide the design of more appropriate interventions and follow-up programs focused on DCP.

Thus, in the present study we aim to map intellectual functioning and EF in people with DCP by comparing their performance with: 1) typically developing controls (TDC) matched for age and sex, and 2) participants with SCP matched

for age, sex, gestational age and motor severity. Following on from previous studies, our primary hypothesis was that intellectual functioning and EF would be poorer in participants with CP compared with TDC. Our second hypothesis was that, with similar motor severity in the two CP groups, intellectual functioning would be higher in participants with DCP than in those with SCP. This hypothesis is in accordance with the studies mentioned above which seem to preliminarily indicate that when people with DCP are comparable to other CP types in terms of motor severity, their cognitive performance tends to be as good as that of the other CP types or better. Furthermore, taking into account the brain lesions described in DCP and the results of the only previous study to analyse EF differences between CP types, we expected performance on EF to be poorer in participants with DCP.

2. METHOD

3.1. Participants

This cross-sectional observational study recruited participants with DSP and a comparison group with SCP from the main hospitals in Barcelona that monitor people with CP (the Pediatric Neurology Department and Rehabilitation and Physical Medicine Department at the Hospital Vall d'Hebron, and the Neurology Department at Hospital Sant Joan de Déu,), other institutions attending people with CP (Health services and rehabilitation services of the ASPACE Cerebral Palsy Association, Centro Ocupacional Sinia and Nadís). Some of them were participants in a previous study [110] who were contacted and invited to participate in the current study. Cases were also compared with a group of TDC composed of relatives/friends of the participants with CP and people recruited through advertisements.

The inclusion criteria for participants with clinical diagnosis of CP with predominant dyskinetic features were (1) age older than 6 years and (2) ability to understand instructions, as evaluated by the Spanish Grammar Screening Test (receptive part) [177]. Exclusion criteria were (1) presence of severe visual

or auditory disability and (2) lack of an intelligible yes/no response. In case of signs of sensory impairment, only participants in whom the deficit was corrected or/and the sensory impairment did not prevent evaluation were included.

After the recruitment of the participants with DCP, participants who had a clinical diagnosis of SCP and met the inclusion and exclusion criteria described above were recruited and matched by sex (male/female) and age with participants with DCP (Supplemental table 1). Since the influence of age on cognitive performance is stronger in younger people, the age matching criterion was more flexible with older participants: <20 years old +/-2 years; 20<30 years old +/-4 years; ≥30 years old +/-8 years.

In order to control for variables other than the CP type, additional inclusion criteria for the SCP group were being matched as term vs preterm (<37 weeks, ≥37 weeks) and as ambulant vs non-ambulant (GMFCS I-II-III vs IV-V) with a participant with DCP. Physicians from the institutions mentioned above informed their patients with DCP or SCP who met the inclusion criteria, or their careers, about the possibility of participating in this project. The diagnosis of CP type was based on the physician's clinical assessment. All physicians agreed to define DCP as the CP type characterized by abnormal patterns of posture and/or movement accompanied by involuntary, uncontrolled, recurring, and occasionally stereotyped movements. Impaired muscle tone regulation, movement control, and coordination may comprise dystonic and choreoathetotic patterns [24].

Only participants who clearly presented predominant dyskinetic symptoms were included in the DCP group. Participants who presented spastic and dyskinetic symptoms to the same extent were not considered eligible. Participants were further contacted by phone to double-check inclusion/exclusion criteria, to explain the participation procedure, and to take part in the study. The recruitment and data collection period was from 2012 to 2016. Typically developing people without brain pathology were matched one-to-one by age and sex with participants with DCP. Controls were ineligible if they had been

born preterm, were diagnosed with a neurological or psychiatric disorder, or were illicit substance consumers.

All procedures performed in the study complied with the ethical standards of the 1964 Helsinki declaration. Ethical approval was obtained by the University of Barcelona's (CBUB) Institutional Ethics Committee, Institutional Review Board (IRB 00003099, assurance number: FWA00004225; http://www.ub.edu/recerca/comissiobioetica.htm) and the Hospital Universitari Vall d'Hebron. Written informed consent was obtained from all participants or their careers.

3.2. Neuropsychological assessment

Tests were carefully chosen to allow most of the participants to answer in an autonomous way and to permit, when possible, the use of assistive technology for communication. Participants were encouraged to use the response technique best suited to their degree of disability and the communication devices they normally used. See Supplemental table 2 for test details and adaptations used.

The Raven's Coloured Progressive Matrices (RCPM) test was used to measure intellectual functioning and the four EF [134] domains were assessed as follows:

Attentional control

- Inhibition and sustained attention components were assessed using an adapted version of the Stop Signal Task (SST) of the Cambridge Neuropsychological Test Automated Battery (CANTAB).
- Selective verbal attention was assessed using the digit forward span from either the Wechsler intelligence scale for children (WISC-IV) or the Wechsler adult intelligence scale (WAIS-III).
- Selective visual attention was assessed using the spatial forward span from the Wechsler nonverbal scale of ability (WNV).

Cognitive flexibility

- Feedback utilization was assessed using the 64-item computerized version of the Wisconsin Card Sorting Test (WCST).
- Verbal working memory was assessed using the digit backward span from either WISC-IV or WAIS-III.
- Visual working memory was assessed using the backward spatial span from the WNV.

Goal setting ability was evaluated by means of the Stockings of Cambridge (SOC) test from the CANTAB. Three scores were used: problems solved in minimum moves, mean moves in tests of two moves and mean moves in tests of five moves.

Information processing was assessed only in verbal participants, using a lexical verbal fluency task.

3.3. Background measures

Gross motor function was determined based on the Gross Motor Function Classification System (GMFCS) [32] while fine motor function was measured by the Manual Ability Classification System (MACS) [34]. The CFCS (Communication Function Classification System) was used to categorize communication [61]. Gestational age and epilepsy status were recorded from parent interviews and medical records.

3.4. Statistical analysis

Statistical analyses were performed using R version 3.3.1 (https://www.r-project.org/). Descriptive statistics were calculated, and a global test based on Kruskal-Wallis and Chi-squared test was used to check differences between groups in matching and descriptive variables. Medians and interquartile ranges

(IQR) were used due to the presence of skewness in the empirical distribution of some numerical variables.

Matched pairs were not included in the analyses as blocks because only one measure was recorded for each pair and, therefore, the block effect could not be separated from error. As a result, global tests based on Kruskal-Wallis (H statistic) were performed to analyse differences in cognitive performance between groups. Pairwise contrasts, based on the Mann-Whitney U test, were performed in cases in which the global test yielded a significant result. The Hodges-Lehmann estimator, as well as a 95% bootstrap-percentile confidence interval, was estimated in order to report the differences between groups. The p values were corrected for multiple comparisons (for global and posteriori contrasts) and we used an alpha level of .05 for all statistical tests. As for the reported effect size, probability of superiority was used. Given its relationship with Cohen's d under certain conditions, probabilities greater than .56, .64, and .71 (or lower than .44, .36, and .29, depending on the order in which groups are compared) could be regarded respectively as small, medium, and large effects. Further details about the statistical analysis are available in Supplemental information.

3. RESULTS

3.1. Participants

The final sample comprised 52 participants with DCP with age range 6-62 and median age 20.5y: 5mo, IQR= 13.75y: 7mo without visual/auditory abnormalities precluding neuropsychological assessment, able to understand instructions and, at least, able to answer yes/no. Five of these 52 participants had sensorineural hearing loss (two mild, one moderate and two severe hearing loss – the last three using hearing aids), 17 subjects with corrected refractive errors (myopia, astigmatism and hypermetropia), four subjects with strabismus (two corrected and two non-corrected), two who showed a slight delay in signal transmission in visual evoked potentials but without pathological values and one

with decreased visual acuity in one eye. The remaining cases did not report any hearing or visual problems. A comparison group of 52 age- and sex-matched typically developing controls with an age range 7-59 and median age of 20y: 4mo, IQR= 12y 7mo were recruited. The final sample for the group with SCP comprised 20 participants (10 females), age range 7-65 and median age of 20.5y: 5.5mo, IQR= 13.75y 9mo. The recruitment process is described in figure 1.

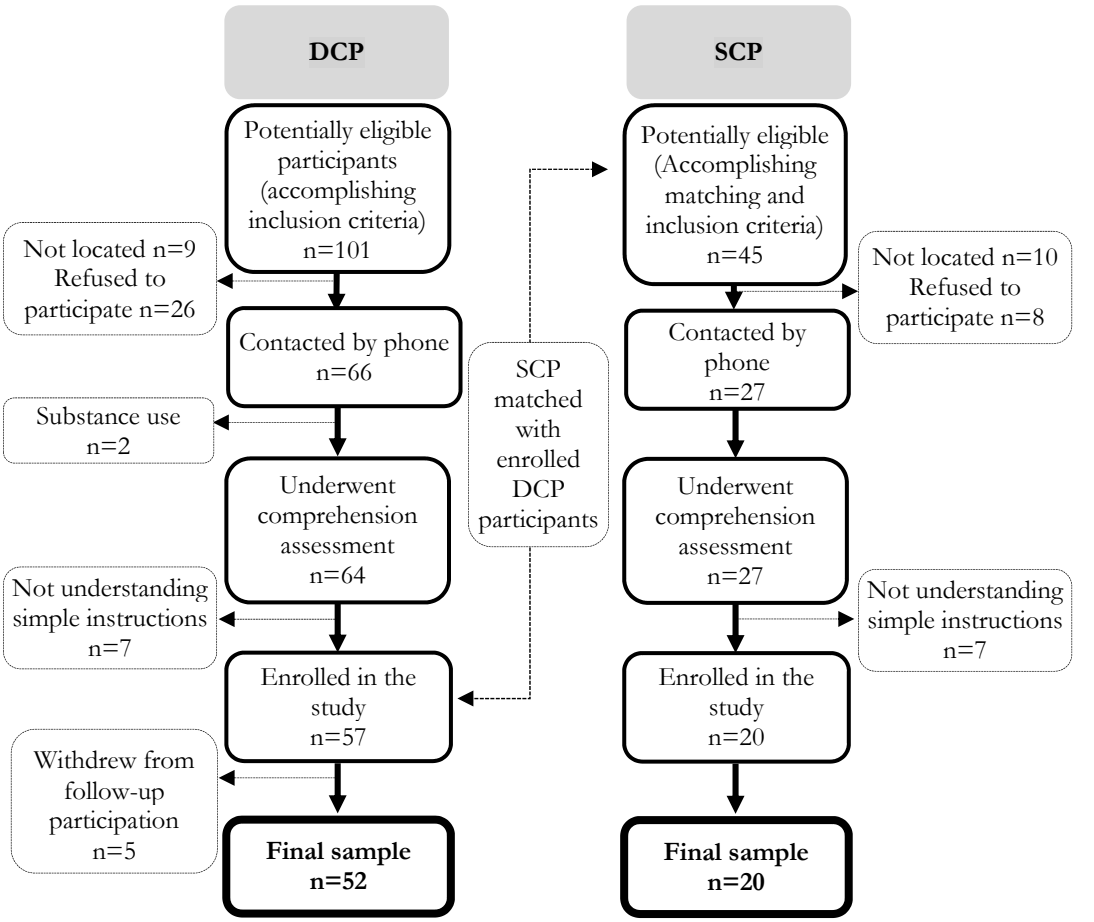

Figure 1. Flowchart showing requitement process for dyskinetic and spastic cerebral palsy participants. DCP, Dyskinetic cerebral palsy; SCP, Spastic cerebral palsy

Given the difficulty of finding participants with SCP who met the matching criteria and due to the completion of the research project, a one-to-one matching was not possible. The range of age and GMFCS of participants were similar in both CP groups. For detailed information on the matching, see Supplemental table 1. There were no significant differences in age and sex between the three groups, as regards the rates of term, pre-term and very preterm participants (x^2=2.67, p=.26) or GMFCS between CP groups. Demographic and clinical data for the three groups are shown in Table 1.

Table 1. Participants' characteristics

Matching variables	DCP	SCP	TDC	Differences: Statistic (*p*-value)*
Age **Md years: months (IQR years: months)**	20.5: 5 (13.75: 7)	20.5: 5.5 (13.7: 9)	20: 4 (12: 7)	H=0.01 (p=.99)
Sex **n (female/male)**	24/28	10/10	24/28	χ^2=0.02 (p=.99)
Gestational age **n (<32 weeks/32-36weeks/≥37 weeks)**	4/6/42	4/1/15	-	χ^2=2.67 (p=.26)
Gestational age participants born pre-term **n / Md weeks (IQR weeks)**	10 / 34 (6.5)	5 / 28 (4.5)	-	z= 1.48 (p=.12)
Gross motor function (GMFCS) (n)	I (15) II (8) III (6) IV (11) V (12)	I (5) II (3) III (4) IV (5) V (3)	-	z= 0.14 (p=.89)

Continuation

Matching variables	DCP	SCP	TDC	Differences: Statistic (*p*-value) *
Other participants' characteristics				
Fine motor function (MACS) (n)	I (5) II (10) III (17) IV (10) V (10)	I (1) II (5) III (5) IV (4) V (4)	-	z= 0.16 (p=.88)
Communication (CFCS) (n)	I (17) II (23) III (6) IV (6)	I (6) II (10) III (2) IV (2)	-	z= 0 (p=1)
Motor distribution n (unilateral / bilateral)	44/8	16/4		
Epilepsy status† n (no epilepsy/ active/resolved)	30/16/6	11/4/5	-	χ^2 = 0.93 (p=.63)
Aetiology[a]				χ^2 = 7.47 (p=.11)
HIE	22	6	-	
Intra-cranial haemorrhage, infarction or hydrocephalus	9	7	-	
Infection	2	2	-	
Kernicterus	2	0	-	
Unclassifiable	17	5	-	

†The International League Against Epilepsy criteria were used to determine epilepsy status; *The level of significance was set at a *p*-value < 0.05 and *p* values were corrected for multiple comparisons (for global and posteriori contrasts); -, not applicable (note that all typically developing controls were born at term); [a] Aetiology classification was based on clinical criteria complemented by the information from available neuroimaging, and HIE criteria were based on Himmelmann et al. [44]; [m] missing values are for participants born at term; CFCS, Communication function classification system; DCP, dyskinetic cerebral palsy; GMFCS, Gross motor function classification system; H, Kruskal-Wallis statistic; HIE, hypoxic-ischemic encephalopathy; MACS, Manual ability classification system; SCP, spastic cerebral palsy; TDC, typically developing controls; IQR, interquartile range; -, not applicable; χ^2, Pearson's Chi-squared test; z, transformed score from Mann-Whitney U test.

3.2. General intellectual functioning differences between the three groups

Both CP groups had significantly lower scores than TDC (Table 2, Figure 2), and participants with DCP had significantly higher scores than participants with SCP. The differences were large for DCP and SCP vs TDC and medium for DCP vs SCP.

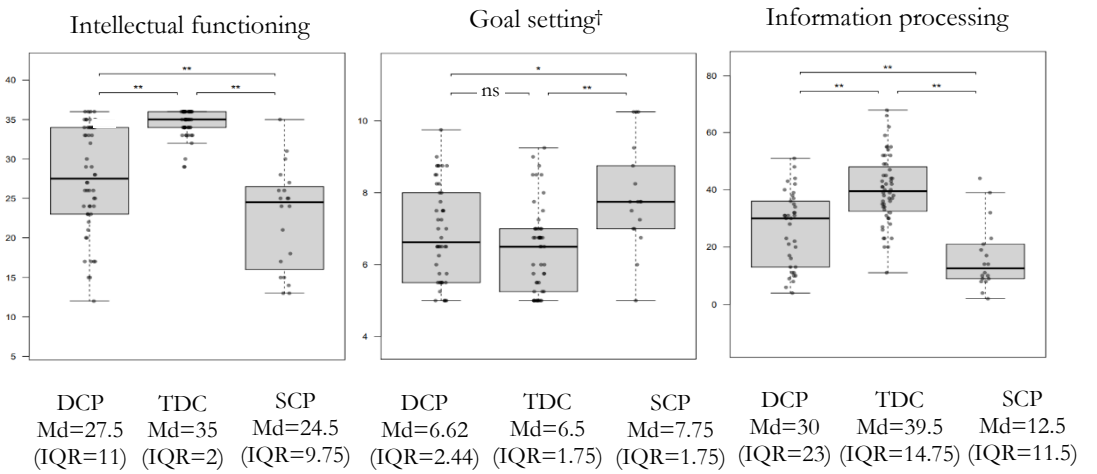

Figure 2. Boxplots showing raw scores (y axis) by groups (x axis) of intellectual functioning, goal setting and information processing. Only boxplots showing significant differences between participants with dyskinetic and spastic cerebral palsy in table 3 are presented. *p < .05; **p <.01; † Higher scores indicate poorer performance in this task; DCP, Dyskinetic cerebral palsy; TDC, typically developing controls; IQR, interquartile range; Md, median; SCP, Spastic cerebral palsy.

Table 2. Descriptive statistics and comparisons of cognitive scores between participants with dyskinetic cerebral palsy, typically developing controls and spastic cerebral palsy

	n / Md (IQR)			General contrasts H (*p* value)*	Posteriori contrasts	Z (adjusted *p* value)	HL estimator (95% CI)	Effect size (probability of superiority)
	DCP	TDC	SCP					
INTELLECTUAL FUNCTIONING								
	52 / 27.5 (11)	52 / 35 (2)	20 / 24.5 (9.75)	55.49 (*p*<0.01)	TDC - DCP	5.96 (*p*<.01)	7 (3;-9)	0.79[L]
					SCP - DCP	-2.51 (*p*=.01)	-5 (-9;-1)	0.29[M]
					SCP - TDC	-6.22 (*p*<.01)	-11 (-15;-9)	0.02[L]
EXECUTIVE FUNCTIONING								
Attentional control								
Inhibition and sustained attention[a]	49 / 283 (17)	52 / 283 (13.25)	18 / 291.5 (18.75)	2.02 (*p*=0.36)	TDC - DCP	-		
					SCP - DCP	-		
					SCP - TDC	-		
Selective verbal attention[a]	47 / 5 (2)	52 / 6 (2)	19 / 5 (2)	24.76 (*p*<0.01)	TDC - DCP	4.61 (*p*<.01)	1 (1;2)	0.68[M]
					SCP - DCP	0.00 (*p*=1)	0 (-1;1)	0.38[S]
					SCP - TDC	-3.36 (*p*<.01)	-1 (-2;-1)	0.16[L]
Selective visual attention[a]	47 / 5 (2)	52 / 6 (1)	19 / 4 (1)	46.21 (*p*<0.01)	TDC - DCP	5.79 (*p*<.00)	2 (1;2)	0.68[M]
					SCP - DCP	-1.64 (*p*=.10)	-1 (-1;0)	0.38[S]
					SCP - TDC	-5.29 (*p*<.00)	-2 (-3;-2)	0.16[L]

Continuation

	n / Md (IQR)			General contrasts H (*p* value)*	Posteriori contrasts	Z (adjusted *p* value)	HL estimator (95% CI)	Effect size (probability of superiority)
	DCP	**TDC**	**SCP**					
Cognitive flexibility								
Feedback utilization†a	50 / 9.5 (8)	52 / 7.5 (4)	18 / 10 (16.25)	7.44 (*p*=0.03)	TDC - DCP	-2.21 (*p*=.04)	-2 (-4;0)	0.34M
					SCP - DCP	0.88 (*p*=.38)	1 (-2;6)	0.55S
					SCP - TDC	2.19 (*p*=.04)	3 (0;9)	0.64S
Verbal working memorya,c	47 / 4 (2)	52 / 5 (2)	19 / 3 (1)	37.06 (*p*<0.01)	TDC - DCP	4.83 (*p*<.01)	2 (1;2)	0.71M
					SCP - DCP	0.00 (*p*=.20)	0 (-1;0)	0.28M
					SCP - TDC	-5.24 (*p*<.01)	-2 (-3;-1)	0.03L
Visual working memorya,c	47 / 5 (2.5)	52 / 6 (0.25)	18 / 4 (1)	50.55 (*p*<0.01)	TDC - DCP	5.85 (*p*<.01)	2 (1;2)	0.75L
					SCP - DCP	-1.54 (*p*=.12)	-1 (-1;0)	0.28L
					SCP - TDC	-5.96 (*p*<.01)	-2 (-3;-2)	0.02L
Goal setting								
Mean moves in tests of two moves†c	48 / 2 (0)	52 / 2 (0)	17 / 2 (0)	5.57 (*p*<0.07)	TDC - DCP	-		
					SCP - DCP	-		
					SCP - TDC	-		
Mean moves in tests of five moves†c	46 / 6.62 (2.44)	52 / 6.5 (1.75)	17 / 7.75 (1.75)	13.79 (*p*<0.01)	TDC - DCP	-1.80 (*p*=.07)	-0.50 (-1;0)	0.36S
					SCP - DCP	2.27 (*p*=.03)	1.12 (0.25;1.75)	0.67M
					SCP - TDC	3.68 (<.01)	1.50 (0.75;2.25)	0.77L

Continuation

	n / Md (IQR)			General contrasts H (*p* value)*	Posteriori contrasts	Z (adjusted *p* value)	HL estimator (95% CI)	Effect size (probability of superiority)
	DCP	**TDC**	**SCP**					
Problems solved in minimum moves[a]	48 / 8 (3)	52 / 9 (2.25)	18 / 7 (3)	24.69 (*p*<0.01)	TDC - DCP	3.48 (*p*<.01)	2 (1;2)	0.64[S]
					SCP - DCP	-1.91 (*p*=.06)	-1 (-3;0)	0.29[M]
					SCP - TDC	-4.55 (*p*<.01)	-3 (-4;-2)	0.10[L]
Information processing								
Lexical verbal fluency[b]	37 / 30 (23)	52 / 39.5 (14.75)	18 / 12.5 (11.5)	36.21 (*p*<0.01)	TDC - DCP	4.32 (<.01)	13 (7;19)	0.76[L]
					SCP - DCP	-2.54 (*p*=.01)	-11 (-20;-2)	0.27[L]
					SCP - TDC	-5.15 (*p*<.01)	-25 (-31;-18)	0.09[L]

*The level of significance was set at a *p*-value < 0.05 and p values were corrected for multiple comparisons (for global and posteriori contrasts); † Higher scores indicate worse performance; -, not applicable; CI, Bootrap-percentile confidence interval based on 10,000 bootstrap samples; DCP, dyskinetic cerebral palsy; HL, Hodges-Lehmann estimator; IQR, interquartile range; Md, median; SCP, spastic cerebral palsy; TDC, typically developing controls; z, transformed score from Mann-Whitney U-test. Reasons for missing data (handled with pairwise deletion): [a]Anarthria accompanied by very severe motor impairments that preclude giving any response system for the test used; [b]Anarthria or severe dysarthria; [c]No comprehension of test instructions; [L], large effect size; [M], medium effect size; [S], small effect size.

3.3. Executive function differences between the three groups

Attentional control: Inhibition/sustained attention measured by the SST did not differ significantly between the three groups. Both selective verbal and visual attention were significantly poorer in DCP and SCP than TDC; there were no differences between CP groups.

Cognitive flexibility: Feedback utilization as well as verbal and visual working memory were significantly poorer in DCP and SCP than TDC. There were no

significant differences between CP groups in any cognitive flexibility component.

Goal setting: The mean number of moves in problems that can be solved in two moves did not differ significantly between the three groups. The mean number of moves in problems that can be solved in five moves was significantly lower in TDC and DCP than in SCP. There were no significant differences between DCP and TDC. Both CP groups had significantly worse global scores (problems solved in the minimum number of moves) than TDC. There were no significant differences between CP groups for this score.

Information processing: Both CP groups showed significantly poorer verbal fluency than TDC. Verbal fluency was significantly higher in DCP than in SCP.

Interestingly, in the variables in which both CP groups performed worse than TDC but did not differ from each other, mean scores were always higher (though not significantly) in participants with DCP (Table 3, Figure 2).

4. DISCUSSION

The present study contributes to the characterization of cognitive impairments in DCP. To our knowledge, it is the first study to compare intellectual functioning and performance in all EF domains in a relatively large sample of people with DCP against samples of TDC and people with SCP who are similar in terms of age, sex, gestational age and motor severity.

As expected, the comparison between TDC and CP groups showed that people with CP had lower intellectual functioning and poorer executive function across all the domains described by Anderson [134]. Differences between CP and TDC in all EF domains have previously been reported in unilateral CP [150]. In the present study, performance did not differ significantly between TDC and CP groups for inhibition/sustained attention and for the easiest items of goal setting. The lack of differences in inhibition/sustained attention is possibly due to the fact that SST may overestimate the performance of CP participants on

"stop trials" (25% of the total score used), as motor slowness precludes inhibition errors. The lack of differences between CP and TDC on the easiest items of goal setting shows that CP performance may be similar that of TDC in very basic planning tasks.

Our results corroborate those of previous studies which have indicated that learning or intellectual disability is more common in spastic tetraplegia than in DCP [106, 111, 112]. Although our results seem to be at odds with those of Sigurdardottir et al. [108], when those authors took account of participants with DCP who could not be assessed by the same test as the rest of the sample (and were therefore assessed by different measures) the highest proportion of children with intellectual impairment was found in the group with spastic tetraplegia. In fact, the authors themselves concluded that cognitive skills might be masked by limitations of motor control [108]. Our results, however, are also at odds with those of other studies [10, 58, 110]. The differences with regard to two of these studies [58, 110] may be due to the small size of the sample of participants with DCP. Himmelmann et al. [10] however, studied a large sample of DCP participants; the differences between our study and theirs may be due to the fact that they did not control for GMFCS and prematurity, and that intellectual functioning was reported dichotomously using an IQ cut-off point of 50. It has been suggested that the more severe the motor impairments, the higher the percentage of cognitive impairment [10] and so DCP has often been associated with poorer cognitive outcomes. However, our results show that, at similar levels of motor severity, dyskinetic forms may present higher intellectual functioning than spastic forms. Accordingly, some studies suggest that intellectual disability, rather than the degree of motor involvement, is a predictor of verbal comprehension abilities [175, 178, 179]. Overall, these findings seem to support the hypothesis that people with DCP, even if they often present a poorer motor outcome than people with SCP, do not necessarily present poorer cognitive functioning.

People with DCP performed significantly better for goal setting and information processing than people with SCP. Better performance in goal setting was

observed for the most difficult items; that is, the CP groups performed similarly on relatively easy items, but people with DCP performed significantly better when more complex planning is required. In fact, their performance on the most difficult items was close to the performance of TDC, since no significant differences were found. Given that information processing was assessed with a verbal task, the conclusions about the better performance observed in DCP than SCP must be limited to verbal participants.

Overall, our results show that people with DCP perform worse than TDC and better than SCP in both intellectual functioning and EF indicating a general tendency, rather than a specific dysexecutive deficit. The performance of people with DCP tends to be closer to TDC on EF than on general intellectual functioning. The executive function results comparing DCP and SCP groups do not confirm DCP as a CP type specifically characterized by an executive dysfunction. Further research including neuropsychological assessment of other cognitive domains is needed to conclusively reject the hypothesis of a dysexecutive deficit in DCP.

The strengths of this study include the recruitment of a large sample of participants with DCP; a wide assessment using reliable and common measures in all participants and the lack of differences in age, sex, GMFCS and prematurity between groups. The limitations include the absence of measurement of dyskinesia using a quantitative scale, the small number of participants with SCP, and the wide age range of the sample. Moreover, neuro-ophthalmological disorders are among the main symptoms in CP [180] and their interaction with manual ability may have an effect on cognitive performance. To control this effect, the execution time was not considered when scoring performance, but SST and verbal fluency are influenced by execution time. In this regard, it is interesting that there were no significant differences in manual ability between DCP and SCP groups ($z= 0.16$, $p=.88$). Finally, participants with SCP included in the present study are not representative of the entire SCP population and caution is therefore required when interpreting the results referring to this group.

In conclusion, the present study identified difficulties across multiple executive function domains compared with TDC and a better cognitive functioning in people with DCP than SCP. The results are clinically relevant as they suggest that cognitive functions may have been underestimated and masked by motor severity in people with DCP. The present study highlights the importance of properly assessing general and specific cognitive functions in CP, even in the most severe cases. Our study may help to broaden the understanding of the clinical consequences of dyskinesia for cognitive function and, by extension, the interaction between cognitive function, muscle tone, and specific brain damage in early childhood. Once again, the results indicate that observations made in SCP cannot be generalized to dyskinetic forms. A comprehensive understanding of cognitive functioning in each CP type would contribute to improving the accuracy of prognosis and also to the design of new educational approaches.

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Supplemental Table 1. Patient characteristics for matching variables

DCP group (n=52)					Control group (n=52)			SCP group (n=20)					Age differences		
No.	Sex	Age y:mo	GMFCS	Term/ Preterm	No.	Sex	Age y:mo	No.	Sex	Age y:mo	GMFCS	Term/ Preterm	DCP vs SCP[a]	DCP vs HC[b]	SCP vs HC
D1	F	6:11	I	P	C1	F	7:05	S1	F	7:06	I	P	1:05	1:06	0:01
D2	M	9:09	III	T	C2	M	9:03	S2	M	10:11	II	T	1:02	0:06	1:08
D3	M	10:11	II	T	C3	M	10:08	S2	M	10:11	II	T	0:00	0:03	0:03
D4	M	11:02	III	T	C4	M	10:04	S2	M	10:11	II	T	1:09	1:02	0:07
D5	F	11:04	V	P	C5	F	11:01							0:03	
D6	M	11:04	I	T	C6	M	12:03	S2	M	10:11	II	T	1:07	1:01	2:08
D7	M	12:09	II	T	C7	M	13:01	S3	M	13:01	III	T	1:08	1:08	0:00
D8	F	12:02	V	T	C8	F	13:04							1:02	
D9	F	13:05	I	T	C9	F	13:07							0:02	
D10	M	13:04	V	T	C10	M	14:08	S4	M	12:08	V	T	1:04	1:04	2:00
D11	F	14:07	III	T	C11	F	14:04							0:03	
D12	M	14:04	V	T	C12	M	14:10	S5	M	15:00	IV	T	1:04	0:06	1:10
D13	M	15:07	I	T	C13	M	15:01	S6	M	14:11	III	T	1:04	0:06	1:10
D14	M	15:04	V	T	C14	M	15:04	S5	M	15:00	IV	T	0:04	0:00	0:04
D15	F	15:02	IV	T	C15	F	15:03							0:01	
D16	M	15:07	II	T	C16	M	15:02	S7	M	15:00	I	T	0:07	0:05	0:02
D17	M	16:03	IV	P	C17	M	16:04							0:01	
D18	M	17:01	II	T	C18	M	17:01							0:00	
D19	F	19:03	III	T	C19	F	18:04	S8	F	18:09	I	T	1:06	1:01	0:05
D20	M	19:09	V	T	C20	M	18:04							1:05	
D21	F	19:07	I	T	C21	F	19:02	S8	F	18:09	I	T	1:02	0:05	1:07
D22	F	19:09	I	T	C22	F	19:07	S8	F	18:09	I	T	1:00	0:02	1:02
D23	F	19:01	I	T	C23	F	19:09	S8	F	18:09	I	T	1:08	0:08	1:00
D24	F	20:10	I	T	C24	F	20:09	S9	F	21:03	I	T	1:07	0:01	1:06
D25	M	20:06	V	T	C25	M	20:09	S10	M	22:03	IV	T	2:03	0:03	2:06
D26	F	20:03	I	T	C26	F	20:10	S9	F	21:03	I	T	1:00	0:07	1:07
D27	F	21:02	IV	T	C27	F	21:01							0:01	
D28	F	21:04	IV	P	C28	F	21:05	S11	F	18:10	IV	P	3:06	0:01	3:05
D29	F	21:09	I	T	C29	F	21:11	S9	F	21:03	I	T	0:06	0:02	0:08
D30	M	22:02	I	P	C30	M	22:10	S12	M	24:10	II	P	2:08	0:08	2:00
D31	F	23:03	IV	P	C31	F	23:10							0:07	
D32	M	23:11	II	P	C32	M	23:06	S12	M	24:10	II	P	1:01	0:05	1:04
D33	M	24:08	III	P	C33	M	24:10	S12	M	24:10	II	P	0:02	0:02	0:00
D34	M	25:09	I	T	C34	M	25:09							0:00	
D35	M	26:00	V	T	C35	M	26:01							0:01	
D36	F	26:07	IV	P	C36	F	27:11	S13	F	25:05	V	P	1:02	1:04	2:06
D37	M	27:07	I	T	C37	M	27:01							0:06	

Continuation

DCP group (n=52)					Control group (n=52)			SCP group (n=20)					Age differences		
No.	**Sex**	**Age y:mo**	**GMFCS**	**Term/ Preterm**	**No.**	**Sex**	**Age y:mo**	**No.**	**Sex**	**Age y:mo**	**GMFCS**	**Term/ Preterm**	**DCP vs SCP[a]**	**DCP vs HC[b]**	**SCP vs HC**
D38	F	28:08	II	T	C38	F	28:04	S14	F	27:09	III	T	1:01	0:04	1:05
D39	F	28:09	IV	T	C39	F	28:03							0:06	
D40	M	31:03	V	T	C40	M	31:04							0:01	
D41	F	31:10	IV	T	C41	F	32:02							1:08	
D42	M	34:02	I	T	C42	M	34:00							0:02	
D43	F	36:11	II	T	C43	F	36:04	S15	F	31:07	II	T	5:04	0:07	5:03
D44	M	37:05	II	T	C44	M	37:02							0:03	
D45	M	41:10	IV	T	C45	M	40:05							1:05	
D46	F	41:01	I	T	C46	F	41:03							0:02	
D47	M	42:02	IV	P	C47	M	42:05	S16	M	41:10	IV	P	1:08	0:03	1:05
D48	F	47:09	V	T	C48	F	47:05	S17	F	42:03	V	T	5:06	0:04	5:02
D49	M	50:05	V	T	C49	M	49:07							1:02	
D50	M	51:01	III	T	C50	M	50:09							1:08	
D51	F	59:10	IV	T	C51	F	59:01	S18	F	65:02	IV	T	6:08	0:09	6:01
D52	M	62:01	V	T	C52	M	59:11							3:10	
								S19[c]	M	20:01	III	T			
								S20[c]	F	27:00	I	P			

DCP, Dyskinetic cerebral palsy; F, female; GMFCS, Gross motor function classification system; HC, healthy controls; M, male; mo, months; No., participant number; P, preterm; SCP, Spastic cerebral palsy; T, term; y, years.

