Mastication Dyspraxia: a neurodevelopmental disorder reflecting disruption of the cerebello-cerebral network involved in planned actions

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Abbreviated Title: Mastication dyspraxia

Abstract

This paper reports longitudinal clinical, neurocognitive and neuroradiological findings in an adolescent patient with non-progressive motor and cognitive disturbances consistent with a diagnosis of developmental coordination disorder (DCD). In addition to prototypical DCD, development of mastication was severely impaired while no evidence of swallowing apraxia, dysphagia, sensorimotor disturbances, abnormal tone or impaired general cognition were found. He suffered from bronchopulmonary dysplasia and was ventilated as newborn for 1.5 months. At the age of three months a ventriculoperitoneal shunt was surgically installed because of obstructive hydrocephalus secondary to perinatal intraventricular bleeding. At the age of five, the patient's attempts to masticate were characterized by rough, effortful and laborious biting movements confined to the vertical plane. Solid food particles had a tendency to get struck in his mouth and there was constant spillage. As a substitute for mastication, he moved the unground food with his fingers in a lateral direction to the mandibular and maxillary vestibule to externally manipulate and squeeze the food between cheek and teeth with the palm of his hand. Once the food was sufficiently soft, the bolus was correctly transported by the tongue in posterior direction and normal deglutition took place. Repeat MRI during follow-up disclosed mild structural abnormalities as the sequellae of the perinatal intraventricular bleeding but this could not explain impaired mastication behaviour. Quantified Tc-99m-ECD SPECT, however, revealed decreased perfusion in the left cerebellar hemisphere, as well as in both inferior lateral frontal regions, both motor cortices and the right anterior and lateral temporal areas. Anatomoclinical findings in this patient with DCD not only indicate that the functional integrity of the cerebello-cerebral network is crucially important in the planning and execution of skilled actions, but also seem to show for the first time that mastication deficits may be of true apraxic origin. As a result it is hypothesized that "mastication dyspraxia" may have to be considered as a distinct nosological entity within the group of the developmental dyspraxias following a disruption of the cerebello-cerebral network involved in planned actions.

Key Words: Cerebellum, developmental coordination disorder, apraxia, SPECT

Conflict of Interest Notification Page

The authors of the manuscript Peter Mariën, Annelies Vidts, Wim Van Hecke, Didier De Surgeloose, Frank De Belder, Paul M Parizel, Sebastiaan Engelborghs, Peter P De Deyn and Jo Verhoeven explicitly disclose no conflicts of interests.

Introduction

Mastication is a skilled motor activity which consists of the complex interaction of orofacial rhythmic processes requiring fine motor coordination of the teeth, temporomandibular joints, the lips, tongue, cheeks and facial muscles. It can be regarded as a stage which prepares the food for swallowing [1] by crushing it, grinding it and mixing it with saliva. The masticatory sequence is the whole set of movements extending from ingestion to swallowing. Lund (1991) [2] makes a distinction between three types of cycles: preparatory cycles (type I), reduction cycles (type II) and preswallowing cycles (type III). The preparatory series is aimed at moving food to the posterior teeth for breakdown by the reduction cycles, while the preswallowing cycles further reduce the food into smaller particles. The preparatory cylces are shortest in duration while the reduction and preswallowing cycles have an intermediate and long duration respectively.

Typical masticatory movements are described as having a 'tear-drop shape' [3], i.e. the beginning of the opening phase is characterized by a slight displacement of the jaw towards the chewing side, while the opposite lateral displacement is observed during the closing phase. This yields a slight rotatory movement. The most lateral point of the chewing cycle is situated halfway through the closing phase. In a vertical plane, the reduction and preswallowing cycles are characterized by a progressively diminishing vertical amplitude of the movements as the size of the food particles becomes smaller. The basic pattern of mastication is generated by pattern generating neurons in the brain stem, while sensory feedback from various intraoral, joint and muscle receptors interact with the central control system to adapt the programme to the characteristics of the food [1].

Mastication has to be learnt and it only occurs after tooth eruption. Although patterns of mastication movement may vary considerably between individuals, chewing becomes well co-ordinated around the age of 4-5. Gum-chewing PET [4] and fMRI [5] experiments in healthy subjects have confirmed significant activations in the oral region of the primary sensorimotor cortex, but have also revealed the involvement of the supplementary motor area, insula, thalamus, and cerebellum. These regions are believed to receive sensory information from the lips, tongue, oral mucosa, gingivae, teeth, mandible, and temporo-mandibular joint and to control the lingual and facial muscles during mastication (Figure 1).

