J Neural Transm (2009) 116:623–629
DOI 10.1007/s00702-009-0191-3

Differentiating attention-deficit/hyperactivity disorder inattentive and combined types: a ^{1}H-magnetic resonance spectroscopy study of fronto-striato-thalamic regions

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Received: 7 July 2008 / Accepted: 28 January 2009 / Published online: 28 April 2009

Abstract Despite the implication of fronto-striatal circuits in attention-deficit/hyperactivity disorder (ADHD), there is a lack of information on the role of these regions, especially the thalamus, in the heterogeneity of ADHD. We assessed the ^{1}H-magnetic resonance spectroscopy profile in ventromedial prefrontal cortex (VMPFC)-thalamic-striatal regions bilaterally in three groups of subjects (age range 18–24 years old): ADHD inattentive type (ADHD-I; $n = 9$), ADHD combined type (ADHD-C; $n = 10$) and non-ADHD controls ($n = 12$). The peaks of N-acetylaspartate, Choline (Cho), myo-inositol (mI), creatine (Cr) and glutamate-glutamine-GABA (Glx) to Cr were calculated. Subjects with ADHD-C showed lower mI/Cr ratio in the right VMPFC than controls, higher Cho/Cr ratio in the left thalamus-pulvinar than the ADHD-I group and higher Glx/Cr ratio in left putamen than individuals with ADHD-I and controls. This metabolic profile suggests a disruption of fronto-striato-thalamic structures in the ADHD-C as a result of lower neuronal energetic metabolism.

Keywords Attention-deficit/hyperactivity disorder · Neuroimaging · Spectroscopy · Inattention · Hyperactivity · Diagnosis

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a prevalent neuropsychiatric disorder affecting 5% of children and adolescents worldwide (Polanczyk et al. 2007; Rohde et al. 1999) and persisting in 60% of subjects during adulthood (Polanczyk and Rohde 2007). Based on the differential frequency of abnormalities in attention, motor activity and impulse control, DSM-IV (APA 1994) criteria subdivide ADHD in three clinical types: predominantly inattentive (ADHD-I), predominantly hyperactive-impulsive (ADHD-HI) and combined (ADHD-C). Because phenotypical features describing each type differ considerably, there has been mounting interest in the validation of such subdivision through epidemiologic and neuropsychological research (Larsson et al. 2006; McBurnett et al. 1999; Rubia et al. 2005; Schmitz et al. 2002). However, there is an on-going debate whether ADHD-C and ADHD-I types represent similar or divergent neurobiological constructs (Barkley 1997). Since these are the two most prevalent ADHD types in clinical (Faraone et al. 1998) and epidemiological samples (Woo and Rey 2005), this issue assumes an even more relevant perspective. In addition, there is a huge debate on the validity of these subtypes for new classificatory systems (Rohde 2008).

Since impairments in fronto-striatal circuits have been implicated in attentional disorders (Barkley et al. 1992; Casey et al. 1997), three initial investigations used ^{1}H-magnetic resonance spectroscopy (MRS) to probe these pathways for neurometabolic profiles that could help differentiating ADHD subtypes (Courvoisie et al. 2004; Hesslinger et al. 2001; Sun et al. 2005). These preliminary studies, however, have yielded different results both in terms of the metabolic abnormalities and the structures involved within the frontal striatal pathways. For instance, Hesslinger et al. 2001) showed that the absolute N-acetylaspartate (NAA) concentration was significantly reduced in the left dorsolateral prefrontal cortex only in patients with ADHD-HI type when compared to those with ADHD-I and healthy controls. In another study, significant reductions in the NAA/Creatine (Cr) ratio were found in the right lenticulate nucleus of patients with ADHD-C when compared to patients with ADHD-I and controls (Sun et al. 2005). Finally, Courvoisie et al. (2004) reported increased glutamate (GLU)/Cr ratios in both frontal lobes and also increased NAA/Cr and Choline (Cho)/Cr ratios in the right frontal lobe of children with ADHD-HI when compared to controls.

Interestingly, there are no previous studies on the thalamic pulvinar metabolism measures in patients with ADHD, despite the fact that this region has been implicated in the attentional process (Pliszka et al. 1996). These diverse and incomplete data clearly suggest the need for more studies. Here, we report ^{1}H-MRS assessments of right and left ventromedial prefrontal cortex (VMPFC)-striatal-thalamic regions in adults with ADHD-C, ADHD-I and controls.

