Kazuistika pacienta s chronickým syndromem derealizace a depersonalizace je příkladem použití ^{18}FDG PET s cílem porozumět patofyziologii relativně raritního a málo prozkoumaného klinického stavu. Zvýšení metabolizmu v pravostranných temporo-parietálních oblastech, které se podílejí na integraci somatosenzorických, zrakových a sluchových modalit může vysvětlit prožitek depersonalizace. Nález v asociační zrakové kůře okcipitální části g. fusiformis je dán do souvislosti s pocitem odcizení od vnímané reality, tedy derealizací. Navržený neuronální model depersonalizačního a derealizačního syndromu nemůže nahradit, ale spíše doplňuje alternativní, především psychodynamické teorie vzniku této poruchy. Vzhledem k ojedinělosti a významu nálezu autoři prezentují tento případ v anglickém jazyce.

Doc. MUDr. Jiří Horáček, Ph.D.

Chronický syndrom depersonalizace a derealizace v obraze ^{18}FDG PET. kazuistika

^{18}FDG PET imaging of chronic depersonalization and derealization syndrome. A case study

MILOSLAV KOPEČEK[1,2,3], MARTIN BAREŠ[1,2], MARTIN BRUNOVSKÝ[1,3], JIŘÍ HORÁČEK[1,2,3]

[1]Psychiatric Centre Prague
[2]Charles University, 3rd School of Medicine in Prague
[3]Centre of Neuropsychiatric Studies in Prague

SUMMARY

Introduction: The aim of our case study was to detect the brain metabolic pattern in a patient with chronic depersonalization-derealization syndrome. **Methods:** We assessed a 36 year old man who has suffered from depersonalization-derealization syndrome (ICD-10) for the last 20 years by the use of 18FDG PET. The control group consisted of 22 psychiatrically healthy volunteers (11 males and 11 females, mean age 37.6±12.3 years). Image analysis was performed using Statistical Parametric Mapping (SPM99) and ANCOVA with age as a nuisance variable. **Results:** We found significantly increased metabolism in the right superior temporal gyrus/inferior parietal gyrus (Brodman area – BA 40), right superior parietal gyrus (BA 7), and left fusiform gyrus in the occipital lobe (BA 19) in the patient with chronic DP/DR compared with controls. We did not find any significant decrease of 18FDG. **Discussion:** The increased metabolism in detected areas in the patient with chronic DP/DR is in agreement with the model of depersonalisation known as asomatognosia occurring after a lesion in the parietal cortex, the model for derealization (visual hypoemotionality) connected with occipito-temporal lesions and dreamy state with temporo-parietal dysfunction.

Key words: depersonalization, derealization, ^{18}FDG, PET, brain metabolism, drug free

SOUHRN

Úvod: Cílem studie bylo detekovat rozdíly v metabolické aktivitě mozku u pacienta s chronickým syndromem derealizace a depersonalizace. **Metody:** Pomocí 18FDG PET byl vyšetřen regionální metabolizmus mozku u 36letého muže trpícího 20 roků syndromem derealizace a depersonalizace (dle MKN-10). Výsledný scan byl porovnán s kontrolní skupinou osob bez duševní poruchy o průměrném věku 37,6 ± 12,3 roku (11 mužů, 11 žen). Analýza dat byla provedena pomocí statistického parametrického mapování (SPM99), ANCOVA s věkem jako kovariantou. **Výsledky:** U pacienta se syndromem depersonalizace a derealizace byl ve srovnání s kontrolní skupinou zvýšený metabolizmus v pravém horním temporálním gyru/dolním parietálním gyru (Brodman area – BA 40), pravém horním parietálním gyru (BA 7) a levém fusiformním gyru okcipitálního laloku (BA 19). Nenašli jsme signifikantní rozdíly týkající se snížení aktivity. **Diskuze:** Zvýšený metabolizmus v detekovaných oblastech u pacienta s chronickým syndromem depersonalizace a derealizace je v souladu s modelem depersonalizace známým jako asomatognózie po lézi v parietální kůře, modelem derealizace (vizuální hypoemocionality) spojené s okcipito-temporální lézí a snovými stavy s abnormitami v temporo-parietální junkci.