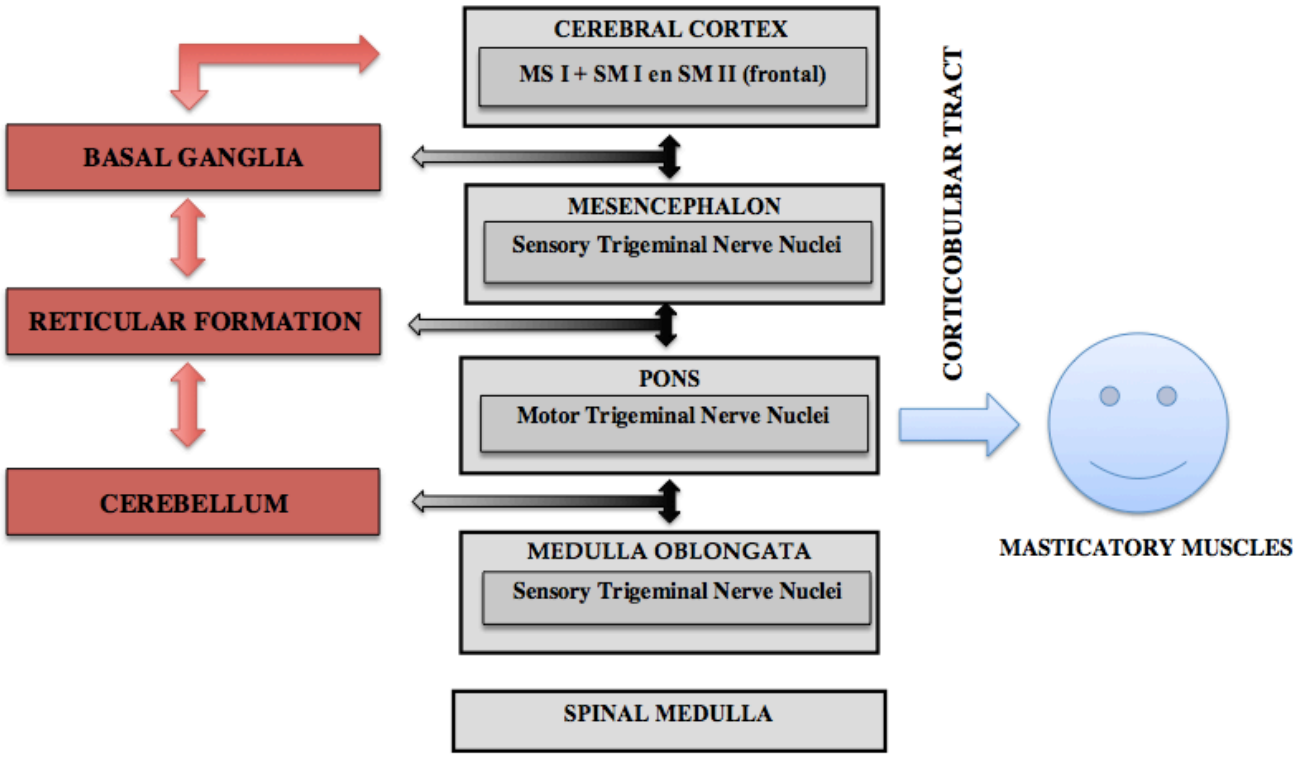

Figure 1: The direct connections of the mastication network are compiled in the corticobulbar tract (grey arrows) responsible for the voluntary movements. The corticobulbar tract rises from the primary somatomotor area (MS I) and the primary and secondary somatosensory area (SM I and SM II). These fibres continue to the medulla oblongata. On different levels they send off branches to the basal ganglia, reticular formation and cerebellum. These fibres are part of the multisynaptic extrapyramidal system, responsible for automatic movements (red arrows). The corticobulbar tract is involved in refined movements, including those of the oral system. The cerebellum also plays an important role in the motor control, planning and coordination of the masticatory movements.

Apraxia, a term originally proposed by Steinthal in 1881, is nowadays broadly defined as a disorder of skilled motor actions not caused by motor weakness, akinesia, deafferentiation, abnormal tone or posture, movement disorders (e.g. tremor, ataxia, chorea, ballismus, myoclonus), sensory-perceptual deficits, language comprehension deficits, general cognitive impairment or uncooperativeness [6,7]. Many distinct forms of apraxia have been identified that involve various parts of the human body. There has been a long tradition in neuropsychological research which has investigated different forms of apraxia at the interface between cognitive processing and motor action: eyelid apraxia, oro-facial apraxia, apraxia of

speech, swallowing apraxia, forelimb apraxia (limb-kinetic apraxia, ideomotor apraxia, ideational apraxia, dissociation apraxia, conceptual apraxia, callosal apraxia, diagnostic apraxia, pure agraphia, visuo-constructive apraxia, drawing apraxia, dressing apraxia) and gait apraxia. To the best of our knowledge there are no studies in which apraxic disruption of the mastication process has been documented. This paper, however, describes the longitudinal clinical, neurocognitive and (functional) neuroimaging findings in a 19-year-old right-handed patient who presented with severely disrupted mastication behaviour following extended periods of tube feeding during the first years of his life.

Case Report

Propositus was born prematurely by Caesarian section after 29 weeks of gestation due to pregnancy toxicosis. The newborn suffered from bronchopulmonary dysplasia and was ventilated for 1.5 months. At the age of three months a ventriculoperitoneal shunt was installed because of obstructive hydrocephalus secondary to perinatal intraventricular bleeding. Until the age of six months the boy was tube fed. Because attempts to start bottle-feeding were unsuccessful (absence of the suck reflex) syringe feeding was started. At the age of 21 months the patient was re-admitted because of progressive weight loss (-1.1 kg) (body weight = 8.5 kg; < percentile 3). He refused food that required chewing and vomited after the intake of non-liquid or soft food substances. The swallowing of liquids and pudding was normal as confirmed by videofluoroscopy. Mild oesophagitis and gastro-oesophageal reflux were found. Nocturnal nasogastric tube feeding was started and continued until the age of 30 months. An oral feeding training programme was concomitantly started but the patient remained unable to chew solid substances. At the age of 36 months he was diagnosed with gastric volvulus which was treated surgically. His eating habits did not change after the operation and he remained unable to chew.

Acquisition of motor milestones as well as onset of speech production (around age 2.5 years) was delayed. At the age of 4.5 years, deviant development of articulated speech was formally diagnosed as developmental apraxia of speech (DAS). Speech therapy was started to complement feeding and oral-motor therapy. A Wechsler Preschool and Primary Scale of Intelligence performed at this age showed a normal verbal IQ level of 88. A developmental non-verbal delay of approximately 1.5 years was objectified by means of the 'Snijders-Oomen Non-verbale Intelligetietest' (SON-R) [8]. The kintergarten reported behavioural and affective

problems. These included the avoidance of social contacts and difficulties in establishing and maintaining relationships with peers. Family history was negative for developmental disorders and learning disabilities.

At the age of 5.5 years the boy was referred to the neurological department of ZNA Middelheim General Hospital because little progress had been made in acquiring a mature mastication pattern, even after several months of intensive oral-motor and feeding therapy. Instead of coordinated chewing movements, mastication behaviour consisted of rough, effortful and laborious biting movements. Chewing was restricted to vertical movements of the jaw without any noticeable lateral or rotatory motion. Bigger food particles had a tendency to get stuck in his mouth and there was constant spillage. The patient moved the unground food particles with his fingers in a lateral direction to the mandibular and maxillary vestibule; the bolus was then externally manipulated and squeezed between his teeth and cheek with the palm of his hand. Once the bolus was sufficiently soft, normal deglutition took place immediately. Neurological examination revealed severe developmental delay (> 2.5 years) of gross and fine motor functions, dysdiadochokinesia and marked clumsiness but no motor or sensory abnormalities were found to explain abnormal mastication. However, various dyspraxic deficits across different modalities were observed. In addition to DAS, the patient presented with severe bucco-labio-lingual, constructional and drawing apraxia. In-depth stomatological and maxillo-facial examinations did not reveal any motor or sensory abnormalities. A repeat videofluoroscopy study was normal. CT and MRI of the brain as well as EEG recordings did not reveal any abnormalities.