Materials and methods

Participants

Patients were consecutively recruited from the Psychiatry Outpatient Clinic of the University Hospital (Hospital São Lucas - PUCRS) having acquisition of images performed at the same place. Control subjects were students. All provided written informed consent. The protocol was approved by the Research Ethics Committee from Hospital São Lucas da PUCRS.

All individuals underwent a comprehensive psychiatric assessment including the use of specific modules for ADHD and disruptive behavior disorders of the Portuguese version of K-SADS (Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiological Version-K-SADS-E) (Mercadante et al. 1995). These modules were adjusted in terms of wording to evaluate DSM-IV criteria for adolescent and adults (Grevet et al. 2005). The Portuguese version of the SNAP-IV (Swanson et al. 2001) was used to score severity of inattention and hyperactivity/impulsivity (Mattos et al. 2006). The structured clinical interview for DSM-IV axis I. Disorders, patient edition. SCID-I/P, Version 2.0, (First et al. 1998) was carried out to evaluate current and lifetime comorbid psychiatric disorders in both patients and controls. To assess comorbidity with substance use disorder, biochemical analysis of urine was carried prior to examinations of MRS both in patients with ADHD and in controls subjects.

Patients with ADHD

Nineteen patients were enrolled, nine with ADHD-I and ten with ADHD-C. All were right handed, ranging from 18 to 24 years of age (mean age $= 20.84 \pm 2.43$). Inclusion criteria to assign patients to specific ADHD types were as follows:

1. ADHD-I: To assure a relatively homogeneous ADHD-I subpopulation, all had at least seven DSM-IV symptoms of inattention but at most three symptoms of hyperactivity/impulsivity. We have been using this strategy in previous investigations on ADHD-I (Schmitz et al. 2006a, b). Two presented comorbidity with dysthymia.
2. ADHD-C: All patients had at least six symptoms of inattention and at least six symptoms of hyperactivity/impulsivity. In addition, four had oppositional defiant disorder as comorbidity.

Exclusion criteria

(a) patients with metallic devices precluding magnetic resonance imaging; (b) history of significant medical disorder or head trauma; (c) comorbidity with dyslexia, bipolar or substance use disorder (drug, alcohol or tobacco), psychosis, mental retardation; (d) use of any psychotropic medications in the 6 months before recruitment; (e) presence of structural MRI abnormalities.

Control subjects

Twelve individuals matched for age, sex, schooling, ethnicity and handedness with cases, and without history of previous neurological or psychiatric disorders and of school failure agreed to participate as controls. According to DSM-IV ADHD criteria, these subjects had at most two symptoms of inattention and/or hyperactivity/ impulsivity.

Magnetic resonance imaging and spectroscopy acquisition

^{1}H-magnetic resonance spectroscopy scans were acquired on a 1.5T Siemens Magneton Vision Plus scanner at the

Center for Imaging Diagnosis, HSL-PUCRS. Point resolved spectroscopy (PRESS) sequence with 16 × 16 phase encoding steps was used with the following acquisition parameters: repetition time (TR) of 1,500 ms, echo time (TE) of 30 ms, field of view (FOV) of 24 cm, 2,000 Hz spectral bandwidth, 512 complex data points, 20 mm thickness, one measurements and acquisition time of 06 min 36 s. To localize the anatomical regions of interest a T1 gradient echo (TR 400/TE 4.7/flip 70°/matrix 180 × 256/NEX 1/thick 5 mm/spacing 1.5 mm/FOV 240 × 240) in the sagittal and coronal planes and a turbo spin echo FLAIR (TR 9000/TE 110/flip 180°/ matrix 180 × 256/NEX 1/thick 5 mm/spacing 0.9 mm/FOV 240 × 240 mm) in the axial plane were acquired and all planes covered the whole brain. The PRESS sequence defined the anterior/posterior and right/left dimensions of the region-of-interest defined in the axial slices. We established for quality criteria a maximum 8 Hz full width at half maximum of the water peak during the shimming procedure.