Klíčová slova: depersonalizace, derealizace, ^{18}FDG, PET, mozkový metabolizmus

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Introduction

The symptom of depersonalization (DP) has been defined in the Diagnostic and Statistical Manual of mental disorder, 4th Edition (DSM-IV) as an experience of feeling detached from and as if an outside observer of one's mental processes or body, while maintaining intact reality testing; derealization (DR) has been defined as the sensation that the external world is strange or unreal (APA 1994). DP and DR are considered to consist of an altered perception of the self and the environment and hence is classified under dissociative disorders in the DSM-IV. However, in the ICD-10, depersonalization-derealization syndrome is classified as a separate neurotic disorder (WHO, 1992). The expression of depersonalization-derealization syndrome as a neurotic disorder implies that psychological factors play the crucial role in its etiology. But neuroscience has shown in the last 20 years that even neurotic disorders, such as obsessive-compulsive disorder (Saxena et al., 1992) or panic disorder (Praško et al., 2004) have neuronal correlates and the biological and psychological factors are indistinguishable.

Only one neuroimaging study has used ^{18}FDG PET to find the cerebral glucose metabolism pattern of depersonalization (Simeon et al., 2000). In comparison with healthy subjects, the patients with depersonalization disorder showed significantly lower metabolic activity in the right-sided Brodmann's areas 22 and 21 of the superior and middle temporal gyri and had significantly higher metabolism in the parietal Brodmann's areas 7B and 39 and left occipital Brodmann's area 19. Dissociation and depersonalization scores among the subjects with depersonalization disorder positively correlated with metabolic activity in the area 7B (Simeon et al., 2000). The aim of our case study was to detect the resting brain metabolic pattern in a patient with chronic DP and DR and compare it with the results from Simeon's study (2000).

Methods

Case report

Using ^{18}FDG *PET,* we assessed a 36 year old man who has suffered from depersonalization and derealization (diagnosed according to ICD-10) for the last 20 years. The patient described his feelings: "I feel like in a dream-state, as if I am not alive. Things look unreal, unsubstantial – etheric. People and things seem as though they are only colored air". He rationally knows that he is not experiencing a dream but reality; nevertheless his sensations do not reflect so. He feels that his senses are blunted. He has lost clarity and depth of sensual perception. He has lost self-awareness of his soul, his life and the feeling that he is a living person. He feels like a dead person. He feels alienated from people, especially from his relatives. Very often he is not able to feel connection with his parents and sister. He does not understand normal emotions such as the feeling of love. He thinks he has lost about 80 % of his feeling ability. He has also described the worsening of time perception, he feels that time is passing very quickly. He is able to work but the work consumes a lot of energy. He reports his sense of unreality to be more expressed during a very sunny day or in a dark or even after low doses of alcohol. The first clear signs of similar symptoms only appeared transiently in his 15th year after he was raped by a school-mate at a children's camp. The symptoms appeared again between the ages of 16 and 17 and became more stable. There were no psychiatric disorders in his family medical history and any severe somatic diseases, brain or psychodynamic traumas were also not detected in his personal history. He has no experiences with cannabis, psychostimulants or hallucinogens. The patient has normal results from baseline routine laboratory evaluation and a magnetic resonance scan. Electroencephalography showed mild abnormity due to slowing of background activity 7–8 Hz, but no focal abnormity was detected. EEG cordance showed discordance in the delta band over bilateral temporal and left parietal region. The EEG result was suspected of encephalopathy.

The patient has been psychiatrically treated for 3 years. The symptoms were refractory to therapy using fluvoxamine, lamotrigine, sulpiride, risperidone, clomipramine and 20 sessions of high frequency rTMS on the left dorsolateral prefrontal cortex. The patient transiently responded to citalopram together with clonazepam but the effect diminished after one month. A further trial of citalopram with clonazepam was not successful.

