Chapter 7:

Crossed Cerebellar Diaschisis in Alzheimer’s Disease


Abstract:

**BACKGROUND:** We describe the phenomenon of crossed cerebellar diaschisis (CCD) in four subjects diagnosed with Alzheimer’s disease (AD) according to the National Institute on Aging - Alzheimer Association (NIA-AA) criteria, in combination with 18F-FDG PET and 11C-PiB PET imaging.

**METHODS:** 18F-FDG PET showed a pattern of cerebral metabolism with relative decrease most prominent in the frontal-parietal cortex of the left hemisphere and crossed hypometabolism of the right cerebellum. 11C-PiB PET showed symmetrical amyloid accumulation, but a lower relative tracer delivery (a surrogate of relative cerebral blood flow) in the left hemisphere. CCD is the phenomenon of unilateral cerebellar hypometabolism as a remote effect of supratentorial dysfunction of the brain in the contralateral hemisphere. The mechanism implies the involvement of the cortico-ponto-cerebellar fibers. The pathophysiology is thought to have a functional or reversible basis but can also reflect in secondary morphologic change. CCD is a well-recognized phenomenon, since the development of new imaging techniques, although scarcely described in neurodegenerative dementias.

**RESULTS:** To our knowledge this is the first report describing CCD in AD subjects with documentation of both 18F-FDG PET and 11C-PiB PET imaging. CCD in our subjects was explained on a functional basis due to neurodegenerative pathology in the left hemisphere. There was no structural lesion and the symmetric amyloid accumulation did not correspond with the unilateral metabolic impairment.

**CONCLUSION:** This suggests that CCD might be caused by non-amyloid neurodegeneration. The pathophysiological mechanism, clinical relevance and therapeutic implications of CCD and the role of the cerebellum in AD need further investigation.

Introduction:

Diaschisis is defined as a distant neurophysiological change caused by focal injury\(^1\). The term ‘diaschisis’ was first introduced by Monakow (1914), to explain temporary functional impairment in a non-damaged area as a remote effect of acute brain lesions\(^2\). In this way ipsilateral or contra-lateral patterns of diaschisis have been identified. Feeney and Baron modernized this controversial and often misunderstood theory of diaschisis in their landmark review in Stroke (1986), also based on the findings from early PET studies\(^3\). Nearly 30 years later, Carrera et al.\(^1\) describes diaschisis as a multiform open concept, evolving in parallel with further understanding related to the development of new tools to access brain function. They distinguishes two types of diaschisis. Focal diaschisis which is based on the ‘classic’ understanding of the original
definition of Von Monakow, including four key aspects: the presence of focal brain lesion; a remote loss of excitability or ‘functional stillstand’; the interruption of the connections between the lesion and remote areas; and a clinical and dynamic nature of the progress that decreases over time. The second type of diachisis is a non-focal diachisis, with changes in the structural and functional neural network connectivity, involving areas distant from the lesions. Crossed cerebellar diachisis (CCD) consists of a reduction in metabolism in the cerebellar hemisphere contralateral to supratentorial lesions. Since the development of functional imaging techniques, involving Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) CCD is a well-recognized phenomenon. Recently, CCD was also illustrated using Magnetic Resonance Imaging (MRI) by dynamic susceptibility contrast and perfusion images. CCD is frequently described after stroke. Other focal lesions which may cause CCD include malignant glioma, epilepsy, head injury and encephalitis.

CCD results from the interruption of the cerebro-cerebellar pathways and cortico-ponto-cerebellar fibers, projecting via the ipsilateral pontine nuclei and cerebral peduncle to the contralateral cerebellar peduncle. This pathway has long been regarded as an open-loop circuit, providing information from sensory, motor and cognitive domains to control movement, serving as an output stage of the premotor cortex. Arguments that CCD may result from functional disconnection, and not necessarily structural interruption, are derived from e.g. the immediate occurrence following contralateral hemisphere ischemia or the reversible CCD seen during Wada test by which activity of one cerebral hemisphere is temporarily blocked. Disruption of the thalamic nucleus, an important relay station, could lead to antegrade-retrograde inactivation of the contralateral cerebellar hemisphere. Antegrade CCD occurs when a thalamic lesion induces ipsilateral cortical deactivation, i.e. thalamo-cortical diachisis, while alternatively, retrograde inactivation via the dentorubrocerebellar pathway (feedback) has been suggested. More recently, the demonstration of multiple closed-loop circuits in cerebro-cerebellar connections also concerning non-motor domains, supports the concept that the cerebellum participates in a much wider range of functions. Beyond motor control, this includes higher-order processes concerning affect and other cognitive functions. The impact of the cerebellum and CCD on network dynamics in neurodegenerative dementia is not yet clear and is focus of further investigations.