Post-acquisition data processing

Data were analyzed by a trained MRS imager blind for the clinical diagnoses. We used the Luise software (Siemens, Erlangen, Germany) that runs under the Siemens Magneton Vision Plus platform to shift a particular voxel (within the 16 × 16 voxel-matrix) superimposed on axial images over 08 regions of interest: left (L) and right (R) VMPFC; L and R pulvinar (thalamus posterior); L and R putamen; L and R caudate head (Fig. 1). A post-processing protocol was defined to minimize variation between analyses. A Gaussian filter, water signal subtraction, and raw data interpolation (zero filling) to achieve 1,024 data points were applied for each voxel before the phase and baseline correction. The curve fitting was performed based on predefined part per million values for each metabolic peak (Fig. 2). The integral value for each peak was calculated by a Gaussian curve type fitting. None of the subjects required a sedative for completion of the procedure.

Data analyses

A one-way ANOVA with level of significance set at $P = 0.05$ compared ^{1}H MRS findings among the three groups of patients (ADHD-I, ADHD-C and controls). An analysis of co-variance was used to control for the effect of the occurring comorbidities that were not exclusion criteria. Post hoc Bonferroni tests were conducted to detect the difference of the peak-area ratios of the: NAA peak at 2.0 ppm; Cho at 3.22 ppm; Glutamate-glutamine-GABA (Glx) between 2.1 and 2.5 ppm; myo-inositol (mI) between 3.56 and 4.06 ppm and Cr between 3.03 and 3.94 ppm of the metabolic spectrum (Provencher 1993) (Fig. 2). Results are given as ratios of the different metabolites to Cr, whose peak is stable and considered as a useful internal reference

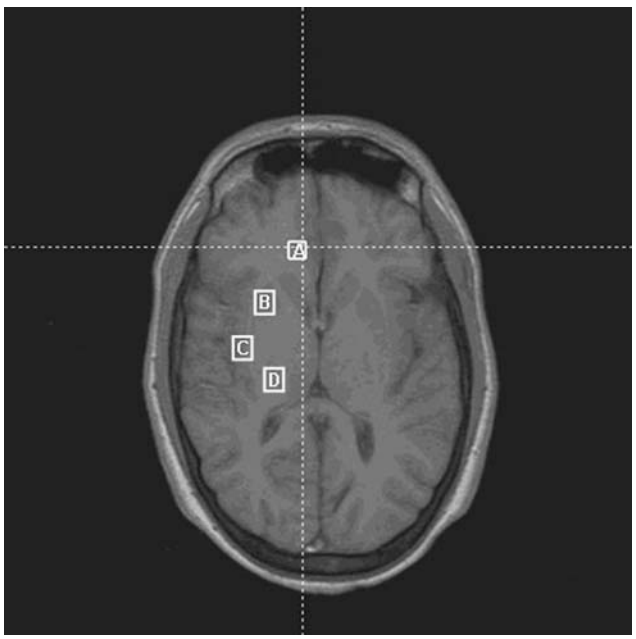

Fig. 1 Voxel placement in **a** prefrontal ventromedial cortex, **b** caudate, **c** putamen and **d** pulvinar. Measurements were performed bilaterally in homologous areas

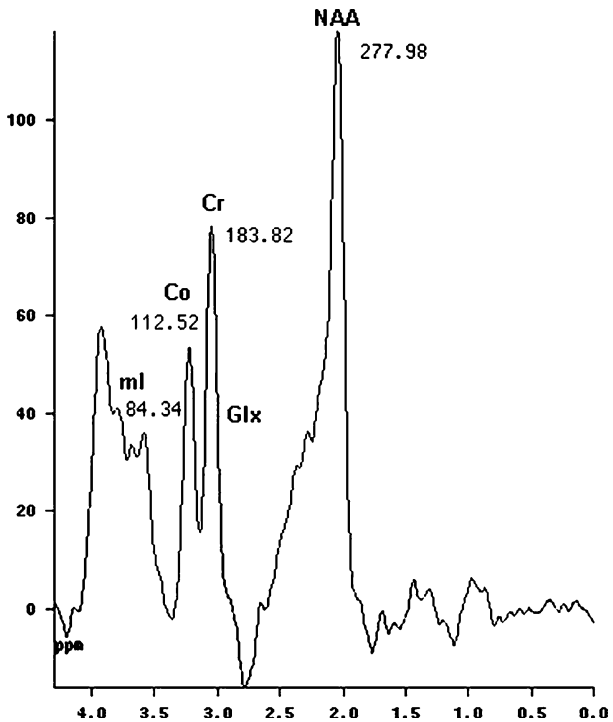

Fig. 2 Sample spectra demonstrating metabolic peaks of, respectively, *NAA* N-acetylaspartate, *Glx* glutamate/glutamine/γ-aminobutyric acid, *Cr* creatine/phosphocreatine, *Cho* choline compounds

(Deicken et al. 2000). The SPSS 10.0 (Statistical Package for the Social Sciences) software was used for the analyses.

