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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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 analyse 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 wellbeing 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 wellbeing, 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.

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.

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 foetal 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], stuctures that have been related to executive functions [6].

Because CP is a permanent disorder, current treatment programmes 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 wellbeing. The Cerebral palsy quality of life questionnaire (CP QOL) fits the World health organization’s definition of QOL and embraces wellbeing 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, 40] 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 [21, 22, 27] domains in children and adolescents with CP. However, research has yet to analyse 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, 22, 28–30] 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 [31], 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 [32]. Associations between QOL and executive functions have been described in the general population and in other neurological and psychiatric conditions [33–38]. 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 [39].

Thus, executive function is not exclusive to cognitive (cool) processes, but is also characterized in emotional responses and behavioral actions (hot processes) [40]. 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 [41]. Therefore, when studying executive functions it is also important have hot executive functions paradigms into account such as decision-making under conditions of risk, as they have an affective, motivational, or incentive/reward component [42], and are associated with behavior

problems [43, 44] 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 [45].

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 with 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 [38–40], 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 with some clinical outcomes in CP, research has yet to examine the neural substrate underlying QOL in CP. Dyskinetic CP is an specially suitable context for a study of this kind, since it is characterized by a homogeneous brain injury pattern among affected individuals. In sum, studing 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 analyse 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 [46] (2) age 12 years or over (3) for the neuropsychological assessment, being able to understand instructions, as evaluated by the Spanish Grammar Screening Test (receptive part). 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 5 cases, congenital brain malformations in 2 cases and signs of infection in 2 cases. In 6 subjects the perinatal antecedents were unknown. In order to undertake the cortical thickness analysis, all participants were asked to undergo a brain 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 artefacts. 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 [47], an instrument comprising the following seven domains: general wellbeing and participation, communication and physical health, school wellbeing, social wellbeing, 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. Cronbach's alphas for the scales range from 0.81 to 0.96 indicating an acceptable internal consistency. Test–retest reliability range 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 [47]. 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 wellbeing domain, and were adapted by asking adult respondents to think about the institutions they currently attended (occupational therapy centre, 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) [48]. 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) [49] and the Bimanual Fine Motor Function (BFMF) [50]. 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 [51]. 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 [51].

Cognitive assessment

Verbal IQ was assessed using the Peabody Picture Vocabulary Test Third Edition (PPVT-III) [52]. Nonverbal IQ was computed by means of Raven's Coloured Progressive Matrices (RCPM) [53]. 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 are required [54].

Three main subdomains comprising executive functions [41] 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) [55, 56]; goal setting was evaluated by means of the Stockings of Cambridge (SOC) test form the Cambridge Neuropsychological Test Automated Battery [57]; and cognitive flexibility was assessed using the 64-item computerized version of the Wisconsin Card Sorting Test (WCST) [58]. In order to assess risk taking, participants also completed the youth version of the Balloon Analogue Risk Task (BART-Y) [59], 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 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 €2,700 (level VI).

Magnetic resonance imaging (MRI) 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 9º; 320 x 307 matrix and voxel size 0.7 mm x 0.7 mm x 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 [60]. 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 [61], automated Talairach transformation, intensity normalization [62], tessellation of the gray matter/white matter boundary, automated topology correction [63, 64] and surface deformation to optimally place the gray/white matter and gray matter/cerebrospinal fluid boundaries [60]. The result in representation of cortical thickness is calculated as the distance between tissue boundaries [60]. 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 [65, 66] 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 labelled according to the Desikan atlas [67]. 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 is 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 wellbeing. 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 wellbeing (small effect size). The CFCS was only

weakly associated with School wellbeing and Feelings about functioning. Regarding cognitive functions, both verbal and non-verbal IQ were positively associated with a medium effect size to three domains (General wellbeing and participation and Communication and physical health), and only verbal IQ with a medium effect size with Feelings about functioning. Executive functions was the cognitive area associated with the highest number of CP QOL domains. Specifically, it correlated positively and at least moderately with General wellbeing 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 wellbeing 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 wellbeing 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 do not predict School wellbeing (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, istmus 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, Figure 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 (Figure 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 [68]. Moreover, the association between QOL and cognitive flexibility, as measured by the WCST, has previously been reported in other health-related conditions [37, 38, 69, 70].