The variety of patient descriptions with CCD in neurodegenerative dementia is summarized in Table 1. CCD in AD is scarcely described using 18F-FDG PET imaging. CCD has also been described in Lewy Body Dementia (DLB), dementia with amyotrophic lateral sclerosis (ALS) and Creutzfeldt-Jacob disease.
Table 1: Crossed Cerebellar Diaschisis in Neurodegenerative Dementia

<table>
<thead>
<tr>
<th>Dementia</th>
<th>Patients</th>
<th>Crossed Cerebellar Diaschisis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>4 (of 24)</td>
<td>18F-FDG PET: asymmetric cerebellar metabolism in AD cases (without mention of hypometabolism in the contralateral cerebral hemisphere)22</td>
</tr>
<tr>
<td>AD</td>
<td>7 (of 26)</td>
<td>18F-FDG PET: frontotemporal-parietal hypometabolism; 2 patients basal ganglia hypometabolism, hypometabolism contralateral cerebellum21</td>
</tr>
<tr>
<td>DLB</td>
<td>1</td>
<td>18F-FDG PET: hypometabolism parietal temporal and occipital left &gt; right and right cerebellar lobe23</td>
</tr>
<tr>
<td>ALS</td>
<td>4</td>
<td>C15O2 PET: decreased rCBF and rCMRO2 bilateral frontal, right temporal and bilateral cerebellar cortices24</td>
</tr>
<tr>
<td>CJD</td>
<td>1</td>
<td>18F-FDG PET: regional hypometabolism left pons and right cerebellum25</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s Disease, ALS: Amyotrophic Lateral Sclerosis, CJD: Creutzfeldt Jacob Disease, DLB: Lewy Body Dementia, PET: Positron Emission Tomography, rCBF: relative cerebral blood flow

The diagnosis of Alzheimer’s disease (AD) rests largely on characterization of the cognitive profile, supported by neuroimaging26. A typical AD syndrome is characterized by early episodic memory loss, followed by various combinations of attention-executive, language and visuospatial impairment27. Since the publication of the National Institute on Aging -Alzheimer Association criteria-(NIA-AA)28, the use of cerebrospinal fluid (CSF) and PET imaging as biomarkers in clinical diagnosis has increased: CSF Aβ42, 11C-PiB PET as biomarkers of amyloid β depositions and CSF tau and 18F-FDG PET as biomarkers of downstream neuronal degeneration. Postmortem studies of AD suggest that tau pathology follows a specific spreading pattern from the locus coeruleus29, entorhinal cortex/ hippocampus, to cortical association areas30. Involvement of the cerebellum in this neuropathological process is mentioned only in the final stage of disease31. Therefore the cerebellar cortex is recommended as reference region in PET quantification32. AD-related change in 18F-FDG uptake is characterized by bilateral reduction in the posterior cingulate, temporal-parietal and prefrontal association
cortex\textsuperscript{33}. Using the Scaled Subprofile Modeling/Principal Component Analysis (SSM/PCA), a multivariate analysis method to identify disease-specific cerebral brain patterns in neurodegenerative diseases, the “AD profile” shows bilaterally decreased temporo-parietal- and relative increased metabolic activity in the subcortical white matter, cerebellum and sensorimotor cortex\textsuperscript{34}. Notwithstanding bilateral involvement, the majority AD cases visually display an asymmetric pattern at \textsuperscript{18}F-FDG PET\textsuperscript{35}. Amyloid deposition can also be asymmetric\textsuperscript{36}. Asymmetric AD pathology can reflect atypical focal cortical presentations as Progressive Non-Fluent Aphasia (PNFA), Posterior Cortical Atrophy (PCA) and Corticobasal Syndrome (CBS)\textsuperscript{37}.