Diagnosis of depersonalisation was confirmed by assessment by two psychiatrists (due to ICD-10 criteria). Dissociative symptoms were quantified by the Dissociative Experiences Scale (DES) (Bernstein and Putnam, 1986) and Cambridge depersonalisation scale (CDS) (Sierra et al., 2000). The CDS score was 194. The highest scores of the DES were for the depersonalization and derealization items, numbers 12, 13 and 28.

PET investigation

The regional brain metabolism was investigated by the use of ^{18}FDG PET. The patient was fasted for at least 6 hours before imaging. He did not use any psychotropics for 5 weeks before the PET scan. In a dimly-lit and quiet room, 3 MBq/kg of ^{18}FDG was administered via a peripheral vein catheter. The patient then rested for 30 minutes in the same room. This condition has been described as Random Episodic Silent Thinking (REST) (Andreasen et al 1995). Next, a 2D "hot" transmission scan of the brain was performed, and lasted between 5 and 10 minutes (transmission scanning time was corrected to allow for decay of the transmission sources). The data were acquired using the ECAT EXACT 922 (CTI/Siemens, Knoxville, TN) PET scanner. The scan was immediately followed by 3D emission scanning which lasted 15 minutes. The data acquired were reconstructed by iterative OS-EM algorithm (matrix: 1282, brain mode, 47 slices, zoom: 2, subsets: 16, iterations: 6, Hann filter: 5 mm) and implemented using ECAT 7.2 software.

PET data analysis and statistics

The data analysis was performed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm) implemented by Matlab (Mathworks, USA). Our patient with DP/DR was compared with the control group comprised of a sample of 22 psychiatrically healthy volunteers (11 males and 11 females, mean age 37.6 ± 12.3 years) from the oncological register of PET Centre Hospital Na Homolce. All subjects were medically screened for remission of oncological disease. Only subjects with negative structural (MRI) and PET brain imaging findings and no serious somatic or psychiatric disorders (except the history concerning the neoplasm) confirmed by the structured interview, without somatic or psychotropic medication intake were included in the control sample. All of the subjects were of Caucasian origin. Applicants with significant medical problems, a history of head trauma and alcohol or

drug abuse within the last 6 months were excluded. Written informed consent was obtained from all subjects. The PET scans were converted into the Analyze format, interpolated from 47 to 68 slices and normalized into standard stereotactic space by the use of bilinear sinc interpolation. PET images were smoothed with an isotropic Gaussian filter (full width at half maximum of 12 mm). The data pre-processing procedure resulted in the generation of a spatially normalized image of ^{18}FDG uptake for every voxel in 68 horizontal slices of the brain. The ANCOVA with age as a nuisance variable was used to determine the differences between the patient with DP and DR and the control group (Signorini et al., 1999). Global intensity differences were corrected using proportional scaling (global mean to 50, analysis threshold 0.8) and global calculation was performed by the mean voxel value. Statistical parametric maps of T-values were created and the anatomical locations of the activated areas were determined in the normalized space. The p-values at voxel-level for all identified regions were $\leq | 0.005$ achieving height threshold T = 2.84 (Z score of 2.58). This threshold is based on studies showing a low level of Type I error using this cut-off as the criteria (Reiman et al., 1997). We report only the peaks that contain more than 50 adjacent voxels and that agree with previously dysfunctional areas found with depersonalization-derealization syndrome. Every peak has been defined by the number of contiguous significant voxels that constitute the peak and by the standard Talairach atlas coordinates (Talairach, 1988).

Results

We found a significantly increased metabolism in the right superior temporal gyrus/inferior parietal gyrus (Brodman area -BA 40), right superior parietal gyrus (BA 7) and left fusiform gyrus in the occipital lobe (BA 19) in the patient with chronic DP/DR compared with the control group (Table 1 and Figure 1, 2). We did not find any significant decrease of ^{18}FDG.