Results

Group comparisons revealed no differences regarding age ($P = 0.46$), gender ($P = 0.47$), level of education ($P = 0.81$) or ethnicity ($P = 1.00$). ^{1}H-MRS metabolite ratios for each brain region in patients with ADHD-C, ADHD-I and controls are shown in the Table 1. After adjusting for the effect of comorbidities, three significant metabolic differences were found: (1) decreased ratio of mI/Cr in right VMPFC in ADHD-C as compared to controls ($P = 0.003$); (2) increased ratio of Glx/Cr in the left putamen in ADHD-C as compared to both ADHD-I and controls ($P = 0.044$) and (3) increased ratio of Cho/Cr in the left thalamus-pulvinar (thalamus posterior) in ADHD-C as compared to ADHD-I ($P = 0.017$).

No differences related to NAA/Cr in the VMPFC, striatum and thalami were observed.

Discussion

The nosological validity of differentiating patients with the three proposed DSM-IV ADHD types (predominantly inattentive, hyperactive/impulsive and combined) is still under debate. Here, we showed that groups of patients with ADHD-C and ADHD-I types have some metabolic differences in gray matter structures along fronto-striato-thalamic circuits. Overall, the group of patients with combined ADHD type presented slightly different metabolic patterns in frontal, striatal and thalamic structures from inattentive

Table 1 1H-magnetic resonance spectroscopy metabolite ratios in fronto-striato-thalamic structures according to ADHD subtypes

Anatomical regions	^{1}H-MRS metabolite ratios	ADHD subtypes[1]			P value[2]	P value[3]
		ADHD-C ($n = 10$)	ADHD-I ($n = 9$)	Controls ($n = 12$)		
R VMPFC	NAA/Cr	1.84 ± 0.20	1.77 ± 0.27	1.70 ± 0.26	0.418	0.871
	Cho/Cr	0.96 ± 0.09	0.86 ± 0.11	0.94 ± 0.11	0.111	0.144
	mI/Cr	0.51^{a} ± 0.12	0.58^{ab} ± 0.13	0.65^{b} ± 0.12	0.031	0.003
	Glx/Cr	1.17 ± 0.33	1.25 ± 0.61	0.98 ± 0.39	0.386	0.770
L VMPFC	NAA/Cr	1.89 ± 0.24	1.71 ± 0.45	1.59 ± 0.33	0.145	0.077
	Cho/Cr	0.93 ± 0.08	0.79 ± 0.24	0.89 ± 0.11	0.149	0.055
	mI/Cr	0.51 ± 0.12	0.64 ± 0.33	0.72 ± 0.16	0.086	0.152
	Glx/Cr	0.97 ± 0.25	1.18 ± 0.71	0.94 ± 0.40	0.504	0.561
R putamen	NAA/Cr	1.73 ± 0.28	1.46 ± 0.29	1.61 ± 0.16	0.062	0.052
	Cho/Cr	0.70 ± 0.12	0.59 ± 0.12	0.64 ± 0.10	0.160	0.111
	mI/Cr	0.50 ± 0.13	0.39 ± 0.08	0.48 ± 0.08	0.061	0.052
	Glx/Cr	1.20 ± 0.36	0.87 ± 0.27	1.05 ± 0.34	0.105	0.078
L putamen	NAA/Cr	1.52 ± 0.20	1.46 ± 0.16	1.38 ± 0.11	0.120	0.344
	Cho/Cr	0.71 ± 0.13	0.68 ± 0.04	0.63 ± 0.09	0.129	0.324
	mI/Cr	0.47 ± 0.14	0.43 ± 0.06	0.44 ± 0.13	0.794	0.832
	Glx/Cr	1.34^{b} ± 0.27	1.00^{a} ± 0.31	0.96^{a} ± 0.32	0.046	0.044
Right pulvinar	NAA/Cr	1.90 ± 0.25	1.81 ± 0.16	1.87 ± 0.28	0.712	0.722
	Cho/Cr	0.92 ± 0.13	0.82 ± 0.07	0.84 ± 0.09	0.113	0.137
	mI/Cr	0.54 ± 0.12	0.58 ± 0.09	0.60 ± 0.18	0.654	0.757
	Glx/Cr	1.38 ± 0.44	1.18 ± 0.26	1.11 ± 0.25	0.156	0.284
Left pulvinar	NAA/Cr	1.92 ± 0.16	1.77 ± 0.15	1.77 ± 0.20	0.093	0.132
	Cho/Cr	0.93^{b} ± 0.14	0.78^{a} ± 0.08	0.73^{a} ± 0.09	0.014	0.017
	mI/Cr	0.60 ± 0.10	0.52 ± 0.09	0.60 ± 0.13	0.202	0.226
	Glx/Cr	1.42 ± 0.60	1.10 ± 0.30	1.03 ± 0.27	0.084	0.111