Obviously, the relation between CCD and the neurodegenerative process in AD is not well established. It is therefore important to obtain more data on well documented cases, preferably with imaging data, not only of the brain metabolism but also on amyloid and tau depositions. The strategy in our memory clinic to recruit dementia patients in an ongoing PET study combining \textsuperscript{11}C-PiB PET and \textsuperscript{18}F-FDG PET imaging yielded four amyloid positive AD cases with clear-cut CCD on visual inspection of FDG images. In the present paper, we describe the clinical characteristics and PET results and discuss the implications of these findings.

Material and Methods:

Subjects were recruited from 2013 until 2017 at the memory clinic of the University Medical Center of Groningen (UMCG). Standard dementia screening was performed, including medical history, physical and neurological examinations, screening laboratory tests and T1-weighted brain MRI. Standard cognitive test battery included Rey Auditory Verbal Learning test (REAVL)\textsuperscript{38}, Visual Association Test (VAT)\textsuperscript{39}, Rey Complex Figure Test (RCFT-IR)\textsuperscript{40}, Immediate Recall Location Learning Test (LLT-IR)\textsuperscript{41}, Delayed Recall (LLT-DR)\textsuperscript{42}, Doors Test A/ B\textsuperscript{43}, Trail Making Test A/B (TMT)\textsuperscript{44}, Semantic Fluency\textsuperscript{45} and Geriatric Depression Scale (GDS)\textsuperscript{46}. CSF samples were collected in polypropylene tubes, transported to the laboratory, centrifuged, and measured or stored at \textsuperscript{–}80°C until use. The Enzyme-Linked Immuno Sorbent Assay’s were used, according to the manufacturers’ protocol for the determination of A\textsubscript{β42} (INNOTEST® β-AMYLOID (1–42)), t-tau (INNOTEST® TAU Ag) and p-tau (INNOTEST® PHOSPHO-TAU (181P)). Clinical diagnosis was established by multidisciplinary team consensus according to the NIA-AA criteria\textsuperscript{47}.

Included subjects were between 50 and 80 years old. Exclusion criteria were major psychiatric illness, medications which may affect outcome, cerebrovascular disease (Fazekas-score 2 or higher), mentally incompetent to understand consequence of written informed consent and cognitive deficits explained by non-neurodegenerative condition. The study considered 5 groups of 20 patients with clinical diagnosis of mild cognitive impairment (MCI), probable AD, Frontotemporal Dementia (FTD), Lewy Body
Dementia (DLB) and 20 healthy controls. The ethics committee of the UMCG approved the study. The time between the different investigations was less than 3 months.

All subjects underwent a dynamic $^{11}$C-PiB and a static $^{18}$F-FDG PET scan on the same day under standard resting conditions with eyes closed. Siemens Biograph 40 and 64 mCT PET/CT scanners were used. Radiotracers were manufactured at the radiopharmacy facility of the nuclear medicine department and synthesized according to the Good Manufacturing Procedure, and administered intravenously. The dynamic 60 minutes $^{11}$C-PiB data acquisition was started at the time of tracer injection ($387 \pm 18$ MBq). The static $^{18}$F-FDG PET was acquired 30 minutes after $^{18}$F-FDG injection ($208 \pm 8$ MBq), at least 90 minutes after $^{11}$C-PiB injection. Obtained images were visually assessed by experts during a multidisciplinary consensus meeting. Changes in FDG uptake were classified as mild (+), moderate (++) or severe (+++). PET images were subsequently processed and analyzed with PMOD v3.8 (PMOD Technologies Ltd., Switzerland). Hammers atlas was used to define the anatomical brain regions of interest, after which the standard brain was transformed onto the individual subject brain. Only gray matter tissue was included for the analysis of cortical regions. Pharmacokinetic analysis was performed of $^{11}$C-PiB PET data, using the simplified reference tissue model 2 (SRTM2) to obtain R1 (tracer delivery normalized to the gray matter of the cerebellum) as an indicator of relative cerebral blood flow (rCBF) and the non-displaceable binding potential ($B_{ND}$) values. Standardized Uptake Values (SUV), normalized to body weight, were calculated for $^{11}$C-PiB images (40-60 minutes interval) and $^{18}$F-FDG images. Descriptive PET results are given as mean difference (MD) between the left side minus the right side of the brain and its Standard Error(SE). Statistical differences between the left and the right side of the brain were explored using Paired Samples T-test. P values <0.05 were considered significant (uncorrected for multiple comparisons).