[a] Age matching between DCP and SCP participants was more flexible for older participants. Specifically, participants with DCP and <20 years old were matched with participants with SCP with +/-2 years; participants with DCP and 20<30 years old were matched with participants with SCP with +/-4 years; participants with DCP and ≥30 years old were matched with participants with SCP with +/-8 years.

[b] Age matching between DCP and TDC was the same for all age range participants. That is, healthy controls were eligible if age difference with matched DCP participant was +/- 2 years.

[c] Two participants with SCP were not matched with a participant with DCP because their two DCP matched pairs withdrew the study when the SCP participant was already enrolled.

Supplemental Table 2. Description of tests used and adaptations needed

	Brief description	Adaptations needed
Raven's Coloured Progressive Matrices [181] **/ total raw score**	It consists of 36 items, grouped into three sets of 12 items of increasing difficulty within each set. Each item contains a pattern problem with one part removed and the participant has to choose which of the six alternatives completes the pattern.	Participants answered orally (n DCP/SCP=40/18), pointing (with the finger (n DCP/SCP=2/0), hand (n DCP/SCP=3/0), gaze (n DCP/SCP=2/2) or an adapted pointer on the head (n DCP/SCP=2/0). In those cases in which autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice. These latter subjects answered "yes" or "no" by means of vocalisations, movement of head, facial miming or gestures with other parts of the body (n DCP/SCP=3/0).
Stop Signal Task [182] **/ total correct score on stop and go trials**	The test instructs participants to respond as fast as possible to a simple arrow stimulus on a computer screen. The participant was told to press the left button when they see a left-pointing arrow and the right button when they see a right-pointing arrow. On some trials, an auditory stop signal was presented, and participants are instructed to try and stop or inhibit their response. In the original version of the test, at the end of each assessed block, a feedback screen was displayed showing a graphical representation of the participant's performance. These resting stops were removed in the present study in order to increase the attentional component of the task.	The task was switch adapted and participants were therefore able to respond pressing the buttons by hand (n DCP/SCP=42/17), cheek (n DCP/SCP=4/0), chin (n DCP/SCP=1/0), head (n DCP/SCP=0/1), arm (n DCP/SCP=1/0) or neck (n DCP/SCP=1/0) to allow autonomous responses.
Digit Span subtest of the Wechsler Adult Intelligence Scale-III or Wechsler Intelligence Scale for Children-IV [183, 184] **/ span raw score**	It comprises two series: the forward condition, in which the examinee is read a sequence of numbers and recalls the numbers in the same order; and the backward condition, in which the examinee must recall the numbers in reverse order.	Participants answered the test orally (n DCP/SCP=40/18). For participants with non-verbal communication the answer was given by pointing with the finger (n DCP/SCP=2/0), hand (n DCP/SCP=3/0), gaze (n DCP/SCP=1/1) or an adapted pointer on the head (n DCP/SCP=1/0) to written numbers placed in front of them. Every time the numbers were dictated, the written numbers were hidden to avoid the possibility that the response was based on visual rather than on verbal component.

Continuation

	Brief description	Adaptations needed
Spatial Span subtest of the Wechsler Nonverbal Scale of Ability [185] **/ span raw score**	It comprises two series: the forward condition, in which the examiner points out some cubes and the examinee must indicate the same cubes in the same order; and backward, in which the examinee must indicate the cubes in the reverse order. In both conditions, the length of the sequences is gradually increased.	Participants answered pointing with their finger (n DCP/SCP=40/16), hand (n DCP/SCP=3/0), fixing the gaze (n DCP/SCP=1/0) or with an adapted pointer on the head (n DCP/SCP=3/2). When the gaze was used, the examiner pointed to the item the subject was looking at to confirm that the subject was referring to it.
64-item computerized version of the Wisconsin Card Sorting Test [186] **/ perseverative errors†**	This task consists of four reference cards and 64 response cards with geometric figures that vary in colour, shape and number. The participant has to pair each response card with one of the four reference cards and discover the correct classification principle by trial and error and the computer feedback.	To access the test, a mouse/joystick controlled by hand (n DCP/SCP=33/8) or with the chin (n DCP/SCP=1/0) and one switch (pressed by hand, cheek, head or foot) were used. In some cases, the participant pointed to the screen (n DCP/SCP=10/3) or said the answer orally (n DCP/SCP=2/6) and the examiner executed the action on the computer. In cases where an autonomous response was not possible the examiner indicated the various response alternatives while asking the participant if it was his/her choice, and then the examiner executed the action (n DCP/SCP=4/1).
Stockings of Cambridge test [182] **/ problems solved in minimum moves, mean moves in tests of two moves and mean moves in tests of five moves†**	The participant is shown two displays containing three coloured balls. The participant must move the balls in the lower display to copy the pattern shown in the upper display.	To access the test, a mouse/joystick controlled by hand (n DCP/SCP=36/9) or with the chin (1/0) and one switch (pressed by hand, cheek, head or foot) were used. In some cases, the participant pointed to the screen (n DCP/SCP=9/3) or said the answer orally (n DCP/SCP=1/5) and the examiner executed the action on the computer. In cases where an autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice, and then the examiner executed the action (n DCP/SCP=1/1).
Lexical verbal fluency task [187] **/ total raw score**	The test requires participants to generate as many words as possible beginning with P, M, and R during a minute.	This rest requires speaking so it was assessed only in verbal participants.

† Higher scores indicate worse performance; DCP, Dyskinetic cerebral palsy; SCP, Spastic cerebral palsy.

Supplemental information. Additional statistical information

Probability of superiority

It quantifies the probability of randomly drawing an individual from the first population with a higher score than another individual drawn at random from the second population.

Hodges-Lehmann estimator

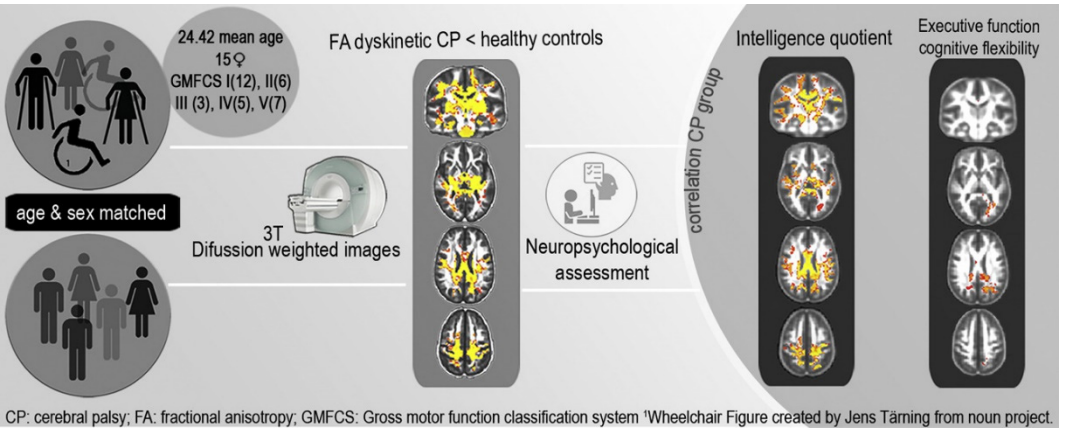
It quantifies the median of the differences between groups; it is an unbiased estimator of the location shift.

3.3 Study 3

Reference

Laporta-Hoyos, O., Pannek, K., Ballester-Plané, J., Reid, L.B., Vázquez, E., Delgado, I., Zubiaurre-Elorza, L., Macaya, A., Póo, P., Meléndez-Plumed, M., Junqué, C., Boyd, R., Pueyo, R. (2017). White matter integrity in dyskinetic cerebral palsy: Relationship with intelligence quotient and executive function. *NeuroImage: Clinical, 15*, 789-800.

Graphical Abstract



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White matter integrity in dyskinetic cerebral palsy: Relationship with intelligence quotient and executive function

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ABSTRACT

Background: Dyskinetic cerebral palsy (CP) is one of the most disabling motor types of CP and has been classically associated with injury to the basal ganglia and thalamus. Although cognitive dysfunction is common in CP, there is a paucity of published quantitative analyses investigating the relationship between white matter (WM) microstructure and cognition in this CP type.

Aims: This study aims (1) to compare brain WM microstructure between people with dyskinetic CP and healthy controls, (2) to identify brain regions where WM microstructure is related to intelligence and (3) to identify brain regions where WM microstructure is related to executive function in people with dyskinetic CP and (4) to identify brain regions where the correlations are different between controls and people with CP in IQ and executive functions.

Patients and methods: Thirty-three participants with dyskinetic CP (mean ± SD age: 24.42 ± 12.61, 15 female) were age and sex matched with 33 controls. Participants underwent a comprehensive neuropsychological battery to assess intelligence quotient (IQ) and four executive function domains (attentional control, cognitive flexibility, goal setting and information processing). Diffusion weighted MRI scans were acquired at 3T. Voxel-based whole brain groupwise analyses were used to compare fractional anisotropy (FA) and of the CP group to the matched controls using a general lineal model. Further general linear models were used to identify regions where white matter FA correlated with IQ and each of the executive function domains.

Results: White matter FA was significantly reduced in the CP group in all cerebral lobes, predominantly in regions connected with the parietal and to a lesser extent the temporal lobes. There was no significant correlation between IQ or any of the four executive function domains and WM microstructure in the control group. In participants with CP, lower IQ was associated with lower FA in all cerebral lobes, predominantly in locations that also showed reduced FA compared to controls. Attentional control, goal setting and information processing did not correlate with WM microstructure in the CP group. Cognitive flexibility was associated with FA in regions known to contain connections with the frontal lobe (such as the superior longitudinal fasciculus and cingulum) as well as regions not known to contain tracts directly connected with the frontal lobe (such as the posterior corona radiata, posterior thalamic radiation, retrolenticular part of internal capsule, tapetum, body and splenium of corpus callosum).

Conclusion: The widespread loss in the integrity of WM tissue is mainly located in the parietal lobe and related to IQ in dyskinetic CP. Unexpectedly, executive functions are only related with WM microstructure in regions

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containing fronto-cortical and posterior cortico-subcortical pathways, and not being specifically related to the state of fronto-striatal pathways which might be due to brain reorganization. Further studies of this nature may improve our understanding of the neurobiological bases of cognitive impairments after early brain insult.

1. Introduction

Cerebral palsy (CP) describes a group of permanent disorders of the development of movement and posture, causing activity limitations, that are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain (Rosenbaum et al., 2007). The predominant motor types in CP can be classified in three groups: spastic, dyskinetic, and ataxic (Surveillance of Cerebral Palsy in Europe, 2000). Dyskinetic CP is the second largest CP group, comprising between 3 and 15% of CP cases with higher rates among children born at term and among children with normal birth weight (Himmelmann et al., 2009). Together with spastic quadriplegia, people with dyskinetic CP have poorer motor and cognitive outcomes than people with other CP motor types (Sigurdardottir et al., 2008). Most studies of cognition in CP, however, have focused on unilateral CP, and their results may not be generalized to bilateral cases. There are few studies examining cognition and neuroimaging in people with dyskinetic CP (Scheck et al., 2012), possibly due to the challenges associated with performing these assessments in this group of patients.

The main CP subtypes (spastic and dyskinetic) are associated with different brain lesions (Krageloh-Mann and Cans, 2009). Qualitative neuroimaging studies indicate that spastic CP mainly presents periventricular leukomalacia, while dyskinetic CP is associated with damage to the cortical grey matter as well as the basal ganglia and thalamus (Bax et al., 2006). Quantitative neuroimaging studies further indicate that abnormalities also tend to be more severe and diffuse in participants with dyskinetic CP than in participants with spastic CP (Yoshida et al., 2013; Yoshida et al., 2011). Studies of dyskinetic CP have reported cortico-subcortical lesions (Himmelmann and Uvebrant, 2011), white matter (WM) damage (Yoshida et al., 2013; Yoshida et al., 2011), as well as normal or non-specific neuroimaging findings (Towsley et al., 2011).

In addition to motor disorders, one in two people with CP have intellectual disability (Novak et al., 2012) and specific cognitive difficulties have been described as well (Straub and Obrzut, 2009). Studies that have focused on executive functions have reported difficulties with inhibitory control, shifting and categorization (Bottcher, 2010; Christ et al., 2003; Jenks et al., 2009; Kolk and Talvik, 2000) which can explain difficulties in everyday life (Whittingham et al., 2014). Lesions of the basal ganglia and thalamic systems may impair focused attention and executive function (Bottcher, 2010). These brain lesions are frequently described in people with dyskinetic CP (Bax et al., 2006; Himmelmann and Uvebrant, 2011) but only one study has focused on executive function (executive function) and brain magnetic resonance imaging (MRI) in this CP subtype (Laporta-Hoyos et al., 2017). Although executive functions depend on the integrity of the entire brain, they are mainly mediated by the frontal lobes and its connections with posterior and subcortical brain regions (Anderson, 2008; Bodimeade et al., 2013). Analysing the association between executive function and WM microstructure with advanced imaging techniques may help in understanding neuroplastic mechanisms that take place after disturbances in the foetal or infant brain. To date there is a lack of brain imaging studies investigating executive function in dyskinetic CP.

Research in the field of intelligence has emphasized the crucial role of WM tracts underlying fronto-parietal association cortices, such as the superior longitudinal fasciculus (Jung and Haier, 2007). A previous study of our group showed that in dyskinetic CP, intelligence quotient (IQ) was related to the volumes of the basal ganglia, thalamus, and superior longitudinal fasciculus, retrolenticular part of the internal capsule, cingulum and superior corona radiata (Ballester-Plané et al., 2016). That previous study did not aim to analyse microstructure and did not include a control group (Ballester-Plané et al., 2016). Lesions of the thalamus and basal ganglia as well as features of lesions such as lesion type (periventricular leukomalacia vs arterial ischemic stroke) and lesion severity have been associated with the severity of cognitive impairment in spastic CP (Riva et al., 2012).

A recent review concluded that dyskinetic CP should be considered separately to other motor types, looking at the relationship to clinical measures in order to provide further insight into the pathogenesis of this condition (Scheck et al., 2012). Our study aims to investigate how intelligence and executive function relate to brain microstructure in people with dyskinetic CP. To analyse WM integrity and organization, diffusion MRI was used. By probing the random motion of water molecules, measures of fractional anisotropy (FA; often reported as a surrogate marker for WM 'integrity') and mean diffusivity (MD) were computed (Basser and Pierpaoli, 1996). There is evidence that decreased FA and increased MD correlate with measures of clinical severity of CP and provide information about corticomotor reorganization (Reid et al., 2016); however networks associated with cognition have been less thoroughly studied (Scheck et al., 2012). Diffusion imaging studies in CP provide new insight into the specific injury and reorganization of WM motor pathways; however, current data are limited and focused on unilateral and spastic diplegia (Rai et al., 2013; Scheck et al., 2015). Furthermore, dyskinetic CP is generally undersampled and is thought to be accompanied by significantly different diffusion properties than unilateral and spastic CP in many brain regions (Scheck et al., 2012).

This study aims (1) to compare brain WM microstructure between people with dyskinetic CP and healthy controls, (2) to identify brain regions where WM microstructure is related to intelligence and (3) to identify brain regions where WM microstructure is related to executive function in people with dyskinetic CP and (4) to identify brain regions where the correlations are different between controls and people with CP in IQ and executive functions.

In this study our primary hypothesis was that FA would be reduced in participants with CP compared to healthy controls in several regions, reflecting impaired WM organization. Our second hypothesis was that, for some of the regions showing significant differences to controls, FA would be correlated with cognitive performance. Specifically, that IQ would correlate with FA in structures such as the superior longitudinal fasciculus and the cingulum, in accordance with previous studies (Ballester-Plané et al., 2016). We further hypothesised that executive function would correlate with FA and MD of the fronto-striatal loop. We expected FA to correlate with executive function performance in different regions in participants with dyskinetic CP and controls, due to compensatory neural development.

2. Materials and methods

2.1. Participants

All procedures performed in the study were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval was obtained by the University of Barcelona's (CBUB) Institutional Ethics Committee, Institutional Review Board (IRB 00003099, assurance number: FWA00004225; http://www.ub.edu/recerca/comissiobioetica.htm) and the Hospital Universitari Vall d'Hebron. Written informed consent was obtained from all participants included in the study or their parents/legal guardian.

The study sample included a subset of participants of a larger project that recruited people with dyskinetic CP from the Hospital Vall

d'Hebron (Pediatric Neurology Department and Rehabilitation and Physical Medicine Department) (n = 27), the Hospital Sant Joan de Déu (n = 3) (Neurology Department), the Cerebral Palsy Association ASPACE (n = 1) (Health services and rehabilitation) in Barcelona, Spain as well as from a previous study (n = 2) (Pueyo et al., 2009). Physicians from the above mentioned institutions informed their patients with dyskinetic CP or their parents/legal guardian about the possibility to participate in this research project. Patients where further contacted by phone to check inclusion/exclusion criteria, to explain the participation procedure and to offer to participate in the study. Participants were recruited and data were collected between 2012 and 2015.

Inclusion criteria for the study were (1) clinical diagnosis of CP with predominant dyskinetic features; (2) being older than 6 years; (3) an intelligible yes/no response system; and (4) for the neuropsychological assessment, being able to understand instructions, as evaluated by the Spanish grammar screening test (receptive part) (Toronto, 1973). Exclusion criteria were the presence of severe visual or auditory disability that precludes neuropsychological assessment.

Thirty-three participants with dyskinetic CP aged 6–59 years, 15 female, who satisfied the inclusion criteria were able to successfully undergo an MRI (Table 1). Thirty-three typically developing people without brain pathology and matched by age and sex were also included in all analyses as controls. Inclusion criteria were therefore to have same sex and similar age (± 1 year) as a participant with dyskinetic CP. Controls were ineligible if they were born preterm, were suffering from a neurological or psychiatric disorder, or were illicit substance consumers. The control group was composed of 20 friends and relatives of the participants with CP, while the remaining 13 controls were recruited through advertisements.

2.2. Neuropsychological assessment

Tests used were carefully chosen to allow the majority of the participants to answer in an autonomous way. All but two of the tests were computerized and allowed for use of assistive technology for communication. Participants were encouraged to use the response technique best suited to their degree of disability and the communication devices they normally used.

2.2.1. Intelligence quotient

The Raven's coloured progressive matrices (RCPM) test was used to measure intelligence quotient (Raven et al., 2001). This test is recommended for people with physical disabilities, aphasia, deafness or CP (Strauss et al., 2006), and has been shown to be sensitive to brain structure in dyskinetic CP (Ballester-Plané et al., 2016). The RCPM have also been commonly used in research with healthy controls (Strauss et al., 2006). Raw scores were used in the neuroimaging analyses. Raw scores range from 0 to 36 and can be converted into IQ scores using normative data for children (Raven et al., 2001) and normative data for adults (Measso et al., 1993). For adolescents, we used a linear interpolation, as previously described (Ballester-Plané et al., 2016). The different ways of response used were: orally (saying the item number), pointing (with the finger, hand or an adapted pointer on the head), or, in cases in where an autonomous response was not possible, the examiner indicated each response alternative while asking the participant if it was his/her choice. Subjects further answered “yes” or “no” by means of vocalisations, movement of head, facial miming or gestures with other parts of the body.

2.2.2. Executive function

A comprehensive neuropsychological test battery was used to assess the four domains of executive function according to Anderson (2008): attentional control, cognitive flexibility, goal setting and information processing.

Attentional control was assessed using the Stop signal task (SST) of the Cambridge neuropsychological test automated battery (CANTAB) (Cambridge Cognition, 1999). The test instructs participants to respond as fast as possible to a simple arrow stimulus on a computer screen. The participant was told to press the left button when they see a left-pointing arrow and the right button when they see a right-pointing arrow. The task was switch adapted and participants were therefore able to respond pressing the buttons by hand, cheek, chin, head or feet to allow autonomous responses. On some trials, an auditory stop signal was presented, and participants are instructed to try and stop or inhibit their response. In the original version of the test, at the end of every assessed block, a feedback screen was displayed showing a graphical representation of the participant's performance. These resting stops were removed in the present study in order to increase the attentional component of the task. The number of correct responses on “stop” and “go” trials represents the total score. Higher scores indicate better performance.

Cognitive flexibility was assessed using the 64-item computerized version of the Wisconsin card sorting test (WCST) (Kongs et al., 2000). This task, which is one of the most widely used tests of executive function in clinical and experimental neuropsychology, consists of four reference cards and 64 response cards with geometric figures that vary in colour, shape and number. The participant has to pair each response card with one of the four reference cards and discover the correct classification principle by trial and error and the computer feedback (Kongs et al., 2000). The score used was the number of perseverative errors. Higher scores indicate poorer performance and raw scores were converted into z scores using normative data provided with the test manual. To access the test, a mouse/joystick (controlled by hand or with the chin) and one switch (pressed by hand, cheek, head or foot) were used. In cases where an autonomous response was not possible,

Table 1
Demographics and clinical data of subjects with dyskinetic cerebral palsy and healthy age and sex matched controls.

	CP group	Control group
Sex n (female/male)	15/18	15/18
Age Mean (SD)/range	24.42 (12.61)/ 6–59	24.42 (12.44)/ 7–59
Gestational age n (< 32 weeks/32–36 weeks/ ≥ 37 weeks)	2/4/27	0/0/33
Epilepsy status n (no epilepsy/active/resolved)	23/8/2	33/0/0
Aetiology, n		
HIE	14	
Intra-cranial haemorrhage/infarction/ hydrocephalus	3	–
Infection	1	
Kernicterus	1	
Unclassifiable	14	
Gross motor function (GMFCS) (n)	I (12) II (6) III (3) IV (5) V (7)	–
Fine motor function (MACS) (n)	I (5) II (8) III (11) IV (2) V (7)	–
Communication (CFCS) (n)	I (14) II (13) III (2) IV (4) V (0)	–
Motor distribution (tetraplegia/ hemiplegia/monoplegia)	28/4/1	–

CFCS: Communication function classification system; CP: cerebral palsy; GMFCS: Gross motor function classification system; HIE: hypoxic-ischemic encephalopathy; MACS: Manual ability classification system; SD: standard deviation.

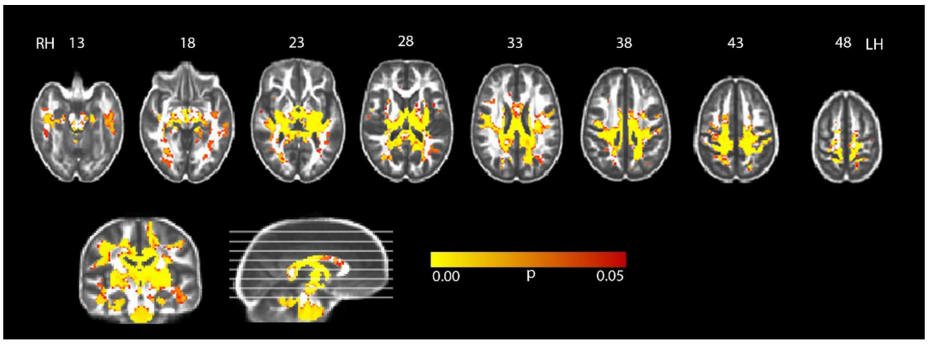

Fig. 1. Regions where fractional anisotropy was significantly lower in a sample of 33 subjects with dyskinetic cerebral palsy compared with 33 age and sex matched healthy controls. Results are shown at $p < 0.05$ corrected for multiple comparisons and overlaid on the group mean fractional anisotropy. RH: right hemisphere; LH: left hemisphere.

the examiner indicated the various response alternatives while asking the participant if it was his/her choice, and then the examiner executed the action.

Goal setting was evaluated by means of the Stockings of Cambridge (SOC) test of CANTAB (Cambridge Cognition, 1999). The SOC is a spatial planning test in which the participant is shown two displays containing three coloured balls. The participant must use the balls in the lower display to copy the pattern shown in the upper display. The outcome measure used for the analysis was the number of problems solved in minimum moves (Cambridge Cognition, 1999). Higher scores indicate better performance. Raw scores were converted into z scores using normative data provided with the test manual. To access the test, a mouse/joystick (controlled by hand or with the chin) and one switch (pressed by hand, cheek, head or foot) were used. Some participants responded the test by pointing to the computer screen (with the finger, hand or an adapted pointer on the head). In cases where an autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice, and then the examiner executed the action.

Information processing was measured using the performance in a lexical verbal fluency task with three initial-letters (Gramunt-Fombuena and Pen, 2009), a frequently used task in clinical practice. The test requires participants to generate as many words as possible beginning with P, M, and R and the score used was the number of words that the participant were able to say. Higher scores indicate better performance.

2.2.3. Statistical analysis

Descriptive statistics of neuropsychological performance were calculated. The cognitive performances of the CP and control groups against their matched controls were compared using *t*-tests or Mann–Whitney *U* tests, depending on the distribution of the data. Statistical analyses of neuropsychological data were performed using SPSS version 24 (IBM SPSS Statistics, IBM Corp. NY, USA). The level of significance was set at p-value < 0.05. Missing data were handled with pairwise deletion.

2.3. Neuroimaging

2.3.1. Image acquisition

MRI data were acquired on a Siemens Magnetom TRIO 3 Tesla scanner (Erlangen, Germany) at the Hospital Universitari Vall d'Hebron (Barcelona, Spain), TQ-engine Tim (45 mT/m, slew rate 200 T/m/s), using a 12 element Tim head array.

Diffusion weighted images were acquired in 30 noncollinear directions and 65 axial slices. Parameters were: 2 mm slice thickness; field of view 240 × 240 mm; TR/TE 8400/90 ms; and acquisition matrix 122 × 122, voxel size 1.96 × 1.96 mm. Images were acquired at b = 1000 s/mm^2, along with one minimally diffusion weighted image (b = 0). The acquisition time was 4:47 min.

In order to minimize movement during MRI, diazepam was administered in 13 patients (dose between 2.5 and 10 mg depending on each participant) and 6 were sedated with pentobarbital and propofol. The drug was prescribed by a physician in accordance with the protocol detailed and reviewed by the ethics committee.

2.3.2. Diffusion preprocessing

An extensive preprocessing procedure was used. Volumes containing within-volume motion or scanner artefacts were visually identified, and excluded from further analysis. Participants whose datasets contained more than three volumes showing motion artefacts were excluded entirely from further analyses. Brain masks where created using FSL BET (Smith, 2002) and further manually edited as required. FSL EDDY (Andersson and Sotiropoulos, 2015) was used to correct for eddy current-induced distortions and head movements between volumes, including rotation of the b-vectors. DTI maps including FA and MD were calculated for each participant using FSL DTIFIT.

2.3.3. Voxelwise analysis

Whole brain groupwise analyses of FA images were carried out using a variation (Schwarz et al., 2013) of the original tract based spatial statistics (TBSS) pipeline (Smith et al., 2006) shown to improve reliability. A study specific template was created from the FA maps of all participants, and FA maps of all participants were subsequently nonlinear registered to this template using ANTS-SyN (http://picsl.upenn.edu/software/ants/) (Avants et al., 2012; Fonslow et al., 2013). Greedy SyN was used as the transformation model. Probability mapping was used as the metric, GradStep = 0.25, regularization sigma = 2.0, 4 iterations of template construction, number of iterations per level 30 × 90 × 20.

Registration accuracy was assessed visually, and data with registration errors were excluded from further analysis. Creation of the study specific template was repeated excluding these participants. A Gaussian smoothing kernel with sigma of 2 mm was applied. A WM mask was created by first eroding the average brain mask by 3 voxels, applying a group average FA threshold of 0.2 and retaining only voxels that were non-zero in all participants.

A permutation-based modelling approach (Nichols and Holmes, 2001) implemented in FSL RANDOMISE with 5000 iterations was used to perform all statistical analyses. The resultant statistical maps were thresholded at $p < 0.05$ corrected for multiple comparisons with threshold-free cluster enhancement (Smith and Nichols, 2009). Although our primary hypotheses were one-tailed, the opposite contrast was also investigated to confirm absence of significant differences. A

voxelwise analysis for participants with dyskinetic CP compared to healthy controls was performed to explore differences in FA between the CP and control participants. A correlation between IQ and FA was then performed, controlling for age and sex, for all participants with CP and controls separately to ascertain regions where injury severity was specifically associated with IQ. Finally, four separate general linear models were employed to identify regions where FA correlated with scores in each one of the executive function domains in the CP and control group (controlling for age and sex). All analyses were also further performed for MD (see Supplementary material). Anatomical naming of WM regions containing significant clusters was performed using the John Hopkins University (JHU) WM atlas (Hua et al., 2008) included in FSL. The Harvard-Oxford cortical structural atlas (http://www.cma.mgh.harvard.edu/fsl_atlas.html) was further used to report cortical structures that were close to significant WM results. Only clusters containing at least five voxels are presented.

3. Results

3.1. Demographic and clinical information

From a total of 101 potentially eligible patients, 9 could not be located, 26 refused to participate in the study, 2 were excluded for being treated for substance use disorder, 7 did not meet the criterion of understanding simple instructions, and 5 withdrew from follow-up participation.

Among the 52 remaining cases some were not included in the present study because 2 could not be scanned due to metal devices implanted, 3 refused to undergo MRI, and 5 did not complete scans due to anxiety. From the remaining 42 cases, 6 were excluded due to excessive head movement artefacts or signal-to-noise problems on the MRIs and 3 could not be adequately processed by the software.

The final sample comprised 33 participants with dyskinetic CP aged 6–59 years without visual/auditory abnormalities, able to understand instructions and, at least, able to answer yes/no, as well as 33 age and sex matched healthy controls. The majority of the participants (n = 27; 81%) were born at term as expected in this CP type (Himmelmann et al., 2007). In the CP group 8 (24%) participants had active epilepsy, the most frequent classifiable aetiology being hypoxic-ischemic encephalopathy (n = 14; 42%) and the vast majority had tetraplegia (n = 28; 85%). Participants' gross and fine motor function (GMFCS: Gross motor function classification system, and MACS: manual ability classification system) ranged from I to V and communication (CFCS: Communication function classification system) from I to IV (Table 1).

The neuropsychological performance of the sample is reported in Table 2. Eight participants with dyskinetic CP had an IQ equal to or below 70 (24%) indicating intellectual disability according the criterion A of DSM-5 (American Psychiatric Association, 2013). There was more variability in the CP group in almost all cognitive function scores. The only domain where the control group showed higher variability in their performance was information processing which was measured by a task that requires being able to speak.

3.2. Neuroimaging

3.2.1. Differences between dyskinetic CP and control participants

The voxel-based analysis of white matter FA (Fig. 1) and MD (Supplementary Fig. 1) detected an extended decrease in white matter FA and increase MD in the CP group in all cerebral lobes relative to controls. These differences were particularly prominent in the WM underlying the parietal lobe and, to a lesser extent, the temporal cortex. Differences in WM of the frontal and occipital lobes where less extended than those of the temporal and parietal lobes. Specifically, differences in frontal lobe were circumscribed in the anterior corona radiata, the genu of corpus callosum, the anterior part of the cingulate gyrus and the anterior part of the superior longitudinal fasciculus. Differences were further extended to the corticospinal tract, inferior and superior cerebellar peduncles and medial lemniscus.

3.2.2. Relationship between IQ and white matter microstructure

There was no significant correlation between IQ and WM microstructure in the control group. In the CP group, FA was significantly positively correlated with IQ in all cerebral lobes (Figs. 2a and 3; Table 3). Specifically, FA significantly correlated with IQ in six clusters. Fractional anisotropy and IQ correlated in almost the entire sagittal axis of the fornix and corpus callosum. A significant correlation was also observed bilaterally in the cerebral and cerebellar peduncles. Parts of the posterior thalamic radiation within the internal capsule and superior and posterior corona radiata were also significantly correlated with IQ, as were the external capsule, the cingulum, the superior longitudinal fasciculus and the superior fronto-occipital fasciculus. A significant correlation was further observed in the anterior limb of the internal capsule. Specifically, in the right hemisphere, FA was significantly correlated with IQ in the tapetum and sagittal stratum.