Abbreviations as in the text

Same small superscript letters do not differ by the Bonferroni test

[1] Mean ± standard deviation of the mean

[2] One-way ANOVA

[3] ANCOVA adjusted to effect of comorbidities

patients and normal controls, whereas the latter two had similar metabolic patterns. This suggests that ADHD-C patients may have a more distinctive neuronal metabolic profile.

Before dwelling into the main metabolic findings, it should be noted that our results apply to older adolescents and young adults with ADHD within the homogeneous age range of 18–24 years of age. They were all evaluated with standard psychiatric scales probing for both childhood and adulthood ADHD symptomatology. In addition, none had comorbidities with dyslexia, bipolar or substance use disorder or psychosis. On the other hand, roughly one-third of our patients had comorbid oppositional-defiant disorder or dysthymia. We believe the high frequency of these two comorbidities in the ADHD population in general justifies the retention of these patients. In fact, their exclusion might render our results less applicable to a 'real world' ADHD population, in which comorbidity with oppositional-defiant disorder or dysthymia is often present. Other authors have elected this same strategy (Sun et al. 2005; Carrey et al. 2003).

The main finding in the present study is the combination of a decreased mI/Cr ratio in the right VMPFC with an increase in the ratio of Glx/Cr in the left putamen and Cho/Cr in the left pulvinar in patients with ADHD combined type. It is noteworthy that this is the first ADHD investigation on the thalamic-pulvinar metabolic profile as well as the first study to provide these comparisons among ADHD types.

The reduced mI/Cr in the right VMPFC and the increased Cho/Cr in the left thalamic-pulvinar found in the group with ADHD-C may be related to the cellular energy cycle, since these metabolites may influence second messenger systems bearing upon cyclic-AMP production (Moore et al. 2000, 2006; Malhi et al. 2002). Furthermore, a putative mechanism for increased Glx/Cr ratio in the left putamen in ADHD-C is again related to cellular energy mechanisms. Because the synaptic clearance of GLU is effected by an astrocyte-neuronal lactate shuttle (Todd and Botteron 2001), abnormalities in the latter lead to accumulation of GLU and therefore to an increase in Glx (Carrey et al. 2003). Therefore, the neuronal metabolic profile reported here is in line with the ADHD theory of an 'energetic deficit' (Todd and Botteron 2001) in fronto-thalamic-striatal structures.

There are at least two additional possible mechanisms to explain the increased left putamen Glx/Cr ratio, a neuroanatomic region that may be especially relevant to ADHD. First, it could express overall increased levels of glutamine and GLU related to reduction in the conversion of GLU to GABA (via glutaminic acid decarboxylase) or by increased back transformation of GABA to GLU (via GABA transaminase) (Courvoisie et al. 2004). Interestingly, MacMaster et al. (2003) showed an increase in glutamatergic resonance (Glx/Cr) in the right prefrontal cortex and striatum of 14 ADHD children relative to healthy control subjects. In another study, these authors (Carrey et al. 2003) showed that pharmacologic treatment decreased this ratio.