Results:

Among a series of eighty-four subjects, twenty-nine were $^{11}$C-PiB PET positive and four cases with $^{11}$C-PiB PET positive AD and CCD were identified. The neuropsychological characteristics and details of PET imaging are reported in Table 2 and 3, respectively.

Report of the cases:

1. A 67 year-old right-handed male interior decorator presented with a gradual onset of memory complaints since two years. Medical history noted extirpation of a parotid adenoma and a continuous positive airway pressure (CPAP) treated sleep apnea. He consumed two glasses of wine daily and had no neurological familial antecedents. The neurological examination showed no abnormalities. The neuropsychological tests revealed deficit in several cognitive domains, most pronounced in memory and executive functions. An MRI scan of the brain showed Global Cortical Atrophy (GCA) and symmetric
Medial Temporal lobe Atrophy (MTA) grade 1 and two microbleeds. CSF analysis disclosed an Alzheimer profile with decreased Aβ42 (470 ng/L) and increased t-tau (949 ng/L) and p-Tau (131 ng/L). The ¹⁸F-FDG PET scan showed general but mostly left-sided hypometabolism, including the mediofrontal cortex (+), parietal cortex (left ++/right +), symmetric involvement of the basal ganglia and a mild right-sided hypometabolism of the cerebellum. In the following years, the patient’s cognitive complaints gradually worsened. Repeated ¹⁸F-FDG PET three-and-a-half years later showed progressive general and persistent most left-sided hypometabolism in the parietal (left ++++, right ++), temporal (left ++++, right ++), left frontal (+/+++) cortex, left thalamus (+) and right cerebellar cortex (+). ¹¹C-PiB PET showed evident symmetric accumulation in the fronto-parietal-temporal cortex. The symptoms aggravated and, nursery home placement became unavoidable.

2. A 63 year-old right-handed woman noticed progressive cognitive deficits since three years; she failed to assist clients in her job as a civil servant, could no longer carry out knitting-work and experienced difficulties orienting whilst driving. Medical history noted fibromyalgia and anxiety disorder, for which she used selective serotonin-reuptake-inhibitors. Her family history was negative for neurodegenerative disorders. Neuropsychological examination revealed only a non-fluent aphasia. Neuropsychological test scores were decreased in the cognitive domains memory, language and executive functions, of which memory and executive functions were most pronounced. MRI scan of the brain showed some vascular white matter lesions (Fazekas 1) and symmetric GCA and MTA grade 1. CSF examination demonstrated decreased Aβ42 (234 ng/L), increased t-tau (482 ng/L) and p-tau (90 ng/L) levels. The ¹⁸F-FDG PET scan revealed hypometabolism most prominently in the left frontoparietal (left ++/ right +) cortex and the right cerebellum(+). A ¹¹C-PiB PET accumulation was most prominent in the left fronto-parietal cortex. The clinical course was characterized by a gradual decline of cognitive functions.

3. A 73 year-old right-handed women presented with gradually progressive language difficulties since one year, with relatively normal comprehension. Her movements became clumsy. Medical history noted hypertension and renal insufficiency. She used an ACE-inhibitor, diuretic and proton-pump-inhibitor. Her family history was unremarkable. Neurological examination showed severe non-fluent aphasia with concretism, bradykinesia, and ideomotor apraxia. Neuropsychological tests revealed severe deficits in language production and executive functions, with preservation of non-verbal memory. CSF analysis showed extreme high t-tau (2260 ng/L) and p-tau (232 ng/L) and decreased Aβ42 (245 ng/L) levels. MRI scan of the brain showed global, mostly left sided, cortical atrophy with an MTA score of 2 and diffuse white matter lesions (Fazekas 1). The ¹⁸F-FDG PET scan showed bilateral hypometabolism with a left-sided predominance of the fronto-parieto-temporal cortex (left ++++, right
++) and left striatal (+) together with right-sided hypometabolism of the cerebellum (+) (figure 1). $^{11}$C-PiB PET accumulation of amyloid was visual mostly left-sided in the parietotemporal cortex. The patient was diagnosed with a CBS- phenotype of Alzheimer’s disease. The clinical course was rapidly progressive and three years after presentation she suffered from end-stage dementia requiring placing in a nursing home.