Intelligence quotient was also associated with WM microstructure close to several cortical regions: mainly the parietal cortex and the temporal cortex including the parahippocampal gyrus. These regions were not covered by the JHU atlas and were therefore labelled according to the Harvard-Oxford cortical structural atlas (Table 3). Four smaller significant clusters within the WM (not labelled with the JHU atlas) were located close to the frontal orbital cortex, superior frontal gyrus, subcallosal cortex and the superior division of the lateral occipital cortex.

The significant correlation between MD and IQ embraced fewer

Table 2
Descriptive statistics of neuropsychological performance of subjects with dyskinetic cerebral palsy and age and sex matched healthy controls.

		n	Score	CP group		Control group		Differences
				Range	Mean (SD) or Median (IQR)	Range	Mean (SD) or Median (IQR)	
IQ	Intelligence quotient†	33	Raw	12–36	*29 (12)*	29–36	*35 (2)*	* < 0.001; U = 217
			IQ	33–127	*94 (41)*	95–128	*113 (7)*	* < 0.001; U = 257
EF	Attentional control†	31[a]	Raw	244–316	*283.60 (12)*	266–312	*283.84 (14)*	NS. U − 462.50
	Cognitive flexibility†,+	31[a]	Raw	4–35	*8 (7)*	2–23	*7 (5)*	NS. U = − 401
			z	− 2.70–3	*− 0.30 (1.30)*	− 2.10–3	*− 0.30 (1.10)*	NS. U = 451.50
	Goal setting	30[a]	Raw	3–12	7.93 (2.35)	6–12	9.40 (1.57)	*0.006 t = 2.85
			z	− 2.52–1.91	0.02 (1.11)	− 1.04–1.91	0.70 (0.76)	0.007 t = − 2.79
	Information processing	26[b]	Raw	4–51	28.42 (12.60)	11–68	40.04 (13.65)	*0.002 t = 3.19

CP: cerebral palsy; EF: executive function; IQ: intelligence quotient; IQR: interquartile range; NS: no significant; SD: standard deviation. Reasons for missing data: [a]Anarthria accompanied by very severe motor impairments that preclude to use an appropriate response system for the test used; [b]Anarthria or severe dysarthria.
*Bonferroni correction for multiple-comparison was applied and significance is at level set of 0.006.
†Data in one or both groups is not normally distributed, thus, non-parametric test is applied and median (IQR) is indicated in italic.
+Higher scores indicate worse performance.

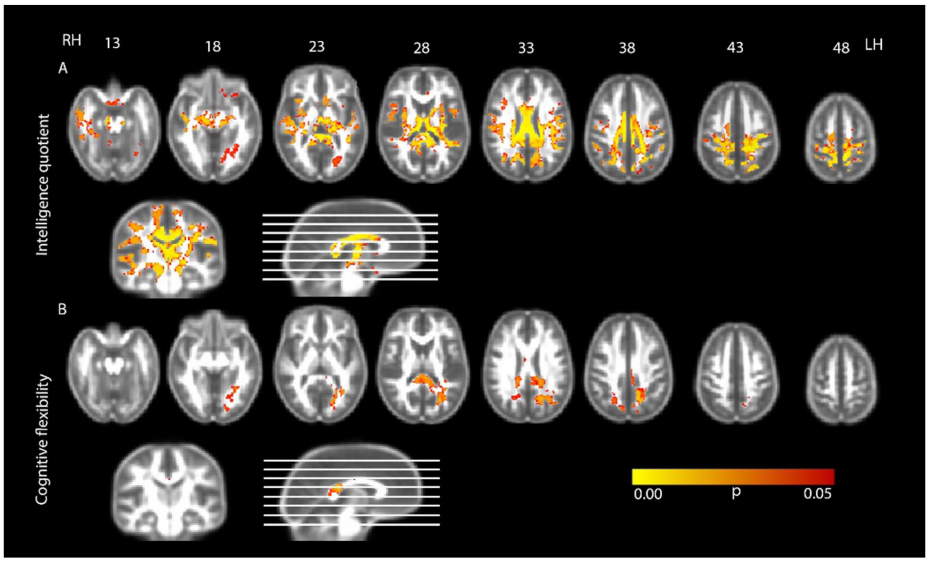

Fig. 2. Regions where fractional anisotropy correlated A) positively with intelligence quotient (Raven's coloured progressive matrices) B) negatively with cognitive flexibility (Wisconsin card sorting test). Results are shown at $p < 0.05$, corrected for multiple comparisons, controlled for age and sex and overlaid on the group mean fractional anisotropy image. RH: right hemisphere; LH: left hemisphere.

regions than that of FA and showed only one significant cluster. Specifically, FA was significantly correlated with IQ in the genu of corpus callosum, the middle cerebellar peduncle, the posterior thalamic radiation, the tapetum, sagital stratum and hippocampus section of the cingulum as defined by the JHU white matter atlas. Mean diffusivity was not related with these regions. Significant correlations between FA and IQ were also extended to more regions not covered by the JHU atlas than significant correlations between MD and IQ. The left uncinated fasciculus was the only region showing a significant correlation between MD and IQ but not FA and IQ. The relationship between MD and IQ is reported in Supplementary Table 1, and Supplementary Figs. 2 and 3. Differences between FA and MD results are indicated in Table 3 as well as Supplementary Table 1.

3.2.3. Relationship between executive function and white matter microstructure

There were no significant correlations between FA and executive function domains observed in the control group for any of the four analyses. Attentional control, goal setting and information processing did not correlate with WM microstructure in the CP group, however FA was significantly negatively correlated with WCST scores (which measure cognitive flexibility) in the CP group. These results indicate that higher FA is associated with better performance in cognitive flexibility (i.e. lower scores on the WCST). Specifically, there was a statistically significant negative correlation between cognitive flexibility (WCST scores) and FA in four clusters (Figs. 2b and 4; Table 4). The largest cluster was extended along the body and splenium of the corpus callosum including the left tapetum. For this cluster, FA was also correlated with WCST scores in bilateral WM regions in the posterior corona radiata. Fractional anisotropy of the retrolenticular part of the internal capsule, posterior thalamic radiation, the cingulate gyrus and the superior longitudinal fasciculus was further correlated with executive function in the left hemisphere. Regions where FA was correlated with cognitive flexibility were extended bilaterally to the WM below the posterior division of the cingulate gyrus according to the Harvard-Oxford cortical structural atlas. The relationship between WM microstructure and executive function was located in different regions in the left hemisphere near the precentral, postcentral, lingual, occipital fusiform and supramarginal gyrus. In this hemisphere, correlations were also found in WM near the intracalcarine, supracalcarine and cuneal cortex as well as the planum temporale and the inferior temporal gyrus. The second largest cluster was located in the right hemisphere, and executive function correlations were found in the WM near to the lateral occipital, superior parietal and precuneus cortex. For the two remaining smaller clusters, FA was correlated with WM close the superior parietal lobe and the anterior division of the cingulate gyrus.

The significant correlations between MD and executive function embraced smaller volume than those of FA and were mainly located in the left hemisphere. While MD was not significantly related with executive function in some of the previously mentioned regions (body of corpus callosum, tapetum, retrolenticular part of internal capsule, posterior thalamic radiation and the cingulum), it was related in the superior corona radiata and the superior fronto-occipital fasciculus (according to the JHU white matter atlas). The relationship between MD and executive function is reported in Supplementary Table 2, and Supplementary Figs. 2 and 4. Discrepancies between FA and MD results are indicated in Table 4 as well as Supplementary Table 2.

4. Discussion

To our knowledge, this is the first study to examine the association between WM microstructure and executive function in a relatively large sample of people with dyskinetic CP ($n = 33$) compared to a group of age and sex matched healthy controls. Although dyskinetic CP has been classically characterized by deep grey matter injury (playing an important role in the specific movement disorder), this study shows that WM microstructure is also impaired in all cerebral lobes in both sensorimotor and non-motor-related regions. These impairments may explain

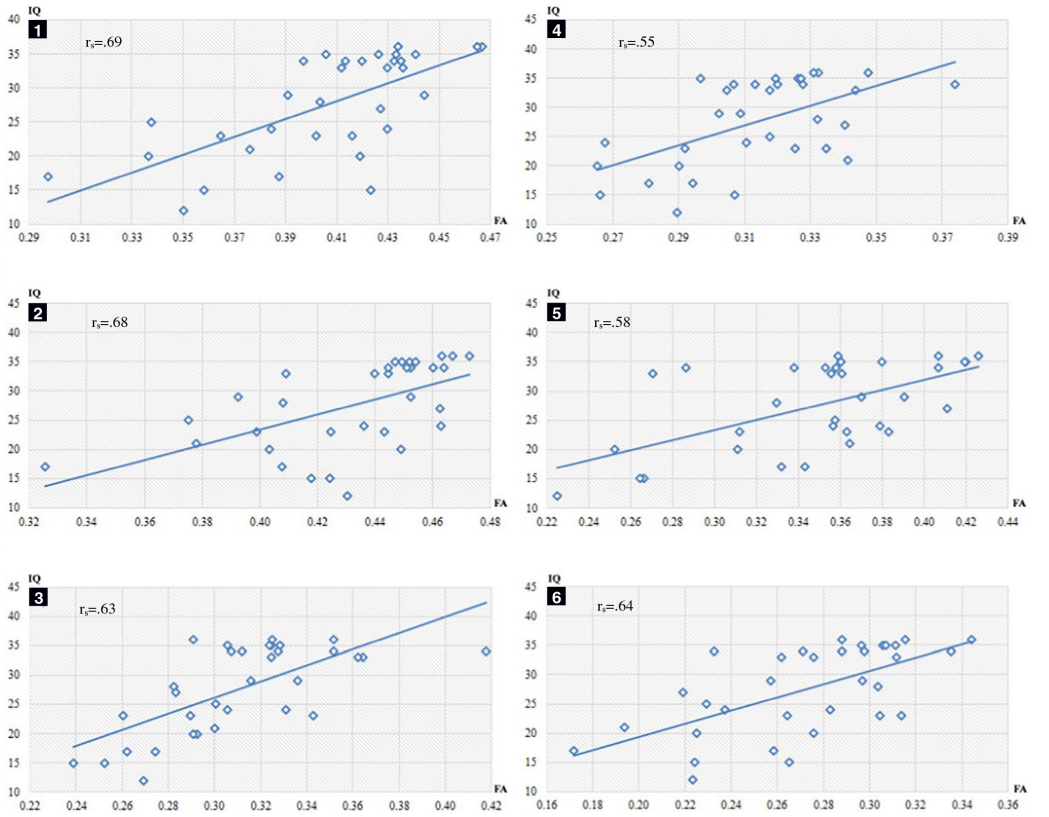

Fig. 3. Scatterplot between IQ (intelligence quotient) (y-axis; raw score) and mean FA (fractional anisotropy) (x-axis) in significant clusters ($p < 0.05$). Clusters sorted by size (largest first) and labelled by the same numbers as Table 3.

other comorbidities such as cognitive difficulties in dyskinetic CP. It is noteworthy that the loss in the integrity of the WM in dyskinetic CP is predominantly underlying the parietal and, to a lesser extent, the temporal cortex. Our larger sample confirmed the early observations of Yoshida et al. (2013) in a sample of seven children with dyskinetic CP. Yoshida et al. (2013) performed analysis of 205 atlas-defined regions, and reported that extended WM changes were present along the main four brain lobes.

Regarding our investigation of the correlation between cognitive function and WM microstructure, we cannot compare findings in CP against our control group because none of the cognitive functions assessed were significantly related with FA in the control group. A previous study exploring the association between FA and perseverative responses of the WCST in typically developing subjects did not find any significant correlation (Ohtani et al., 2017), in agreement with our results. To understand the neuroimaging results it is necessary to keep in mind the cognitive performance of our sample. We hypothesise that the restricted range of neuropsychological scores prevented finding significant associations between brain microstructure and function in the control group, unlike the CP group scores with a wider spread of neuropsychological scores, for whom significant correlations were revealed. The higher variability in the CP group in almost all neuropsychological scores, as well as their differential relationship with the WM microstructure, are signs that the biological basis of cognition in dyskinetic CP could be different to the general population. While findings in CP cannot be compared against the control group, interesting conclusions may be drawn from the associations observed in people with dyskinetic CP.

Intelligence quotient was related to WM integrity in the majority of regions that also showed a decrease in FA relative to the control group. These results for IQ are consistent with the literature reporting the importance of undisrupted information transfer in cortico-cortical long association fibres in intelligence (Deary et al., 2010) such as the superior longitudinal fasciculus, sagittal stratum, superior fronto-occipital fasciculus or the cingulum. Our results are also consistent with a previous study in an overlapping cohort of dyskinetic CP participants reporting a correlation between RCPM and the WM volume in the superior longitudinal fasciculus, the internal capsule and the cingulum using WM voxel based morphometry analysis of T1-weighted images (Ballester-Plané et al., 2016). Interestingly, a previous study showed specific reduction in long-range connectivity in severe versus moderate CP (Englander et al., 2013). Although the study by Englander et al. (2013) did not focus on dyskinetic CP and did not include participants with GMFCS level V, all participants were diagnosed with bilateral CP and included some participants with dyskinetic features. Other regions that showed significant associations with IQ in our study, such as the corpus callosum and the fornix are also involved in non-motor functions (Fling et al., 2016; Leech and Sharp, 2014). Intelligence quotient was further associated with WM microstructure in some regions consistent with the

Table 3
Regions showing a positive correlation between fractional anisotropy and intelligence quotient in the cerebral palsy group.

Cluster number	Cluster size (mm^3)	Mean FA (SD) (CP/ controls)		Anatomical regions	
				JHU white matter atlas	Harvard-Oxford cortical structural atlas
1	143,218	0.393 (0.099)/ 0.418 (0.105)	MS	Genu, **body and splenium of corpus callosum** **Column and body of fornix** Middle cerebellar peduncle	
			B	**Fornix (cres)** *Cerebral peduncle* Posterior thalamic radiation (include optic radiation) **Posterior limb and retrolenticular part of internal capsule** **Superior and posterior corona radiata** **External capsule** **Cingulum (cingulate gyrus** and hippocampus) **Superior longitudinal fasciculus** **Superior fronto-occipital fasciculus (**could be a part of anterior internal capsule**)** **Anterior limb of internal capsule**	**Insular cortex** **Superior,** *middle* and inferior (pars opercularis) **frontal gyrus** **Precentral gyrus** Superior temporal gyrus (anterior and posterior division) Middle temporal gyrus (posterior division and temporo-occipital part) **Postcentral gyrus** **Superior parietal lobe** Supramarginal gyrus (anterior and posterior division) **Cingulate gyrus (**anterior and **posterior division)** Precuneous cortex Parahippocampal gyrus (anterior division) Supplementary motor cortex **Central and parietal opercular cortex** Planum polare **Planum temporale** Lateral occipital cortex (superior division) Angular gyrus Heschl's gyrus (includes H1 and H2)
			LH		**Frontal operculum cortex**
			RH	Tapetum Sagittal stratum (include inferior longitudinal fasciculus and inferior fronto-occipital fasciculus)	Inferior frontal gyrus (pars triangularis) Cuneal cortex Parahippocampal gyrus (posterior and anterior division) Temporal fusiform cortex (posterior division) Temporal occipital fusiform cortex Inferior temporal gyrus (posterior division and temporo-occipital part)
2	3359	0.432 (0.087)/ 0.443(0.093)	LH	Posterior thalamic radiation (include optic radiation)	Intracalcarine cortex Lingual gyrus Occipital fusiform gyrus Temporal occipital fusiform cortex
3	1184	0.310 (0.036)/ 0.322 (0.037)	B		*Frontal orbital cortex* Subcallosal cortex
4	890	0.314 (0.042)/ 0.315 (0.042)	LH		**Frontal orbital cortex** Subcallosal cortex
5	147	0.349 (0.069)/ 0.352 (0.070)	LH		**Superior frontal gyrus**
6	54	0.272 (0.024)/ 0.296 (0.028)	LH		Lateral occipital cortex (superior division)

B: bilateral; CP: cerebral palsy; FA: fractional anisotropy; JHU: John Hopkins University; LH: left hemisphere; MS: medial structure; RH: right hemisphere; SD: standard deviation. Discrepancies between fractional anisotropy and mean diffusivity results are indicated as follows. Bold indicates regions that are significant with both fractional anisotropy and mean diffusivity. Italics indicate regions that only show the same result between fractional anisotropy and mean diffusivity in one hemisphere.

fronto-striatal circuit, such as the anterior limb of the internal capsule, which is involved in cognition (Oberlin et al., 2016). This result is not surprising as the basal ganglia are involved in both executive function and IQ as are crucial elements in the circuits that confer human reasoning (Leisman et al., 2014). It is also noteworthy that we found that regions of association between FA and IQ extended to the superior section of the tracts close to the frontal cortex which have been reported to be involved in general cognitive functioning (Ohtani et al., 2017). Other WM regions close to the parietal and occipital cortex and involved in perception also showed correlations between FA and IQ. The association between WM microstructure and IQ in the parahippocampal and temporal cortex could be due to injury in the hippocampus in some participants of our CP group, as has been previously reported in infants asphyxiated at term (De Haan et al., 2006). This form of injury also seems to be associated with damage to the basal ganglia and thalamus. Thus, the relationship between IQ and FA in these regions could reflect a degree of covariance between the level of asphyxia and IQ.

While some regions that show a significant relationship between brain microstructure and IQ play a crucial role in the general cognitive functioning in dyskinetic CP, others might be underlying the motor impairment which is highly associated with the intellectual ability (Gabis et al., 2016). The FA was also related with IQ in specific WM regions associated with sensori-motor skills. These cortico-subcortical pathways, including the superior and posterior corona radiata and their projections to the precentral and postcentral gyrus, or the posterior thalamic radiation, may reflect a degree of covariance between motor function and IQ, as previously suggested (Smits-Engelsman and Hill, 2012). The association was further extended to the cerebral and cerebellar peduncles.

It is important to highlight the main differences between FA correlations with IQ and the FA differences between the CP and control group. While clusters resulting from the contrast between the CP and control group were extended to the left inferior temporal gyrus and to the inferior parts of the cerebrum, the IQ were not associated with FA in

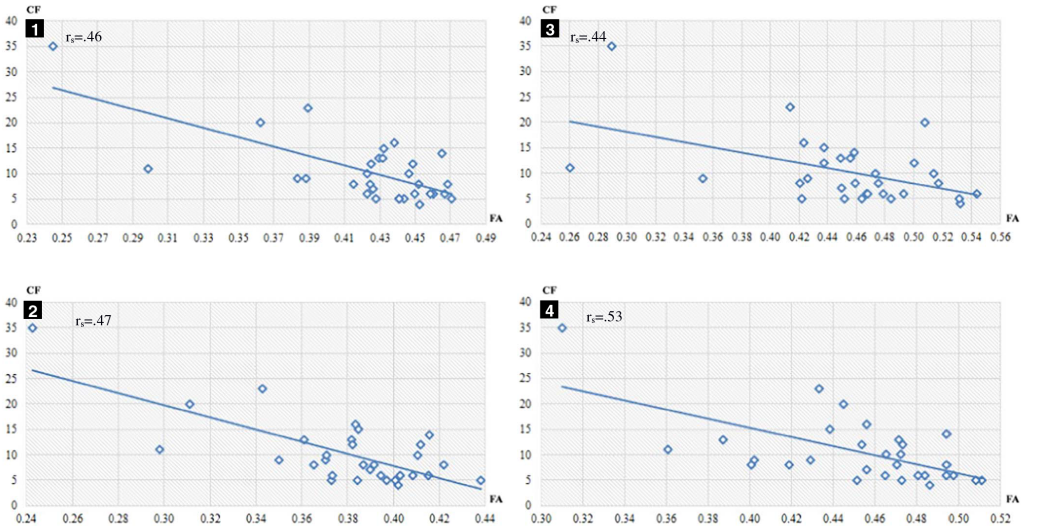

Fig. 4. Scatterplot between CF (cognitive flexibility) (y-axis; raw score) and mean FA (fractional anisotropy) (x-axis) in significant clusters ($p < 0.05$). Clusters sorted by size (largest first) and labelled by the same numbers as Table 4.

these brain regions. Overall, reduced FA correlated with lower IQ in several cortico-cortical and cortico-subcortical regions. This is in accordance with the general consensus that intelligence does not reside in a single, narrowly circumscribed brain region but requires a widespread network (Deary et al., 2010).

Cognitive flexibility measured by the WCST was sensitive to the WM integrity in our CP sample. Our results are consistent with previous studies in other CP samples showing that WM features are associated with executive function (Scheck et al., 2015) and specifically with WCST (Skranes et al., 2008). In particular, a study investigating quantitatively the relationship between executive function and connectivity in unilateral CP reports the involvement of the anterior cingulate (Scheck et al., 2015) while in dyskinetic CP we mainly found significant associations in the WM of the middle and posteriors parts of the cingulum. This difference may be due to the fact that the study of Scheck et al. (2015) focused on unilateral CP while our participants have dyskinetic CP.

Cognitive flexibility was associated with FA in regions known to contain connections with the frontal lobe such as the cingulate gyrus and the superior longitudinal fasciculus in the left hemisphere but also in regions not directly connected with the frontal lobe such as the posterior corpus callosum and superior and posterior corona radiata,

Table 4
Regions showing a negative correlation between fractional anisotropy and cognitive flexibility in the cerebral palsy group.

Cluster number	Cluster size (mm^3)	Mean FA (SD) (CP/ controls)		Anatomical regions	
				JHU white matter atlas	Harvard-Oxford cortical structural atlas
1	20,951	0.450 (0.104)/ 0.479 (0.110)	MS	Body and **splenium of corpus callosum**	
			B	*Posterior corona radiata*	*Cingulate gyrus (posterior division)*
			LH	Tapetum	**Precentral gyrus**
				Retrolenticular part of internal capsule	**Postcentral gyrus**
				Posterior thalamic radiation (include optic radiation)	Lingual gyrus
					Occipital fusiform gyrus
				Cingulum (cingulate gyrus)	Supramarginal gyrus (anterior and posterior division)
				Superior longitudinal fasciculus	Intracalcarine cortex
					Supracalcarine cortex
					Cuneal cortex
					Planum temporale
					Inferior temporal gyrus (temporo-occipital part)
2	245	0.379 (0.070)/ 0.392 (0.074)	RH		*Lateral occipital cortex (superior division)*
					Superior parietal lobe
					Precuneous cortex
3	69	0.379 (0.070)/ 0.392 (0.074)	RH		*Superior parietal lobe*
4	54	0.453 (0.080)/ 0.474 (0.085)	RH		Cingulate gyrus (anterior division)

B: bilateral; CP: cerebral palsy; FA: fractional anisotropy; JHU: John Hopkins University; LH: left hemisphere; MS: medial structure; RH: right hemisphere; SD: standard deviation. Discrepancies between fractional anisotropy and mean diffusivity results are indicated as follows. Bold indicates regions that are significant with both fractional anisotropy and mean diffusivity. Italics indicate regions that only show the same result between fractional anisotropy and mean diffusivity in one hemisphere.

the retrolenticular part of internal capsule and the posterior thalamic radiation. This is not surprising because WM disturbances in non-frontal regions can affect the connectivity of the entire brain, impairing communication between frontal lobe and other brain regions, and thereby causing executive function difficulties (Bettcher et al., 2016). Cognitive flexibility did not correlate directly with FA in the anterior part of the frontal lobe. The most anterior location where we found a correlation between WM microstructure and executive function was located in the WM near the precentral gyrus. Our results are located in more posterior regions compared with those reported by Ohtani et al. (2017) in a typically developing sample. Specifically, higher FA values in the right anterior middle orbital frontal cortex and the rostral anterior cingulate cortex were associated with more correct responses on the WCST in Ohtani et al. (2017). In agreement with Ohtani et al. (2017) another study reported that WM hyperintensities in the prefrontal region were independently associated with age-related increases in perseverative errors on the WCST (Gunning-Dixon and Raz, 2003). These results also seem to be contradictory to our findings that did not show such relationships in any prefrontal region. Impairments in executive function have been reported to be due to cortical-subcortical damage even when the frontal lobe is not directly damaged (Little et al., 2010). Accordingly, a study using a different measure of cognitive flexibility suggested the basal ganglia and the fronto-striato-thalamic circuit play crucial role in cognitive flexibility in healthy adults (Van Schouwenburg et al., 2014). Unexpectedly, there was neither significant relationship between FA and executive function near the fronto-striatal pathways in our study. This may be due to the fact that fronto-striatal circuits interact with other complex, cortical-subcortical circuits relevant to behaviour, such as the visual association regions of the temporal cortex, the hippocampus and the amygdala (Chudasama and Robbins, 2006) which could play an important role in the WCST performance in our sample. Interestingly, a study using another measure of cognitive flexibility found that higher FA was associated with better cognitive flexibility in posterior brain regions in children (Treit et al., 2014). Further research is needed to elucidate whether the negative finding in anterior regions might be a sign of neuroplastic reorganization.

The relationship between FA and cognitive flexibility was more predominant on the left hemisphere. The laterality observed in cognitive flexibility is not consistent with a previous study in unilateral CP assessing the four executive function domains (Bodimeade et al., 2013) but it was consistent with a previous study of cortical thickness in dyskinetic CP including 28 of the participants included in the present study (Laporta-Hoyos et al., 2017). This interhemispheric difference observed with the WCST has also been previously described in other neurological conditions (Jodzio et al., 2016).

All mean diffusivity results were relatively similar to FA. Even so, it is important to point out that FA and MD results are not completely coincident. These slight differences are not surprising as FA and MD are different measures of microstructure and previous studies focused on CP also found few differences between FA and MD results (Scheck et al., 2015; Yoshida et al., 2011). While high FA index reflects preserved WM and coherence of diffusion, MD is a measure of the total diffusion within a voxel and high values indicates tissue alteration (Le Bihan et al., 2001; Mori & Zhang, 2006). Overall, MD results for correlations seem to be less extended and the correlation between MD and executive function is more left sided than the correlation between FA and executive function. In the light of these results, it is important to take into account that although DTI does not allow examination of the cytoarchitecture of the WM tissue, increased FA in crossing-fiber regions could be reflecting a decrement in FA in a contributing fiber bundle (Douaud et al., 2011; Groeschel et al., 2014).

There are some potential limitations to our study. First, the performance observed in our sample cannot be generalized to the broad population of dyskinetic CP because we have included only subjects with adequate comprehension. It is also noteworthy that the study of cognitive function is only possible in this subsample of dyskinetic CP who had a minimum comprehension level. Second, the MRI requires to hold still or agreement to be sedated, therefore some participants satisfying the inclusion criteria were not able to be included in this study. Further participants were removed because of registration errors, because the method can only be used when brain pathology is not substantial. Third, the control group presents an above average cognitive functioning indicating that a larger sample size would be more representative of the general population. Fourth, although the age range is very wide, age-corrected raw scores had to be used because not all tests provide standardized scores. A replication of the analyses using a narrower age band would help to strengthen the present results. Fifth, the speed of response is a potential confound in some tasks such as information processing and attentional control because participants are encouraged to respond as fast as possible which may cause additional stress for the CP participants. In the attentional control task, it is further noteworthy that motor impairment might actually overestimate the performance of CP participants on "stop trials" (25% of the total trials) as motor slowness might preclude inhibition errors. Even so, reaction time scores are not taken into account for the analyses and SST is a computerized test with a low motor component because the stimulus does not disappear from the screen until the participant responds. Sixth, although the sample size may be considered large taking into account the characteristics of the sample and the previous studies, it is small in terms of statistical power.

5. Conclusion

Despite the difficulties in the assessment, brain structure and cognition can be studied in dyskinetic CP. It was demonstrated that dyskinetic CP was associated with widespread WM microstructural changes in sensori-motor and non-motor areas. Significant FA differences between dyskinetic CP and healthy controls were widespread in all lobes but are more extended near the parietal cortex. Lower IQ was correlated with widespread damage, including the superior section of tracts showing a reduced FA. While some of these regions play a crucial role in the IQ in dyskinetic CP and should be targets for future research, others might be underlying the motor impairment which is highly associated with the intellectual ability. Regarding executive function domains, their correlation with white matter FA was only significant for cognitive flexibility. Preserved cognitive flexibility was associated with regions known to contain cortico-cortical pathways, some of which are highly connected with the frontal lobe, and cortico-subcortical pathways not directly connected with frontal lobe. Although basal ganglia and thalamus injury are associated with dyskinetic CP, executive function seems not to be specifically related to the WM of the fronto-striatal circuit as expected. Further research is needed to elucidate whether the negative finding in this region might be a sign of neuroplastic reorganization.

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Supplementary Table 1. Regions showing a negative correlation between mean diffusivity and intelligence quotient in the cerebral palsy group.

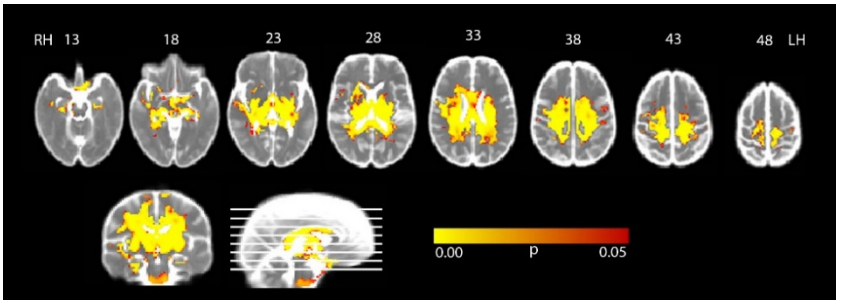
Cluster size (mm^3)	Mean MD (SD) CP/controls (10^{-3} s/mm^2)		Anatomical regions	
			JHU white matter atlas	Harvard-Oxford cortical structural atlas
55355	0.828 (0.213) / 0.921 (0.261)	MS	Body and splenium of corpus callosum Column and body of fornix	
		B	Fornix (cres) Superior and posterior corona radiata Posterior limb and retrolenticular part of internal capsule External capsule Cingulum (cingulate gyrus) Superior longitudinal fasciculus Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) Anterior limb of internal capsule	Insular cortex Superior frontal gyrus Precentral gyrus Postcentral gyrus Superior parietal lobe Juxtapositional lobe cortex Cingulate gyrus (posterior division) Central and parietal opercular cortex Planum temporale
		LH	*Cerebral peduncle* Uncinate fasciculus	*Middle frontal gyrus* Frontal orbital cortex

B: bilateral; CP: cerebral palsy; JHU: John Hopkins University; LH: left hemisphere; MD: mean diffusivity; MS: medial structure; RH: right hemisphere; SD: standard deviation. Discrepancies between fractional anisotropy and mean diffusivity results are indicated as follows. Bold indicates regions that are significant with both fractional anisotropy and mean diffusivity. Italics indicate regions that only show the same result between fractional anisotropy and mean diffusivity in one hemisphere.

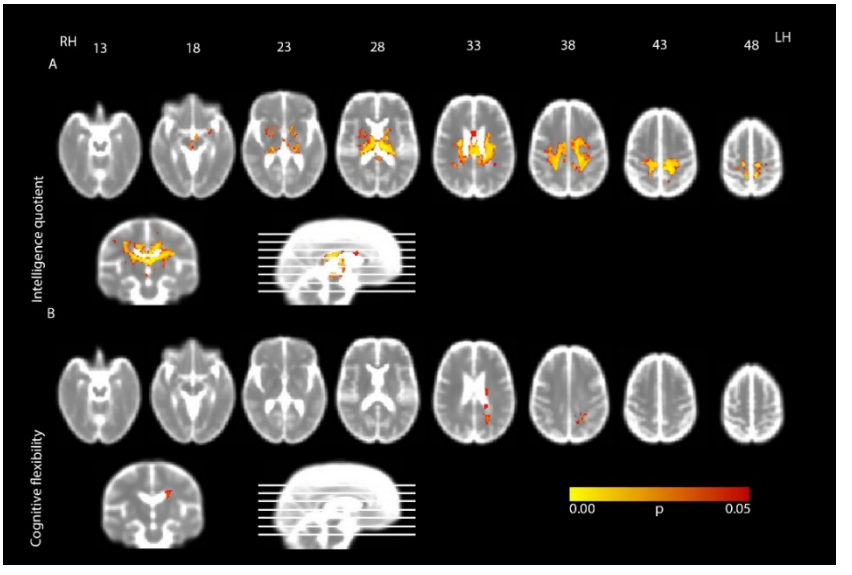
Supplementary Table 2. Regions showing a positive correlation between mean diffusivity and cognitive flexibility in the cerebral palsy group.