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 [71]. Poor mental flexibility undermines a person's ability to function independently, especially in new situations, affecting adaptive behaviour and socialization skills [72], 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 [50] it being more focused on wellbeing than on the specific capacity to grasp, hold, and manipulate, which is what is measured by the BFMF. Our findings consistent with previous studies indicating 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 wellbeing. Specifically, having more communication difficulties was related to feeling better at currently-attended institutions (school, college, occupational therapy centre, 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 centres 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 wellbeing 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 with 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 neighbouring areas have reciprocal corticocortical connections [73]. 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 [73]. Perfusion in the posterior cingulate and precuneus has been associated with wellbeing and HRQOL in patients with major depressive and post-traumatic stress disorders [74, 75]. However, in these patients the perfusion was negatively associated with wellbeing, 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 wellbeing. 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 [76]. 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 [73]. 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 with 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 [77]. 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 [73], 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 preliminay 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 [78]. 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 [79] 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 requieres 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 [47]. 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. 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 programmes 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.

COMPLIANCE WITH ETHICAL STANDARDS

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

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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

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.

CP QOL DOMAINS	N*	Mean (SD)	Range
General wellbeing and participation	50	69.95 (11.93)	41.67 - 94.64
Communication and physical health		71.79 (10.87)	42.97 - 91.41
School wellbeing		74.59 (14.46)	29.69 - 100
Social wellbeing		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
MOTOR STATUS	**N**	**Level (n)**	**Range**
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	**N**	**Level (n)**	**Range**
CFCS	50	I (18), II (20), III (6), IV (5), V (1)	I - V
IQ	**N**	**Mean (SD)**	**Range**
Verbal			
PPVT-III (IQ)	49[a]	71.53 (18.59)	55 - 119
Non verbal			
RCPM (IQ)	49[a]	87.04 (26.31)	26 - 129
EXECUTIVE FUNCTIONS	**N**	**Mean (SD)**	**Range**
Attentional control			
WISC/WAIS digit span (z)	42[a, b, c]	-0.94 (0.92)	-2.75 - 0.77
Goal setting			
SOC total scores (z)	43[a, b, c]	-0.25 (1.39)	-4 - 1.91
Cognitive flexibility			
WCST completed categories (z)	46[a, c]	-1.48 (0.62)	-2.67 - -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 - 1.70
ANXIOUS AND DEPRESSIVE SYMPTOMS	**N**	**Mean (SD)**	**Range**
ASEBA (CBCL, ASR or ABCL as applicable) (T)	49[d]	57.58 (6.74)	48.52 - 75.95
SOCIOECONOMIC STATUS	**N**	**Mean (SD)**	**Range**
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 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 coloured 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.

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 wellbeing and participation	IQ		
	Verbal: PPVT-III	$.35_s$	.014
	Non-verbal: 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
	Non-verbal: RCPM	$.35_s$	.015
	Executive functions		
	Cognitive flexibility: WCST perseverative responses (T)	.36	.013
	Risk taking: BART-Y (z)	.38	.010
School wellbeing	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 coloured progressive matrices; WAIS: Wechsler adult intelligence scale; WCST: Wisconsin card sorting test; WISC: Wechsler intelligence scale for children.

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

* p≤.05; ** p≤.01; ***p≤.001; 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.

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 (mm2)	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, istmus and pericalcarine cortices	4763.44	-13.0	-35.2	39.4	4.122	<.001
LH	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

LH: Left hemisphere; QOL: Quality of life; RH: Right hemisphere; WCST: Wisconsin card sorting test.