4. A right-handed 68 year-old woman presented with progressive language difficulties. Until recently, she was employed as director in public transportation. She feared developing dementia, as her mother and grandmother had both experienced the first symptoms of a dementing disorder at the age she had reached now. Medical history noted glaucoma and mastopathy. Neuropsychological tests showed severe deficits in language production and attention. Test scores in the domain of executive functions were decreased but not impaired. Non-verbal memory was preserved. CSF revealed an abnormal increase of protein t-tau (828 ng/L) and p-tau (99 ng/L), with a normal level $\beta_42$ (636 ng/L). MRI scan of the brain showed left-sided frontoparietal cortical atrophy and an MTA score of 4. The $^{18}$F-FDG PET showed marked hypometabolism of the left parietal (++) and fronto-temporal (+) cortex and right cerebellum (+) and marginal hypometabolism of the left striatum and thalamus (Figure 1). The $^{11}$C-PiB PET clearly showed left-sided fronto-temporal accumulation of amyloid. The clinical diagnosis was a PNFA phenotype of Alzheimer’s disease.

Neuropsychological testing revealed that patients 3 and 4 were severely impaired in language production (table 2) which implied that verbal memory could not be assessed properly. Therefore, only nonverbal memory tests were applied. Language comprehension was unimpaired as assessed by means of standardized observation during testing. In three of our cases we found decreased volume on MRI in the brainstem (-6%, -1% and -3%, for cases 1, 2 and 4 respectively) and in two cases (cases 2 and 3) of the post-central gyrus (case 2: -4%, and case 4: -11%). Table 3 and figure 2 show the mean difference(MD) and standard error (SE) in PET results of the subjects. Statistically significant lower $^{18}$F-FDG PET uptake can be found in the left cingulate gyri, frontal, occipital, parietal and temporal lobes, thalamus and white matter (MD±SE is -0.54±0.2) as compared with the right hemisphere. It seems, therefore, that a global reduction of the $^{18}$F-FDG PET uptake was found in most of the cortical regions, and as expected on visual inspection, an opposite effect was found in the cerebellum, with a lower $^{18}$F-FDG uptake at the right than at the left side (MD±SE is 0.33±0.04). A similar effect was observed for the rCBF values extracted from the $^{11}$C-PiB PET (R1: relative tracer delivery), with statistically significant lower R1 values in the left cingulate gyri, frontal, parietal and temporal lobes, thalamus and white matter (MD±SE is -0.06±0.02) as compared with the right hemisphere; and higher R1 values in the left cerebellum than in the right side (MD±SE is 0.03±0.003). Interestingly, no statistical differences were found between hemispheres in the $^{11}$C-PiB uptake (SUV or BPND).
Table 2: Neuropsychological test scores of AD cases with CCD:

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal memory</strong></td>
<td>impaired</td>
<td>impaired</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RAVLT-DR (raw score, perc)</td>
<td>1, P1</td>
<td>3, P1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Non-verbal memory</strong></td>
<td>impaired</td>
<td>borderline</td>
<td>Unimpaired</td>
<td>unimpaired</td>
</tr>
<tr>
<td>Test (raw score, perc)</td>
<td>VAT (1/12, P1)</td>
<td>RCFT-IR (6/36, P7)</td>
<td>RCFT-IR (11/36, P31)</td>
<td>Doors-A (11/12, P75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LLT-IR (11, P60-70)</td>
<td>LLT-DR (0, P100)</td>
<td>Doors-B (8/12, P75)</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>borderline</td>
<td>unimpaired</td>
<td>borderline</td>
<td>impaired</td>
</tr>
<tr>
<td>TMT-A</td>
<td>55, P10</td>
<td>47, P16</td>
<td>77, P8</td>
<td>83, P1</td>
</tr>
<tr>
<td>(raw score, perc)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>borderline</td>
<td>borderline</td>
<td>impaired</td>
<td>impaired</td>
</tr>
<tr>
<td>Fluency</td>
<td>16, P10</td>
<td>15, P7</td>
<td>0, P1</td>
<td>8, P1</td>
</tr>
<tr>
<td>(raw score, perc)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Executive Functions</strong></td>
<td>Impaired</td>
<td>impaired</td>
<td>impaired</td>
<td>unimpaired</td>
</tr>
<tr>
<td>TMT-B B/A index (score, perc)</td>
<td>discontinued</td>
<td>discontinued</td>
<td>5.7, P1</td>
<td>2.0, P16</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDS15</td>
<td>5</td>
<td>1</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