Cluster number	Cluster size (mm^3)	Mean MD (SD) CP/controls (10^{-3} s/m m^2)		Anatomical regions	
				JHU white matter atlas	Harvard-Oxford cortical structural atlas
1	2035	0.900 (0.172) / 0.813 (0.105)	MS	**Splenium of corpus callosum**	
			LH	**Superior longitudinal fasciculus** *Posterior corona radiata*	**Precentral gyrus** **Postcentral gyrus** *Superior parietal lobe* *Lateral occipital cortex (superior division)* *Cingulate gyrus (posterior division)* *Precuneous cortex*
2	565	0.001 (0.151) / 0.805 (0.084)	LH	Superior corona radiata Superior fronto-occipital fasciculus (could be a part of anterior internal capsule)	
3	170	0.855 (0.032) / 0.821 (0.027)	LH		*Precuneous cortex*

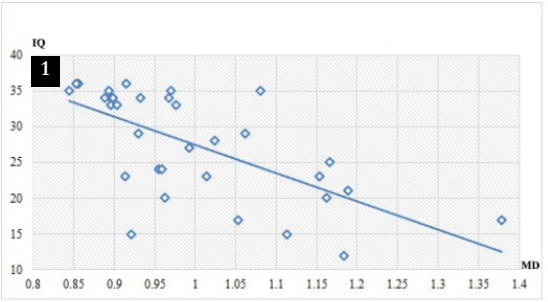
B: bilateral; CP: cerebral palsy; JHU: John Hopkins University; LH: left hemisphere; MD: mean diffusivity; MS: medial structure; RH: right hemisphere; SD: standard deviation. Higher scores in cognitive flexibility indicate worse performance. Discrepancies between fractional anisotropy and mean diffusivity results are indicated as follows. Bold indicates regions that are significant with both fractional anisotropy and mean diffusivity. Italics indicate regions that only show the same result between fractional anisotropy and mean diffusivity in one hemisphere.



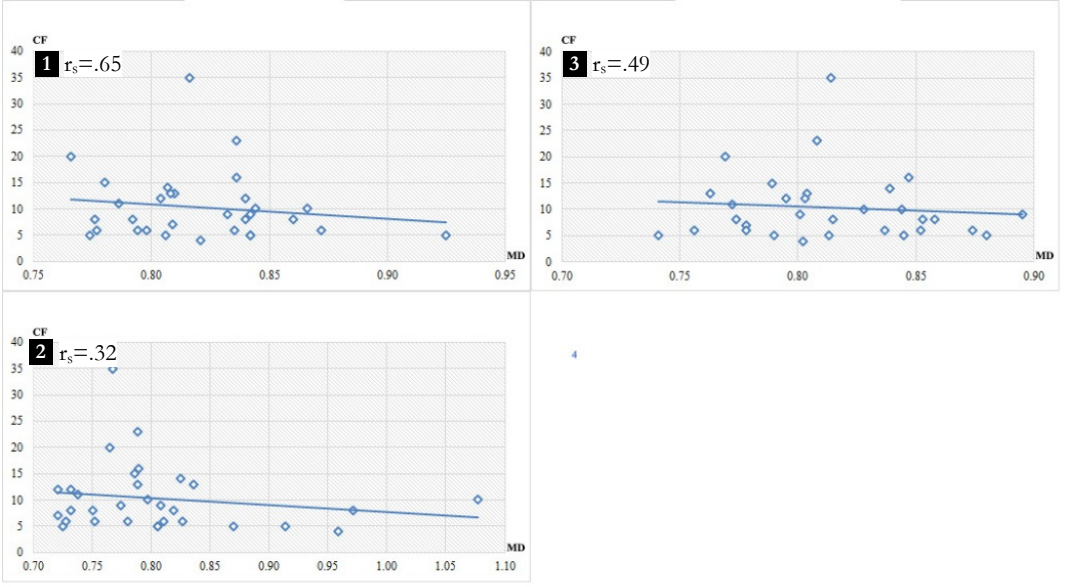
Supplementary Figure 1. Regions where mean diffusivity was significantly higher in a sample of 33 subjects with dyskinetic cerebral palsy compared with 33 age and sex matched healthy controls. Results are shown at p<0.05 corrected for multiple comparisons and overlaid on the group mean diffusivity image. RH: right hemisphere; LH: left hemisphere.



Supplementary Figure 2. Regions where mean diffusivity correlated A) negatively with intelligence quotient (Raven's coloured progressive matrices) B) positively with cognitive flexibility (Wisconsin card sorting test). Results are shown at p<0.05, corrected for multiple comparisons, controlled for age and sex and overlaid on the group mean fractional anisotropy image. RH: right hemisphere; LH: left hemisphere.



Supplementary Figure 3. Scatterplot between IQ (intelligence quotient) (y-axis; raw score) and mean MD (mean diffusivity) (x-axis) in significant clusters ($p<0.05$).



Supplementary Figure 4. Scatterplot between CF (cognitive flexibility) (y-axis; raw score) and mean MD (mean diffusivity) (x-axis) in significant clusters ($p<0.05$). Clusters sorted by size (largest first) and labelled by the same numbers as Supplementary Table 2.

3.4 Study 4

Reference

Laporta-Hoyos, O., Fiori, S., Pannek, K., Ballester-Plané, J., Leiva, D., Reid, R.B., Pagnozzi, A.M., Vázquez, E., Delgado, I., Macaya, A., Pueyo, R., Boyd, R. (2018). Brain lesion scores obtained using a simple semi-quantitative scale from MR imaging are associated with motor function, communication and cognition in dyskinetic cerebral palsy. *NeuroImage: Clinical, 19*, 892-900.

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Brain lesion scores obtained using a simple semi-quantitative scale from MR imaging are associated with motor function, communication and cognition in dyskinetic cerebral palsy

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ABSTRACT

Purpose: To characterise brain lesions in dyskinetic cerebral palsy (DCP) using the semi-quantitative scale for structural MRI (sqMRI) and to investigate their relationship with motor, communication and cognitive function.

Materials and methods: Thirty-nine participants (19 females, median age 21y) with DCP were assessed in terms of motor function, communication and a variety of cognitive domains. Whole-head magnetic resonance imaging (MRI) was performed including T1-MPRAGE, T2 turbo spin echo (axial plane), and fluid attenuated inversion recovery images (FLAIR). A child neurologist visually assessed images for brain lesions and scored these using the sqMRI. Ordinal, Poisson and binomial negative regression models identified which brain lesions accounted for clinical outcomes.

Results: Brain lesions were most frequently located in the ventral posterior lateral thalamus and the frontal lobe. Gross (B = 0.180, $p < .001$; B = 0.658, $p < .001$) and fine (B = 0.136, $p = .003$; B = 0.540, $p < .001$) motor function were associated with global sqMRI score and parietal involvement. Communication functioning was associated with putamen involvement (B = 0.747, $p < .028$). Intellectual functioning was associated with global sqMRI score and posterior thalamus involvement (B = −0.018, $p < .001$; B = −0.192, $p < .001$). Selective attention was associated with global sqMRI score (B = −0.035, $p < .001$), parietal (B = −0.063, $p = .023$), and corpus callosum involvement (B = −0.448, $p < .001$). Visuospatial and visuoperceptive abilities were associated with global sqMRI score (B = −0.078, $p = .007$) and medial dorsal thalamus involvement (B = −0.139, $p < .012$), respectively.

Conclusions: Key clinical outcomes in DCP are associated with specific observable brain lesions as indexed by a simple lesion scoring system that relies only on standard clinical MRI.

1. Introduction

Dyskinetic cerebral palsy (DCP) is the second largest cerebral palsy (CP) group comprising between 3 and 15% of CP cases (Himmelmann et al., 2009). Motor disturbances are the primary component of CP, but the main drivers of reduced quality of life tend to be other factors (Laporta-Hoyos et al., 2017a). Communication is impaired in 25% of all CP cases (Novak et al., 2012) which influences quality of life (Colver et al., 2015). Furthermore, almost 50% of the CP population have intellectual disability (Novak et al., 2012) which has been reported to be

Abbreviations list: Cerebral palsy, (CP); Dyskinetic cerebral palsy, (DCP); Fluid attenuated inversion recovery images, (FLAIR); Gross motor function classification system, (GMFCS); Magnetic resonance images, (MRI); Semi-quantitative scale for brain structural MRI, (sqMRI)

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associated with psychological and social functioning as measured by the Strengths and difficulties questionnaire (Parkes et al., 2008). Specific neuropsychological impairments such as visuospatial, visuoperceptive, memory and executive functions have also been described (Straub and Obrzut, 2009), some of which seem to impair quality of life (Laporta-Hoyos et al., 2017a).

Studies that have utilised qualitative categorical descriptions of computed tomography and magnetic resonance images (MRI) have suggested that the most frequent brain abnormalities observed in DCP may be in the basal ganglia and thalamus, which in some cases are accompanied by periventricular leukomalacia, but some patients are without any apparent brain injury (Aravamuthan and Waugh, 2016; Benini et al., 2013; Himmelmann and Uvebrant, 2011; Krägeloh-Mann and Cans, 2009; Monbaliu et al., 2015; Towsley et al., 2011). These findings have provided critical insights, but the literature currently lacks quantitative analyses for moderately sized DCP cohorts. Quantitative neuroimaging studies in DCP have shed light on the pathogenesis of different CP subtypes (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b; Yoshida et al., 2011) but their translatability to routine clinical settings is limited. Ideally, such findings are best translated into clinical practice in a manner that utilises tools and imaging that clinicians are already familiar with. The semi-quantitative scale for brain structural MRI (sqMRI) is one such tool (Fiori et al., 2015; Fiori et al., 2014). It has been tested for reliability (Fiori et al., 2014) and construct validity in unilateral CP (Fiori et al., 2015) and can be robustly scored despite some motion artefacts that are highly likely to occur in DCP.

Longitudinal studies exploring long-term consequences of early brain injury provide unique opportunities to uncover information that may aid development of prognostic models. Unfortunately, studies of this nature are highly costly to conduct, and can take years before imaging can be compared with developmental outcomes. Given that brain lesions in CP are not progressive (Rosenbaum et al., 2007), a cross-sectional study might elucidate the association between brain lesions and concurrent clinical outcomes in older children or adults with DCP. The purpose of the present cross-sectional study was to (A) characterise a moderate-sized sample of participants with DCP using the sqMRI scale (Fiori et al., 2014), and (B) investigate the relationship between sqMRI scoring and key clinical outcomes in CP: motor, communication and cognitive function. We hypothesised that the primary feature of the DCP patients would be a brain lesion of the basal ganglia and thalamus. The second hypothesis was that the severity of the brain lesion would be negatively associated with clinical outcomes.

2. Materials and methods

2.1. Participants

All procedures performed in the study were in accordance with the ethical standards of the 1964 Helsinki declaration. Ethical approval was obtained by the University of Barcelona's Institutional Ethics Committee, Institutional Review Board (IRB 00003099 assurance number: FWA00004225; http://www.ub.edu/recerca/comissiobioetica.htm) and the Hospital Universitari Vall d'Hebron. Written and verbal informed consents were obtained from all participants or their legal guardian.

This study included 39 participants (19 male with median age 20 years, 20 females with median age 22.5 years) recruited from two hospitals of Barcelona, and three other institutions. The inclusion criteria for the study were (A) clinical diagnosis of CP with predominant dyskinetic features, (B) older than 6 years, and (C) for the neuropsychological assessment, being able to understand instructions as evaluated by the Spanish grammar screening test (receptive part) (Toronto, 1973). Exclusion criteria were (1) presence of severe visual or auditory disability that precludes neuropsychological assessment, and (2) lack of an intelligible yes/no response system.

2.2. Magnetic resonance imaging

Magnetic resonance images (MRI) were acquired on a Siemens Magnetom TRIO 3 T scanner (Erlangen, Germany). Fluid attenuated inversion recovery images (FLAIR) were acquired in 25 axial slices (9040 ms TR, 86 ms TE, 0.43 × 0.43 mm, slice thickness 5.2 mm). High-resolution three-dimensional T1-weighted images were acquired in the sagittal plane with a MPRAGE sequence (1900 ms TR, 2.46 ms TE, inversion time 900 ms, voxel size 0.7 mm × 0.7 mm × 1 mm). T2 turbo spin echo (axial plane) images (5150 ms TR, 103 ms TE, flip angle of 120°, 0.43 × 0.43 mm, slice thickness 5.2 mm) were acquired, also in 25 axial slices, where time permitted. Prior to scanning, 21 participants took either diazepam (n = 15; 2.5-10 mg) or pentobarbital and propofol (n = 6), supervised by a physician in accordance with the protocol reviewed by the ethics committee.

2.3. Scoring

The sqMRI scoring was performed by a child neurologist (SF) according to the procedure and calculation detailed in Fiori et al. (2014). Abnormalities on FLAIR images were crosschecked with the axial T2 images and sagittal T1 images when available. Briefly, this system provides scores by brain region, assigning progressively higher scores for increased lesion involvement, as assessed by inspection of structural images. Each periventricular, middle and cortico/subcortical layer of the frontal, parietal, temporal and occipital lobes was scored as 0 or 1, and summed to provide a score ranging from 0 to 3 for each lobe. All lobar scores were summed to provide a hemispheric score (range: 0–24). As in Fiori et al. (2014), the corpus callosum, cerebellum and basal-ganglia-and-brainstem were each scored. For the cerebellum, the score ranged from 0 to 3, by assigning 1 point to the involvement of each vermis, right and/or left hemisphere. For corpus callosum, the score ranged from 0 to 3, by assigning 1 point to the involvement of each anterior, middle and/or posterior corpus callosum. In the original paper, the basal-ganglia-and-brainstem score ranged from 0 to 5, by assigning 1 point to the involvement of each caudate, lenticular, posterior limb of internal capsule, thalamus and/or brainstem. In the present study including DCP, as we were interested in deep grey matter injury, we extended the latter score to also detail the specific involvement of the thalamic nuclei (anterior thalamus, ventral posterior lateral thalamus, medial dorsal thalamus, posterior thalamus). We also extended the lenticular involvement by detailing the involvement of globus pallidus and/or putamen. As in the original paper, we assigned a score of 1 to the involvement of each of the detailed structure, thus resulting in a larger score range for the basal-ganglia-and-brainstem of 0 to 9 on each side (right or left). In the present study, no lateralization was considered for lesion severity. We thus included in the statistical analysis the sum of right and left scores for lateralized measures. The sum of all the summary scores according to the original template (Fiori et al., 2014) provided a global score ranging from 0 to 40, ranged from 0 to 48 in the present study due to the revision of basal-ganglia-and-brainstem score. Brain lesion types were also classified by using the Krägeloh-Mann categories (Krägeloh-Mann, 2004) as these were common categorical descriptions used in previous studies (Himmelmann and Uvebrant, 2011; Krägeloh-Mann and Cans, 2009; Towsley et al., 2011).

2.4. Clinical measures

Gross and fine motor functions were classified according to the Gross motor function classification system (GMFCS) and the Manual ability classification system. Communication was assessed with the Communication function classification system. Intellectual functioning was measured using Raven's coloured progressive matrices (Raven et al., 2001). Four domains of executive functions were assessed:

- Attentional control: Inhibition and sustained attention using the Stop signal task (Cambridge Cognition, 1999). Selective visual and

verbal attention using the digit span (Wechsler, 2003; Wechsler, 1999) and the spatial span (Wechsler and Naglieri, 2006).
- Cognitive flexibility: Wisconsin card sorting test (Kongs et al., 2000).
- Goal setting: Stockings of Cambridge test (Cambridge Cognition, 1999).
- Information processing: Lexical verbal fluency test (Peña-Casanova et al., 2009).

Visual/verbal short and long term memory were assessed using the Pattern/Verbal recognition memory task (Cambridge Cognition, 1999). Benton's facial recognition test (Benton, 1994) and Benton's judgment of line orientation test (Benton, 1994) were used to assess visuo-perceptual and visuospatial abilities. The Peabody picture vocabulary test third edition (Dunn, 1997) was used to assess vocabulary. All clinical measures were assessed by two trained neuropsychologists (OLH and JBP).

2.5. Statistics

We examined relationships between each clinical measure and both (A) sqMRI global scores and (B) sqMRI subscores. A top-down approach was followed to find the best models. Specifically, a first model including all relevant predictors correlating with sqMRI scores (Supplementary Table 1) was estimated (Supplementary Table 2) and simplified by manually removing those predictors that yielded non-significant results and validated by inspecting information criteria and multicollinearity measures (Supplementary Information 1).

The sqMRI scores that were significantly correlated with motor and communication status (ordinal variables) (Supplementary Table 1) were entered into separate ordinal regression models to identify the best predictive sqMRI scores for each function. Proportional odds assumptions were checked for ordinal models. The sqMRI scores that showed significant correlations with cognitive function scores (count data) were entered into separate Poisson regression models to identify the best predictors (i.e. sqMRI sub-scores) for each cognitive domain. All statistical assumptions were assessed and binomial negative models were used when Poisson regression models condition of equidispersion was not met. Cook's distance was used to measure the influence of data points. Data points showing a Cooks distance > 4/(n-k-1) (n = number of participants, k = independent variables included in the model) were removed from the Poisson regression model. In instances where results remained substantially stable after removal of these points, the data points were included in the final model. Age was included as a covariate in all models considering cognitive functioning. The level of significance of the model predictors was set at $p < .05$ after false discovery rate correction for multiple comparisons.

3. Results

From a total of 101 eligible participants, 39 (6-62y, 19 female) were included in the study (Fig. 1; Table 1).

3.1. Characterization of participants with DCP using the sqMRI scale

Frequencies of the sqMRI scores included in the analyses are reported in Fig. 2, Supplementary Table 3 and Supplementary Table 4. The most frequent brain lesion location reported by the sqMRI scale was the ventral posterior lateral thalamus ($n = 23$; 59%; Fig. 3A). Other lesions identified by the sqMRI scale were in the posterior ($n = 14$; 36%), middle ($n = 5$; 13%) and anterior (n = 5; 13%) thalamus; posterior limb of internal capsule ($n = 17$; 44%), putamen (n = 17; 44%); globus pallidus ($n = 3$; 8%); brainstem (n = 3; 8%), and caudate nucleus (n = 2; 5%).

Regarding hemispheric involvement, lesions frequently involved frontal lobe ($n = 20$; 51%; Fig. 3B), followed by the parietal ($n = 16$; 41%) and temporal lobes ($n = 12$; 31%). Only 21% ($n = 8$) of participants presented a lesion involving the occipital lobe. Although frontal lesions were the second most frequent, their sqMRI score was generally lower (≤ 3.5 out of 6 in all cases), indicating less severe lesions (in terms of extent) than those observed in the parietal lobe, where 59% of those with non-zero score had a score > 3.5. Interestingly, all participants, except eight who had no observable lesion (GMFCS: I $n = 4$, II $n = 3$, IV $n = 1$; aetiology: unclassifiable $n = 6$, kernicterus $n = 2$), presented with a lesion of the basal ganglia or thalamus. One third of participants with a visible brain lesion had lesions constrained to the basal ganglia and thalamus. Finally, no participant had an observable lesion in anterior corpus callosum or vermis.

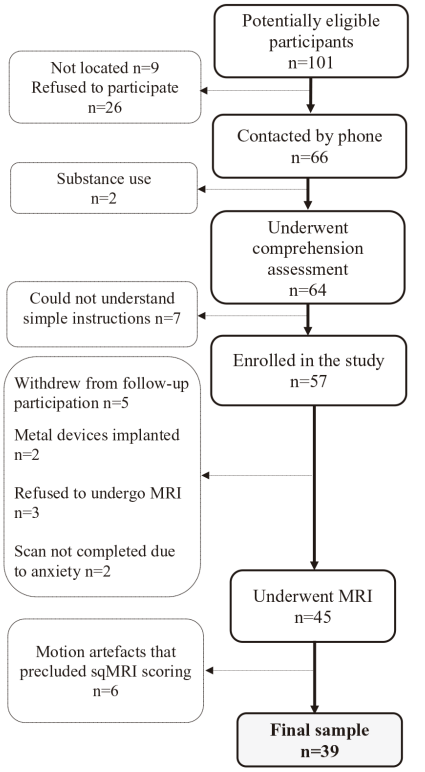

Fig. 1. Flowchart showing requitement process for participants.

3.2. Association between sqMRI scoring and clinical outcomes

The final regression models examining the effects of sqMRI scores on clinical outcomes are presented in Table 2 and Fig. 4.

3.2.1. Motor status

For clarity, results deriving from ordinal regression are reported henceforth using odds instead of log-odds. The odds of a higher GMFCS levels was 20% greater when the global sqMRI score increased by one unit ($p < .001$). When the parietal sqMRI score increased by one unit, the odds of higher levels in GMFCS was 93% ($p < .001$). Regarding fine motor function, the odds of higher levels in Manual ability classification system increased by 15% ($p = .003$) for each unit increase in the global sqMRI score, whereas it increased 72% ($p < .001$) as a result of a unit increase in parietal score (Fig. 5A).

Table 1
Demographics and clinical data of dyskinetic cerebral palsy cohort (n = 39).

Sex	
n (female/male)	19/20
Age	
Median (interquartile range)/range	21 (13)/6–62
Gestational age	
n (< 32 weeks/32-36 weeks/≥ 37 weeks)	3/5/31
Epilepsy status	
n (no epilepsy/active/resolved)	26/10/3
Type of lesion (Krägeloh-Mann categories, 2007)	
n (CDGM/PWM/miscellaneous/normal)	23/8/0/8
Aetiology, n	
HIE	15
Intra-cranial haemorrhage/infarction/ hydrocephalus	5
Infection	1
Kernicterus	2
Unclassifiable	16
Motor distribution	
n (tetraplegia/hemiplegia/monoplegia)	32/6/1
Gross motor function (GMFCS)$^{+}$, levels (n)	I (15); II (7); III (3); IV (5); V (9)
Manual ability (MACS)$^{+}$, levels (n)	I (5); II (10); III (12); IV (3); V (9)
Communication (CFCS)$^{+}$, levels (n)	I (15); II (16); III (4); IV (4); V (0)

		Median (interquartile range)†/range†/n*
Intellectual functioning (RCPM)		29 (11)/12–36/39
Executive function	**Inhibition and sustained attention** (SST)	283 (16)/237–316/35
	Selective verbal attention (Digit span)	13 (8)/4–22/35
	Selective visual attention (Spatial span)	14 (8)/4–21/37
	Cognitive flexibility (WCST)$^{+}$	8 (7)/4–35/36
	Goal setting (SOC)	8 (3)/1–12/36
	Information processing (Lexical verbal fluency)	31 (18)/4–51/30
Visuoperception	**Visuospatial abilities** (BJLOT)	14 (8)/4–21/37
	Visuoperceptual abilities (BFRT)	13 (8)/4–22/39
Memory	**Visual short term** (PRM)	19.5 (5)/13–24/38
	Verbal short term (VRM)	23 (4)/13–24/38
	Visual long term (PRM)	8.5 (3)/3–12/38
	Verbal long term (VRM)	22 (4)/12–24/38
Vocabulary (PPVT-III)		136 (47)/45–182/39

BFRT: Benton's facial recognition test; BJLOT: Benton's judgment of line orientation test; CDGM: cortical and deep grey matter; CFCS: Communication function classification system; GMFCS: Gross motor function classification system; HIE: hypoxic-ischemic encephalopathy; MACS: Manual ability classification system; PPVT-III: Peabody picture vocabulary test-3rd; PRM: Pattern recognition memory; PWM: Periventricular white matter; RCPM: Raven's coloured progressive matrices; SOC: Stockings of Cambridge; SST: Stop signal task; VRM: Verbal recognition memory; WCST: Wisconsin card sorting test. +Higher scores indicate worse performance. † Raw scores. *Despite the adaptations used (Supplementary table 5) missing data are due to the fact that some subjects present anarthria accompanied by very severe motor impairments that preclude using an appropriate response system for the test used.

3.2.2. Communication

The odds of higher Communication function classification system levels would increase 111% (p = .028) as a result of a unit increase in the putamen score (Fig. 5B).

3.2.3. Cognition

A unit increase in the posterior thalamus sqMRI subscore was associated with a 17.47% decrease in the Raven's coloured progressive matrices score (B = −0.192; p < .001; Fig. 5C). This effect contributed to the significant relationship between Raven's coloured progressive matrices scores and global sqMRI score (decrease of 1.78% per unit sqMRI increase; B = −0.018; p < .001).

Regarding executive functions, sqMRI scores were not associated with cognitive flexibility, goal setting, information processing, selective verbal attention or inhibition and sustained attention. By contrast, selective visual attention, measured by spatial span, was significantly associated with different models. The global model for spatial span indicated that a unit change in the sqMRI global score reduced the spatial span direct score by 3.44% (B = −0.035; p < .001). This appeared to be primarily driven by parietal and corpus callosum subscores, for which a unit increase would decrease the spatial span direct score by 6.11% (B = −0.063; p = .023) and 36.12% (B = −0.448; p < .001), respectively (Fig. 5D).

Visuospatial abilities were observed to decrease 7.5% as a result of a unit increase in the sqMRI global score (B = −0.078; p = .007) and visuoperceptive scores decreased by 12.98% as a result of a unit change in the medial dorsal thalamus score (B − −139; p − .012; Fig. 5E). Memory and vocabulary were not associated with any sqMRI score.

4. Discussion

Overall, results indicate that (A) observable lesions in DCP most commonly occur in the lateral thalamus and frontal lobe, and (B) motor, communication and cognitive functioning are associated with brain lesion severity as measured by a simple lesion scoring system. By performing standardised sqMRI scoring, clinicians might use the weights from the presented models to predict several patient outcomes that can guide treatment.

In order to assist in the earlier detection of DCP, the frequency and location of brain lesions and their relationships with clinical outcomes should be understood. Previous neuroimaging studies of DCP have been based on qualitative analyses of pathogenesis (Himmelmann and Uvebrant, 2011; Krägeloh-Mann and Cans, 2009; Towsley et al., 2011) or advanced neuroimaging protocols that cannot be easily utilised in a clinical context (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b; Yoshida et al., 2011). To enable clinical translation, in the present study brain lesions and their association with clinical outcomes have been characterized using a semi-quantitative scale for brain lesion severity on MRI, that is clinically accessible due to its relative simplicity and reliance only on standard clinical images. Basal ganglia and thalamus regions' involvement was evaluated in more detail than the original version of the sqMRI scale. Owing to the semi-quantitative scale's relatively accessible approach, the present study has a moderately good sample size considering the CP subtype and the wide range of cognitive assessments.

The present work reveals that the ventral posterior lateral thalamus is the most common brain lesion location in DCP. This is in agreement with the well-known pattern of brain involvement in diffuse hypoxic-ischemic injury of term neonates (Barkovich and Raybaud, 2005). The ventral posterior lateral thalamus has a fundamental role as a relay on S1 ascending projections influencing sensorimotor control (Chien et al., 2017; De Lafuente and Romo, 2005; Vazquez et al., 2012). The posterior thalamus also was frequently involved in our sample (36%). There are suggestions that the pulvinar critically supports an early visual pathway and plays a broad role in human cognition (Bridge et al., 2016). Congruent with these suggestions, in the present study posterior thalamic status was associated with intellectual functioning, as assessed by a visual reasoning task. By contrast, the medial dorsal thalamus and anterior thalamus were rarely impaired by lesions, but sufficiently so that medial dorsal thalamic status was associated with visuoperceptive abilities (evaluated by a facial recognition test). This is consistent with findings that medial dorsal thalamus is involved in familiarity detection (Kafkas and Montaldi, 2014) which seems to be influenced by face perception (Yan et al., 2017). Overall, regions involved by lesions in our group correspond to those reported in term children with hypoxic-

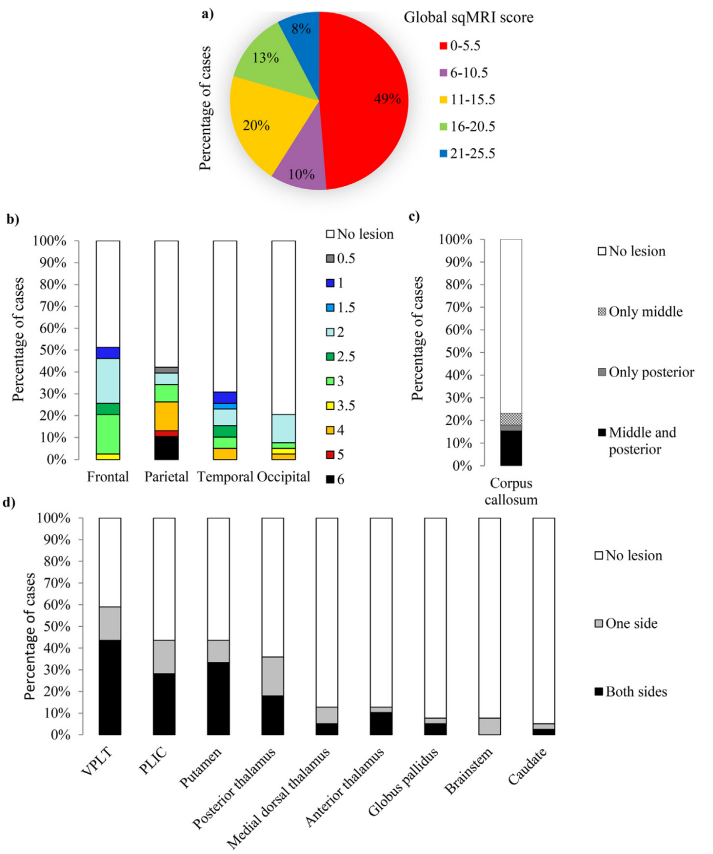

Fig. 2. Percentage of cases presenting different lesion severity according sqMRI scores a) global score (maximum score of 40) to b) ranging from 0 to 6 for each lobar score (including right and left side) c) ranging from no lesion, middle and posterior lesion for corpus callosum and d) ranging from none, unilateral and bilateral lesion for basal ganglia, thalamus, brainstem and cerebellum. PLIC: posterior limb of internal capsule; VPLT: ventral posterior lateral thalamus.

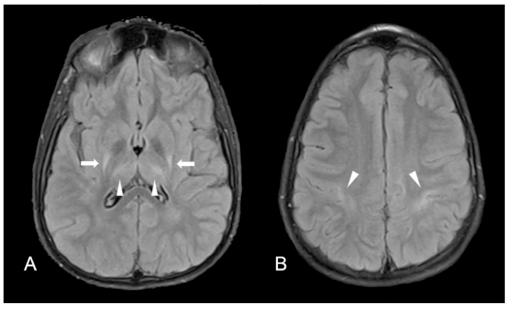

Fig. 3. Axial FLAIR images of a 14 year old male, showing an example of the most common involvement observed, including ventral posterior lateral thalamus (A, arrowheads) and frontal perirolandic cortex (B, arrowheads). In this subject also putamina are involved (arrows).

ischemic encephalopathy, kernicterus or other known etiopathogenetical factors which typically result in DCP (Graham et al., 2016; Krägeloh-Mann et al., 2002). A typical example of this is the involvement of basal ganglia–thalamus pattern mostly affecting the central grey nuclei and perirolandic cortex (Fig. 3). Each structure was, however, deliberately considered independently in the analyses.

With regards to cerebral lobes, results agreed with previous reports that white matter injury can occur in all cerebral lobes (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b). Frontal lobe damage was the second most common observable lesion (but the most common lobar involvement). This is consistent with the frequent abovementioned pattern of lesion reported in term neonates with hypoxic encephalopathy (Barkovich and Raybaud, 2005). Interestingly, although less frequent, parietal lobe lesions were more severe than frontal lobe lesions and were associated with poorer motor functioning. Of note, participants were diagnosed with CP with predominant dyskinetic features, thus lobar involvement might reflect the co-existence of spastic symptoms. This is consistent with the idea that sensory deficits

Table 2
Final regression models showing the association between sqMRI scores, motor functioning, communication and cognitive domains.