After one year the patient had learned some gross chewing movements but mastication of hard substances was still impossible. He could not move his tongue or jaw in a lateral direction on command, he could not lick his lips or protrude his tongue towards the tip of his nose. Rapid and smooth alteration between different articulatory positions /p–t–k/, was not possible. He was not able to blow up his cheeks and hold for at least 3 seconds. Furthermore, he was unable to whistle or blow out a candle. Results of the neurological examination remained unremarkable. Food aversion was suspected but a psychiatric assessment disclosed no evidence of a psychogenic disorder. Since there were reports of problems at school, cognitive investigations were repeated. A screening of general cognition by means of the Wechsler Intelligence Scale for Children-R [9] disclosed a significant discrepancy of 20 IQ-points between a low average verbal IQ (80) and a profoundly depressed non-verbal level

(performance IQ = 60) (Table 1). Scaled scores ≤-2 standard deviations (SD) were obtained for all but one of the performance subtests (picture arrangement). At the verbal level, the subtests 'digit repetition', 'arithmetics' and 'similarities' scored ≤-2 SD. Distorted visual-motor integration skills (scaled score 69), and borderline visual-motor coordination (scaled score 74) were reflected by the results on the Beery Developmental Test of Visual-Motor Integration [10]. A low score (pct. <10) was found on copying of the Rey-Osterrieth figure [11]. As demonstrated by the Differentieller Leistungstest [12] (< pct 5) and the Bourdon-Vos Test [13] (< pct 5) borderline results were obtained for sustained visuo-motor attention. In addition to DAS, formal investigation of linguistic functions by means of the Taaltest voor Kinderen [14] showed a borderline score at the level of receptive vocabulary (word comprehension = pct. 4). Verbal memory was normal (pct. 69) as measured by the 15 words test of the PINOK [15]. Physical therapy was started to complement oral-motor and feeding therapy and the boy was referred to special needs education.

As shown in table 1 the neurocognitive profile did not substantially change. A consistent discrepancy between superior verbal and inferior non-verbal cognitive skills was found again one year later and attentional deficits and executive dysfunctions persisted as well. During follow-up an improvement of bucco-labio-lingual praxis and mastication skills was reported. At the age of 19 years he was able to perform lateral as well as rotatory chewing movements but the process was executed in a markedly slow, gross and laborious way. Oral searching behaviour to position and transport the bolus (groping) with effortful lingual movements was regularly observed when the patient put food in his mouth. Notwithstanding the long duration of the chewing process, the patient swallowed relatively big food particles with considerable difficulty. A lack of control over the mastication process was observed and as soon as he was distracted from the mastication act, he stopped chewing. The Nordic Orofacial Test-Screening (NOT-S) [16] was administered to investigate orofacial function and ad hoc normative data for this test were collected in an age and education-matched control group of 40 subjects (19-year-old pupils trained at the same level of special education). The NOT-S assesses 12 domains of orofacial function, six by means of a structured interview and six by clinical evaluation of the participant performing various tasks using a manual consisting of 13 pictures. A positive or defective response results in one point with a maximum total score on the test of 12 points. The domains evaluated in the NOT-S interview are: (I) sensory function, (II) breathing, (III) habits, (IV) chewing and swallowing, (V)

drooling, and (VI) dryness of the mouth. The patient obtained a total score in the NOT-S interview of 4/6 with failures situated in the following fields: (I) sensory function (1 positive response on 2 questions), (II) breathing (2 positive responses on 2 questions), (III) habits (2 positive responses on 2 questions), and (IV) chewing and swallowing (2 postive responses on 5 questions). No evidence for (V) drooling (1 question) and (VI) dryness of the mouth (2 questions) was found. The clinical part of the in the NOT-S examination consists of: (1) the face at rest (4 evaluation criteria), and a variety of tasks evaluating (2) nose breathing (1 task), (3) facial expression (3 tasks), (4) masticatory muscle and jaw function (2 tasks), (5) oral motor function (4 tasks), and (6) speech (2 tasks). The patient obtained a score of 4/6 on this subpart with positive scores situated in the following domains: 1) the face at rest which was marked by a slight asymmetry (4) abnormal masticatory muscle and jaw function characterized by asymmetrical activity, (5) deviant oral motor function characterized by the inability to reach outside of the Vermillion border of the lips with the tip of the tongue, to reach the corners of the mouth and to blow up the cheeks and hold for at least 3 seconds, and (6) unclear speech with some indistinct sounds. The patient obtained a NOT-S total score of 8 points which is statistically significantly different (One sample Wilcoxon Signed Rank Test, $p < 0.001$) from the mean of 3.3 points (SD = 1.4) in the control population. In addition, the patient and the controls were examined by means of the Test for Assessing Nonverbal Oral Movement Control and Sequencing [17]. This test consists of 10 oral-motor tasks each of which is scored on a 1 to 4 point scale (higher points indicate normality. The following tasks have to be performed: 1) coughing, 2) clicking the tongue, 3) blowing, 4) biting the lower lip, 5) puffing out the cheeks, 6) smacking the lips, 7) sticking out the tongue, 8) licking the lips, 9) biting the lower lip and then clicking the tongue, and 10) smacking the lips and then coughing. The mean score in the control population was 39/40 (SD = 1.5). The patient obtained a significantly lower total score of 27/40 (One sample Wilcoxon Signed Rank Test, $p < 0.001$). He was not able to puff out his cheeks (score 1) and displayed trial and error searching movements when he had to smack his lips (score 2), to stick out his tongue (score 2), to lick his lips (score 2), and to smack his lips and then cough (score 2). Coughing (task 1) and biting of the lower lip and then clicking the tongue (task 9) were accurate but awkwardly and slowly produced (score 3). Tasks 2, 3, and 4 required no effort and were immediately and accurately performed. Detailed clinical neurological examination in which cerebellar functionality was studied with the Brief Ataxia Rating Scale (BARS) revealed very mild

ataxia, reflected by a total score of 4/30 (normality is indicated by lower points) [18]. Lowering of the heel was performed in a continuous axis but the movement was decomposed in several phases (BARS score = 1). In the finger-to-nose test, oscillating movements of the arm and hand without decomposition of the movement were observed (BARS score = 1). Motor speech was mildly disrupted by a few articulation errors, a laboured articulatory setting and oral diadochokinesis (BARS score = 1) which are consistent with sequelae of DAS. There were mild oculomotor abnormalities consisting of slightly slowed pursuit (BARS score = 1). Repeat EEG was normal. Repeat MRI of the brain (Fig. 1A-F) showed slight atrophy of the corpus callosum (Fig 1A), irregular but normal-sized ventricles and the linear trajectory of intraventricular drain insertion (1C-F) when the patient was 3 months old (Fig 1C-D). In addition, slightly abnormal aspect of the white matter suggests discrete hypomyelination as the possible sequellae of the perinatal intraventricular bleeding (Fig 1C-E). A gliotic reaction surrounding a periventricular white matter lesion is demonstrated on Fig 1E. No infra- or supratentorial abnormalities were found in the primary sensorimotor cortices, the supplementary motor area, insula, thalamus, brainstem or the cerebellum that could relate to the pattern of neurobehavioural deficits.