RAVLT: Rey Auditory Verbal Learning test, VAT: Visual Association Test, RCFT-IR: Rey Complex Figure Test – Immediate Recall, LLT-IR: Location Learning Test – Immediate Recall, LLT-DR: Location Learning Test – Delayed Recall, Doors – A/B: Doors Test (from 11/12, P75)
Doors and People Test) version A and B, TMT-A/B: Trail Making Test A or B, Fluency: Semantic Fluency (# animals in 1 minute), GDS15: 15 item Geriatric Depression Scale.

Table 3. Mean PET results of AD cases with CCD:

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>$^{18}$F-FDG (SUV)</th>
<th>$^{11}$C-PiB (SUV)</th>
<th>$^{11}$C-PiB (R1)</th>
<th>$^{11}$C-PiB (BPnd)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (± SE)</td>
<td>$p$-value</td>
<td>Mean (± SE)</td>
<td>$p$-value</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.33 (0.04)</td>
<td>0.005</td>
<td>0.00 (0.01)</td>
<td>0.543</td>
</tr>
<tr>
<td>Basal_ganglia</td>
<td>-0.42 (0.14)</td>
<td>0.054</td>
<td>-0.02 (0.02)</td>
<td>0.325</td>
</tr>
<tr>
<td>Cingulate_gyri</td>
<td>-0.51 (0.12)</td>
<td>0.025</td>
<td>0.02 (0.01)</td>
<td>0.095</td>
</tr>
<tr>
<td>Frontal_lobe</td>
<td>-0.71 (0.14)</td>
<td>0.015</td>
<td>0.01 (0.01)</td>
<td>0.637</td>
</tr>
<tr>
<td>Insula</td>
<td>-0.41 (0.15)</td>
<td>0.073</td>
<td>0.01 (0.02)</td>
<td>0.715</td>
</tr>
<tr>
<td>Occipital_lobe</td>
<td>-0.29 (0.09)</td>
<td>0.044</td>
<td>0.01(0.02)</td>
<td>0.466</td>
</tr>
<tr>
<td>Parietal_lobe</td>
<td>-0.76 (0.07)</td>
<td>0.002</td>
<td>0.02 (0.03)</td>
<td>0.428</td>
</tr>
<tr>
<td>Temporal_lobe</td>
<td>-0.79 (0.18)</td>
<td>0.021</td>
<td>0.03 (0.03)</td>
<td>0.364</td>
</tr>
<tr>
<td>Thalamus</td>
<td>-0.66 (0.10)</td>
<td>0.008</td>
<td>-0.02 (0.01)</td>
<td>0.246</td>
</tr>
<tr>
<td>White_matter</td>
<td>-0.30 (0.05)</td>
<td>0.007</td>
<td>0.00 (0.01)</td>
<td>0.938</td>
</tr>
</tbody>
</table>

SUV: Standardized Uptake Value (measured activity concentration/ normalized by injected dose divided by subject characteristics)  
R1: ratio of the delivery in the tissue region to the reference region  
BPnd: binding potential relative to non-displaceable binding ratio of the concentration of the ligand specifically bound over the concentration of the ligand in a given compartment at equilibrium)  
SE: Standard Error. Descriptive PET results are given as mean difference between the left side minus the right side of the brain and its Standard Error(SE). Statistical differences between the left and the right side of the brain were explored using Paired Samples T-test. P values < 0.05 were considered significant.
Discussion:

We describe four AD subjects, according to the NIA-AA criteria with CCD. CCD has been described mainly in lateralized brain lesions and scarcely in neurodegenerative dementias. The definition of diaschisis is based on the ‘classic’ understanding of Von Monakow and involves changes of structural and functional neural network connectivity in areas distant from the lesion. Previous reports already described a total of 11 AD subjects with CCD. To our knowledge this is the first report of CCD in AD subjects with documentation of both $^{18}$F-FDG PET and $^{11}$C-PiB PET imaging.