Function assessed (test used)				sqMRI scores (predictors)	B	Std. Error	P	Omnibus test (global test)			AIC/BIC
								Likelihood ratio chi-square	Degrees of freedom	Adjusted p	
Motor status[o]	**Gross motor function**	(GMFCS)[+]	Global model	Global score	0.180	0.050	< 0.001***	16.067	1	< 0.001***	–
			Subscores model	Parietal total	0.658	0.172	< 0.001***	18.041	1	< 0.001***	50.028/58.346
	Fine motor function	(MACS)[+]	Global model	Global score	0.136	0.045	0.003**	10.556	1	0.004**	
			Subscores model	Parietal total	0.540	0.165	< 0.001***	12.482	1	< 0.001***	50.003/58.320
Communication[o]		(CFCS)[+]	Subscores model	Putamen	0.747	0.340	0.028*	5.119	1	0.033*	33.666/40.320
Intellectual functioning[p]		(RCPM)	Global model	Global score	−0.018	0.005	< 0.001***	15.799	2	< 0.001***	–
			Subscores model	Posterior thalamus	−0.192	0.043	< 0.001***	21.752	2	< 0.001***	229.961/ 234.711
Executive function	**Attentional control**[p]	**Inhibition and sustained attention** (SST)	ns								
		Selective visual attention (Spatial span)	Global model	Global score	−0.035	0.008	< 0.001***	25.511	2	< 0.001***	–
			Subscores model	Parietal total	−0.063	0.028	0.023*	44.011	3	< 0.001***	191.770/ 197.991
				Corpus callosum	−0.448	0.094	< 0.001***				
		Selective verbal attention (Digit span)	Subscores model	Posterior thalamus	−0.128	0.065	0.049*	4.707	2	0.095	205.115/ 209.781
	Cognitive flexibility (WCST)[b+]		ns								
	Goal setting (SOC)[p]		Global model	Global score	−0.023	0.010	0.019*	5.789	2	0.060	–
	Information processing (Lexical verbal fluency)[b]		ns								
Visuoperception	**Visuospatial abilities** (BJLOT)[b]		Global model	Global score	−0.078	0.029	0.007**	7.010	2	0.036*	–
	visuperceptual abilities (BFRT)[p]		Subscores model	Medial dorsal thalamus	−0.139	0.055	0.012*	7.372	2	0.033*	241.630/ 246.620
Memory[p]	**Short term**	**Visual** (PRM)	ns								
		Verbal (VRM)									
	Long term	**Visual** (PRM)									
		Verbal (VRM)									
Vocabulary[b]	(PPVT-III)		ns								

BFRT: Benton's facial recognition test; BJLOT: Benton's judgment of line orientation test; CFCS: Communication function classification system; GMFCS: Gross motor function classification system; MACS: Manual ability classification system; PPVT-III: Peabody picture vocabulary test-3rd; PRM: Pattern recognition memory; RCPM: Raven's coloured progressive matrices; SOC: Stockings of Cambridge; sqMRI: Semi-quantitative scale for structural MRI; SST: Stop signal task; VRM: Verbal recognition memory; WCST: Wisconsin card sorting test. [b] Binomial negative model; [p] Poisson regression model; [o] Ordinal regression model; *p ≤ .05; **p ≤ .01; ***p ≤ .001 after false discovery rate correction for multiple comparisons in the global test. [+]Higher scores indicate worse performance. AIC and BIC values are only provided for subscores models.

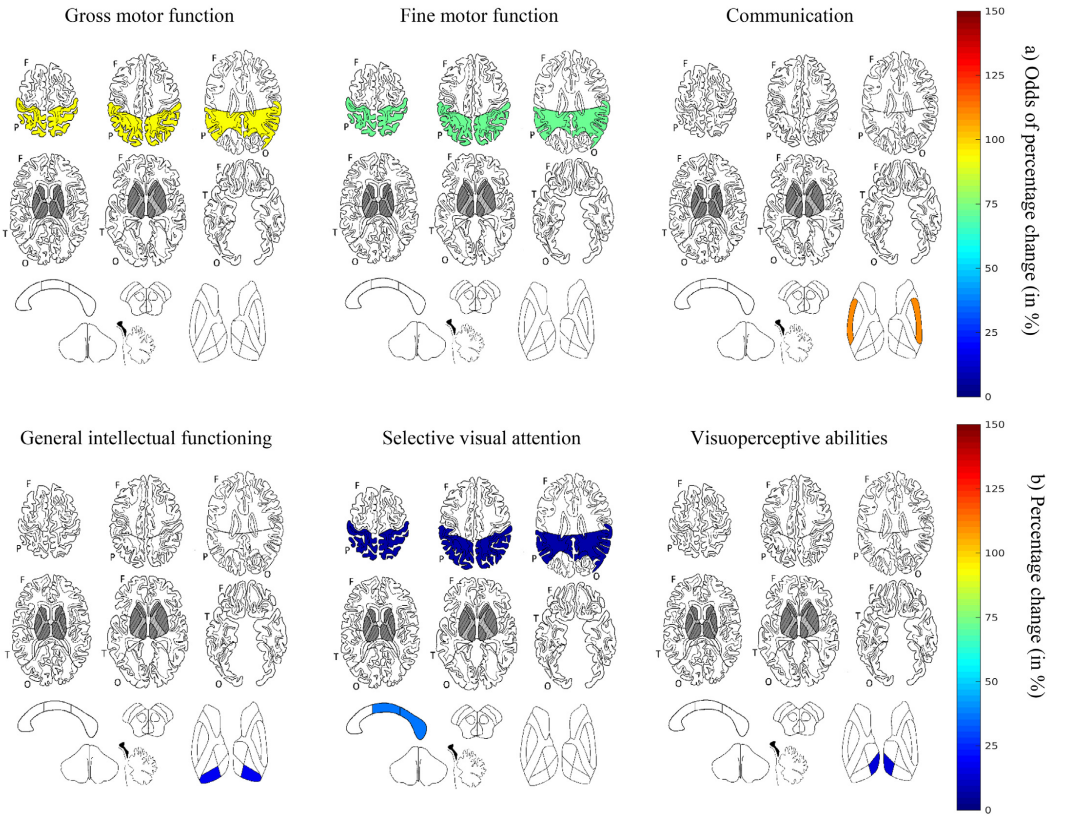

Fig. 4. An illustration of the results of the regression models obtained for the subscores regression models presented in Table 2. F: frontal, O: occipital, P: parietal, T: temporal. The colour bar indicates a) the percentage of odds change in each clinical outcome when the sqMRI score in this region increases by one unit b) the percentage change in clinical outcome when the sqMRI score in this region increases by one unit.

may alter motor coordination (Tsao et al., 2014). Additionally, more severe presentations in DCP have been reported to include cortical involvement (i.e. spastic symptoms) together with subcortical involvement (i.e. dyskinetic symptoms) (Monbaliu et al., 2017). Quantitative neuroimaging analyses previously reported associations between parietal structural connectivity and motor function in dyskinetic (Ballester-Plané et al., 2017), and in spastic CP (Arrigoni et al., 2016; Pannek et al., 2014; Tsao et al., 2015). The present study focused on motor severity in terms of GMFCS, rather than severity of dystonia which may explain why the association was not found with deep grey matter injury. Although quantitative neuroimaging studies report other associations between motor function and areas beyond the parietal lobe such as basal ganglia, thalamus and frontal cortex (Arrigoni et al., 2016; Ballester-Plané et al., 2017; Pannek et al., 2014; Tsao et al., 2015), at observable levels, these regions were not individually associated with motor functioning in the present study. A possible explanation for these differences with some of the studies above mentioned, might be due to the clinical measures used to assess motor outcome. Another reason may be that the sqMRI scale indexes the appearance of lesions on structural images, which are expected to be relatively static, whilst previous studies utilised measurements such as fractional anisotropy (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b; Yoshida et al., 2011), that may be affected by altered brain development and plasticity (Deng et al., 2017). Finally, the association found between the severity of parietal injury and selective visual attention may be due to the involvement of the visual dorsal stream (Culham et al., 2006).

Despite the models here not relying on any form of prior knowledge, plausible associations between lesions in the remaining regions and clinical outcomes further add value to the potential clinical utilisation of the sqMRI. Specifically, abnormalities of the middle and posterior corpus callosum were associated with selective visual attention, a function this region has been associated with (Hines et al., 2002). Furthermore, damage occurring in the basal ganglia predominantly presented in the putamen was associated with communication ability. This aligns with a number of previous findings: that the putamen connects the basal ganglia with language regions (Ford et al., 2013), is heavily involved in semantic processes (Vinas-Guasch and Wu, 2017) and, when stimulated, induces dysarthria (Duffau, 2005).

Unexpectedly, no sqMRI score was associated with cognitive flexibility. Previous studies show that Wisconsin Card Sorting Test is sensitive to the white matter microstructural status and cortical thickness in DCP (Laporta-Hoyos et al., 2017a; Laporta-Hoyos et al., 2017b) but the present study implies that Wisconsin Card Sorting Test profiles might not be sensitive to macrostructural characteristics of observable lesions. For visuospatial abilities, global sqMRI score was the only score associated with performance, whilst in other domains global sqMRI

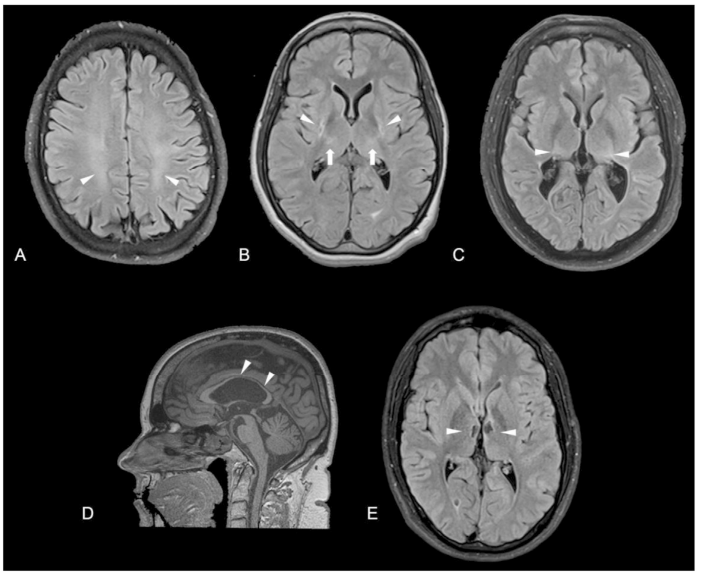

Fig. 5. Top row: Axial FLAIR images showing an example of the regions which showed an association with clinical measures. (A) Axial FLAIR: parietal white matter involvement (arrowheads); (B) Axial FLAIR: posterior putamina involvement (arrowheads); here with ventral posterior lateral thalamus involvement (arrows); (C) Axial FLAIR: posterior thalamic involvement (arrowheads); (D) Sagittal T1: thinning of middle and posterior corpus callosum (arrowheads); (E) Axial FLAIR: medial dorsal thalamus involvement (arrowheads). Images correspond to a (A) 50 year old male; (B) 21 year old female; (C) 42 year old male (D) 41 year old female and a (E) 17 year old male.

scores were less strongly associated than region-specific sqMRI scores. As such, it is recommended to use region-specific sqMRI scores when aiming to estimate any of the clinical outcomes assessed except for visuospatial domains. It is worthy of note that motor function and intellectual functioning have been shown to be associated with different observable lesions in the present study. This is interesting, as previous quantitative analyses that have relied on less regionally-specific methods, were unable to clearly differentiate which areas were involved with motor versus intellectual functioning (Ballester-Plané et al., 2017; Laporta-Hoyos et al., 2017b). Finally, further research with the revised scoring system for deep grey matter used is encouraged.

A limitation of the current work is the wide age range of participants assessed. Given that lesions are thought to be non-progressive, these results are promising, and encourage replication of the current findings in a longitudinal study in which imaging is performed during infancy and clinical outcomes assessed during later childhood and adolescence. Nevertheless, it is important to keep in mind that there have been years of plasticity and environmental factors that might have affected the structure-function relationship in this cohort. It must be also noted that people with severe communication difficulties cannot be included in a study of this nature, which indirectly precludes the inclusion of some participants at the highest GMFCS levels. Moreover, participants with higher GMFCS levels were less likely to be able hold still while undergoing the scan. These facts might have biased the cohort towards a less severe GMFCS motor level, which should be taken into account when considering the generalizability of our results to the whole spectrum of people with DCP. Furthermore, predominance of dystonia versus choreoathetosis was not considered in this study. As dystonia or choreoathetosis might have different neuroanatomical substrates, future studies including a comprehensive clinical assessment will be encouraged to clarify in more detail their neuroanatomical correlates. Finally, further studies are needed to assess the reliability of the updated version of the sqMRI scale used in the present study in order to support the generalizability of our results in different cohorts of people with DCP.

One major goal in CP research is the ability to provide early diagnoses and prognoses of outcomes, enabling enrolment of children into early-intervention programs, which may lead to more effective motor, communication and cognitive functions. For neuroimaging tools to provide this service, they must not only demonstrate meaningful and plausible associations between measurements and clinical outcomes, but also do so in a manner that integrates easily with clinicians' facilities and expertise. Here we demonstrated that the clinically accessible sqMRI scale is associated with outcomes in DCP. Taking into account that CP disturbances in the brain are not progressive, this scoring may enable clinicians to determine future clinical outcomes associated with the early brain injury.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2018.06.015.

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Appendix A. Supplementary data

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Supplementary Table 1. Correlation matrix between sqMRI scores and clinical measures (motor status, communication and cognitive performance)

	n	Global score	Frontal	Parietal	Temporal	Occipital	Anterior thalamus	Medial dorsal thalamus	Ventral posterior lateral thalamus	Posterior thalamus	PLIC	Putamen	Globus pallidus	Brainstem	Caudate	Cerebellum	Corpus callosum
GMFCS+	39	.402 / .001***	.400 / .002**	.484 / .000***	.144 / .150	.119 / .204	.041 / .388	.203 / .081	.289 / .020*	.410 / .002**	.447 / .001***	.301 / .017*	-.068 / .321	-.073 / .311	.034 / .408	.205 / .083	.292 / .021*
MACS+	39	.346 / .003**	.355 / .004**	.053 / .351	.015 / .457	.427 / .001***	.104 / .238	.263 / .035*	.297 / .017*	.411 / .002**	.350 / .006**	.293 / .019*	.004 / .489	.056 / .352	.105 / .235	.202 / .085	.227 / .056
CFCS+	39	.105 / .208	.143 / .154	-.155 / .139	.205 / .071	-.107 / .235	.000 / .500	.165 / .136	.160 / .135	.165 / .129	.142 / .164	.294 / .023*	-.051 / .368	-.056 / .357	.021 / .446	.051 / .370	.008 / .479
RCPM	39	-.312 / .004**	-.251 / .024*	-.241 / .029*	-.122 / .174	-.125 / .175	-.129 / .172	-.311 / .011**	-.160 / .111	-.450 / .000***	-.259 / .024*	-.066 / .310	-.144 / .145	-.142 / .151	-.175 / .101	-.175 / .083	-.343 / .005**
SST	37	.063 / .299	.115 / .185	.238 / .032*	.064 / .312	.184 / .087	-.186 / .089	-.290 / .018*	.079 / .277	.132 / .163	.135 / .157	-.096 / .237	-.140 / .156	-.214 / .063	-.187 / .089	.033 / .407	-.034 / .403
Spatial span	35	-.372 / .001***	-.338 / .006**	-.374 / .003**	-.219 / .055	-.260 / .034*	-.030 / .418	-.227 / .057	-.120 / .195	-.469 / .000***	-.36 / .004**	-.094 / .252	.072 / .309	-.116 / .212	-.226 / .059	-.231 / .056	-.512 / .000***
Digit span	35	-.162 / .098	-.218 / .052	-.202 / .067	.060 / .332	.082 / .282	.067 / .320	-.123 / .196	-.199 / .077	-.244 / .041*	-.200 / .076	-.141 / .157	.031 / .415	.056 / .350	-.103 / .238	-.145 / .160	-.062 / .333
WCST+	37	.239 / .025*	.340 / .005**	.252 / .027*	.249 / .031*	.177 / .099	-.065 / .321	.127 / .182	.057 / .338	.392 / .002**	.257 / .029*	-.054 / .347	.147 / .148	.162 / .126	.294 / .018*	.073 / .302	.389 / .003**
SOC	36	-.323 / .005**	-.324 / .008**	-.239 / .038*	-.337 / .007**	-.287 / .022*	-.140 / .168	-.366 / .006**	-.023 / .434	-.248 / .039*	-.208 / .069	-.049 / .365	-.203 / .082	-.199 / .087	-.319 / .014**	-.085 / .280	-.411 / .002**
Lexical verbal fluency	30	.095 / .240	.139 / .169	.069 / .316	.042 / .385	.063 / .339	.133 / .194	.115 / .227	.058 / .347	-.112 / .229	.113 / .225	.226 / .066	.186 / .114	.207 / .091	.153 / .163	-.189 / .112	-.086 / .285
BJLOT	37	-.308 / .005**	-.202 / .059	-.167 / .097	-.096 / .233	-.244 / .036*	-.142 / .153	-.294 / .017*	-.269 / .022*	-.364 / .003**	-.16 / .107	-.034 / .400	-.085 / .270	-.133 / .172	-.182 / .095	-.020 / .444	-.330 / .008**
BFRT	39	-.028 / .408	-.120 / .176	-.134 / .149	.057 / .332	.024 / .431	-.108 / .217	-.256 / .032*	.098 / .232	-.228 / .045*	.00 / .473	.022 / .434	.214 / .062	-.011 / .468	-.022 / .436	-.100 / .237	-.048 / .363
Short term PRM	38	-.104 / .196	-.140 / .142	-.208 / .055	.002 / .494	-.081 / .277	.007 / .481	-.094 / .251	-.156 / .126	-.168 / .110	-.00 / .477	.038 / .392	.255 / .035*	-.039 / .392	.023 / .435	.098 / .245	-.047 / .366
Short term VRM	38	.033 / .397	-.069 / .304	.073 / .294	.095 / .244	.194 / .086	-.145 / .159	-.285 / .024*	.179 / .101	-.076 / .294	.039 / .390	-.117 / .204	.049 / .369	-.158 / .139	-.161 / .134	.034 / .407	-.037 / .397
Long term PRM		-.199 / .052	-.165 / .107	-.149 / .130	.019 / .444	-.028 / .421	-.051 / .359	-.116 / .207	-.244 / .039*	-.245 / .038*	-.098 / .239	-.176 / .103	.151 / .145	-.079 / .292	-.028 / .421	.053 / .356	-.053 / .352
Long term VRM	38	.082 / .252	-.011 / .467	.063 / .316	.145 / .142	.390 / .003**	-.127 / .186	-.290 / .020*	.130 / .174	-.114 / .205	-.006 / .483	-.093 / .251	.043 / .383	-.237 / .050*	-.189 / .093	-.085 / .115	-.085 / .273
PPVT-III	39	-.021 / .427	-.016 / .448	.012 / .463	.219 / .042*	.100 / .224	-.020 / .442	-.173 / .097	-.082 / .263	-.246 / .029*	-.012 / .462	-.072 / .291	.042 / .376	.039 / .386	-.047 / .363	.012 / .465	-.085 / .259

BFRT: Benton's facial recognition test; BJLOT: Benton's judgment of line orientation test; CFCS: Communication function classification system; GMFCS: Gross motor function; MACS: Manual ability classification system; PPVT-III: Peabody Picture Vocabulary Test-3rd; PLIC: Posterior limb of internal capsule; PRM: Pattern recognition memory; RCPM: Raven's coloured progressive matrices; SOC: Stockings of Cambridge; SST: Stop signal task; VRM: Verbal recognition memory; WCST: Wisconsin card sorting test. * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$; +Higher scores indicate worse performance.

Supplementary Table 2. First regression models including all relevant predictors and showing the effects of sqMRI scores on clinical measures (motor status, communication and cognitive performance)

Function assessed (Test used)				sqMRI scores (predictors)	B	Std. Error	P	AIC/ BIC	AIC/ BIC final models†
Motor status°	Gross motor function	(GMFCS)+	Global model	Global score	0.180	0.050	<.001***	-	-
			Subscores model	Frontal total	-1.065	0.626	.089	90.647/108.766	50.028/58.346
				Parietal total	0.981	0.376	.009**		
				PLIC	-0.053	0.624	.932		
				Putamen	0.931	0.451	.039*		
				Ventral posterior lateral thalamus	0.018	0.391	.962		
				Posterior thalamus	0.252	0.629	.689		
				Corpus callosum	1.173	0.640	.067		
	Fine motor function	(MACS)+	Global model	Global score	0.136	0.045	.003**	-	-
			Subscores model	Frontal total	-0.396	0.448	.337	97.364/115.663	50.003/58.320
				Parietal total	0.729	0.307	.018*		
				PLIC	-0.395	0.586	.500		
				Putamen	0.631	0.392	.107		
				Ventral posterior lateral thalamus	0.270	0.373	.470		
				Medial dorsal thalamus	1.215	0.723	.093		
				Posterior thalamus	0.549	0.597	.358		
Communication°		(CFCS)+	Subscores model	Putamen	0.747	0.340	.028*	33.666/40.320	

Continuation

Function assessed (Test used)				sqMRI scores (predictors)	B	Std. Error	P	AIC/ BIC	AIC/ BIC final models†
Intellectual functioning[p]		(RCPM)	Global model	Age	0.005	0.003	.063	-	-
				Global score	-0.018	0.005	<.001***		
			Subscores model	Age	-0.002	0.003	.542	233.957/246.625	229.961/234.711
				Frontal total	0.019	0.056	.733		
				Parietal total	-0.027	0.032	.402		
				Medial dorsal thalamus	-0.189	0.111	.090		
				Posterior thalamus	-0.155	0.062	.012*		
				PLIC	0.080	0.059	.171		
				Corpus callosum	-0.063	0.058	.279		
Executive function	Attentional control [p]	Inhibition and sustained attention (SST)	Subscores model	Age	0.000	0.001	.852	-	-
				Medial dorsal thalamus	-0.018	0.062	.776		
				Parietal total	0.005	0.006	.422		
		Selective visual attention (Spatial span)	Global model	Age	0.003	0.004	.518	-	-
				Global score	-0.035	0.008	<.001***		
			Subscores model	Age	0.000	0.005	.991	193.993/206.436	191.770/197.991434
				Frontal total	0.219	0.101	.030*		
				Parietal total	-0.155	0.062	.013*		
				Occipital total	-0.010	0.070	.891		
				PLIC	0.027	0.092	.768		
				Posterior thalamus	-0.103	0.097	.287		
				Corpus callosum	-0.540	0.134	<.001***		
		Selective verbal attention (Digit span)	Subscores model	Age	-0.002	0.004	.545	205.115/209.781	
				Posterior thalamus	-0.128	0.065	.049*		

Continuation

Function assessed (Test used)			sqMRI scores (predictors)	B	Std. Error	P	AIC/ BIC	AIC/ BIC final models†
Executive function	Cognitive flexibility (WCST) [b+]	Global model	Age	-0.001	0.016	.930	-	-
			Global score	0.034	0.026	.193		
		Subscores model	Age	0.006	0.019	.767	-	-
			Frontal total	0.166	0.380	.661		
			Parietal total	-0.082	0.234	.725		
			Temporal total	-0.013	0.224	.953		
			PLIC	-0.044	0.344	.899		
			Posterior thalamus	0.178	0.359	.619		
			Corpus callosum	0.254	0.404	.531		
			Caudate	-0.125	0.739	.866		
	Goal setting (SOC) [p]	Global model	Age	0.005	0.005	.329	-	-
			Global score	-0.023	0.010	.019*		
		Subscores model	Age	0.002	0.008	.797	-	-
			Frontal total	-0.014	0.120	.910		
			Parietal total	0.000	0.085	1.000		
			Temporal total	-0.061	0.114	.591		
			Occipital total	-0.005	0.104	.964		
			Posterior thalamus	0.006	0.108	.959		
			Medial dorsal thalamus	-0.162	0.160	.310		
			Corpus callosum	-0.080	0.149	.589		
			Caudate	-0.567	0.388	.144		
	Information processing (Lexical verbal fluency) [b]	ns						

Continuation

Function assessed (Test used)				sqMRI scores (predictors)	B	Std. Error	P	AIC/ BIC	AIC/ BIC final models†
Visuoperception	Visuospatial abilities (BJLOT) [b]		Global model	Age	0.032	0.015	.040*	-	-
				Global score	-0.078	0.029	.007**		
			Subscores model	Age	0.020	0.014	.160	-	-
				Occipital total	-0.068	0.221	.758		
				Ventral posterior lateral thalamus	-0.237	0.208	.253		
				Posterior thalamus	-0.423	0.284	.137		
				Medial dorsal thalamus	-0.438	0.344	.204		
				Corpus callosum	-0.191	0.330	.562		
	Visuoperceptive abilities (BFRT) [p]		Subscores model	Age	0.001	0.002	.586	243.005/ 249.660	241.630/ 246.620
				Posterior thalamus	-0.027	0.034	.431		
				Middle thalamus	-0.127	0.058	.028*		
Memory[p]	Short term	(PRM)	Subscores model	Age	0.000	0.003	.871	-	-
				Globus pallidus	0.110	0.098	.259		
		(VRM)	Subscores model	Age	0.001	0.003	.619	-	-
				Medial dorsal thalamus	-0.089	0.077	.246		
	Long term	(PRM)	Subscores model	Age	0.006	0.004	.154	-	-
				Ventral posterior lateral thalamus	-0.065	0.065	.320		
				Posterior thalamus	-0.076	0.079	.339		
		(VRM)	Subscores model	Age	-0.001	0.003	.826	-	-
				Occipital total	0.044	0.031	.154		
				Medial dorsal thalamus	-0.092	0.091	.312		
				Brainstem	-0.041	0.159	.799		

Continuation

Function assessed (Test used)		sqMRI scores (predictors)	B	Std. Error	P	AIC/ BIC	AIC/ BIC final models†
Vocabulary[b]	(PPVT-III)	Age	0.008	0.015	.580	-	-
		Temporal	0.041	0.163	.800		
		Posterior thalamus	-0.176	0.216	.414		

BFRT: Benton's facial recognition test; BJLOT: Benton's judgment of line orientation test; CFCS: Communication function classification system; GMFCS, Gross motor function classification system; MACS: Manual ability classification system; PLIC: Posterior limb of internal capsule; PPVT-III: Peabody picture vocabulary test-3rd; PRM: Pattern recognition memory; RCPM: Raven's coloured progressive matrices; SOC: Stockings of Cambridge; SST: Stop signal task; WCST: Wisconsin card sorting test; VRM: Verbal recognition memory; [b] Binomial negative model; [p] Poisson regression model; [o] ordinal regression model; * $p \leq .05$; ** $p \leq .01$; *** $p \leq .001$. For comparison proposes, AIC and BIC values are provided in subscores models showing significant predictors and included in the final regression models. †AIC and BIC indexes displayed in this column correspond to the final models presented in Table 3; ⁺Higher scores indicate worse performance. Italic indicates the predictor showing signs of multicollinality. Therefore, this predictor was further removed when performing the final model.

Supplementary Table 3. Semi-quantitative scale for brain structural MRI scores for the individual participants

		sqMRI lobar score (sum of right and left scores)				Anterior thalamus		Medial dorsal thalamus		Ventral posterior lateral thalamus		Posterior thalamus		PLIC		Putamen		Globus pallidus		Brainstem		Caudate		Cerebellum		Corpus callosum		
No.	Global score	Frontal total	Parietal total	Temporal total	Occipital total	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	A	M	P
1*	2									1	1																	
2	5	1	2							1	1																	
3	10	2	3	1	2						1		1															
4*	6									1	1	1	1			1	1											
5	11	2	3	2	2					1	1																	
6*	2									1	1																	
7*	2															1	1											
8	14.50	2.50							1	1	1	1	1		1	1	1					1	1				1	1
9	18	3	6							1	1	1	1	1	1	1	1										1	
10	15	3	4							1	1	1	1	1	1	1	1											
11	13	2	4							1	1		1	1	1	1	1											
12*	2															1	1											
13	11					1	1		1		1		1	1	1	1	1	1	1									
14	15	2	4	3									1		1									1	1		1	1
15*	2									1	1																	
16	15	3	6							1	1			1	1	1	1											
17	0																											
18	16	2	3.50	2.50	4					1	1																1	1
19	16	3.50	5	2.50							1		1		1	1	1											
20	19	3	6	2	2					1	1			1	1	1	1											
21	3	2														1												
22	16.50	3	4	1.50	2							1	1	1	1												1	1
23	4					1	1							1	1													
24	24	3	3	3	2		1		1		1		1	1	1		1	1	1		1		1				1	1
25	9	2.50	.50	1						1				1		1				1							1	
26	0																											
27*	4									1	1					1	1											

Continuation

No.	Global score	sqMRI lobar score (sum of right and left scores)				Anterior thalamus		Medial dorsal thalamus		Ventral posterior lateral thalamus		Posterior thalamus		PLIC		Putamen		Globus pallidus		Brainstem		Caudate		Cerebellum		Corpus callosum		
		Frontal total	Parietal total	Temporal total	Occipital total	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	R	L	A	M	P
28	21	2	4	4	3					1	1	1	1	1	1												1	1
29	15.50	2	2	4	3.50						1		1		1													1
30	0																											
31*	2									1	1																	
32	0																											
33	0																											
34	6	1		2											1		1		1									
35	0																											
36*	4					1	1	1	1																			
37	0																											
38	22	3	6			1	1	1	1	1	1	1	1	1	1	1	1				1							
39	**0**																											

A: Anterior; L: Left hemisphere; M: Middle; No: Participant number; P: Posterior; PLIC: Posterior limb of internal capsule; R: Right hemisphere; sqMRI: Semi-quantitative scale for brain structural MRI. Empty cells indicate that there is no lesion. *Indicate subjects presenting only deep grey matter lesions.

Supplementary Table 4. Frequency table presenting sqMRI subscores: lobar scores (ranging from 0 to 6), basal ganglia, thalamus, brainstem and cerebellum scores (ranging from none, unilateral or bilateral lesion) and corpus callosum (ranging from no lesion to middle and posterior lesion)

sqMRI global score													
Median (interquartile range) / Range	6 (13) / 0-24												
	sqMRI lobar score (sum of right and left scores)												
	0	**0.5**	**1**	**1.5**	**2**	**2.5**	**3**	**3.5**	**4**	**4.5**	**5**	**5.5**	**6**
Frontal total (n)	19	0	2	0	8	2	7	1	0	0	0	0	0
Parietal total (n)	22	1	0	0	2	0	3	1	5	0	1	0	4
Temporal total (n)	27	0	2	1	3	2	2	0	2	0	0	0	0
Occipital total (n)	31	0	0	0	5	0	1	1	1	0	0	0	0

	Number of hemispheres showing a lesion		
	None	**Unilateral**	**Bilateral**
VPLT (n)	16	6	17
PLIC (n)	22	6	11
Putamen (n)	22	4	13
Posterior thalamus (n)	25	7	7
Medial dorsal thalamus (n)	34	3	2
Anterior thalamus (n)	34	1	4
Globus pallidus (n)	36	1	2
Brainstem (n)	36	3	0
Caudate (n)	37	1	1
Cerebellum (n)	38	0	1

	Number of sections showing a lesion*			
Corpus callosum (n)	**None**	**Only middle**	**Only posterior**	**Middle and posterior**
	30	2	1	6

* No participant presented brain lesions in the anterior corpus callosum according the sqMRI. PLIC: Posterior limb of internal capsule; sqMRI: Semi-quantitative scale for brain structural magnetic resonance imaging; VPLT: Ventral posterior lateral thalamus

Supplementary Table 5. Description of tests used to assess cognitive domains and adaptations needed

Domain	Test / score used	Brief description	Adaptations needed
Gross motor function	GMFCS	Distinguishes between levels based on functional abilities, the need for assistive technology, including hand-held mobility devices or wheeled mobility, and to a much lesser extent, quality of movement. Higher scores indicate worse performance.	-
Fine motor function	MACS	Classifies how people with CP use their hands when handling objects in daily activities. Higher scores indicate worse performance.	-
Communication	CFCS	Distinguishes different levels of everyday communication according to the activity/participation level of the World Health Organization's International classification of functioning, disability and health. Higher scores indicate lower levels of communication ability in terms of effectiveness and velocity of the communication.	-
Intellectual functioning	Raven's coloured progressive matrices / total raw score	Consists of 36 items, grouped into three sets of 12 items of increasing difficulty within each set. Each item contains a pattern problem with one part removed and the participant has to choose which of the six alternatives completes the pattern. The use of this test is recommended for people with physical disabilities, aphasia, deafness or CP and has been shown to be sensitive to brain structure in DCP.	Participants answered orally (n=31), pointing with the finger (n=1), hand (n=1), gaze (n=2) or an adapted pointer on the head (n=2). In those cases in which autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice. These latter subjects answered "yes" or "no" by means of vocalisations, movement of head, facial miming or gestures with other parts of the body (n=2).

Continuation

Domain		Test / score used	Brief description	Adaptations needed
Executive function	Attentional control: Inhibition and sustained attention	Stop signal task (adapted version) / total correct score on stop and go trials	Instructs participants to respond as fast as possible to a simple arrow stimulus on a computer screen. Participants were told to press the left button when they saw a left-pointing arrow and the right button when they saw a right-pointing arrow. On some trials, an auditory stop signal was presented, and participants were instructed to try to stop or inhibit their response.	The task was switch adapted and participants were therefore able to respond pressing the buttons by hand (n=32), cheek (n=3), chin (n=1), or neck (n=1) to allow autonomous responses. In the original version of the test, at the end of each assessed block, a feedback screen was displayed showing a graphical representation of the participant's performance. These resting stops were removed in the present study in order to increase the attentional component of the task.
	Selective visual attention	Spatial Span subtest of the Wechsler Nonverbal Scale of Ability / total raw score	It comprises two series: the forward condition, in which the examiner points out some cubes and the examinee must indicate the same cubes in the same order; and backward, in which the examinee must indicate the cubes in the reverse order. In both conditions, the length of the sequences is gradually increased. Each correct response is worth one point; with a maximum of 32 for the total score.	Participants answered pointing with their finger (n=30), hand (n=1), fixing the gaze (n=1) or with an adapted pointer on the head (n=3). When the gaze was used, the examiner pointed to the item the subject was looking at to confirm that the subject was referring to it.
	Selective verbal attention	Digit Span subtest of the WAIS-III or WISC-IV / total raw score	Comprises two series: the forward condition, in which the participants is read a sequence of numbers and recalls the numbers in the same order; and the backward condition, in which the participants must recall the numbers in reverse order. Each correct response is worth one point; with a maximum of 32 and 30 for WISC-IV and WAIS-III respectively.	Participants answered the test orally (n=32). For participants with non-verbal communication the answer was given by pointing with the finger (n=2) or gaze (n=1) to written numbers placed in front of them. Every time the numbers were dictated, the written numbers were hidden to avoid the possibility that the response was based on visual rather than on verbal component.
	Cognitive flexibility	64-item computerized version of the Wisconsin card sorting test / perseverative errors	This task consists of four reference cards and 64 response cards with geometric figures that vary in colour, shape and number. The participant has to pair each response card with one of the four reference cards and discover the correct classification principle by trial and error and the computer feedback. Higher scores indicate worse performance.	To access the test, a mouse/joystick controlled by hand (n=27) or with the chin (n=1) and one switch (pressed by hand, cheek, head or foot) were used. In some cases, the participant pointed to the screen (n=5) or said the answer orally (n=1) and the examiner executed the action on the computer. In cases where an autonomous response was not possible the examiner indicated the various response alternatives while asking the participant if it was his/her choice, and then the examiner executed the action (n=3).
	Goal setting	Stockings of Cambridge test / problems solved in minimum moves	The participant is shown two displays containing three coloured balls. The participant must move the balls in the lower display to copy the pattern shown in the upper display.	To access the test, a mouse/joystick controlled by hand (n=29) or with the chin (n=1) and one switch (pressed by hand, cheek, head or foot) were used. In some cases, the participant pointed to the screen (n=6) and the examiner executed the action on the computer.
	Information processing	Lexical verbal fluency task / total raw score	Requires participants to generate as many words as possible beginning with P, M, and R during a minute.	This rest requires speaking so it was assessed only in verbal participants (n=30).