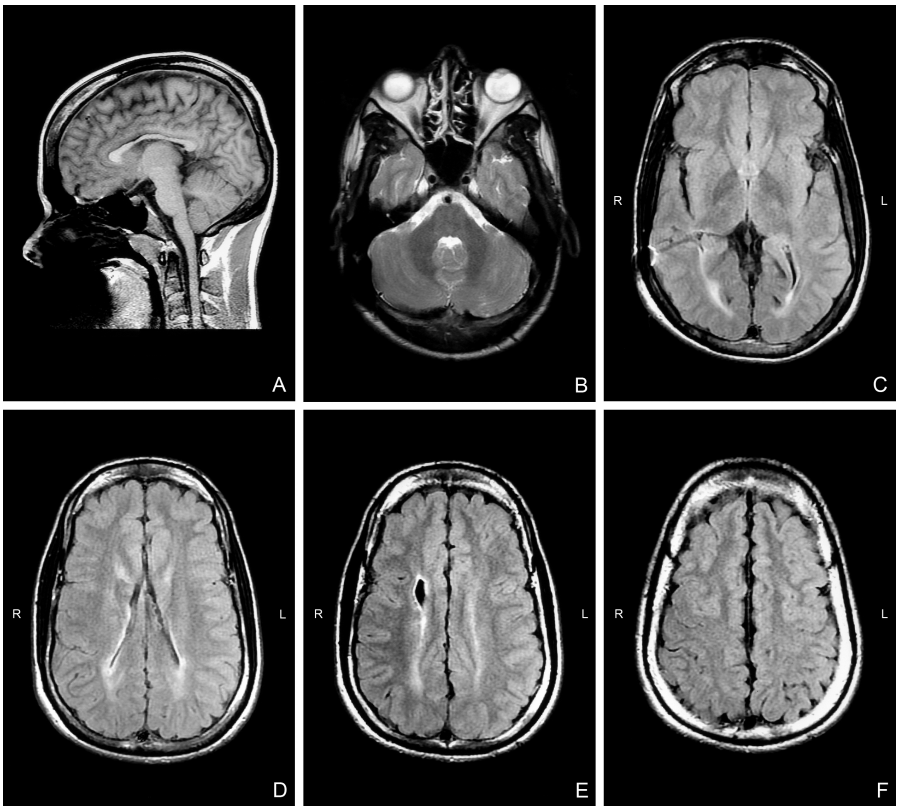

Figure 2 (A-H): Mid-saggital T1-weighted Brain MRI slice (1A) at the age of 19-years showing an irregular and slightly atrophic callosal body. Axial FSE T2-weighted Brain MRI slice (1B) shows normal cerebellar structures. Axial FLAIR images (1C-F) disclose irregular lateral ventricular volumes, a linear trajectory of the intraventricular drain installation when the patient was 3 months old and slightly abnormal white matter indicating discrete hypomyelination as the possible sequelae of the perinatal intraventricular bleeding. A gliotic reaction surrounding a periventricular white matter lesion is demonstrated as well (1E).

Since T2- and FLAIR sequences did not show focal white matter lesions and to limit exposure time in the scanner single voxel MRI spectroscopy instead of volumetric spectroscopy was conducted to exclude metabolic disease, which may be expected to involve the whole white matter. Single voxel MRI spectroscopy was acquired on a 3T MRI (Siemens) in the deep white matter of the left cerebral hemisphere. To this end, 128 averages were obtained within a single but representative voxel of 2x2x2 cm^3, which was the maximum volume of white matter to include without including grey matter with a TE of 135 ms and a TR of 2000 ms. As shown in Figure 3, normal N-acetyl aspartate (NAA), creatine (Cr), and choline (Cho) peaks were found. The ratio Cho/Cr (=0.84) is low but within normal limits (0.8-1.4).

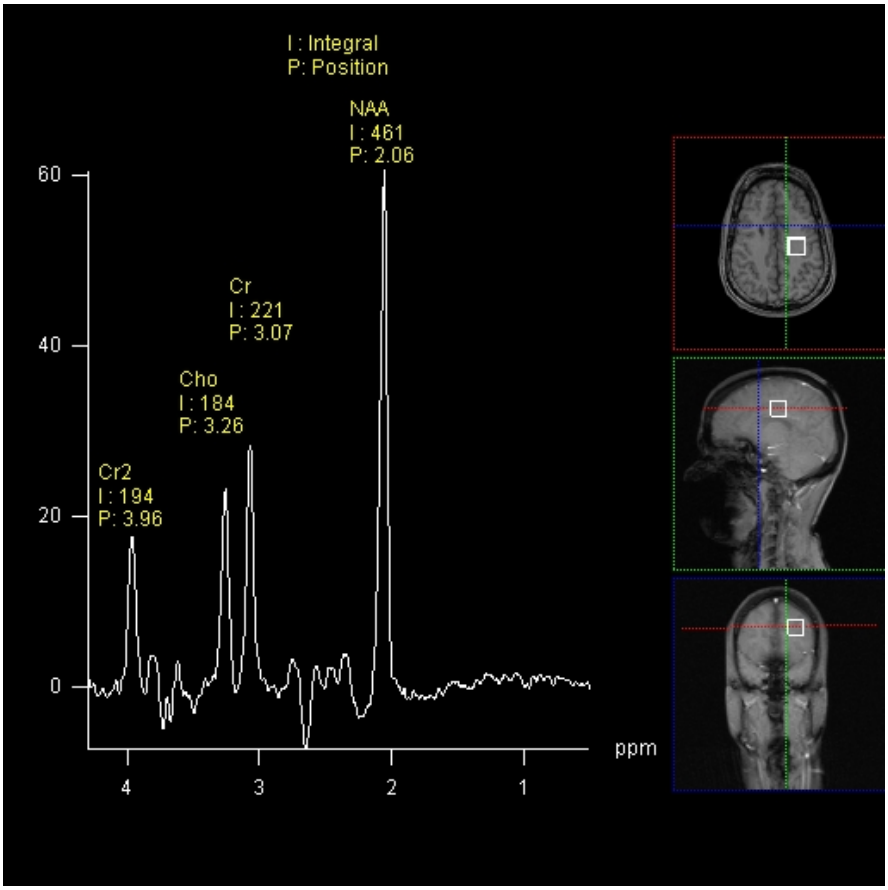

Figure 3: Spectrum of a single voxel in the deep white matter of the left hemisphere, showing normal N-acetyl aspartate (NAA), creatine (Cr), and choline (Cho) peaks. The ratio Cho/CR (=0,84) is low but within normal limits (0.8-1.4).