The four AD subjects had a clinical phenotype within the heterogeneous spectrum of AD; subject 1 and 2 matched a typical AD syndrome and subject 3 and 4 presented as focal cortical AD syndromes CBS and PNFA. Although all subjects had wide-spread hypometabolism in both hemispheres, there was a left-sided predominance of hypometabolism (most significantly in the frontal, parietal and temporal cortices) combined with crossed right cerebellar hypometabolism. None of our subjects had evident asymmetric neurological deficits at physical examination, except for language dysfunction. There were no structural or cerebellar lesions on MRI scan of the brain. Other associated diagnoses have been ruled out. Asymmetric cerebellar hypometabolism was therefore interpreted in the context of CCD, as a remote effect of cortical AD pathology.

The neurophysiological basis of CCD is not fully understood, but is based on a remote effect in brain activity in response to a distant lesion. Focal diaschisis can be subdivided in functional or dynamic diaschisis. These changes normalize over time and are related to functional recovery. An asymmetric neurodegenerative process is proposed by Carrera (2014) as a new subtype of non-focal diaschisis, subdivided in connectional or connectomal diaschisis, with remote changes in network connectivity and the functional integrity. There is mounting evidence that diaschisis may be help understanding clinical findings that cannot be explained by local pathology alone. The phenomenon of CCD in AD may be explained according to the concept of transneuronal degeneration, from early (potentially reversible) synaptic dysfunction, to irreversible neuronal loss. In the study of Akiyama no gross cerebellar atrophy or evidence of significant neuronal loss in the cerebellum or pontine gray matter was found in 3 autopsy-proven AD cases with CCD. Other studies suggest that anterograde transneuronal degeneration is responsible for the irreversible component of the phenomenon, reflecting in secondary morphologic change and cerebellar atrophy. In three of our cases we found decreased volume on MRI in the brainstem (cases 1, 2 and 4) and in the post-central gyrus (case 2 and 4). In one AD case, subject 1, repeated $^{11}$C-PiB PET and $^{18}$F-FDG PET scan after 3.5 years showed a persistent and even progressive phenomenon of CCD. Following the decreased volume and persistent CCD in our subjects, we hypothesize that CCD has both a functional, and a neurodegenerative basis.
AD is characterized by gradual bilateral neurodegeneration. A mechanism that may account for CCD in AD is asymmetric neuropathology. However, we did not find significant asymmetry in amyloid accumulation in our subjects. Brain uptake of PET tau tracers is highly correlated with $^{18}$F-FDG PET hypometabolism. It is conceivable that the mechanism of CCD is explained by asymmetric tau-burden. The relationship between regional tau-burden and the functional connectome in AD is also described by Cope et al; In that study, analysis of $^{18}$F-AV-1451 PET scans showed that neurodegenerative tauopathies preferentially affect ‘hub’brain regions, with the functional consequence of progressive weakening of large scale connectivity networks throughout the cortex. Apparently, a lesion anatomically located in the parietal junction has most impact on brain organization. In our subjects with CCD, we found global left-sided hypometabolism, which was more pronounced in the frontal, parietal and temporal lobes. Akiyama et al similarly found a highly significant correlation of CCD with frontal hypometabolism. This could be explained by a dominance of cortico-ponto-cerebellar fibers from the frontal-parietal cortical areas associated with CCD. We found lower relative tracer delivery of $^{11}$C-PiB (R1) in the left cerebral hemisphere and the right cerebellum, which can be interpreted as reduced perfusion. Cerebral blood flow correlates with amyloid burden across the spectrum from cognitively healthy to AD, which could be in part consequential, and in part contributing to impaired amyloid clearance. Although we did not demonstrate an evident 1:1 correlation between $^{11}$C-PiB (R1) and $^{18}$F-FDG, one may speculate that this asymmetric reduction in cerebellar blood flow also reflects CCD.