Continuation

Domain	Test / score used	Brief description	Adaptations needed
Visuospatial abilities	Benton's judgment of line orientation test / total raw score	Consists of 30 test items in which participants are asked to match two angled lines to a set of 11 lines that are arranged in a semicircle. Each correct response (considered when the two lines of each item are correct) is worth one point; with a maximum of 30 points. The short form developed by Calamia et al. [188] was applied.	Participants answered orally (saying the item number) (n=31), pointing (with the finger, hand or an adapted pointer on the head) (n=3), or, in those cases in which autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice (n=3). These latter subjects answered "yes" or "no" by means of vocalisations, movement of head, facial miming or gestures with other parts of the body.
Visuoperceptual	Benton's facial recognition test / total raw score (long form)	Participants are presented with a target face above six test faces, and they are asked to indicate which of the six images match the target face. For some of the items, only one answer is correct, and the correct target image and the test image are identical. In other items, three of the test faces match the target face, and the poses or lighting conditions are different. Each correct response is worth one point. Short form was applied in our study and long form scores were obtained (54 maximum points).	Participants answered orally (saying the item number) (n=31), pointing (with the finger, hand, an adapted pointer on the head or fixing the gaze) (n=5), or, in those cases in which autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice (n=3). These latter subjects answered "yes" or "no" by means of vocalisations, movement of head, facial miming or gestures with other parts of the body. When the gaze was used, the examiner pointed to the item the subject was staring at and confirmed that the subject was referring to it.
Memory	Pattern Recognition Memory subtests of the CANTAB (computer administered version) / no. of correct trials (short and long term)	Participants were presented with a series of visual patterns, one at a time, in the centre of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, participants are required to choose between a pattern they have already seen and a novel pattern. This is then repeated, with new pattern. The second recognition phase can be given either immediately or after a 20-min delay.	To access the test, a mouse/joystick (controlled by hand or with the chin) and two switches – one for each visual stimulus – (pressed by hand, cheek or head) were used (n=32). In those cases in which autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice, and then the examiner executed the action (n=6).
	Verbal recognition memory subtests of the CANTAB (computer administered version) / no. of correct trials (short and long term)	The participant is shown a list of words and then asked to recognise the words they have seen before from a list containing the original words and distractors, right after the presentation and after 20 minutes.	Due to the difficulties or reading disabilities of subjects with CP, this test was applied orally to all participants (also to the control group). The examiner read the list of words to subjects followed by a short and long term recognition task. Participants answered orally (n=33) or by means of vocalisations, movement of head, facial miming or gestures with other parts of the body (n=5).

Continuation

Domain	Test / score used	Brief description	Adaptations needed
Vocabulary	Peabody picture vocabulary Test-III / total raw score	The adaptation for the Spanish population of this test consists of 192 items sorted by level of difficulty and grouped into sets of 12 items. Each element consists of four illustrations in black and white. The task of the participant is to select the image that best represents the meaning of the word provided orally by the examiner. It is a measure of verbal comprehension and/or receptive vocabulary. Because of its non-verbal aspect it is appropriate for those cases with severe expressive language impairment and it has been widely used in CP.	Participants answered orally (saying the item number) (n=31), pointing (with the finger, hand, an adapted pointer on the head or fixing the gaze) (n=5), or, in those cases in which autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice (n=3). These latter subjects answered "yes" or "no" by means of vocalisations, movement of head, facial miming or gestures with other parts of the body. When the gaze was used, the examiner pointed to the item the subject was staring at and confirmed that the subject was referring to it.

CANTAB, Cambridge Neuropsychological test automated battery; CP, cerebral palsy; DCP, dyskinetic cerebral palsy; CFCS, Communication function classification system; GMFCS, Gross motor function classification system; MACS: Manual ability classification system; WAIS-III Wechsler adult intelligence scale–third edition; WISC-IV, Wechsler Intelligence test for children-fourth edition.

4 General discussion

4.1 Main findings

The previous chapters addressed the four major aims (see Section 2, Aims) of this thesis as follows. The first aim was addressed by Study 1 that determined that executive function impacts QOL in people with DCP together with fine motor status, communication, and socioeconomic status. Importantly, executive functioning is a key outcome as it predicts the Cerebral Palsy Quality of Life Questionnaire (CP QOL) total score and it is associated with almost all QOL domains.

As for the second aim, Study 2 showed that people with DCP perform worse than TDC and better than SCP in both intellectual functioning and executive function which does not indicate a specific dysexecutive deficit. In some goal setting tasks assessed, performance in people with DCP seems to be similar than performance in TDC.

The third aim of this thesis was addressed in Studies 3 and 4, which found that both observable white matter and grey matter lesions as well as white matter microstructure are involved in DCP. Although the ventral posterior lateral thalamus was the most frequently found lesion location in our sample, all participants, except the eight who had no observable lesion, presented with a lesion of the basal ganglia or thalamus. Interestingly, one third of participants with a visible brain damage had lesions constrained to the basal ganglia and thalamus. The frontal lobe was also frequently involved, and white matter microstructure was also impaired in all cerebral lobes. Specifically, the loss in the integrity of the white matter in DCP was predominantly found in the parietal and, to a lesser extent, temporal cortices. Other lesions identified by the sqMRI scale were in the posterior, middle and anterior thalamus, posterior limb of internal capsule, putamen, globus pallidus, brainstem and caudate.

Fourth, regarding our investigation of the correlation between cognitive function and brain structure, both white matter microstructure and observable brain lesions were related to general intellectual functioning and specific executive function domains. Specifically, general intellectual functioning was related to

lower FA in several cortico-cortical and cortico-subcortical regions and with global sqMRI score and posterior thalamus involvement. As for executive function, cognitive flexibility was associated with FA in regions known to contain connections with the frontal lobe such as the cingulate gyrus and the superior longitudinal fasciculus in the left hemisphere but also in regions not directly connected with the frontal lobe such as the posterior corpus callosum and superior and posterior corona radiata, the retrolenticular part of internal capsule and the posterior thalamic radiation. At odds with these results, no sqMRI score was associated with cognitive flexibility. Selective attention, however, was associated with global sqMRI score, parietal lobe and corpus callosum involvement. Unexpectedly, neither in terms of white matter microstructure nor in terms of observable lesions, was there a significant relationship between executive function and the fronto-striatal pathways (Study 3 and Study 4).

Finally, it is important to note for clarity purposes that some aspects explored in the articles but not directly linked with the aims of this thesis will not be discussed in this section. This includes the association between cortical thickness and CP QOL total score (Study 1) and the association between sqMRI scores and motor status, communication, visuoperception, memory and vocabulary (Study 4).

4.2 Achievement of aims and further discussion

4.2.1 Aim I

Study 1 achieved the first aim of the present thesis, which was to elucidate the impact of executive function on QOL in people with DCP taking into account other variables that have been demonstrated to effect QOL in CP and other populations. That is, verbal and nonverbal IQ, gross motor functioning, fine motor functioning, communication and economic status. In accordance with our hypothesis, which was based on the importance of executive function for the successful completion of daily activities, executive function predicted QOL in our sample of people with DCP. Specifically, among all variables considered, cognitive flexibility was the only one predicting CP QOL total score. As mentioned in the

discussion of Study 1, the association between QOL and cognitive flexibility, as measured by the Wisconsin card sorting test (WCST), has previously been reported in other health-related conditions. In the current section, we will discuss in more detail these studies together with the updated literature. For example, Barf et al. [5] found that both cognitive flexibility (completed categories of WCST) and divided attention (execution time of Trial Making Test B-A) were significant determinants of subjective QOL in young adults with spina bifida and hydrocephalus. Intelligence, memory and word production, however, were not related to subjective QOL [5]. These results, in a sample of adults with a congenital disorder that may result in some similar neurological deficits to CP, align well with ours as IQ was also considered but was not a significant predictor of QOL in the regression model.

Other studies reporting the association between QOL and WCST in psychiatric conditions, however, further show the role of other variables such as IQ and anxious and depressive symptoms. Aksaray et al. [189], for example, found that QOL was associated not only with non-perseverative errors of WCST but also with negative symptoms and extrapyramidal side effects in patients with schizophrenia. Also in participants with schizophrenia, categories achieved in WCST and depression/anxiety were related with QOL but attentional control measured by the Continuous Performance Test was not related with QOL [190]. Similarly, Sota et al. [191] showed that WCST (perseverative errors and categories completed) and IQ were related with QOL in participants with schizophrenia. However, verbal memory function was not found to be related with QOL indicating the relevance of executive function over other functions. Finally, a recent study found correlations between the BRIEF and well-being, cognition, and behaviour domains of the QOL measure used [192]. Importantly, the working memory subscale on the BRIEF was the sole significant predictor of HRQOL. In spite of some minor differences in the results between these studies and ours, findings in populations other than CP seem to be consistent with those of Study 1 as executive function seems to be an important driver of QOL. The fact that some of these studies also report a relevant role of other measures considered is probably due to differences between health conditions and

methodological issues such as the QOL measure used or statistical analysis performed.

Here we have modestly added to the pool of knowledge about the role of executive function in QOL by exploring this association in the most common cause of physical disability in childhood. Although there are a number of studies describing executive function difficulties in CP, IQ was the only cognitive domain so far whose association with QOL had been explored [55, 57, 59, 60, 142, 193]. Study 1 of the present thesis is, therefore, the first to consider executive function as a potential determinant of QOL in CP.

As for the role of IQ, both verbal and nonverbal IQ were positively associated with a medium effect size to two QOL domains (General Well-Being and Participation, Communication and Physical Health), and only verbal IQ was associated with a medium effect size with the Feelings About Functioning domain. However, when IQ variables where introduced into a multiple linear regression model in order to clarify which combination of variables best predicts QOL, general intellectual functioning did not feature in any predictive model. Overall, results of Study 1 suggest that cognitive flexibility has a greater effect on QOL than IQ.

The lack of predictive power of IQ for QOL was also mirrored by a lack of gross motor function predictive power for QOL. Fine motor functioning was similar, predicting scores solely on the Feelings About Functioning domain of CP QOL. Such lack of findings seem to be consistent with the disability paradox [194] which postulates that many people with significant functional limitations report good QOL while better levels of functioning may be associated with lower life satisfaction [55, 195]. The occurrence of the disability paradox for cognitive disabilities is not well known and our results might shed some light to this issue. It could happen that the disability paradox only occurs when participants are below a certain general intellectual or motor function level. If we have a closer look to the studies exploring the association between IQ and QOL, no firm conclusion can be drawn on this regard as cognitive and motor severity levels of participants are different between studies and a wide variety of different IQ measures are used

(Table 8). It is interesting to note, however, that no study includes a large percentage of participants at the high GMFCS levels, and that the study finding a negative association between IQ and QOL includes a high percentage of participants with an IQ below 70. Further research specifically comparing this association in mild and severe CP cases could shed light on this issue.

Table 8. Studies exploring the association between intelligence quotient and quality of life in cerebral palsy

Reference	n	Age	GMFCS IV-V$^{\Delta}$ (%)	IQ < 70 (%)	QOL measure	IQ measure	Positive association between IQ and QOL^{+}	Negative association between IQ and QOL^{+}
Rapp et al., 2017 [193]	551	12y-18y	35%	53%	KIDSCREEN (parent-reported)	Parents provided information	**5 of 10 domains** (Psychological wellbeing; Moods and emotions; Self-perception; Relationship with parents; School life)	
Colver et al., 2015 [57]	431	13y-17y	21%	34%	KIDSCREEN (self-reported)	Parents provided information	**1 of 10 domains** (Social support and peers)	
Arnaud et al., 2008 [59]	728-744	8y-12y	32%	53%	KIDSCREEN (parent-reported)	Formal IQ assessment or a cognitive description completed by the parents	**1 of 10 domains** (Social support and peers)	**2 of 10 domains** (Mood and emotions; Self-perception)
Majnemer et al., 2007 [55]	95	6y-12y	35%	35%	Child Health Questionnaire and Pediatric Quality of Life Inventory	Leiter International Performance Scale-Revised		
Dickinson et a., 2007 [196]	500	8y-12y	14%	27%	KIDSCREEN (self-reported)	Parents provided information	**2 of 10 domains** (Mood and emotions; Anatomy)	
Aran et al., 2007 [142]	39	6y-18y	36%	mean IQ 94*	Child Health Questionnaire (parent-reported)	WISC-R		

$^{\Delta}$Note that analyses where performed including the whole sample, not only those participants at the IV-V GMFCS levels; $^{+}$Results for specific domains are presented; *Only mean IQ is reported; GMFCS, Gross Motor Function Classification System; IQ, intelligence quotient; QOL, quality of life; WISC-R, Wechsler Intelligence Scale for Children-Revised; y, years.

While our results regarding IQ and gross motor function seem not to be contradictory with the disability paradox, our results regarding cognitive flexibility are. A key question is why executive functioning plays a more relevant role in QOL than IQ and motor function. Poor mental flexibility undermines a person's ability to function independently, especially in new situations, affecting adaptive behaviour and socialization skills [197]. Some studies highlight the association between cognitive flexibility and emotional experiences and social aptitudes. For example, it has been suggested that cognitive flexibility and emotional neurodevelopment are entwined as positive emotions seem to increase the cognitive flexibility [198] and activation of the left dorsolateral prefrontal cortex is associated with both cognitive flexibility and preschool irritability [199]. Furthermore, deficits in executive functions seem to be linked with to theory of mind and to account for the social-cognitive impairments associated with autism traits [131, 200]. It can be hypothesised that the link existing between cognitive flexibility and social cognition and emotions may promote its association with QOL. Taking into account the prevalence of autism spectrum disorders in children with CP [63-67] further research of this nature should consider autism traits as a potential determinant of QOL.

4.2.2 Aim II

The second aim of this thesis, to map general intellectual functioning and executive function in people with DCP, was achieved in Study 2. Study 2 is the first to date to specifically explore executive function performance in people with DCP and to describe general cognitive functioning in a moderate sample of participants with DCP against participants with SCP matched by age, sex, term/preterm and motor severity.

Versus typically developing controls

As expected, people with DCP perform poorer than TDC in both intellectual functioning and executive function. This finding aligns with the idea that higher order skills can rely on diffuse activation patterns and, so, be relatively prone to brain injury. Further in line with this idea, recent evidence suggests that executive deficits are present following early brain injury, regardless of lesion location [201].

In spite of this, performance on goal setting ability in our sample of people with DCP is close to that of TDCs, indicating adequate functional development of this executive function domain. A possible explanation as to why goal setting but no other cognitive domains are similar to TDC is that this executive function component seems to be more complex than others, lending itself more to compensatory strategies that allow adequate performance in the face of altered neurodevelopment. Although counter-intuitive, similar patterns of impairment have been reported in other conditions and domains. For example, stroke can commonly reduce motor performance in simple and moderately complex tasks, but very high level goals, such as pointing or reaching tasks, often show no measured impairment due to compensatory strategies as atypical muscle use [202, 203]. Consistent with the suggestion that goal setting as a very high-level function is that goal setting is the last executive function domain to develop. For example, it is not until the gains in cognitive flexibility during the fourth years of life or gains in working memory around the 9 years, that children show the first strategies which draw or improve the beginning of planning and goal directed behaviour [134].

Versus spastic cerebral palsy

People with DCP may present with intellectual and executive functioning difficulties compared with TDC but, compared with SCP, display a better

general intellectual level and executive functioning in terms of goal setting and information processing.

Regarding general intellectual functioning, results confirm the hypothesis that people with DCP do not present poorer general intellectual functioning than people with SCP. Our hypothesis was based in the fact that some studies found that learning or intellectual disability is more common in spastic tetraplegia than in DCP [106, 111, 112]. Moreover, our results seem to agree with those of Sigurdardottir et al. [108], as when participants with important motor severity who could not be assessed using standard intelligence tests were considered, the highest proportion of children with intellectual impairment was found in the group with spastic tetraplegia. Our results, however, are at odds with those of other studies [10, 58, 110] that found that people with DCP performed poorer than those with SCP. We hypothesise that the differences with these studies may be due to the fact that they did not control for GMFCS and prematurity, and that intellectual functioning was reported dichotomously [10]. Another reason for the differences may be the small size of the sample of participants with DCP in two of these three studies [58, 110].

As for executive functioning, the better performance in DCP than SCP in goal setting and information processing might be due to average neuroanatomical differences between CP types, but the lesion-outcome relationships here are not straightforward to interpret.

The first factor complicating an understanding of these differences is lesion timing. Timing periods of occurrence of the lesions may affect some of the variables influencing reorganization after early brain injury. Early insults would potentially lead to disruption of cell characteristics and neural and network connections, as well as functional organization [204, 205]. The most commonly observed lesions in children with spastic motor type are periventricular white matter lesions which occur during the early parts of the third trimester. Basal ganglia, thalamus and cortico-subcortical areas of the central region, however, appear to be more vulnerable during the late third trimester and are observed in

DCP [72, 74, 81]. Taking into account the early vulnerability model, it could be hypothesised that the earlier brain insults in SCP than DCP entail more severe cognitive difficulties. It is important to highlight that investigating the effects of age at insult in isolation may be misleading as this factor interacts with others such as nature (diffuse versus focal), site, insult severity and distribution of the neural network underpinning the impaired skills (focal or distributed representation) [206].

The second factor complicating a comparison between SCP and DCP brain structure is a present lack of published studies adequately designed to answer these questions. Moreover, lesions typically associated with DCP can also be found in the SCP and vice versa. Specifically, basal ganglia lesions can be, in some occasions, found in SCP [82] and white matter lesions can be found in DCP and seem to be more common than previously thought [94]. In this line, severe presentations of DCP have been reported to present cortical involvement (i.e. spastic symptoms) together with subcortical involvement (i.e. dyskinetic symptoms) [207]. As for quantitative comparisons of brain structure between CP types, Yoshida et al. [94] found that diffusion-tensor imaging abnormalities in DCP tend to be more widespread, with involvement of deep grey and white matter structures, than that in children with SCP. In this study, however motor severity of participants was not reported and, thus, brain lesion differences may have been partly related to differences in GMFCS levels. At an observable level there is agreement, however, that basal ganglia and grey matter injury are more often seen in DCP, while PVL is more common in SCP [20, 70].

In addition, although there is not total consensus, brain resposnses to small focal lesions appear to be most effective when early brain insult is bilateral (as tends to happen in DCP) as large lesion size is associated with greater impairment suggesting the need for the presence of some healthy tissue for optimal recovery [206]. Although Yoshida et al. [94, 95] reported more severe lesions in DCP than SCP, one of these studies did not report on motor severity [94] and the other include DCP participants at the III-V range of GMFCS and SCP participats at the range I-III of GMFCS. In fact, one could hypothesise that the

opposite pattern could be true: when these two CP types are comparable in terms of motor severity (that is, participants with SCP and high GMFCS levels) lesions might tend to be more widespread in SCP than in DCP, resulting in a poorer cognitive functioning. Some lines of evidence hint toward this possibility. Firstly, a reduction in total white matter connectivity throughout the brain has been found in severe versus moderate bilateral spastic CP, including but not limited to regions associated with the sensorimotor system [79]. Secondly, Krägeloh-Mann et al. [90] reported purely dyskinetic CP presented on MRI with patterns of mild lesions, whereas purely spastic CP was more related to the severe pattern. Thirdly, this suggestion is consistent with the finding that white matter damage of immaturity (PVL and periventricular haemorrhage) tends to be more widespread in spastic tetraplegia involving posterior, middle and anterior regions than in spastic diplegia [11].

Is DCP characterized by an executive function deficit?

The better performance in DCP than SCP in executive functioning was counter to our hypothesis that DCP would be characterized by a larger executive function deficit. Nevertheless, executive impairments where identified for all executive function domains in DCP being their performance closer to TDC on executive function than on general intellectual functioning. To conclusively reject the hypothesis of a specific executive function deficit in DCP, cognitive domains other than executive functioning should be taken into account to check if there is a greater tendency towards executive function deficits than this found for other cognitive domains.

Further highlighting this non-executive function specific deficit are results from another study of our research group [208]. This study shows that, in comparison to typically developmental controls, people with DCP present poorer functioning not only in executive function but also in a variety of cognitive domains (visuoperception, receptive vocabulary, basic grammar comprehension, verbal learning, and visual memory). In fact, if we look at the effect size of all cognitive domains considered in this study, cognitive flexibility

is the cognitive domain whose effect size is smaller, and it is only significantly different from TDC in those participants with DCP at the IV and V GMFCS levels.

4.2.3 Aim III

The third aim, to identify brain structure alterations in participants with DCP was addressed by Studies 3 and 4.

On one hand, results aligned with the classic idea that DCP is characterized by deep grey matter injury as one third of participants with a visible brain lesion had lesions constrained to the basal ganglia and thalamus. In fact, all participants, except eight who had no observable lesion, presented with a lesion of the basal ganglia or thalamus. This is in accordance with 84% of studies on Table 3 that report basal ganglia and thalamus injury as the most common lesion in DCP. As described in Study 4, this was in agreement with our hypothesis and with the well-known pattern of brain involvement in diffuse hypoxic-ischemic injury of term neonates, kernicterus, or other known etiopathogenetic factors which typically result in DCP [25, 90, 209]. Furthering the work of studies listed in Table 3, our use of a simple but detailed scoring procedure that considers the extent of the lesions [103, 104] has identified the ventral posterior lateral thalamus as the most frequently found lesion location in our sample.

On the other hand, and also in accordance with our hypothesis, white matter was involved in our participants with DCP. Studies 3 and 4 confirmed the early observations of Yoshida et al. in a sample of seven [95] and nineteen [94] children with DCP and results found in another work of our research group [210], both of which found that white matter involvement in DCP is more present than previously thought. This may be due to both the primary disturbance that caused CP (most likely seen at an observable level in Study 4) and secondary results from deep grey matter injury (most likely seen at a microstructural level in Study 3). As an example of this second idea, the observed involvement of ventral posterior lateral thalamus may explain some of

the white matter involvement in our sample as it has a fundamental role as a relay on S1 ascending projections influencing sensorimotor control [211–213].

As for the location and extension of white matter involvement, Studies 3 and 4 indicated that white matter may be impaired in all cerebral lobes, including both sensorimotor and non-motor-related regions. Importantly, some white matter microstructural differences between people with DCP and TDC in the fronto-striatal circuitry were found but they were circumscribed in the anterior corona radiata close to the anterior part of the cingulate gyrus (Study 3).

That said, such impairment appeared to be primarily disrupted in more-posterior brain regions: the anterior regions of the frontal lobe appeared to be relatively preserved. This is, no observable involvement of the anterior corpus callosum was found (Study 4) and white matter FA was predominantly reduced in regions connected with the parietal and to a lesser extent the temporal lobes (Study 3). This idea is also consistent with results for another work of our research group [210] that found that structural brain connectivity in DCP is disrupted in posterior brain regions with relative preservation of prefrontal areas.

In 2007 there was an agreement that knowledge about neuroimaging in CP was insufficient to recommend any specific classification scheme based on neuroimaging findings [16]. During the last ten years an important number of works focused on describing neuroimaging characteristics in different CP types have been published. While most of these studies are focused on SCP, Studies 3 and 4 of the present thesis contribute to the neuroimaging description of DCP. This thesis includes the study with what is so far the largest sample of participants with DCP exploring white matter microstructure (see Table 4 for previous works). Moreover, Study 4 is the first to specifically score brain lesions by using a semi-quantitative MRI scale that is not only easily applicable by clinicians, but it is also based on a well described procedure for its utilization and has been tested for both reliability [104] and construct validity [214]. Unlike previous procedures used to describe brain lesions in large samples of people

with DCP (see Table 3) [26, 27], Study 4 of this thesis used a more sophisticated scoring procedure that considers not only the different pathogenic groups but also the extent of the lesions.

To increase our knowledge, studies comparing structural and microstructural characteristics between CP types are needed. This is, for example, studies quantitatively comparing brain structure characteristics between DCP and SCP and between people at different GMFCS levels. Study 4 contributes toward such knowledge by presenting the association between motor severity and brain lesion severity (as measured by global or parietal sqMRI score) in DCP. In the light of our above presented hypothesis, such associations might suggest that people with DCP at higher GMFCS levels could be more similar to people with SCP in terms of neuroimaging findings.

Following the ideas presented in the previous section, studies of this nature could help to better understand not only motor but also cognitive differences between CP types.

4.2.4 Aim IV

The fourth aim, to investigate the neural correlate of executive functioning and general intellectual functioning in participants with DCP, was also addressed by Studies 3 and 4.

Regarding general intellectual functioning, in healthy people, higher IQ scores have been associated with larger total, grey, and white matter volumes, specifically in parieto-frontal pathways [169, 170]. Subcortical structures such as the basal ganglia also play a relevant role in intelligence in healthy children and adults [171–173]. Our results are in accordance with the general consensus that general intellectual functioning does not reside in a single, narrowly circumscribed brain region but is supported by a widespread network [170]. That is, lower intellectual functioning was associated with lower FA in all cerebral lobes (Study 3) and with higher sqMRI global score (Study 4). Given

that Studies 3 and 4 already include a detailed discussion about each different region associated with general intellectual functioning, in the following lines we will focus on other aspects of both articles, discussed together.

Our results for the Study 4 are consistent with the idea that large lesion size are associated with greater impairment [206] as more extended lesions seem to be related with lower general intellectual functioning. Moreover, in accordance with the Parieto-Frontal Integration Theory of Intelligence and findings in typically developing people [215], white matter microstructure in all cerebral lobes was associated with general intellectual functioning in Study 3 and with total sqMRI score in Study 4. In our sample of participants with DCP, however, posterior networks seem to play a more relevant role than anterior networks with regards to general intellectual impairments. Taken together, results of Studies 3 and 4 agree with the idea that general intellectual functioning relies on a widespread brain network, but that the status of posterior regions seem to play a more important role on the level of performance in DCP.

We hypothesise that this tendency for associations with general intellectual functioning to be more widespread in more-posterior regions might be due to two different but non-mutually-exclusive reasons. First, microstructural and observable abnormalities in our sample are more severe in the parietal lobe (Aim 3, Studies 3 and 4) and, thus, it is more likely to find significant results in this area. Second, general intellectual functioning was assessed by a visual reasoning task which is consistent with the results for pulvinar nuclei in Study 4. There are suggestions that the pulvinar nuclei critically supports an early visual pathway and plays a broad role in human cognition [216]. These results are consistent with the relationship between the extension of periventricular white matter damage to parietal and occipital regions and the degree of impairment of visual functions [119, 217, 218]. This is supported by the association found between visual reasoning and white mater integrity of the posterior thalamic radiation connecting with the parietal cortex (Study 3).

As for the neural correlate of executive function, an association between brain structure and cognitive flexibility (feedback utilization component) and attentional control (selective visual attention) was found. Specifically, cognitive flexibility was sensitive to white matter microstructural status (Study 3) but no sqMRI score was associated with this executive function domain (Study 4). Therefore, WCST performance seems not be sensitive to the macrostructural characteristics of observable lesions but it is sensitive to the white mater integrity in regions known to contain connections with the frontal lobe (such as the superior longitudinal fasciculus and cingulum), and regions not known to contain tracts directly connected with the frontal lobe (such as the posterior corona radiata, posterior thalamic radiation, retrolenticular part of internal capsule, tapetum, body and splenium of corpus callosum). Interestingly, these structural-functional relationships did not hold true for all executive function domains: the severity of parietal injury and lesions in the middle and posterior corpus callosum regions were indicative of selective visual attention (Study 4) whereas white matter integrity was not an indicative of this cognitive domain (Study 3). Results from Study 3 are consistent with the association found between executive function and corpus callosum sqMRI score in children with spastic diplegia [146]. Differing from the results reported here for DCP, results of this study suggest a relevant role of the anterior portions of the corpus callosum in executive function.

Overall, our results align with the idea that posterior brain regions appear to underlie executive function in people with DCP. That is, neuroanatomical correlates for executive function seemed to be circumscribed to non-frontal regions. At this point it is important to note that despite frontal regions seeming to be relatively preserved in DCP, some white matter microstructural differences between people with DCP and TDC in the fronto-striatal circuitry were found (Study 3). Contrary to our hypothesis, executive functioning was not associated with microstructural characteristics of these fronto-striatal pathways in DCP. Rather, these functions seemed to be related to damage of posterior cortico-subcortical pathways and the white matter tracts connecting

the prefrontal and posterior brain regions. These results seem to be consistent with those found in extremely low–birth-weight infants with PVL [219], indicating that superior occipitofrontal and longitudinal fasciculi, which play a role in higher cerebral function, were involved. These results make sense in the context of our finding that DCP seems not to be characterized by a specific executive function deficit (Aim II).

Although no one of our results regarding the association between executive function and brain structure are greatly different from those found in TDC [220, 221], we would expect to find some indications of fronto-striatal circuitry underlying executive function in DCP. Our hypothesis was based on the fact that DCP has classically been characterized by basal ganglia and thalamus injury and that basal ganglia and the fronto-striato-thalamic circuit play crucial role in cognitive flexibility in TDC [222]. One possible reason for the lack of associations between executive function and fronto-striatal microstructural status in Study 3 is neuroplastic processes taking place after early brain insult: that is, reorganisation as to which areas are primarily responsible for certain aspects of executive functioning. Among the different scenarios for functional reorganization, intrahemispheric reorganization could have occurred, mainly for executive function, in our sample of participants with DCP. Interhemispheric reorganization is less likely as only 15% our sample of participants with DCP were presenting unilateral CP and only 10% of all participants whose MRI were visually assessed presented unilateral lesions. An alternative option to consider is the possibility of intrahemispheric maintenance. That is, the possibility that skills subsumed by damaged tissue are maintained within that tissue, resulting in maximum dysfunction [206]. However, although intrahemispheric maintenance has been said to be more likely following bilateral or diffuse insults, such as cerebral infection or hypoxic–ischaemic encephalopathy [206], this possibility seems less likely for executive function but might be more likely for general intellectual functioning. This suggestion is based into the fact that executive function seems to be less impaired in DCP (closer to TDC performance) than SCP (Study 2) and that this function was not associated with white matter

microstructure in fronto-striatal pathways as expected in TDC [223] and other neurological conditions [224]. The results of Studies 3 and 4 are not conclusive enough, however, to draw firm conclusions regarding this issue. To shed further light to this issue a tractography study specifically checking the integrity of the fronto-striatal circuitry is warranted.

4.3 Advances in knowledge

This thesis includes the first study to investigate a group of possible predictors of QOL in people with DCP showing the importance of executive function on QOL. It also includes the first study to compare intellectual functioning and performance in all executive function domains in a relatively large sample of people with DCP against samples of TDC and people with SCP who are similar in terms of age, sex, gestational age and motor severity. Although results indicate that DCP seems not to be specifically characterised by a dysexecutive deficit, it has been shown that people with DCP present difficulties in all executive function domains.

Our results further reinforce previous findings about the involvement of basal ganglia and thalamus in DCP, further suggesting the importance of ventral posterior lateral thalamus involvement, which was the most frequently found in our sample. Finally, our larger sample confirmed the early observations of Yoshida et al. [95] regarding grey and white matter involvement at an observable and microstructural level.

Combining these two important facets of DCP, this thesis is the first to report the association between brain structure and cognitive function (general intellectual functioning and executive function), showing that fronto-striatal pathways are not the main driver of executive function difficulties in DCP.

4.4 Clinical implications

From a clinical point of view, our results highlight the importance of proactive screening for executive dysfunction in DCP in order to identify those at risk of poor QOL. Our results also highlight the importance of studying the potential role of interventions to improve executive functions as part of intervention programmes designed to improve the QOL of people with CP.