Repeat neuropsychological investigations confirmed prior findings, i.e. a consistent discrepancy between the verbal IQ (VIQ=79) and the nonverbal IQ (PIQ=64). The Wisconsin Card Sorting Test (WCST) [19] revealed an impaired ability to form abstract concepts, to shift and maintain goal-oriented cognitive strategies in response to changing environmental contingencies. The patient did not manage to complete any category within 128 trials (< pct 1). Visual search and sequencing (Trail Making Test) [20] were below normal levels and a subclinical score on the Stroop Colour-Word test (percentile 12) [21] provided evidence of a depressed ability to inhibit a competing and more automatic response set**.** Apart from these disrupted visuo-spatial cognition, attentional deficits and executive dysfunctions, no other cognitive defects were found. Results on the Wechsler Memory Scale-Revised (WMS-R) [22] showed that verbal learning (index = 87), nonverbal learning (index = 93) and recent memory (index =93) were well within the normal range. Formal language testing by means of the BNT (visual confrontation naming) [23], a verbal fluency task (one minute oral production of words belonging to a specific semantic or phonological category) as well as repetition, word reading and writing to dictation [24] yielded normal results. Persisting affective and social difficulties were recorded. In addition to difficulties in establishing and maintaining social contacts with peers the patient had developed strong feelings of worthlessness and emotional instability.

[INSERT TABLE 1 NEAR HERE]

Functional neuroimaging with SPECT and MRI

A quantified Tc-99m-ECD SPECT study was carried out. Using a previously fixed butterfly needle 740 MBq (20 mCi) Tc-99m-ECD was administered to the patient sitting in a quiet and dimmed room, eyes open and ears unplugged. Acquisition was started 40 min after injection using a three-headed rotating gamma camera system (Triad 88; Trionix Research Laboratory, Twinsburg, Ohio, USA) equipped with lead super-fine fanbeam collimators with a system resolution of 7.3 mm FWHM (rotating radius 13 cm). Projection data were accumulated in a

128 x 64 matrix, pixel size 3.56 mm, 15 seconds per angle, 120 angles for each detector (3° steps, 360° rotation). Projection images were rebinned to parallel data, smoothed and reconstructed in a 64 x 64 matrix, using a Butterworth filter with a high cut frequency of 0.7 cycles/cm and a roll-off of 5. No attenuation or scatter correction was performed. Trans-axial images with a pixel size of 3.56 mm were anatomically standardized using SPM and compared to a standard normal and SD image obtained from ECD perfusion studies in a group of 15 normally educated healthy adults consisting of 8 men and 7 women with an age ranging from 45 to 70 years. Using a 31 ROI template, Z-scores (SD) were calculated for each region. A regional Z-score of >2.0 was considered significant. In comparison to normal database findings the quantified Tc-99m-ECD SPECT study showed a significant decrease of perfusion in the anterior and medial part of the left cerebellar hemisphere (-2.22 SD) including the dentate nucleus and middle cerebellar peduncle as well as a hypoperfusion in the right temporal region (-2.76 SD), the right motor cortex (-2.15 SD) and the right inferior frontal region (Figure 4). Decreased perfusion in the right anterior temporal (-1.76 SD), the right cerebellar hemisphere (-1.32), the left inferior frontal (-1.77 SD) and left motor cortex (-1.92 SD) nearly reached significance.

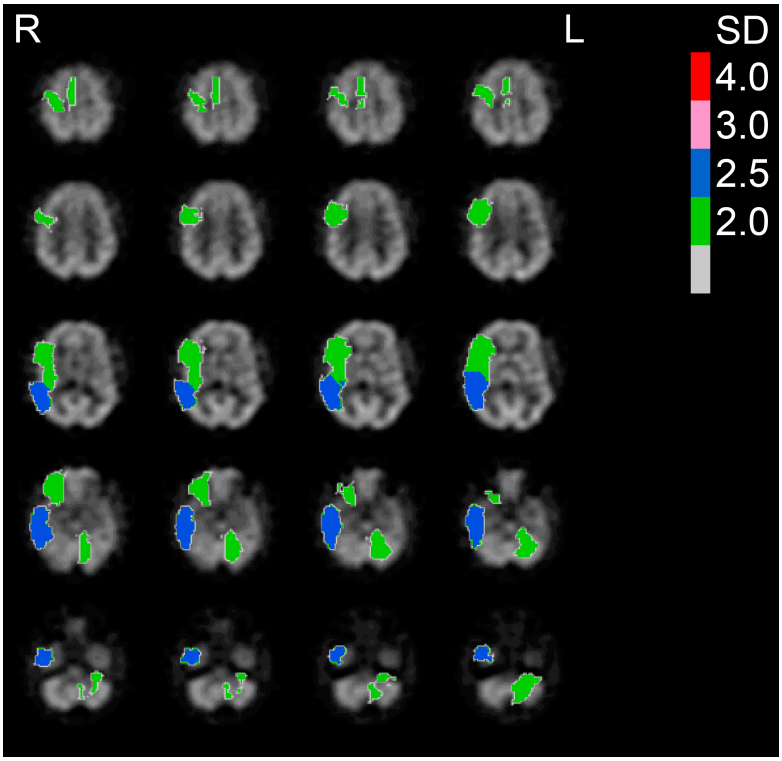

Figure 4: Quantified Tc-99m-ECD SPECT study shows a significant decrease of perfusion in

the right temporal region, the right motor cortex and the right inferior frontal region (upper row) associated with a hypoperfusion in the anterior and medial part of the left cerebellar hemisphere including the dentate nucleus and middle cerebellar peduncle (lower row). Decreased perfusion in right anterior temporal (-1.76 SD), the right cerebellar hemisphere (-1.32), the left inferior frontal (-1.77 SD) and left motor cortex (-1.92 SD) is not indicated as it did not reach a significance level of >-2 SD.