Table 1: ***Higher ^{18}FDG PET metabolism in patient with depersonalization-derealization syndrome compared to control group. The uncorrected p-values at voxel-level for all identified regions was < 0.005.***

Region (Brodman area)	number of voxels	Z score of Maximum value voxel	Talairach coordinates		
			x	y	z
R sup. temporal g /inf. parietal g. (BA 40)	188	3.65	51	–23	14
R sup. parietal g. (BA 7)	51	3.06	24	–46	68
L fusiform g. (BA 19) occipital lobe	71	2.84	–22	–61	–12

Discussion

The association between depersonalization and temporal lobe dysfunction has long been reported (review Lambert et al., 2002). Jackson and Colman in 1898 described the "dreamy state" of a patient with temporal lobe epilepsy (TLE) secondary to a lesion in the left uncinate gyrus. Induction of a "dream-like" state is described after electrical stimulation of the medial temporal lobe in patients undergoing assessment for epilepsy surgery (Penfield and Perot, 1963). However, the specific anatomical site or even the hemisphere that would habitually produce the particular experimental sensation when stimulated has not been identified (Gloor et al., 1982; Lambert et al., 2002). An increased metabolism in the parietal cortex (BA 7B and 39) of patients with DP/DR was detected in Simeon et al. study (2000). The right superior temporal gyrus/inferior parietal gyrus BA 40 detected in our study is adjacent to area BA 39 and may only differ from Simeon's finding due to the spatial resolution of the PET method or due to interindividual variability. BA 40 represents a multimodal association area and is implicated in somatosensory-visual-auditory integration, which could be disturbed in DP/DR. Functional disturbancies in BA 39/40 could lead to autoscopy or out-of-body experiences (Blanke et al., 2004) which have partially similar fenomenology as DP. We detected increased metabolism in the patient with DP/DR in the right parietal area BA 7 which is the same result found by Simeon et al. (2000). BA 7 represents the somatosensory association area, an area in which dysfunction could lead to symptoms of body alienation. Depersonalization due to dysfunction in the parietal cortex is in agreement with the neurological model for depersonalisation (body alienation) known as asomatognosia or „hemidepersonalisation" that may result from a lesion in the parietal cortex (Sierra et al., 2002). Tumours in the inferior parietal and angular gyrus

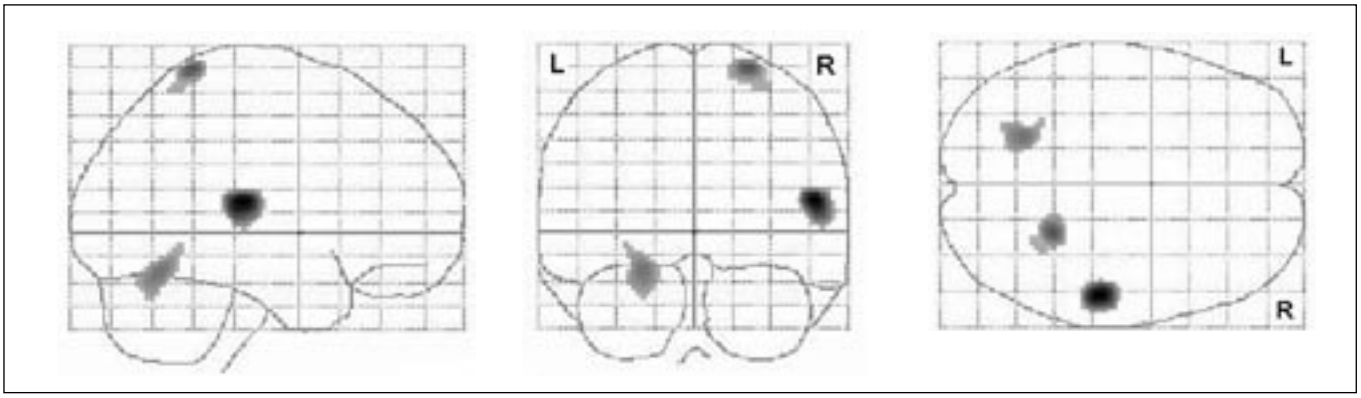

Figure 1: ***Higher ^{18}FDG PET metabolism in patient with depersonalization-derealization syndrome compared to control group (n = 22). The clusters exceeding the extent threshold of 50 voxels and the the uncorrected p-values at voxel-level < 0.005. Detailed characteristic of detected area are in the Table 1.***