An alternative neurochemical perspective suggested by our findings concerns the relationships among GLU, dopamine and acetylcholine in fronto-thalamic-striatal circuits. GLU modulates the release of dopamine while dopaminergic activity leads to mildly elevated levels of cholinergic (Jin et al. 2001) and glutamatergic neurotransmission in the striatum (Carrey et al. 2002, 2003; MacMaster et al. 2003). Imbalances in this neurochemical profile in ADHD patients may interfere with the gating of sensory information in striato-frontal pathways, possibly resulting in frontal lobe dysfunction (Casey et al. 1997).

Finally, the increased Cho/Cr ratio in the left thalamic-pulvinar region may indicate some degree of dopaminergic hypoactivity. The influence of glutamatergic neurotransmission in both dopaminergic and cholinergic systems (Carrey et al. 2003) may lead to a reduction in overall neuronal energetic metabolism (Moore et al. 2000; Todd and Botteron 2001; Jin et al. 2001; Russell et al. 2006). To our knowledge this is the first evidence of increased thalamic-pulvinar cholinergic activity in ADHD-C, and this finding may contribute to the understanding of the executive dysfunction described in ADHD patients. The most likely mechanism for these alterations involves subtle thalamic-pulvinar abnormalities interfering with its sensory-'gating' role and secondarily with frontal lobe executive (particularly inhibitory) functions (Barkley 1997). The pulvinar region is critical to engage attention on novel stimuli and participates in the posterior attention system, activated when attending to visual stimuli (Pliszka et al. 1996).

N-acetylaspartate levels correlate to neuronal density and mitochondrial energetic metabolism (Fayed and Modrego 2005; Moffetti et al. 2006). In the present study, the NAA/Cr ratio did not differ between ADHD types or between each type and controls. In addition, the fact that we measured NAA in relation to Cr (and not through an absolute quantification) may have contributed to the lack of significance. The findings in different series of patients are heterogeneous in this respect. Courvoisie et al. (2004) and Hesslinger et al. (2001) reported decreased NAA ratios in the prefrontal cortex and Sun et al. (2005) in the lenticulate nucleus in patients with ADHD-C. On the other hand, Fayed et al. (2007) found increased NAA/Cr ratios in the right prefrontal cortex and in the left centrum semiovale in ADHD patients compared to controls. Finally, MacMaster et al. (2003) did not find abnormalities in NAA ratios in prefrontal cortex in ADHD patients.

The present findings should be analyzed in the context of some methodological limitations. Given the nature of the study, sample size is an important issue and correction for multiple comparisons would eliminate the significant results. Therefore, interpretation of the findings should consider the biological plausibility, and definite conclusions should be reached only after independent replications. Instead of analyzing the absolute measurement of metabolites, we used ratios. This approach minimizes potential errors introduced by variable tissue composition and instrumental instability while allowing the evaluation of relative alterations in metabolites (MacMaster et al. 2003). Differences in metabolic ratios occurred in the expected direction, including a gradient of ratio abnormalities between ADHD-C, ADHD-I and controls in the involved structures at all levels along the fronto-striato-thalamic circuitry.

In summary, the preliminary evidence presented here suggest that ^{1}H-MRS of metabolic ratios of mI, Cho and Glx related to Cr may differentiate groups of patients with ADHD-C and ADHD-I, without differentiating the inattentive subtype from normal controls. An intriguing explanation for these findings is that these differential metabolic profiles may, at least in part, reveal a more severe disruption of fronto-striato-thalamic structures in the combined type of ADHD as a result of a reduction in overall neuronal energetic metabolism in this pathway. If confirmed, these finding might be related to a more severe symptomatology in terms of executive dysfunction and impulsiveness/hyperactivity.

Conflict of interest statement Dr Rohde was on the speaker's bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, and Novartis in the last three years. Currently, his only industry related activity is taking part in the advisory board/speaker's bureau for Eli Lilly and Novartis (less than U$ 10,000 per year and reflecting less than 5% of his gross income per year). The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Abbott, Bristol-Myers Squibb, Eli-Lilly, Janssen-Cilag, and Novartis. Dr Palmini is on the speaker's bureau or is a consultant for Janssen-Cilag and Novartis. Dr Abreu is on the speaker's bureau or is a consultant for Janssen-Cilag and Bristol-Myers Squibb. Dr Grevet is on the speaker's bureau or is a consultant for Novartis and Janssen-Cilag.

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