Diffusion tensor imaging (DTI) and functional MRI (fMRI) data sets were acquired on a 3T MRI (Siemens) to study the cortico-spinal tracts, masticatory related motor activation of the jaw and cerebral language dominance. A DTI acquisition with 64 non-colinear directions of gradient was used, with a TE of 88 ms and a TR of 7700 ms. Two block design fMRI data sets were acquired, both with an acquisition time of 4 minutes, a TR of 3000 ms and a TE of 50 ms. These 4 minutes were subdivided in alternating blocks of 30 seconds in which the patient was asked to rest and to perform the task. All tasks and instructions were visually presented to the patient. Since the patient was not able to chew gum an alternative task was performed to study the neural correlates of mastication consisting of moving the jaw in a way masticatory movements are executed. In a language activation task, a standard verbal semantic association task was completed, in which the patient had to think of a semantically related verb in response to a visually presented noun shown on the screen. fMRI data sets were analyzed on a separate workstation using SPM8 software. Motion correction was performed, functional data were coregistered to the anatomical image, and the anatomical image was subsequently normalized to MNI space using a non-affine transformation. This transformation was then applied to all registered functional images. After smoothing the functional images with a FWHM of 8 mm, contrasts were calculated. Results were corrected, with a false discovery rate (FDR) threshold of 0.05.

Figure 5 shows the cortico-spinal tracts in the left (green) and right (red) hemisphere. No abnormalities were observed in these tracts which had an average fractional anisotropy value of 0.54. In addition, tractography was performed using regions of interest (ROI) in the dentate nuclei and the anterior part of the motor lobe. On the colour-encoded axial FA slice (Figure 6) the regions of interest used to reconstruct the tracts from the dentate nucleus are shown in white. Tractography results are visualized in Figure 7. The FA and MD in the dentate nuclei tracts was 0.43 and 0.00086 mm^2/s, respectively. The FA and MD of the motor anterior lobe tracts was 0.39 and 0.00080 mm^2/s, respectively. Interestingly, tracts were found from the dentate nucleus towards the thalamus, but not to the motor cortex. As demonstrated

in Figure 8, the left and right primary motor cortex, left supplementary motor area (SMA) were activated during the mastication movement of the jaw. No brain activation was found in the cerebellum at the FDR (0.05) level. However, this pattern of activation should be interpreted with caution, as the patient performed additional head movements during this task, due to the inability to properly execute masticatory movements. The fMRI results of the jaw movement task are summarized in table 2. Figure 8 shows activation of the prefrontal left hemisphere language areas during the verbal association task. In table 3, the MNI coordinates of the significant regions are listed. The superior longitudinal fasciculus, connecting the anterior (Broca's area) and posterior (Wenicke's area) language areas, is displayed in yellow colour in Figure 9.

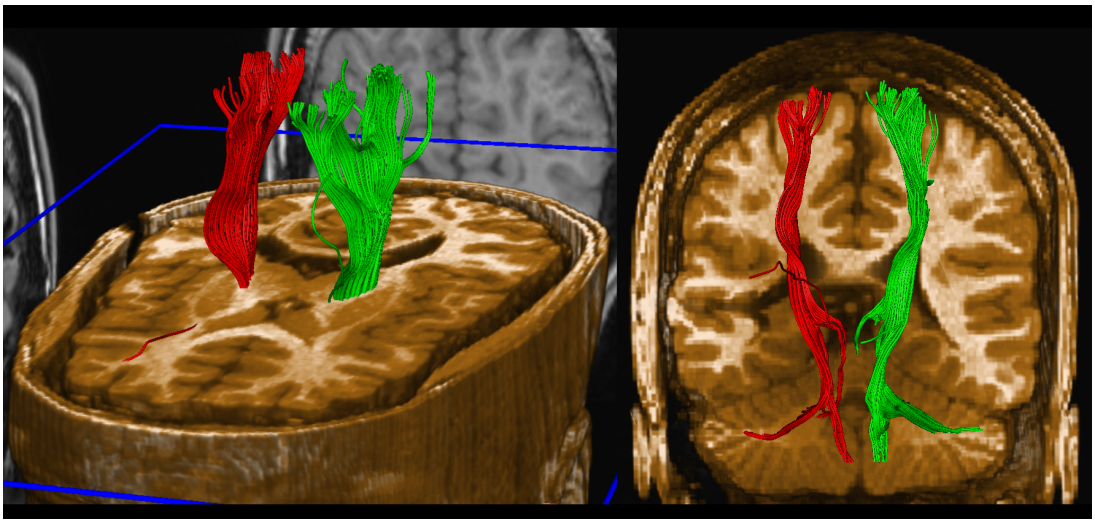

Figure 5: DTI tractography result of the cortico-spinal tracts in the left (green) and right (red) hemisphere.

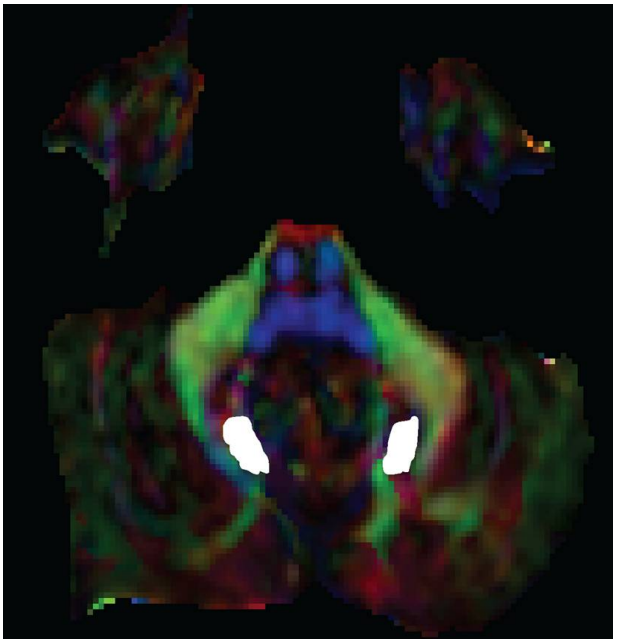

Figure 6: Colour-encoded axial FA slice depicting in white colour the regions of interest used to reconstruct the tracts from the dentate nucleus.