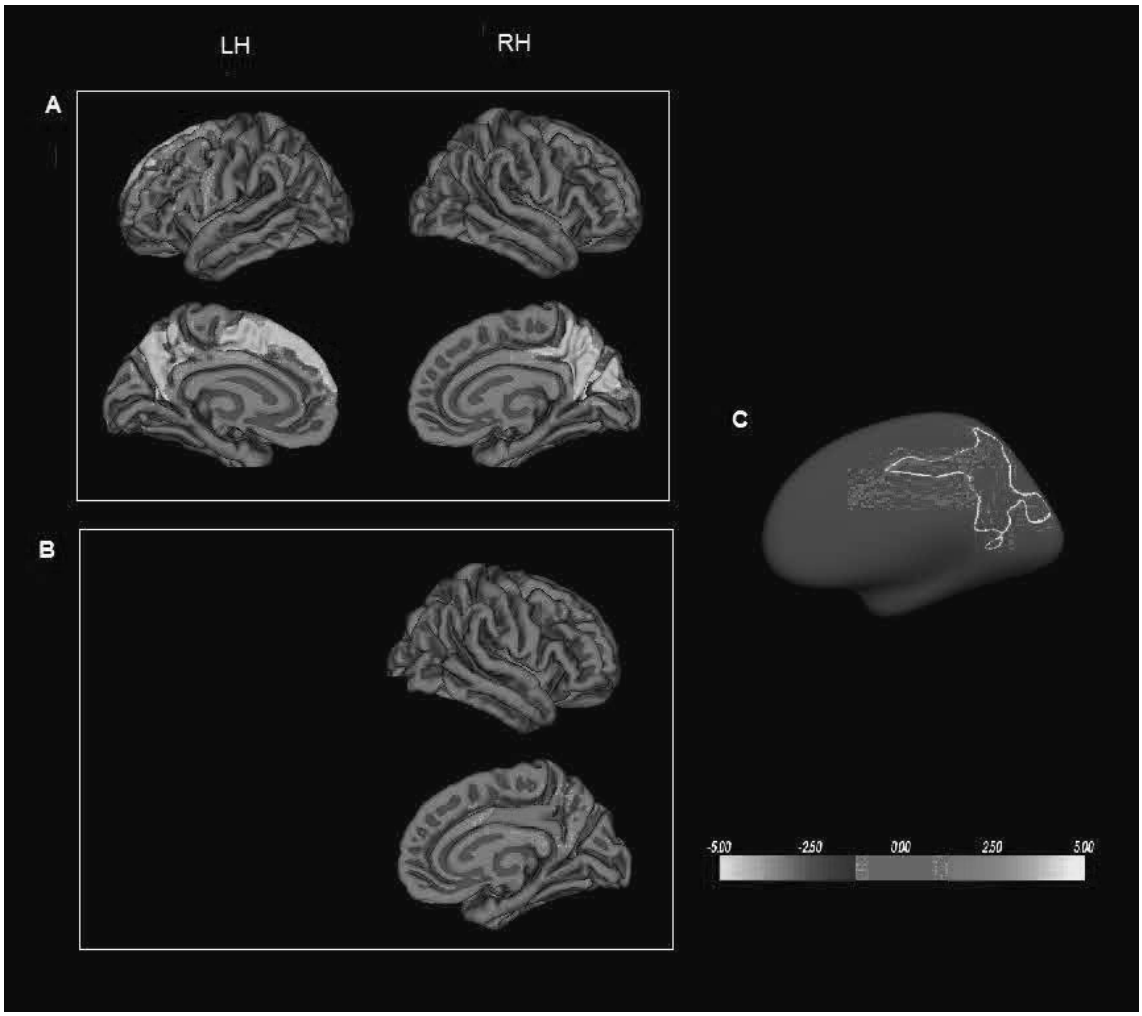

Figure 1. Cerebral areas showing significant positive correlation with: (a) total CP QOL in LH pars opercularis and posterior cingulate and RH precuneus cortices; (b) perseverative responses of WCST in RH posterior cingulate cortex. (c) Overlapping results of both correlations (in RH precuneus and posterior 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 were used. Results were thresholded at a corrected $p \leq .05$ ($Z = 1.3$). LH: Left hemisphere; RH: Right hemisphere.

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 coloured progressive matrices test
SOC	Stockings of Cambridge
WAIS	Wechsler adult intelligence scale
WCST	Wisconsin card sorting test
WISC	Wechsler intelligence scale for children

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