Furthermore, it seems that cognitive functions may have been underestimated and masked by motor severity in people with DCP which emphasises the importance of properly assessing general and specific cognitive functions in CP, even in the most severe cases. Furthermore, characterizing specific cognitive profiles rather than only reporting global estimates of general intellectual functioning takes on great significance in the clinical and educational setting because it would allow designing more efficient rehabilitation and/or educational strategies, fitting better the real needs and capabilities of these people. It is also relevant that observations made in SCP cannot be generalized to dyskinetic forms. This thesis is a minor step forward to a comprehensive understanding of cognitive functioning in each CP type. Further research may contribute to improving the accuracy of prognosis. The better cognitive deficits that are part of the DCP phenotype are identified, the more likely it is patients to benefit from cognitive rehabilitation.

The present thesis further allows to better understand the frequency and location of brain lesions in DCP and their relationships with clinical outcomes in a manner that integrates easily with clinicians' facilities and expertise. Here we demonstrated that the clinically accessible sqMRI scale is associated with outcomes in DCP which may help to assist in the earlier detection of important comorbidities in DCP. This may, in turn, help to enable enrolment of children into early-intervention programs, which may lead to more effective motor, communication and cognitive functions.

4.5 Strengths

The strengths of this thesis include the recruitment of a large sample of participants with DCP. This is of special relevance as DCP is relatively rare, comprising about 7% of CP cases. Indeed, it presents poorer motor outcomes than other CP types [10] which makes specially challenging to perform neuroimaging and cognitive assessments. It is also worth to note the wide cognitive assessment performed using common measures in all participants. Another remarkable aspect is that both advanced neuroimaging analyses of white matter microstructure and a clinically accessible semi-quantitative scale have been used. The fact that this simple semi-quantitative scale was also used makes some results of the present thesis specially translatable to clinical practice.

4.6 Limitations

The limitations of this thesis include the absence of measurement of dyskinesia using a quantitative scale. It would have been very enriching to include a measure of dyskinesia in our study, but unfortunately the research project was already well underway when the Dyskinesia Impairment Scale (a new measurement tool to evaluate dystonia and choreoathetosis in DCP) [225] was published. Therefore, like previous studies [26, 94, 96, 110] our study was based on general clinical criteria. Other scales available were developed especially for people with primary dystonia, and some studies questioned their sensitivity and reliability [226]. To address this limitation, the criteria applied were very strict as only participants who clearly presented predominant dyskinetic symptoms were included; that is, participants presenting spastic and dyskinetic symptoms to the same degree were not considered eligible.

The wide age range of the sample is another limitation. This is because DCP is rare and it makes extremely difficult to reach a moderate-large sample of participants with a narrow age range. To address this issue, the effect of age has been controlled in all studies in different manners. Moreover, although the

sample size may be considered large considering the characteristics of the sample and the previous studies, it is small in terms of statistical power.

An additional limitation of the present thesis is that autism spectrum disorders were not specifically assessed in our sample. Importantly, the majority of studies report rates of autism spectrum disorders ranging from 7 to 8.7% [63, 65–67, 227, 228] although rates in some studies are lower (about 5%) [82] and higher (about 15%) [64]. Additionally, pain was not assessed in CP participants, so we could not include the effect of this variable in any of the analyses performed, being this aspect especially relevant for the Study 1. Recent robust studies [57, 60] have found that pain in childhood or adolescence predicts lower QOL in all domains. It is important to note too that neuro-ophthalmological disorders are among the main symptoms in CP [180] so visual perception and their interaction with manual ability may have an effect on cognitive performance. Moreover, tasks for measuring inhibition/sustained attention (Stop Signal Task) and information processing (Verbal fluency) are influenced by execution time. Although this aspect is a limitation, it should be noted that attention and information processing are executive function abilities that are inherently temporal. To control this effect at the maximum level possible, the execution time was not considered when scoring performance of inhibition/sustained attention task (Stop Signal Task). This is, the number of correct responses on "stop" and "go" trials were considered instead. Moreover, other components of attentional control were assessed by using different tasks. Additionally, no significant result in Studies 1, 3 and 4 was relative to inhibition/sustained attention and information processing, which indicates that no significant result is due to this limitation. Finally, it should be noted that when DCP and SCP groups were compared, there were no significant differences in manual ability between groups ($z= 0.16$, $p=.88$) so it is unlikely the results found for this comparison in Study 2 to be due to the time component.

It is also important to keep in mind that the performance observed in our sample cannot be generalized to the broad population of DCP because we have included only subjects with enough comprehension to perform a

neuropsychological assessment. This is, however, an inner limitation, as the study of cognitive function is only possible in this subsample of DCP who had a minimum comprehension level.

There are some further relevant limitations that are specific to each study, some of which are already mentioned in the studies themselves. Regarding the first study, we had to use the "Teen" version of the CP QOL as there is no a condition-specific tool that can be used to measure the QOL of adults with CP. Thus, important domains for adults such as employment, housing, social networks [229], romantic relationships [230] and urinary problems [231] are not captured by the questionnaire used in Study 1. In favour of the questionnaire used, however, it must be said that a recent study conducting qualitative semi-structured interviews identified that the CP QOL-Child and CP QOL-Teen included more domains identified as important to QOL in children with CP and intellectual disability than other questionnaires such as the Pediatric Quality of Life Inventory -CP, the Caregiver Priorities and Child Health Index of Life with Disabilities and the DISABKIDS-CP) [232]. A recent review of generic preference-based measures for the assessment of QOL in children and adolescents with CP interestingly highlights that the Health Utilities Index—Mark 2 and 3 demonstrated the strongest psychometric properties among the measures considered [233]. Although these results should be taken into account in future research, it is worthy of note that this measure is not condition specific, thus, excludes important facets of HRQOL such as activity limitations and participations that are relevant to the CP population. Another limitation of Study 1 is that visuoperception, despite being a very common well described impairment in CP [117], was not considered as a potential predictor of QOL. Finally, the effect of gender was not controlled. As for the second study, participants with SCP are not representative of the entire SCP population and caution is therefore required when interpreting the results referring to this group. As for neuroimaging studies (mainly Study 3), only participants able to hold still or with agreement to be sedated were included. Therefore, some participants satisfying the inclusion criteria were not able to be included which

must be considered when interpreting the results. In this regard, it is further worthy of note that there were no statistically significant differences in terms of GMFCS level between the 33 DCP participants included in Study 3 and the remaining 19 participants included in the Study 2 (n=52).

4.7 Further research

The results of the studies included in this thesis are a moderate step forward in the current knowledge about the neuroimaging findings and cognitive functioning in DCP. These findings raise several new questions about this topic which should be addressed in further research. Firstly, future studies exploring variables influencing QOL in other CP types should consider executive function as a potential determinant. Given the fact that DCP does not seem to be specifically characterized by an executive function deficit, it is likely that the association found between executive function and QOL in the Study 1 is not only limited to DCP. It would also be interesting to explore whether this association occurs through all severity levels to further shed light on the "disability paradox". Secondly, to conclusively reject the hypothesis of a dysexecutive deficit in DCP, future research should focus on comparing neuropsychological performance between DCP and TDC in cognitive domains other than general cognitive function and executive function. Thirdly, further research is needed to elucidate whether the lack of significant correlations between executive function and regions involved in fronto-striatal pathways might be a sign of neuroplasticity. In order to deepen the subject, we are currently working on a paper focused on exploring independently the integrity of the three relevant circuits with origins in the prefrontal cortex and its association with executive function. As for the use of the sqMRI scale, further research with the revised scoring system for deep grey matter used is encouraged in participants with other CP types which may help to better define how lesion patterns differ across such groups. Finally, in the light of these results, the study of neuropsychological rehabilitation programs focused on executive function is highly encouraged. Several therapy approaches are currently offered to improve

physical symptoms in children with CP but there is little evidence of efficacy of neuropsychological rehabilitation programs [234] being randomized controlled studies in CP based on neuropsychological interventions scarce [154, 235].

5 Conclusions

The conclusions that can be drawn from the results of the studies are the following:

- Cognitive flexibility, an executive function domain, is an important driver of quality of life in people with dyskinetic cerebral palsy.

- People with dyskinetic cerebral palsy present difficulties in both general intellectual and executive functioning. Goal setting abilities are close to those in typically developing controls, indicating some functional development for this executive function domain.

- People with dyskinetic cerebral palsy display a better intellectual and executive functioning than people with spastic cerebral palsy, indicating a general tendency towards a better cognitive performance rather than a specific dysexecutive deficit.

- Observable white and grey matter lesions as well as white matter integrity are involved in dyskinetic cerebral palsy. Specifically:
  - The most common observable lesions include those in the posterior lateral thalamus and the frontal lobe. Lesions in the frontal lobe, however, are less severe than those observed in the parietal lobe.
  - The loss in the integrity of the white matter in dyskinetic cerebral palsy is predominantly underlying posterior regions mainly the parietal cortex and, to a lesser extent, the temporal cortex.

- General intellectual functioning is related to white matter integrity in several cortico-cortical and cortico-subcortical regions and with observable brain lesions, particularly, in the posterior thalamus.

- Posterior brain regions but not fronto-striatal circuitry, support executive function in dyskinetic cerebral palsy. Specifically:
  - Cognitive flexibility is associated with fractional anisotropy in regions containing fronto-cortical and posterior cortico-subcortical pathways.
  - Selective attention is associated with observable brain lesions, particularly, in the parietal lobe and the middle and posterior corpus callosum.

6 Methods

The present thesis consists of four studies using a transversal methodology. The following section provides a general methodological description, given that detailed aspects of the methods can be found in each one of the studies. First, a characterization of the participants included in the studies is provided. Subsequently, the clinical measures, neuropsychological assessmentand and the MRI acquisition procedure administered to the participants are reported. Finally, a description of statistical analyses employed is presented.

6.1 Participants

The project was approved by the University of Barcelona's (CBUB) Institutional Ethics Committee, Institutional Review Board (IRB 00003099, assurance number: FWA00004225; http://www.ub.edu/recerca/comissiobioetica.htm). The research was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants, their parents or their legal guardians.

6.1.1 Participants with dyskinetic cerebral palsy

Participants were recruited, and data were collected between February 2012 and May 2015 from the main institutions attending people with CP in Barcelona. Specifically, the majority of participants were recruited from the Hospital Vall d'Hebron (Pediatric Neurology Department and Rehabilitation and Physical Medicine Department) and the Hospital Sant Joan de Déu (Pediatric Neurology Department). Figure 1 displays information regarding the institutions attending all participants with DCP included in the present thesis.

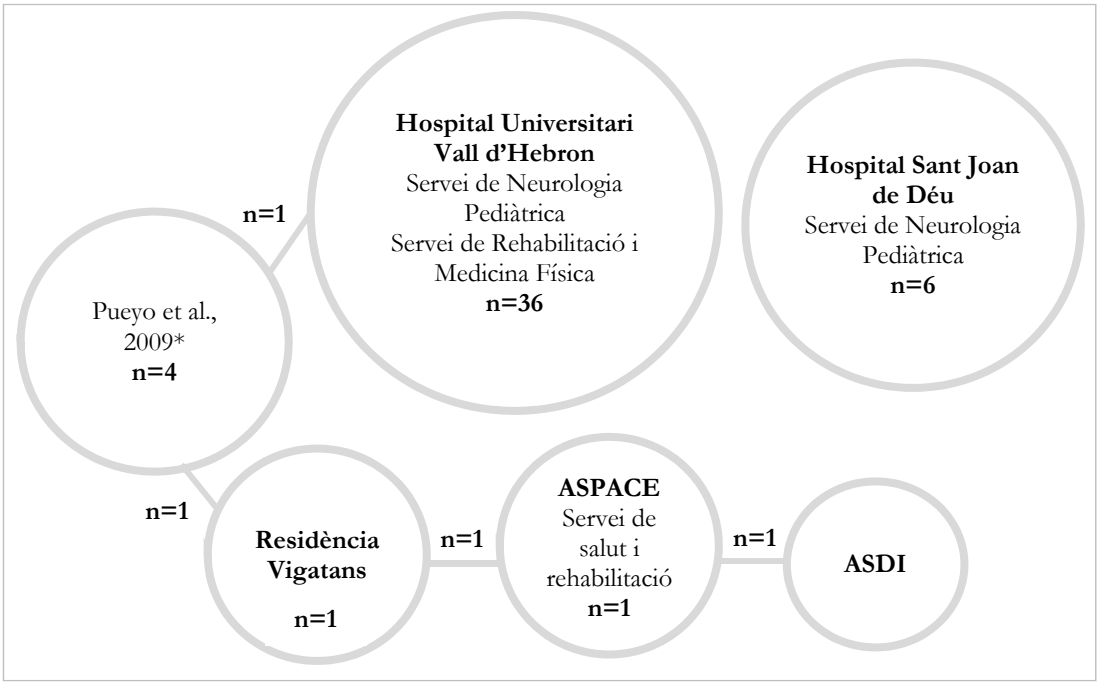

Figure 1. Graphical information about where all fifty-two participants with dyskinetic cerebral palsy included in the present thesis were recruited from.
*Pueyo et al., 2009 [124] refers to a previous study. Lines between circles indicate participants who where "provided" by the two linked sources.

Mainly physicians from the above-mentioned institutions informed their patients with dyskinetic CP or their parents/legal guardian about the possibility to participate in this research project. Patients where further contacted by phone to check inclusion/exclusion criteria, to explain the participation procedure and to offer to participate in the study.

Inclusion criteria were:

- ✓ Clinical diagnosis of CP with predominant dyskinetic features.
- ✓ Age over 6 years old.
- ✓ For the neuropsychological assessment, being able to understand instructions, as evaluated by the Spanish Grammar Screening Test (receptive part) [177]. We established a score ≥30 as the threshold

required to consider that the participant had sufficient verbal comprehension to understand the instructions of the other tasks. A score of 30 corresponds to the 10th percentile for children 6y - 6y:11m old. Noteworthy, this was just a general screening, and comprehension of the instructions of each test was further checked for each task during the assessment.

The task used for the general screening is the Screening Test of Spanish Grammar [177] which consists of 23 items arranged in order of difficulty. Each item is formed by a picture plate with four images that are presented to the examinee while the examiner reads two grammatical expressions. The subject must select the picture that matches with each of the sentences. Each well-matched sentence provides a point, up to a maximum of 46.

Participants answered orally (saying the item number) or pointing indistinctly, only pointing (with the finger, hand, gaze or an adapted pointer on the head) or, in those cases in which autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice. These latter subjects answered "yes" or "no" by means of vocalizations movement of head, facial miming or gestures with other parts of the body. When the gaze was used, the examiner pointed to the item the subject was staring at and confirmed that the subject was referring to it.

Exclusion criteria were:

- ✓ Participants with hearing abnormalities or severe visual difficulties that precluded cognitive assessment were excluded.
- ✓ Lack of an intelligible yes/no response system.

From 101 potentially eligible participants with DCP, 52 people comprised the final sample. The four studies comprising the present thesis include a different number of participants given the specific methodology of each study. Further details about this procedure for each study are given in Figure 2.

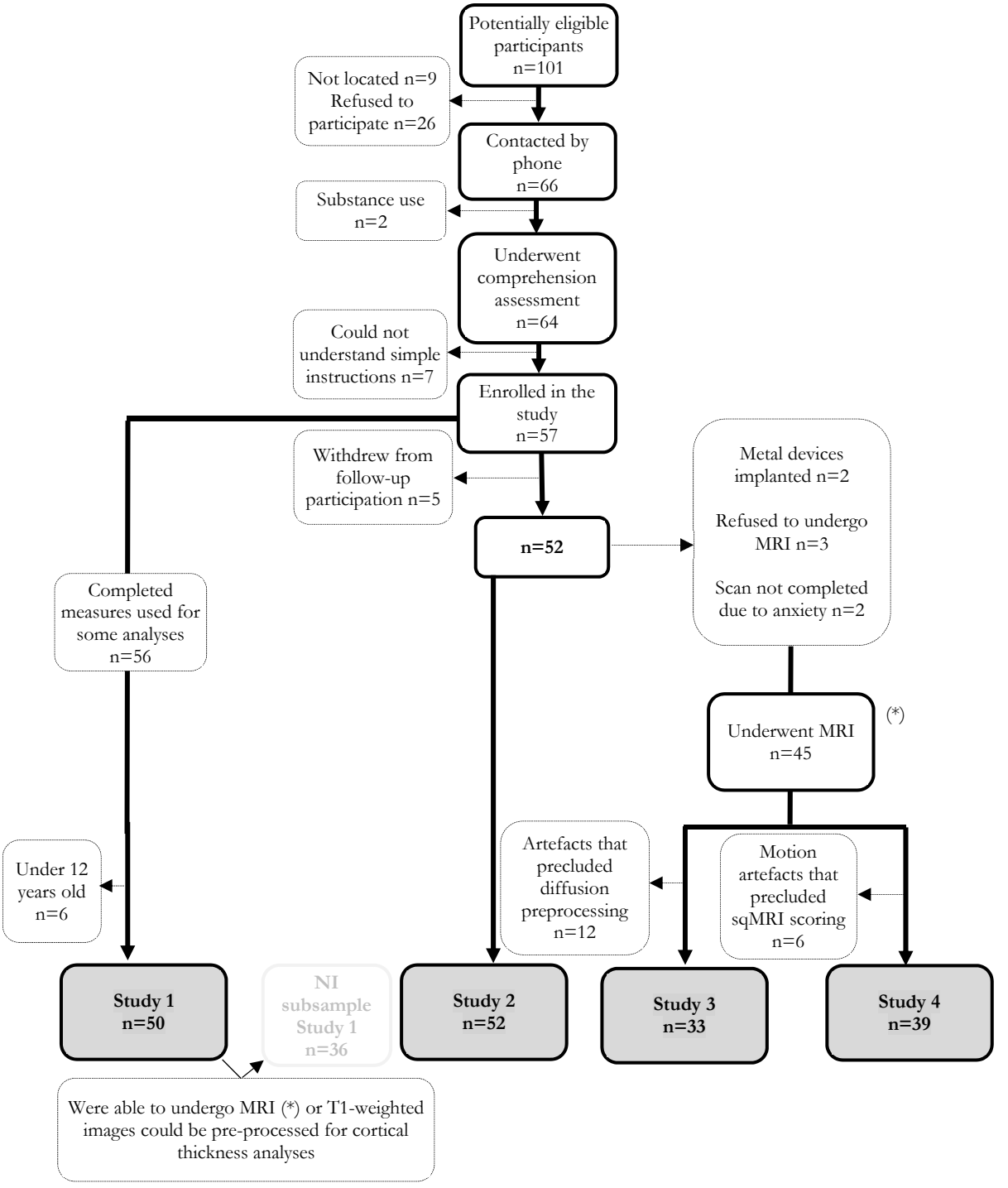

Figure 2. Flowchart showing recruitment process for all participants included in each study. MRI, Magnetic resonance imaging; NI, neuroimaging.

6.1.2 Participants with spastic cerebral palsy

The inclusion criteria for participants with SCP were the same as participants with DCP but with a clinical diagnosis of predominant spastic features.

After the recruitment of the participants with DCP, participants with a clinical diagnosis of SCP were recruited, matching by sex (male/female) and age with participants with DCP. The age matching criterion was more flexible with older participants. That is, participants <20 years old were matched with participants with a maximum difference of +/-2 years; participants between 20 and 30 years old were matched with participants with a maximum difference of +/-4 years; and participants older than 30 years old were matched with participants with a maximum difference of +/-8 years. Furthermore, participants were matched as being term vs preterm (≥37 weeks vs <37 weeks) and as ambulant vs non-ambulant (GMFCS I-II-III vs IV-V) with a participant with DCP. Forty-five people with SCP accomplishing matching and inclusion criteria were potentially eligible as. Of those, ten were not located, eight refused to participate and seven were not able to understand simple instructions. Thus, the final sample comprised twenty participants with SCP. Further details about recruitment process for participants with SCP are available in Study 2.

6.1.3 Typically developing participants

Typically developing people without brain pathology and matched by age and sex were included in all analyses as controls. Most participants in the control group were friends and relatives of the participants with CP. The remaining typically developing participants were recruited through advertisements.

Inclusion criteria were:

- ✓ To have same sex as a participant with DCP.
- ✓ To have similar age (±1 year) as a participant with DCP.
- ✓ Being born at term.

Exclusion criteria were:

- ✓ To be suffering from a neurological or psychiatric disorder.
- ✓ To be illicit substance consumer.

6.2 Clinical measures

Perinatal information was obtained from medical reports and complemented with information provided by participants and/or their relatives. The main perinatal antecedents were: signs of perinatal asphyxia in 22 cases, signs of vascular events in 9 cases, congenital brain malformations in 2 cases and signs of infection in 2 cases. In 17 subjects, the perinatal antecedents were unknown.

6.3 Neuropsychological assessment

Participants underwent a comprehensive neuropsychological assessment of general intellectual functioning, executive functioning and other neuropsychological domains such as memory, visuoperception and vocabulary. Tests used were carefully chosen to allow the majority of the participants to answer in an autonomous way. When creating the neuropsychological protocol, priority was given to those tests that minimized the motor skills involved and that, ideally, did not take into account the execution time, since this could penalize subjects with CP. Most of the final tasks included are extensively used in standard neuropsychological assessments and allow a nonverbal response. All but two of the tests were computerized and allowed for use of assistive technology for communication. Participants were encouraged to use the response technique best suited to their degree of disability and the communication devices they normally used. Adaptations were mainly introduced in order to encourage subjects to answer in an autonomous way. Participants were allowed to use the communication devices they normally used, and the response technique that best fitted their abilities was chosen. It should be noted that the original tests were used and

that the items were not altered for any task of general intellectual or executive functioning. Given the focus of this thesis in general intellectual and executive functioning, the tasks used to measure these cognitive domains are widely presented below.

6.3.1 General intellectual functioning

Non-verbal intellectual functioning was assessed in Studies 1, 2, 3 and 4 by means of the Raven's Coloured Progressive Matrices [181]. This test consists of 36 items, grouped into 3 sets of 12 items of increasing difficulty within each set. Each item contains a pattern problem with one part removed and the participant has to choose which of the six alternatives completes the pattern.

Verbal intellectual functioning was assessed my means of the Peabody Picture Vocabulary Test-3rd [236] and is taken into account only in Study 1. The adaptation for Spanish population of this test consists of 192 items sorted by level of difficulty and grouped into sets of 12 items. Each element consists of four illustrations in black and white and the task of the examinee is to select the image that best represents the meaning of the word provided orally by the examiner. These two tests are widely used and recommended for people with physical disabilities because neither verbalization nor skilled manipulative ability is required [237]. Participants answered the items orally (saying the item number), pointing with the finger, hand, gaze or an adapted pointer on the head. In those cases in which autonomous response was not possible, the examiner indicated the various response alternatives while asking the participant if it was his/her choice. These latter subjects answered "yes" or "no" by means of vocalisations, movement of head, facial miming or gestures with other parts of the body. When the gaze was used, the examiner pointed to the item the subject was staring at and confirmed that the subject was referring to it.

6.3.2 Executive function

Attentional control

Inhibition and sustained attention was assessed in Studies 2, 3 and 4 by means of the Stop signal task [182]. In this task, participants are asked to respond as fast as possible to a simple arrow stimulus on a computer screen. They were instructed to press the left button when they saw a left-pointing arrow and the right button when they saw a right-pointing arrow. On some trials, an auditory stop signal was presented, and participants were instructed to try to stop or inhibit their response. In the original version of the test, at the end of every assessed block, a feedback screen was displayed showing a graphical representation of the participant's performance. These resting stops were removed in the present study in order to increase the attentional component of the task. The task was switch adapted and participants were therefore able to respond pressing the buttons by hand, cheek, chin, or neck to allow autonomous responses. This measure is not included in Study 1 because there is a lack of standardized data for this task and when that study was performed most TDC were not recruited yet.

Selective attention was assessed by both visual and verbal tasks. The visual component was assessed by means of the Spatial Span subtest of the Wechsler Nonverbal Scale of Ability [238] in Studies 2 and 4. In this task the examiner pointed out some cubes and the examinee was asked to indicate the same cubes in the order requested by the examiner. The length of the sequences is gradually increased every two items. Once again, participants answered pointing with their finger, hand, fixing the gaze or with an adapted pointer on the head. When the gaze was used, the examiner pointed to the item the subject was looking at to confirm that the subject was referring to it. *Selective verbal attention* was assessed in Studies 1, 2 and 4 by means of the Digit Span subtest of the Wechsler Adult Intelligence Scale III [184] or the Wechsler Intelligence Scale for Children IV [183]. In this task the participant was asked to recall the numbers previously said by the examiner. The clear majority of participants answered the test orally. In

seven cases, participants with non-verbal communication gave their answer by pointing with the finger or gaze to written numbers placed in front of them. Every time the numbers were dictated, the written numbers were hidden to avoid the possibility that the response was based on visual rather than on verbal component.

Cognitive flexibility

Feedback utilization was assessed in all four studies by means of the 64-item computerized version of the WCST [239]. This task consists of four reference cards and 64 response cards with geometric figures that vary in colour, shape and number. The participant has to pair each response card with one of the four reference cards and discover the correct classification principle by trial and error and the computer feedback. To access the test, a mouse/joystick controlled by hand or with the chin and one switch (pressed by hand, cheek, head or foot) were used. In some cases, the participant pointed to the screen or said the answer orally and the examiner executed the action on the computer. In cases where an autonomous response was not possible the examiner indicated the various response alternatives while asking the participant if it was his/her choice, and then the examiner executed the action.

Working memory was assessed in study 2 by means of the backward condition of the visual (Spatial Span subtest of the Wechsler Nonverbal Scale of Ability [221]) and the verbal (Digit Span subtest of the Wechsler Adult Intelligence Scale III [184] or the Wechsler Intelligence Scale for Children IV [183]) span. The visual backward condition consists into that the examinee must indicate the cubes in the reverse order than presenter by the examiner. Similarly, for the verbal condition the examinee is requested to say the numbers in reverse order to what was said by the examiner.

Goal setting was assessed in all four studies by the Stockings of Cambridge test [182] where the participant is shown two displays containing three coloured balls. The participant must move the balls in the lower display to copy the pattern shown in the upper display. To access the test, a mouse/joystick

controlled by hand or with the chin and one switch (pressed by hand, cheek, head or foot) were used. In some cases, the participant pointed to the screen and the examiner executed the action on the computer.

Information processing was assessed in Studies 2, 3 and 4 by means of a lexical verbal fluency task [187]. This task requires participants to generate as many words as possible beginning with P, M, and R during a minute. This test requires speaking so it was assessed only in verbal participants (71%).

6.4 Magnetic resonance imaging

6.4.1 Acquisition

Magnetic resonance imaging was performed on a Siemens Magnetom TRIO 3.0T scanner (Erlangen, Germany) at the Hospital Universitari Vall d'Hebron (Barcelona, Spain). Prior to scanning, 21 participants took diazepam (2.5-10mg) and 6 pentobarbital and propofol, supervised by a physician in accordance with the protocol reviewed by the ethics committee. Two participants were unable to complete the scan due to anxiety. Given the difficulty for participants to hold still, some images presented motion artefacts that precluded pre-processing for cortical thickness analyses (Study 1), diffusion (Study 3) and sqMRI scoring (Study 4).

The protocol included:

- High-resolution three-dimensional T1-weighted images acquired in the sagittal plane with a magnetization prepared rapid acquisition gradient echo sequence (repetition time 1,900 ms; echo time 2.46 ms; inversion time 900 ms; field of view 220 x 220 mm; flip angle 98; and voxel size 0.7 mm x 0.7 mm x 1 mm). This sequence was used in Study 1 and Study 4.

- Two repetitions of the diffusion weighted imaging sequence acquired at b=1,000 s/mm2, along with one minimally diffusion weighted image (b=0) (repetition time 8,400 ms; echo time 90 ms; field of view 240 x 240 mm; 65 axial slices; 30 diffusion directions; voxel size 2 x 2 x 2 mm with no slice gap). This sequence was used in Study 3.

- Fluid attenuated inversion recovery images (FLAIR) acquired in 25 axial slices (repetition time 9,040 ms; echo time 86 ms; voxel size 0.43 x 0.43 x 5.2 mm). This sequence was used in Study 4.

- T2 turbo spin echo (axial plane) images (repetition time 5,150 ms; echo time 103 ms; flip angle of 120°; voxel size 0.43 x 0.43 x 5.2 mm) were acquired, also in 25 axial slices, where time permitted. This sequence was used in Study 4.

6.4.2 Neuroimaging pre-processing and analysis

Neuroimaging analyses contributed to Studies 1, 3 and 4 of the present thesis. Although specifications of the procedures followed are detailed in the papers themselves, in the following section a general view is provided.

For Study 1, T1-weighted images were processed by using FreeSurfer v5.1.0 (http://surfer.nmr.mgh.harvard.edu). Later, a correlation between cortical thickness and both the CP QOL total score and perseverative responses of WCST was performed using FreeSurfer software. A vertex-by-vertex one-factor general linear model was used, with age being included as a nuisance factor. Resulting locations were labelled according to the Desikan Atlas [240].

For Study 3, diffusion weighted images were pre-processed using an extensive procedure detailed in the methods of this paper. Volumes containing within-volume motion or scanner artefacts were visually identified and excluded from further analysis. Participants whose datasets contained more than three volumes showing motion artefacts were excluded entirely from further analyses. At this

point it should be noted that with at most three rejected volumes, meaningfully-reduced data quality from artefacts is not expected [241]. As for total movement effect within the CP group, there were no significant differences in the total motion between sedated and non-sedated subjects. Moreover, the total motion between the control group and CP group, indexed the value "XXX.eddy_movement_rms" (produced by FSL "eddy"), was marginally higher for the control group (.307) than for the CP group (.258) ($p=.043$, $U=387$).

Brain masks where created using FSL BET [242] and further manually edited as required. FSL "eddy" [243] was used to correct for eddy current-induced distortions and head movements between volumes, including rotation of the b-vectors. DTI maps including FA and mean diffusivity were calculated for each participant using FSL DTIFit. Whole brain voxelwise groupwise analyses of FA and mean diffusivity images were carried out for participants with DCP compared to healthy controls. A correlation between IQ and FA was then performed, controlling for age and sex, for all participants with CP and controls separately to ascertain regions where injury severity was specifically associated with IQ. Finally, four separate general linear models were employed to identify regions where FA correlated with scores in each one of the executive function domains in the CP and control group.

Given that both cortical thickness and white matter microstrucre are well known to be affected by age [244], this variable was included as a nuisance factor in both Study 1 and 3. Gender was further controlled in the Study 3 as a gender influence on white matter microstructure has been reported [245].

As for Study 4, images were scored according to the sqMRI scale detailed in Fiori et al. [104]. Given the focus of this thesis in deep grey matter injury, two deviations from this original protocol were performed according to Fiori's criteria. Firstly the latter score was extended to also detail the specific involvement of the thalamic nuclei (anterior thalamus, ventral posterior lateral thalamus, medial dorsal thalamus, posterior thalamus). Secondly the lenticular

scoring was extended by detailing the involvement of globus pallidus and/or putamen. As in the original paper, we assigned a score of 1 to the involvement of each of the detailed structure, thus resulting in a larger score range for the basal-ganglia-and-brainstem of 0 to 9 on each side (right or left).

6.5 Statistical analysis

With exception of the voxelwise and FreeSurfer analyses that were undertaken with neuroimaging data, statistical analyses were performed by using the IBM SPSS Statistics version 22 (Studies 1, 3 and 4) and R version 3.3.1 (Study 2).

For Study 1, Pearson, Spearman or Kendall bivariate correlations between CP QOL domains/total score and clinical variables were calculated. Variables that showed significant correlations were then entered into multiple linear regression models (stepwise method) to identify the best predictive models of CP QOL. In study 2, global tests based on Kruskal-Wallis (H statistic) were performed to analyse differences in cognitive performance between groups. Pairwise contrasts, based on the Mann-Whitney U test, were performed in cases in which the global test yielded a significant result. The Hodges-Lehmann estimator, as well as a 95% bootstrap-percentile confidence interval, was estimated in order to report the differences between groups. The main statistical analyses for Study 3 are presented in the previous section as they involve neuroimaging by using FSL. In Study 4, a top-down approach was followed to find the best models. A model including all relevant predictors correlating with sqMRI scores was estimated and simplified by manually removing those predictors that yielded non-significant results and validated by inspecting information criteria and multicollinearity measures. The sqMRI scores that were significantly correlated with ordinal variables were entered into separate ordinal regression models to identify the best predictive sqMRI scores for each function. The sqMRI scores that showed significant correlations with count data were entered into separate Poisson regression models. All statistical assumptions were assessed, and binomial negative models were used when Poisson regression models' condition

of equidispersion was not met. Age was included as a covariate in all models considering cognitive functioning. The level of significance of all analyses was set at $p < .05$.

7

Summary

(Catalan version: extended)

7.1 Introducció

La paràlisi cerebral és una de les causes més freqüents de discapacitat física en nens i suposa una condició permanent al llarg de la vida [70]. Concretament, la prevalença mitjana mundial és d' aproximadament de 2 per cada 1000 nascuts vius [36]. El terme paràlisi cerebral inclou un grup de trastorns permanents del moviment i/o la postura a causa d'una afectació en el cervell en desenvolupat o immadur que poden anar acompanyats per diferents comorbiditats [20, 246].