manifest with depersonalisation (Ackner, 1954). Simeon et al. (2000) found positive correlation between metabolic activity in area 7B and the dissociation and depersonalization scores which suggests that dysfunction of this area could be responsible for the quality of depersonalisation.

Further we detected increased metabolism in the occipital cortex in the patient with DP/DR which is the same result as Simeon et al. (2000). The left fusiform gyrus (BA 19) belongs to the visual association area and dysfunction in this localisation could explain symptoms of derealisation, such as the feeling that surrounding things are etheric and people appear like colored air. Sierra et al., 2002 suggest that a neurologic model for derealization (visual derealization) could be the visual hypoemotionality connected with an occipito-temporal lesion.

In our case report we did not replicate the finding of a significantly lower metabolic activity in the superior and middle temporal gyri (BA 21, 22) as found by Simeon et al. (2000). This could be due to different mental activity during the PET scan or to the lower statistical power of our study. We used a resting state in our PET study while Simeon et al. (2000) used a task with visual, speech and memory components. Although we used a resting state our results are highly similar to the only published activation study using ^{18}FDG

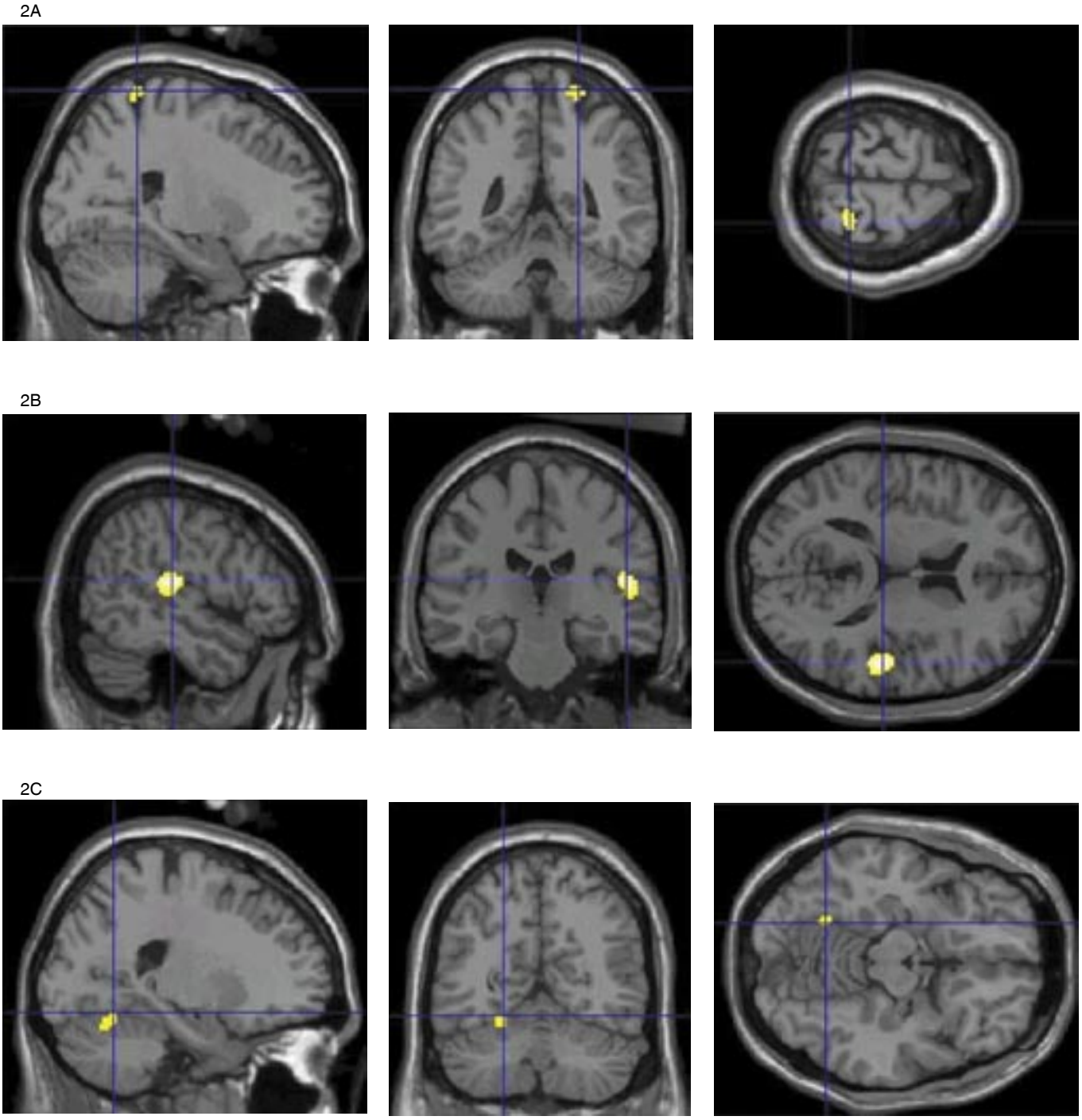

Figure 2 A, B, C: ***Regions with higher ^{18}FDG PET metabolism in patient with DP/DR syndrome compared to controls. 2A right superior parietal gyrus, 2B right superior temporal gyrus/ inferior parietal gyrus, 2C left fusiform gyrus in the occipital lobe. Regions are superimposed to the SPM MR template. Detailed characteristic of detected area are in the Table 1.***

PET in patients with DP/DR. The results are different from DP/DR induction studies in healthy volunteers after THC (Mathew et al., 1999), psilocybin (Vollenweider et al., 1997) or amphetamine (Vollenweider et al., 1998) and it seems that the primary DP/DR syndrome does not share the brain metabolic patterns with phenomenologically similar states induced by psychoactive drugs.