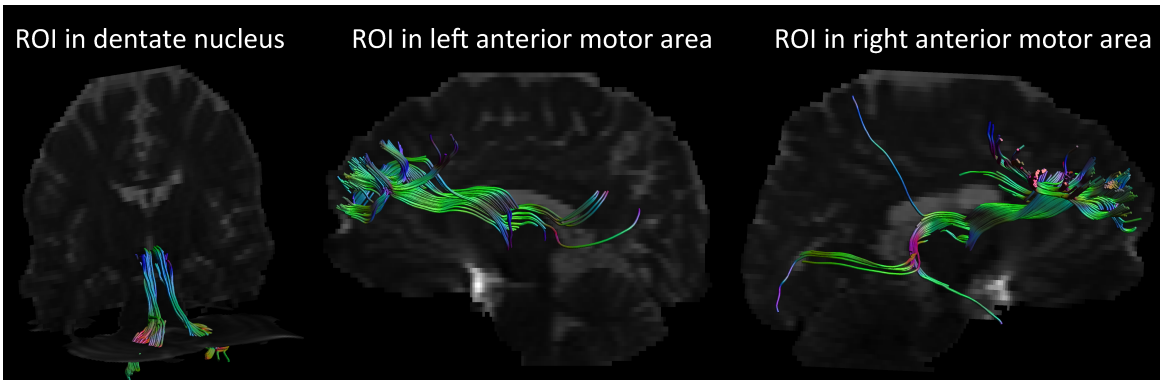

Figure 7

DTI tractography results with ROIs in the dentate nuclei (left plane) and the left (middle plane) and right (right plane) anterior part of the motor tracts.

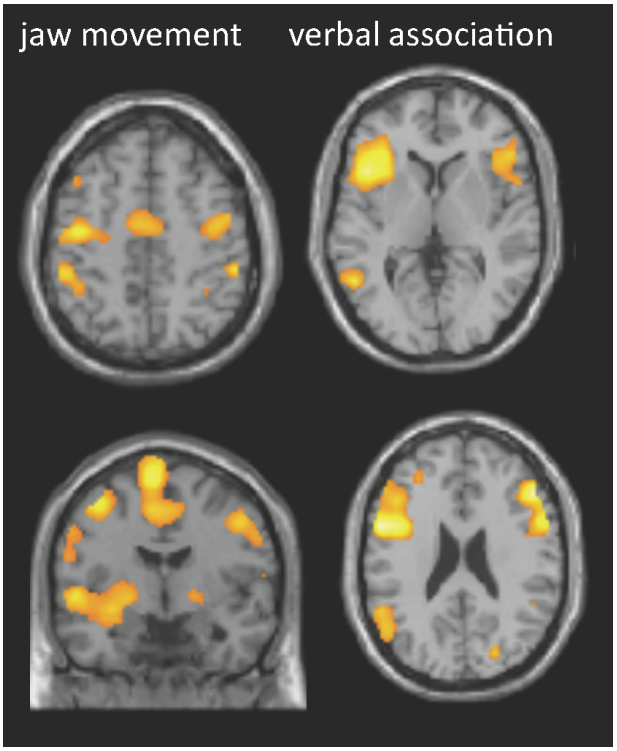

Figure 8: fMRI results: 1) of the jaw movement task showing bilateral motor cortex activations (left plane) and 2) of a noun-verb semantic association task showing prefrontal left hemisphere activity (right plane).

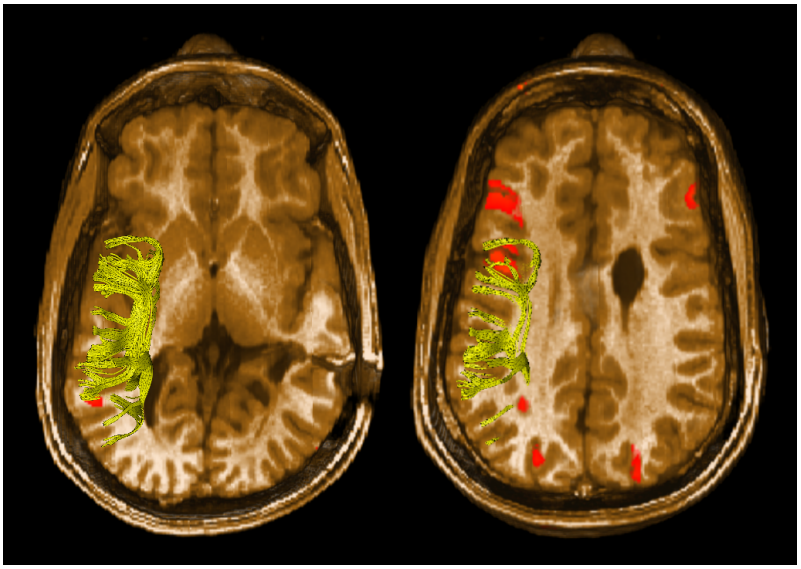

Figure 9: DTI tractography of the fasciculus arcuatus (yellow), connecting the anterior (Broca) and posterior (Wernicke) language areas in the left hemisphere.

[INSERT TABLES 2 & 3 NEAR HERE]

Discussion

This 19-year-old right-handed patient presented with a non-progressive neurodevelopmental disorder characterized by a clearly impaired and delayed acquisition of motor skills, sensorimotor coordination disturbances, impaired non-verbal cognitive skills, attention deficits and executive dysfunction associated with affective and social problems. The clinical set of developmental disturbances affecting the motor, cognitive and affective level suggests a diagnosis of Developmental Coordination Disorder (DSM-IV), which closely relates to the Cerebellar Cognitive Affective Syndrome [25,26]. In addition to the prototypical DCD symptoms this patient also presented with a history of significant developmental mastication impairment.

A number of descriptive studies indicate that a mature pattern of mastication is characterized by the emergence of a highly coordinated rotary motion of the jaw which is readily established during the first 24-30 months of life [27,28]. In this patient, however, jaw motions for chewing at the age of 5.5 years only consisted of roughly cyclic vertical mandibular elevations and depressions, constrained to the inferior-superior dimension of the maxillary-occlusional plane. This primitive chewing pattern is typically found in children of about six months of age in the course of normal mastication development [28]. Despite intensive oral-motor and feeding therapy the next stage in the sequence of early chewing development, i.e. the acquisition of a combination of alternating vertical and lateral jaw movements, had not been achieved when the patient was re-examined at the age of 6.5 and 7.5 years. At the age of 19 he performed rotary motions of the jaw during chewing but no refinement had been achieved in the general coordinative organization of mature masticatory control.