La paràlisi cerebral és una condició heterogènia tant pel que fa a la seva etiologia com en el tipus i la gravetat de l'afectació motriu. En aquest sentit, es considera útil categoritzar als individus amb paràlisi cerebral en grups per proporcionar un major nivell de detall sobre les característiques i necessitats específiques de les diferents persones [16]. Els esquemes de classificació tradicionals s'han centrat principalment en agrupar els casos segons la distribució de les extremitats afectades i el tipus predominant de to o anormalitat del moviment, el que dona lloc a tres grans grups de paràlisi cerebral: l'espàstica, la discinètica i l'atàxica [22]. La present tesi doctoral es centra en l'estudi del segon tipus més freqüent, la paràlisi cerebral discinètica, que es caracteritza per moviments involuntaris, descontrolats, recurrents i, ocasionalment, estereotipats.

Durant els darrers quinze anys, el paper de la ressonància magnètica cerebral ha estat clau per a la comprensió de la patogènesi de la paràlisi cerebral. La majoria d'aquests estudis, però, es centren en el subtipus espàstic essent la paràlisi cerebral discinètica menys estudiada. La majoria dels estudis de neuroimatge en la paràlisi cerebral discinètica es basen en descripcions categòriques qualitatives de tomografia computada i ressonància magnètica, mentre que només cinc treballs han utilitzat anàlisis avançades de neuroimatge [94–96, 100, 102]. Aquests treballs, però, tenen dues limitacions principals que fan difícil treure conclusions generals sobre el patró de lesió cerebral en aquest tipus de paràlisi cerebral. En primer lloc, la majoria d'aquests estudis limiten les anàlisis a regions d'interès seleccionades a priori que normalment estan relacionades amb la

funció sensoriomotriu. En segon lloc, el nombre de participants amb paràlisi cerebral discinètica és molt reduït.

En la paràlisi cerebral s'han descrit tant dèficits en el funcionament intel·lectual general com en dominis cognitius específics. Gairebé un 50% de les persones amb paràlisi cerebral tenen un quocient intel·lectual inferior a 70 [2]. Probablement per aquest motiu, es considera que l'estudi de les funcions cognitives són un aspecte central en la paràlisi cerebral [3] i entre elles, les funcions executives prenen especial rellevància. Això és degut al paper clau que les funcions executives juguen en l'adquisició de noves habilitats i coneixements així com en l'aplicació d'aquests coneixements en la vida diària [4]. En aquest sentit, s'han descrit associacions entre la qualitat de vida i la funció executiva tant en la població general com en algunes malalties neurològiques i psiquiàtriques [5–9]. Aquesta relació, però, no ha estat estudiada fins ara en la paràlisi cerebral.

La paràlisi cerebral discinètica s'associa amb majors dificultats motrius que altres tipus de paràlisi cerebral [10] però no hi ha acord en si aquesta tendència també s'observa en el rendiment cognitiu [10, 58, 108, 110–112]. Els estudis que comparen habilitats cognitives entre persones amb paràlisi cerebral discinètica i altres subtipus de paràlisi cerebral són escassos i, de fet, rarament controlen variables rellevants com ara el nivell de gravetat motriu o la presència de prematuritat.

Tanmateix, cap estudi fins ara s'ha centrat específicament en explorar la funció executiva en aquest subtipus de paràlisi cerebral. Cal tenir en compte que la paràlisi cerebral discinètica es caracteritza per presentar lesions dels ganglis basals i el tàlem [11, 12] i que, donat que els circuits fronto-estriatals juguen un paper crucial en el funcionament executiu dels individus [13, 14], la paràlisi cerebral discinètica es podria caracteritzar per presentar una disfunció executiva. Els estudis de neuroimatge i funcionament executiu en paràlisi cerebral són escassos i no hi ha cap estudi que explori aquesta associació en la paràlisi cerebral discinètica [15].

7.2 Objectius

L'objectiu general de la tesi va ser caracteritzar el funcionament executiu i el rendiment intel·lectual general de les persones amb paràlisi cerebral discinètica, així com aprofundir en les seves bases biològiques en imatges de ressonància magnètica estructural. En el context d'aquest objectiu general es van formular uns objectius específics. Cada objectiu ha estat abordat per un o dos dels articles que comprenen aquesta tesi com s'indica a continuació:

I) Analitzar l'impacte de la funció executiva en la qualitat de vida de les persones amb paràlisi cerebral discinètica tot tenint en compte altres variables que se sap que influencien la qualitat de vida tant en la paràlisi cerebral com en altres poblacions (Estudi 1).

La hipòtesi lligada a aquest objectiu era que la funció executiva seria un important predictor de la qualitat de vida. Aquesta hipòtesi es basa en que les funcions executives són una habilitat cognitiva important per la realització d'activitats quotidianes o noves orientades a objectius complexes i en el fet que aquesta associació s'ha observat en altres poblacions [5–9].

II) Analitzar el funcionament executiu i intel·lectual en persones amb paràlisi cerebral discinètica i comparar-lo amb 1) participants amb un desenvolupament normatiu aparellats per edat i sexe 2) participants amb paràlisi cerebral espàstica i aparellats per edat, sexe, edat gestacional i gravetat motriu (Estudi 2).

Tenint en compte les lesions dels ganglis basals i tàlem freqüentment descrites en persones amb paràlisi cerebral discinètica [25, 53], s'esperava que la funció executiva es veiés afectada en comparació amb els controls i les persones amb paràlisi cerebral espàstica. També s'esperava que les persones amb paràlisi cerebral discinètica no presentessin un funcionament intel·lectual general més pobre que les persones amb paràlisi cerebral espàstica [109, 111, 112].

III) Identificar les alteracions de l'estructura cerebral en les persones amb paràlisi cerebral discinètica tant a nivell de a) microestructura de la substancia blanca com de b) lesions cerebrals observables mesurades amb un sistema semi quantitatiu que ha demostrat ser vàlid i fiable (Estudi 3 i Estudi 4).

Tenint en compte les observacions fetes en estudis previs [38, 75, 96], esperàvem trobar alteracions observables en ganglis basals i tàlem. Es preveia, també, confirmar la presència d'alteracions microestructurals extenses de la substància blanca [94–96, 100, 102].

IV) Investigar l'associació entre l'estructura cerebral i el funcionament intel·lectual general i executiu en els participants amb paràlisi cerebral discinètica tant a nivell de a) microestructura de la substància blanca com de b) lesions cerebrals observables mesurades amb un sistema semi quantitatiu que ha demostrat ser vàlid i fiable (Estudi 3 i Estudi 4).

Donat que la paràlisi cerebral discinètica es caracteritza per les lesions en ganglis basals i tàlem i que els circuits frontal-estriatals juguen un paper important en el funcionament executiu [13, 14], sésperava que la funció executiva estigui relacionada amb la microestructura de la substància blanca en aquelles regions que formen part dels circuits fronto-estriatals i amb la gravetat de les lesions observables en ganglis basals i tàlem. Pel que fa el funcionament intel·lectual general, esperàvem que aquest estigués associat amb la integritat de la substància blanca en tots els lòbuls cerebrals [169, 170], així com amb les lesions pericèntriques de substancia blanca [90] i amb les lesions corticals i subcorticals observables [171–173].

7.3 Mètodes

La present tesi consta de quatre estudis que utilitzen una metodologia transversal. En aquest resum es proporciona només una descripció metodològica general de la mostra, l'avaluació neuropsicològicai el procediment de neuroimage atès que aquells aspectes més concrets es troben en la secció de mètodes de cadascun dels estudis.

Participants

El projecte en el que s'emmarca la tesi va ser aprovat pel Comitè d'Ètica Institucional de la Universitat de Barcelona (IRB 00003099, número d'assegurança: FWA00004225; http://www.ub.edu/recerca/comissiobioetica.htm). Així mateix, la recerca es va dur a terme d'acord amb la Declaració d'Helsinki. Es va obtenir el consentiment informat per escrit de tots els participants, els seus pares o els seus tutors legals.

El procés de selecció dels participants i de recollida de dades va tenir lloc entre febrer de 2012 i maig de 2015. Els participants es van reclutar en les principals institucions que atenen persones amb paràlisi cerebral a Barcelona. Concretament, la majoria dels participants van ser reclutats a l'Hospital Vall d'Hebron (Servei de Neurologia Pediàtrica i Servei de Rehabilitació i Medicina Física) i l'Hospital Sant Joan de Déu (Servei de Neurologia Pediàtrica).

Els metges d'aquestes institucions involucrats en el projecte van informar als seus pacients amb paràlisi cerebral discinètica o els seus pares o tutors legals sobre la possibilitat de participar en aquest projecte de recerca. Els pacients que així ho desitjaven, van ser posteriorment contactats per telèfon per tal de comprovar els criteris d'inclusió/exclusió, explicar el procediment de participació i oferir-los de participar en l'estudi.

Els criteris d'inclusió aplicats van ser:

- ✓ Tenir un diagnòstic clínic de paràlisi cerebral amb característiques discinètiques predominants
- ✓ Tenir una edat superior a 6 anys
- ✓ Per a l'avaluació neuropsicològica, ser capaç de comprendre les instruccions de les proves. Aquesta capacitat va ser avaluada mitjançant el *Test exploratorio de gramática española* (part receptiva) [177]
  Es va establir una puntuació ≥30 com el llindar requerit per considerar que el participant tenia la suficient comprensió verbal per entendre les instruccions de les altres tasques. Aquesta puntuació de 30 correspon al percentil 10 per als nens de 6 a 6 anys i 11 anys d'edat. Cal destacar que aquest procediment fou un primer filtratge general, ja que després es va comprovar la comprensió de les instruccions de cada prova durant la valoració.

Els criteris d'exclusió van ser:

- ✓ Presentar dificultats auditives o visuals greus que impedissin l'avaluació neuropsicològica
- ✓ No tenir un sistema de si i no en la resposta que fos consistent i intel·ligible per les persones que realitzen l' avaluació

Dels 101 participants potencialment elegibles, 52 persones van formar part de la mostra final. Cada un dels quatre estudis que componen aquesta tesi inclouen un nombre diferent de participants depenent de la metodologia específica de cada estudi.

Els criteris d'inclusió per als participants amb paràlisi cerebral espàstica van ser els mateixos que els participants amb paràlisi cerebral discinètica però, en aquest cas, els participants havien de presentar diagnòstic clínic de característiques espàstiques predominants. Després del reclutament dels participants amb paràlisi cerebral discinètica, es van contactar els participants amb paràlisi cerebral espàstica aparellats per sexe i edat amb els participants amb paràlisi

cerebral discinètica. De les 45 persones identificades que complien aquests criteris, deu no van poder ser localitzades, vuit no van voler participar i set no van passar el cribatge de comprensió anteriorment descrit. Així doncs, la mostra final de persones amb paràlisi cerebral espàstica va ser de vint participants.

Els controls amb desenvolupament normatiu eren persones sense patologia cerebral aparellades per edat i sexe amb les persones amb paràlisi cerebral discinètica. A més, els següents criteris d'inclusió van ser aplicats pel grup de controls: ser nascut a terme, no patir cap trastorn neurològic o psiquiàtric i no ser consumidor de substancies il·lícites.

Avaluació neuropsicològica

Els participants van realitzar una avaluació neuropsicològica completa del funcionament intel·lectual general, el funcionament executiu i altres funcions neuropsicològiques com la memòria, la visuopercepció i el vocabulari. Les proves utilitzades van ser acuradament seleccionades per permetre que la majoria dels participants responguessin de forma autònoma a les mateixes. A continuació es presenten les diferent proves neuropsicològiques administrades:

Rendiment cognitiu general:

- ✓ Es va avaluar el funcionament intel·lectual no verbal en els Estudis 1, 2, 3 i 4 mitjançant les matrius progressives de Raven [181].
- ✓ Es va avaluar el funcionament intel·lectual verbal dels mitjançant la prova PEABODY-*Test de Vocabulario en Imágenes* [236]. El rendiment en aquesta tasca es va tenir nomes en compte en l'Estudi 1.

Funcions executives:

- ✓ Pel que fa el control atencional, es van utilitzar diferents mesures. La inhibició i l'atenció sostinguda es van avaluar mitjançant la tasca *Stop Signal Task* [182] i es va incloure en els anàlisis corresponents als estudis 2, 3 i 4. L'atenció selectiva es va avaluar tant a nivell visual com verbal. El component visual es va avaluar mitjançant el subtest d'span espacial

de la *Escala No Verbal de Aptitud Intelectual de Wechsler* [238] en els Estudis 2 i 4.

- ✓ L'atenció verbal selectiva es va avaluar als Estudis 1, 2 i 4 mitjançant el subtest span de dígits de la *Escala de inteligencia de Wechsler para adultos III* [184] o la *Escala de Inteligencia de Wechsler para niños IV* [183].
- ✓ La flexibilitat cognitiva es va mesurar mitjançant la versió computarizada del *Wisconsin Card Sorting Test* [239]. Els resultats d'aquesta prova es van tenir en compte per les anàlisis en els quatre estudis. Per altra banda, també es va avaluar la memòria de treball en l'Estudi 2 amb la modalitat inversa de la prova de dígits [184, 183] i de la memòria espacial [238].
- ✓ La capacitat de planificació es va avaluar mitjançant la tasca informatitzada de l' Stockings of Cambridge [182].
- ✓ Finalment, el domini de processament de la informació es va avaluar només en aquells participants que feien us de la comunicació verbal mitjançant una tasca de fluència verbal fonètica [187].

Imatge per ressonància magnètica

Les imatges es van adquirir en un escàner Siemens Magnetom TRIO 3.0T (Erlangen, Alemanya) a l'Hospital Universitari Vall d'Hebron (Barcelona). Abans de la prova, sota la supervisió d'un metge i d'acord amb el protocol revisat pel comitè d'ètica de l'hospital, 21 participants van prendre diazepam i en 6 es va administrar pentobarbital i propofol. Dos participants no van poder completar l'exploració a causa de l'ansietat. Altres participants van presentar certes dificultats per mantenir-se quiets i per això algunes imatges presentaven artefactes de moviment que van impedir el preprocessament per a l'anàlisi del gruix cortical (Estudi 1), la difusió (Estudi 3) i la puntuació de l'escala semi quantitativa utilitzada (Estudi 4).

El protocol d'imatge incloïa:

- ✓ Imatges tridimensionals d'alta resolució amb ponderació T1 adquirides en el pla sagital amb una seqüència d'eco de gradació d'adquisició ràpida

preparada per magnetització. Aquesta seqüència es va utilitzar en l' Estudi 1 i l' Estudi 4.

- ✓ Dues repeticions de la seqüència d'imatges ponderades de difusió adquirides a b = 1,000 s / mm². Aquesta seqüència es va utilitzar a l' Estudi 3.
- ✓ Imatges de recuperació d'inversió atenuada amb fluid (FLAIR) adquirides en 25 talls axials. Aquesta seqüència es va utilitzar en l'Estudi 4.
- ✓ Imatges de T2 turbo spin echo (pla axial) també en 25 talls axials, on el temps es permet. Aquesta seqüència es va utilitzar en l'Estudi 4.

Preprocessament i anàlisi de neuroimatge

Els estudis 1, 3 i 4 de la present tesi inclouen anàlisis de neuroimatge. Encara que les especificacions dels procediments seguits es detallen en els articles, aquí es proporciona una visió general dels mètodes utilitzats. Per a l' Estudi 1, les imatges ponderades de T1 es van processar amb el programa FreeSurfer v5.1.0 (http://surfer.nmr.mgh.harvard.edu). Posteriorment, es va realitzar una correlació entre el gruix cortical i la puntuació total del qüestionari de qualitat de vida i les respostes perseveratives del *Wisconsin Cards Sorting Test* utilitzant també el programa FreeSurfer. Per a l'Estudi 3, les imatges ponderades de difusió es van processar mitjançant un ampli procediment. Els volums que contenien artefactes es van identificar visualment i es van excloure de les anàlisis. Les adquisicions que contenien més de tres volums amb artefactes per participant també van ser excloses de les anàlisis.

Pel que fa a l'Estudi 4, les imatges es van puntuar segons l'escala semi quantitativa detallada a Fiori et al. [103]. Donada la importància de la substància gris subcortical en la nostra mostra, es van realitzar canvis en el protocol original d'aquesta escala afegint més detalls en les puntuacions dels ganglis basals i el tàlem.

7.4 Resultats

El primer objectiu d'aquesta tesi, abordat per l'Estudi 1, mostra que la funció executiva afecta la qualitat de vida en les persones amb paràlisi cerebral discinètica juntament amb el nivell de motricitat fina, la comunicació i el nivell socioeconòmic. Així doncs, el funcionament executiu és una variable clau per a la qualitat de vida de les persones amb paràlisi cerebral ja que prediu la puntuació total del qüestionari de qualitat de vida utilitzat i s'associa amb gairebé amb tots els dominis de qualitat de vida considerats en el qüestionari.

Pel que fa al segon objectiu, l'Estudi 2 mostra que les persones amb paràlisi cerebral discinètica presenten dèficits tant en el funcionament intel·lectual com executiu. En algunes tasques de planificació, però, el rendiment de les persones amb paràlisi cerebral discinètica sembla ser proper al dels controls amb desenvolupament normatiu.

El tercer propòsit d'aquesta tesi s'ha abordat amb els Estudis 3 i 4. Aquests estudis mostren que les persones amb paràlisi cerebral discinètica presenten lesions observables en la substància blanca i la substància gris així com alteracions en l'estat de la microestructura de la substància blanca. Concretament, les lesions en el tàlem lateral posterior ventral són les més freqüents en la mostra estudiada. A més, tots els participants, excepte els vuit que no tenien una lesió observable, presentaven una lesió dels ganglis basals o el tàlem. Curiosament, d'entre tots els participants que presentaven lesions observables, un terç tenien lesions que estaven limitades nomes als ganglis basals i el tàlem. Les lesions en el lòbul frontal són les segones més freqüentment observades. Tanmateix, es van identificar alteracions en la microestructura de la substància blanca en tots els lòbuls cerebrals. En concret, la pèrdua de la integritat de la substància blanca predomina en el lòbul parietal i, en menor mesura, en el lòbul temporal. Pel que fa a altres alteracions estructurals, s'han identificat lesions en el tàlem posterior, mitjà i anterior, el braç posterior de la càpsula interna, el putamen, el globus pàl·lid, el tronc cerebral i el nucli caudat.

Finalment, pel que fa la relació entre la funció cognitiva i l'estructura cerebral, tant la microestructura de la substància blanca com les lesions cerebrals observables es troben relacionades amb el funcionament cognitiu general i alguns dominis específics de la funció executiva. Concretament, el funcionament intel·lectual general està negativament relacionat amb l'anisotropia fraccional en regions córtico-corticals i córtico-subcorticals així com amb la puntuació global i del tàlem posterior de l'escala semi quantitativa utilitzada. Pel que fa a la funció executiva, la flexibilitat cognitiva es troba associada amb l'anisotropia fraccional en regions que contenen connexions amb el lòbul frontal però també en regions no directament connectades amb el lòbul frontal com el cos callós posterior, la corona radiada superior i posterior, la part retrolenticular de la càpsula interna i la radiació talàmica posterior. L'atenció selectiva, per altra banda, es troba associada amb la puntuació global, la del lòbul parietal i del cos callós de l'escala semi quantitativa utilitzada. Contrari a la nostra hipòtesi, no s'ha identificat cap associació entre la funció executiva i les vies fronto-estriatals (Estudi 3 i Estudi 4).

7.5 Discussió

Aquesta tesi inclou el primer estudi en explorar el paper del funcionament executiu en la qualitat de vida de les perdones amb paràlisi cerebral (Estudi 1) i mostra com la flexibilitat cognitiva és un domini determinant per a la qualitat de vida. L'associació entre la qualitat de vida i la flexibilitat cognitiva s'ha trobat prèviament en altres condicions. Per exemple Barf et al. [5] troben que la flexibilitat cognitiva mesurada amb el *Wisconsin Card Sorting Test* i l'atenció dividida eren determinants per a la qualitat de vida d'adults joves amb espina bífida i hidrocefàlia. Altres estudis demostren aquesta associació en persones amb malalties psiquiàtriques [5–9]. Malgrat existeixen algunes diferències menors entre els nostres resultats i els d'aquests estudis, probablement deguts a les diferències metodològiques i de mostra, aquests estudis recolzen els nostres resultats.

A més a més, l'Estudi 2 compara per primera vegada el funcionament intel·lectual i executiu en una mostra relativament gran de persones amb paràlisi cerebral discinètica amb el rendiment de persones amb desenvolupament normatiu i persones amb paràlisi cerebral espàstica comparables en edat, sexe, edat gestacional i gravetat motora. Els resultats d'aquesta comparació apunten que la paràlisi cerebral discinètica no es caracteritza per un dèficit disexecutiu i que de fet tendeix a un millor rendiment que les persones amb paràlisi cerebral espàstica. Per tal de descartar aquesta possibilitat d'un dèficit executiu específic, seria interessant tenir en compte el rendiment en altres dominis cognitius. En aquest sentit, un altre estudi del nostre grup de recerca [208] apunta que les dificultats a nivell executiu no són les més destacables d'entre les que presenten les persones amb paràlisi cerebral discinètica i que, de fet, les dificultats en flexibilitat cognitiva semblen estar presents només en aquells casos més greus.

Tanmateix, els resultats dels estudis 3 i 4 reforcen les troballes anteriors sobre la implicació de ganglis basals i tàlem en la paràlisi cerebral discinètica i afegeixen que les lesions en el tàlem ventral lateral són especialment habituals. Finalment, els resultats confirmen les troballes de Yoshida et al. sobre la implicació de la substància blanca en la paràlisi cerebral discinètica [95]. En aquest sentit, les alteracions en microestructura cerebral poden ser degudes a la lesió primària que dona lloc a la paràlisi cerebral (probablement identificades en l'Estudi 4) o a danys secundaris derivats d'aquesta lesió. Com a exemple d'aquesta segona idea, la lesió observada en el tàlem lateral ventral podria explicar algunes de les alteracions microestructurals observades en la substància blanca en la nostra mostra, donat el paper fonamental d'aquest nucli del tàlem com a relleu de les projeccions ascendents S1 involucrades en el control sensoriomotor [211–213].

Finalment, aquesta tesi aporta, per primera vegada, informació sobre l'associació entre l'estructura cerebral i la funció cognitiva. Pel que fa al rendiment cognitiu general, els resultats de l'estudi 4 són consistents amb la idea de que lesions més extenses s'associen amb una major gravetat clínica [206]. A més, i d'acord amb la teoria d'integració fronto-parietal i les troballes amb població amb desenvolupament normatiu [215] l'estat de la substància blanca en tots els lòbuls

cerebrals estava associat amb el funcionament cognitiu general en l'estudi 3 i amb la puntuació global de l'escala semi quantitativa en l'estudi 4. Pel que fa el funcionament executiu, els resultants apunten que les vies fronto-estriades no són un substrat determinant en les dificultats de la funció executiva observades en les persones amb paràlisi cerebral discinètica. Una possible raó d'aquesta manca de relació entre la funció executiva i l'estat microestructural fronto-estriatal a l'Estudi 3 podria ser l'existència de processos de plasticitat cerebral que tenen lloc després del dany precoç del cervell.

Des del punt de vista clínic, els nostres resultats posen de relleu la importància d'avaluar de manera detallada la funció executiva en les persones amb paràlisi cerebral discinètica per tal d'identificar un possible factor de risc per una baixa qualitat de vida. Els nostres resultats també posen de relleu la importància d'estudiar el paper potencial de les intervencions centrades en el funcionament executiu com a eina per millorar la qualitat de vida.

A més, tant la comparació amb persones amb paràlisi cerebral espàstica com amb persones amb un desenvolupament normatiu, indiquen que les funcions cognitives poden haver estat subestimades i emmascarades per la gravetat motora en les persones amb paràlisi cerebral discinètica. Novament, aquests resultats posen de relleu la importància d'avaluar adequadament les funcions cognitives generals i específiques en aquesta població, incloent aquells casos que presenten major gravetat motriu. A més, la caracterització de perfils cognitius específics adquireix una gran rellevància en l'entorn clínic i educatiu, ja que permetria dissenyar estratègies educatives i de rehabilitació més eficients, millorant les necessitats reals i les capacitats d'aquestes persones. Cal destacar també que les observacions realitzades en persones amb paràlisi cerebral espàstica no es poden generalitzar a les formes discinètiques.

La present tesi també permet comprendre millor la freqüència i la localització de lesions cerebrals en la paràlisi cerebral discinètica així com les seves relacions amb mesures de rellevant importància clínica. Aquesta relació s'ha estudiat mitjançant una mesura que pot ser fàcilment utilitzada pels clínics, el que pot

afavorir la detecció primerenca de comorbiditats importants en la paràlisi cerebral discinètica i, en última instància, contribuir a millorar els programes d'intervenció primerenca.

7.6 Conclusions

Les conclusions d'aquesta tesi i que es deriven dels resultats dels estudis que la comprenen són les següents:

- ✓ Un domini de la funció executiva, la flexibilitat cognitiva, és un predictor important de la qualitat de vida en persones amb paràlisi cerebral discinètica.

- ✓ Les persones amb paràlisi cerebral discinètica presenten dificultats tant en el funcionament intel·lectual general com executiu. Les habilitats de planificació, però, són properes a les de les persones amb desenvolupament normatiu, el que apunta a un cert desenvolupament d'aquesta capacitat cognitiva.

- ✓ Les persones amb paràlisi cerebral discinètica mostren un millor funcionament intel·lectual i executiu que les persones amb paràlisi cerebral espàstica. Això indica una tendència general cap a un millor rendiment cognitiu en comptes d'un dèficit disexecutiu específic.

- ✓ Les persones amb paràlisi cerebral discinètica presenten lesions observables en la substància gris i la substància blanca, així com una baixa integritat de la substància blanca. Concretament:

Les lesions observables més habituals són les del tàlem lateral posterior i el lòbul frontal. Les lesions en el lòbul frontal, però, són menys greus que les observades en el lòbul parietal.

La pèrdua de la integritat de la substància blanca en la paràlisi cerebral discinètica predomina en regions posteriors, principalment en àrees subjacents a l'escorça parietal i, en menor mesura, l'escorça temporal.

- ✓ El funcionament intel·lectual general està relacionat amb la integritat de la substància blanca en diverses regions córtico-corticals i córtico-subcorticals i amb lesions cerebrals observables (la puntuació global de l'escala semi quantitativa i el tàlem posterior).

- ✓ Les regions cerebrals posteriors, però no els circuits fronto-estriatals, juguen un rol important en el funcionament executiu en la paràlisi cerebral discinètica. Concretament:

La flexibilitat cognitiva s'associa amb l'anisotropia fraccional en regions que contenen vies córtico-subcorticals posteriors i fronto-corticals.

L'atenció selectiva s'associa amb la puntuació global del sistema semi quantitatiu utilitzat, el nivell de lesió observable en el lòbul parietal, el cos callós mig i posterior.

8

Summary

(Spanish version)

La parálisis cerebral es una de las causas más frecuentes de discapacidad física en niños y supone una condición permanente a lo largo de la vida [70]. Concretamente, la prevalencia media mundial es de aproximadamente de 2 por cada 1000 niños nacidos vivos [36]. El término parálisis cerebral incluye un grupo de trastornos permanentes del movimiento y/o postura y de la función motora debido a una afectación en el cerebro en desarrollado o inmaduro que pueden ir acompañados por diferentes comorbilidades [20, 246].

La parálisis cerebral también es una condición heterogénea tanto en cuanto a etiología como en el tipo y gravedad de la afectación motriz. En este sentido, se considera útil categorizar a los individuos con parálisis cerebral en grupos para proporcionar un mayor nivel de detalle sobre las características y necesidades específicas de las diferentes personas [16]. Los esquemas de clasificación tradicionales se han centrado principalmente en agrupar los casos según la distribución de las extremidades afectadas y el tipo predominante de tono o anormalidad del movimiento, lo que da lugar a tres grandes grupos de parálisis cerebral: el espástico, el discinetico y el atáxico [22]. La presente tesis doctoral se centra en el estudio del segundo tipo más frecuente, la parálisis cerebral discinètica, que se caracteriza por movimientos involuntarios, descontrolados, recurrentes y, ocasionalmente, estereotipados.

La resonancia magnética ha aumentado nuestra comprensión de la parálisis cerebral [1], pero mientras que la mayoría de los estudios se centran en la parálisis cerebral espástica, los estudios de neuroimagen centrados en la parálisis cerebral discinética son aun escasos.

Tanto los procesos cognitivos globales como específicos pueden verse afectados en la parálisis cerebral y casi el 50% de la población presenta un cociente intelectual por debajo de 70 [2]. En consecuencia, la consideración de las funciones cognitivas es uno de los aspectos centrales en el estudio de la parálisis cerebral [3] siendo la función ejecutiva de particular interés debido a su papel clave en la adquisición efectiva de nuevas habilidades, conocimiento y la aplicación de estas conocimiento en el día a día [4]. La asociación entre la calidad

de vida y la función ejecutiva se ha descrito en la población general y en otras condiciones neurológicas y psiquiátrica distintas a la parálisis cerebral [5–9].

Existe acuerdo en que la parálisis cerebral discinética presenta mayor gravedad motriz que otros tipos parálisis cerebral [10]. Sin embargo, existen pocos estudios que comparen las capacidades cognitivas entre este tipo de parálisis cerebral y otros subtipos y, de hecho, la mayoría de ellos no controla los resultados por el nivel de gravedad motriz. Ningún estudio hasta la fecha se ha enfocado específicamente en estudiar la función ejecutiva ni su asociación con las características de la estructura cerebral en este subtipo de parálisis cerebral. Las lesiones de los ganglios basales y el tálamo son especialmente frecuentes en personas con parálisis cerebral discinética [11, 12] y, dado que los circuitos fronto-estriatales juegan un papel crucial en el funcionamiento ejecutivo para las personas con un desarrollo normal [13, 14], seria esperable encontrar este correlato anátomo-funcional en la parálisis cerebral discinética. Sin embargo, muy pocos trabajos han estudiado la relación entre la estructura cerebral y el funcionamiento ejecutivo en las personas con parálisis cerebral. De hecho, no existe ningún estudio que analice esta relación en las personas con parálisis cerebral discinética [15].

El objetivo general de la tesis fue caracterizar el funcionamiento ejecutivo y el funcionamiento intelectual general y sus bases biológicas en imagen de resonancia magnética estructural convencional y de difusion en la parálisis cerebral discinética. Específicamente, en la presente tesis se formularon cuatro objetivos que han sido abordados mediante la realización de cuatro estudios. El primero consistió en analizar el impacto de la función ejecutiva en la calidad de vida en personas con parálisis cerebral discinética (Estudio 1). El segundo objetivo fue identificar el perfil de funcionamiento ejecutivo e intelectual en las personas con parálisis cerebral discinética (Estudio 2). En tercer lugar nos propusimos identificar las alteraciones de la estructura cerebral en participantes con parálisis cerebral discinética (Estudio 3 y Estudio 4). Finalmente, el cuarto objetivo fue investigar el correlato neural del funcionamiento ejecutivo e

intelectual general en participantes con parálisis cerebral discinética (Estudio 3 y Estudio 4).

En consecuencia, los principales hallazgos de los estudios son los siguientes. 1) Uno de los componentes de las funciones ejecutivas, la flexibilidad cognitiva, es un predictor importante de la calidad de vida en personas con parálisis cerebral discinética. 2) Las personas con parálisis cerebral discinética presentan dificultades tanto en el rendimiento intelectual general como en el funcionamiento ejecutivo. Sin embargo, las habilidades de planificación parecen ser similares a las de los controles con desarrollo normativo. Además, las personas con parálisis cerebral discinética muestran un mejor funcionamiento intelectual y ejecutivo que las personas con parálisis cerebral espástica, lo que indica una tendencia general hacia un mejor rendimiento cognitivo en lugar de un déficit disejecutivo específico. 3) Existen lesiones observables en la substancia blanca y gris, así como una reducción de la integridad de la substancia blanca en la parálisis cerebral discinética. Concretamente, las lesiones en el tálamo lateral posterior y en el lóbulo frontal son los más comunes en nuestra muestra de personas con parálisis cerebral discinética. Además, la pérdida en la integridad de la sustancia blanca en la parálisis cerebral discinética predomina en regiones posteriores subyacentes, principalmente, a la corteza parietal. 4) El funcionamiento intelectual general está relacionado con la integridad de la substancia blanca en varias regiones cortico-corticales y cortico-subcorticales y con lesiones cerebrales observables principalmente del tálamo posterior. Las funciones ejecutivas se relacionaron con la microestructura de la sustancia blanca en regiones que contienen vías fronto-corticales y cortico-subcorticales posteriores, así como con las lesiones cerebrales observables especialmente en el lóbulo parietal y de cuerpo calloso medio y posterior. Contrariamente a nuestra hipótesis, no se identificaron relaciones significativas entre la función ejecutiva y las vías fronto-estriatales.

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