We found a left-sided dominance in cortical hypometabolism in our subjects, correlated with right-sided cerebellar diaschisis. This left-sided dominance in AD cases with CCD is not specifically described by previously published AD cases, although Akiyama et al describe a tendency for a slightly higher cerebral metabolic rate of glucose in the right hemisphere.

A possible left-hemisphere predominance in the neurodegenerative process of AD is suggested in other imaging studies. One might speculate that handedness could relate to this asymmetry, as described in other neurodegenerative diseases. All four cases were right-handed. The clinical impact of this left sided dominance is unclear, although a higher rate of asymmetry is associated with a faster disease progression. Previous research suggests that CCD could serve as a potential marker of severity and cognitive decline and that this could imply a potential new therapeutic approach in VD. A few clinical trials found that electrical stimulation of the cerebellar fastigal nucleus (FNS) could improve symptoms of dementia in VD. Future investigation will prove the validity of the concept of diaschisis in the therapeutical field.
The left-sided predominance of AD pathology in CCD is previously described by Akiyama et al\textsuperscript{21} and may be indicative of a specific subtype, prone to this phenomenon. The clinical impact of this subtype is still unclear, although a higher rate of asymmetry is associated with a faster disease progression\textsuperscript{61}. This phenomenon may be underdiagnosed and could have pathophysiological and therapeutic importance and therefore warrants further investigation. These four AD subjects with CCD showed a different clinical presentation, though fitting within the heterogeneous spectrum of AD. Possibly the number of subjects was insufficient to contribute to the understanding of the clinical impact of this CCD subtype and further investigation is needed.

A limitation of the present study is the small subject size of CCD in AD, not allowing the assessment of correlations between cerebellar asymmetries and cognitive scores. A future larger study will also benefit from a ‘control group’ of AD patients with asymmetrical hemisphere uptake of \textsuperscript{18}F-FDG but without CCD.

The CCD, which was asymmetrical in our patients, might be an underdiagnosed phenomenon in AD, because the possible occurrence of symmetric bilateral cerebellar hypometabolism in case of symmetrically reduced (parietal) cortex metabolism could remain unnoticed. This would have implications for the interpretation and quantification of PET results, particularly when the cerebellar cortex is used as a reference region. This could potentially confound interpretation of results when normalizing to this region. Pickut et al. described variable cerebellar uptake values occurring between repeat SPECT examinations in AD patients and healthy volunteers\textsuperscript{65}.

Future studies need to clarify whether the use of a cerebellar reference regions in case of CCD needs to be reconciled.

In summary, cerebellar hypometabolism (CCD) as a remote effect of AD-related dysfunction of the contralateral cortical hemisphere is scarcely described. We observed four AD subjects, with symmetrical amyloid accumulation on \textsuperscript{11}C-PiB PET, global left-hemisphere hypometabolism and crossed right cerebellar hypometabolism on \textsuperscript{18}F-FDG PET. All cases had asymmetric, but most prominently frontal-parietal-temporal hypometabolism and decreased left hemispheric perfusion. The presence of CCD in AD may be an early event of transneuronal degeneration. The clinical impact and therapeutic implications of CCD, neurophysiological changes, and the role of the cerebellum in the complexity of brain organization is still unclear. Future research should focus on the analysis of CCD in larger dementia cohorts with the use of different PET and MRI imaging modalities, including tractography and network connectivity analyses.
Figure 1: $^{18F}$-FDG PET scan of AD patient (subject 4) with crossed cerebellar diaschisis and marked hypometabolism of the left parietal (++) and fronto-temporal (+) cortex and right cerebellum (+) and marginal hypometabolism of the left striatum and thalamus.
Figure 2: Mean difference (left- minus right hemisphere) with the standard error. The greybars are statistically significant.

References:


20. Silverman DHS, Small GW, Chang CY. JAMA Network | JAMA | Positron Emission Tomography in Evaluation of DementiaRegional Brain Metabolism and Long-term