Aside from a general developmental delay of gross and fine motor functions, repeat stomatological, maxillo-facial and neurological investigations during longitudinal follow-up did not reveal any anatomical or physiological restrictions which could explain the markedly

impaired development of mastication. In the absence of any muscular weakness, sensorimotor impairments, abnormal tone, comprehension deficits or general cognitive disability it is hypothesized that this disrupted mastication behaviour may represent a genuine dyspraxic disturbance. Repeat investigations consistently disclosed pathological involvement of multiple components of the praxis system. Constructional dyspraxia, drawing dyspraxia and distorted visual-motor integration skills were objectified during follow-up while DAS and bucco-labio-lingual dyspraxia significantly affected speech and voluntary orofacial-motor functioning. At the age of 6.5 and 7.5 years the patient still completely failed to produce oral postures or imitations of them on command which contrasted with the ability to flawlessly realize involuntary productions (such as spontaneously giving a kiss to his mother) in real contextual environments. DAS and bucco-labio-lingual dyspraxia clearly improved during follow-up but depressed scores on the NOT-S [16] and the Test for Assessing Nonverbal Oral Movement Control and Sequencing [17] at the age of 19 years confirmed persistent sequelae of immature and disrupted oral-verbal volitional control.

Long-lasting and recurrent tube feeding -which prevented progressive and systematic introduction of new and solid food consistencies during the crucial stages of early chewing development might be considered to have caused substantial deprivation of essential oral-motor stimulation indispensible to acquire the necessary skills that subserve the normal development of mastication. The combination of a lack of early stimulation associated with a general deficiency to learn skilled movements might have induced a condition of disrupted mastication consistent with a diagnosis of 'developmental mastication dyspraxia'. A deviant coordination of labial, lingual and mandibular movements has to the best of our knowledge only been documented before in the context of swallowing apraxia in patients with acquired neurological damage [29,30]. Some of the early cases with postmortem confirmed lesions to the left lower portions of the pre- and postcentral gyri also presented with concomitant bucco-labio-lingual apraxia and apraxia of speech [29] but an inherent association between these related forms of apraxia has not been consistently found in later studies [31,32].

To the best of our knowledge, this patient is the first in whom apraxic disruption of the mastication process is documented in a developmental context. Although repeat MRI at the age of 19 showed mild structural abnormalities (irregular but normal-sized ventricles, slightly abnormal aspect of the white matter) as the sequelae of the perinatal intraventricular bleeding and surgical insertion of the intraventricular drain (linear trajectory of intraventricular drain

insertion), the brain areas crucially implicated in the mastication process (oral region of the primary sensorimotor cortex, supplementary motor area, insula, thalamus, brain stem and cerebellum) were structurally intact.

Given normal T2- and FLAIR sequences of the white matter, single voxel MRI spectroscopy in the deep white matter of the left cerebral hemisphere, which confirmed the neurobiochemical integrity of the white matter, was considered representative for the whole white matter volume to exclude metabolic disease [33]. Although the metabolite ratio Cho/Cr in our patient was rather low, but still within normal limits, no additional indications for a rare metabolic disorder were found in the other spectra or on T2- and FLAIR sequences. In addition, following a critical review of the literature no indications were found to causally relate the observed structural anomalies to the developmental neurobehavioural deficits However, as demonstrated in Figure 7, DTI-based tractography to study the cerebello-thalamo-cortical and cortico-ponto-cerebellar tracts disclosed an absence of tracts seeded from the dentate nucleus to the motor cortex via the thalamus. As amply documented in animal and human studies the functional integrity of the dentato-thalamo-cortical pathways is of pivotal importance to the neural system subserving voluntary, skilled motricity. It might be hypothesized that this absence of tracts reflects underdevelopmental of the neuroanatomical circuitry subserving skilled motor action, including mastication. However, the quality of the DTI data set and the inherent limitations of DTI tractography in crossing fibre voxels might be an alternative explanation for the absence of tracts seeding from the dentate nucleus to the motor cortex. Motor fMRI to determine motor activation patterns of the jaw during mastication disclosed activation of the left primary motor cortex, the left SMA and the right cerebellum. However, this lateralized pattern of mastication-induced brain neuronal activity which contrast with the findings of a prior fMRI study showing a bilateral increase in the BOLD signals in the sensorimotor cortex, cerebellum, thalamus, supplementary motor area, and insula during chewing [5] should be interpreted with much caution as the patient performed a lot of additional head movements during this task following immature coordination and execution of masticatory movements. The verbal association task resulted in a lateralized increase of the BOLD signal in the left prefrontal regions indicating left hemisphere language dominance.

Functional neuroimaging with SPECT revealed significant perfusion deficits in the anatomoclinically suspected supratentorial regions that subserve mastication (bilateral

primary motor cortex) and the execution of skilled motor actions (prefrontal lobe) and impaired visuo-spatial cognition (right temporal region). In addition, significantly decreased perfusion was found in the in the anterior and medial part of the left cerebellar hemisphere including the dentate nucleus and middle cerebellar peduncle. Decreased perfusion in the right cerebellar hemisphere did not reach significance. These findings not only confirm that the cerebellum is crucially implicated in the pathophysiology of DCD [26] but also in the distributed neural network subserving the development of planning and organization of skilled movements such as mastication and speech production at the oral-motor level. Indeed, crucial involvement of the cerebellum in the modulation of higher cognitive and affective processes is subserved by the cerebello-cerebral network, consisting of close neuroanatomical connections between the cerebellum and the cortical association areas. In patients with cerebellar lesions, disruption of this network is reflected by (crossed) cerebello-cerebral diaschisis, showing the functional impact of cerebellar damage on a distant, anatomically and functionally connected supratentorial area. Cerebellar malfunctioning due to congenital, developmental or acquired disorders may disrupt or reduce the parallel transfer of excitatory impulses from the deep cerebellar nuclei through dentatothalamic connections to the cortical areas that subserve a variety of cognitive and affective processes, among which the planning of skilled motor actions. Data in support of this view are derived from several studies in a variety of etiologically different patient groups with cerebellar lesions, demonstrating a close and significant association between the neurobehavioural repercussions of the cerebellar lesion and the pattern of perfusional deficits at both the cerebellar and structurally intact supratentorial level [e.g. 26,34,35].

Insufficient maturation or functional underdevelopment of the distributed cerebro-cerebellar network that subserves coordinated motor skills, spatial cognition, executive functions and affect might account for the constellation of symptoms characterizing DCD as a possible developmental variant of the Cerebellar Cognitive and Affective Syndrome [25].

Conclusion

Anatomoclinical findings in this patient with DCD not only indicate that the functional integrity of the cerebello-cerebral network is crucially important in the planning and execution of skilled actions, but also seem to show for the first time that mastication deficits may be of true apraxic origin. As a result it is hypothesized that “mastication dyspraxia” may

have to be considered to represent a distinct nosological entity within the group of the developmental dyspraxias following a disruption of the cerebello-cerebral network involved in planned actions [26,36].

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