Results from quantitative EEG showed a slowing of activity which is a similar result as was found in a single subject with alcohol-induced transient depersonalisation who had without a history of other psychiatric illness psychiatric history (Raimo et al., 1999). Our patient was alcohol free but he described a worsening of the sense of unreality, even after low doses of alcohol.

Our study has several methodological limitations. First, the control sample from an oncological register is not an ideal control group. Nevertheless these controls have no psychiatric symptoms, which is essential from our viewpoint. Second, we describe a case report with only one patient therefore our result and generalisations based on this result should be considered with caution. Eventhough we only studied one patient we found similar metabolic patterns as reported in a previously published study. The comparison between one patient and the control group is valid from a clinical perspective. Recently a study aimed to validate the use of SPM to detect nonquantitative regional cerebral metabolic abnormalities ^{18}FDG PET in a single subject (Signorini et al., 1999) and it is valuable to consider the usefullnes of individual PET patterns for individualized rTMS therapy (Martinot et al., 2004). Because chronic DP/DR syndrome is a rare condition it seems necessary to organize a larger multicentric study to establish a more powerful results.

Conclusion

We found a significantly increased metabolism in the right superior temporal gyrus/ inferior parietal gyrus (BA 40), right superior parietal gyrus (BA 7) and left fusiform gyrus in the occipital lobe (BA 19) in a patient with chronic DP/DR compared to a control group. Our results are in agreement with the only published ^{18}FDG PET study of DP/DR.

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Miloslav Kopeček, MD
Psychiatric Centre Prague,
Ústavní 91, Prague 8,
Czech Republic
e-mail: kopecek@pcp.lf3.cuni.cz

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