Mastocytosis is a rare disease in which chronic symptoms are related to mast cell accumulation and activation. Patients can display depression–anxiety-like symptoms and cognitive impairment. The pathophysiology of these symptoms may be associated with tissue mast cell infiltration, mast cell mediator release or both. The objective of this study is to perform morphological or functional brain analyses in patients with mastocytosis compared with 33 healthy controls. In the test cohort of 39 mastocytosis patients with psycho-cognitive complaints, we found that 49% of them had morphological brain abnormalities, mainly abnormal punctuated white matter abnormalities (WMA). WMA were equally frequent in cutaneous mastocytosis patients and indolent forms of systemic mastocytosis patients (42% and 41% of patients with WMA, respectively). Patients with WMA showed increased perfusion in the putamen compared with patients without WMA and with healthy controls. Putamen perfusion was also negatively correlated with depression subscores. This study demonstrates, for we believe the first time, a high prevalence of morphological and functional abnormalities in the brains of mastocytosis patients with neuropsychiatric complaints. Further studies are required to determine the mechanism underpinning this association and to ascertain its specificity.
environment and treatment. Although some symptoms are strongly suggestive of mast cell activation (flush, anaphylactic reaction, and drug or food intolerances), most, if not all, mast cell mediator release symptoms are unspecific (for example, fatigue, musculoskeletal pains, gastrointestinal complaints, palpitations and malaise).

A large panel of neurological and psychiatric symptoms is also frequently reported by patients with mastocytosis including headaches, neuropathic pains, dizziness, attention and memory changes, anxiety, emotional over-reactivity, depressive-like symptoms and sleeping disorders. In a retrospective series of adult patients with a diagnosis of mastocytosis who were referred to a neurologist, multiple sclerosis has been found to be over-represented. We have shown that 40 to 60% of mastocytosis patients present with psycho-cognitive manifestations including attention and memory impairments and depression.

Although the number of publications on this topic is extremely scarce and the exact prevalence and specific characteristics are still not precisely validated, these symptoms tend to be considered authentic mast cell mediator release symptoms and should be carefully considered in medical coverage.

The present prospective comparative and monocentric study aimed to investigate relationships between psycho-cognitive complaints assessed via systematic psychiatric evaluation and objective medical data using magnetic resonance imaging (MRI) with morphological and perfusion sequences (arterial spin-labeled perfusion). In other systemic diseases such as systemic lupus erythematosus with neuropsychiatric symptoms (for a recent review, see Mikdashi, 2016) or even without (Mak et al., 2012), Sjögren’s syndrome or Behçet’s disease, MRI helped to characterize brain alterations related to psychiatric, cognitive or neurological symptoms. In mastocytosis, coupled psychiatric evaluation and MRI could not only demonstrate brain lesions and their correlates but could also pinpoint the involvement of mast cells in cognitive and depressive symptoms in a broader perspective.

MATERIALS AND METHODS

Subjects

Patients registered in the French National Reference Centre for Mast-cell diseases (centre de référence des mastocyteses, CEREMAST) were proposed to be enrolled in a French, prospective, monocentric clinical study. No formal sample size calculation was performed because mastocytosis is a rare condition and no preliminary data have allowed defining the size or even the type of neuroimaging results. Consecutive patients were recruited during 18 months at Necker Children’s Hospital (Paris, France). Inclusion criteria included a diagnosis of a CM, ISM or SSM type of mastocytosis and the existence of psycho-cognitive symptoms/complaints. The diagnosis of mastocytosis and its subtype was made by trained specialized medical doctors and characterized as either CM, ISM or SSM based on the WHO classification criteria. Systemic involvement relied on a bone marrow biopsy and/or aspirate with the presence of atypical mast cells expressing the immunostaining CD2 and/or CD25 as well as the presence of a D816V mutation in the C-KIT gene (see Supplementary Table). A diagnosis of CM was confirmed when either bone marrow analysis and blood tests indicated the absence of systemic involvement (no major criteria and less than three minor criteria, five patients) or when bone marrow analysis was not available (due to procedure failure or patient refusal, seven patients). Psycho-cognitive symptoms/complaints consisted of recurrent or continuous anxiety, depression or cognitive impairment, with consecutive feelings of dissatisfaction and/or disability in their current life.

Exclusion criteria included the presence of a known neurological disease such as epilepsy, multiple sclerosis or any identified comorbid systemic condition.

A control group including healthy volunteers free of mastocytosis as well as of any neurological and/or psychiatric disorders was constituted to perform brain imaging.

The investigational review board of Necker Children's Hospital approved this study supported by the AFIRM (Association Française pour l'Initiative et la Recherche sur le Mastocyte et les Mastocytoses). The study was approved by the local ethics committee (Comité de Protection des personnes Ile de France 6—CPP IDF 6, number 9300). All the subjects gave their written informed consent. The use of a computer database to store personal information was authorized by the French National Data Protection Commission (CNIL authorization #1445939).

Clinical evaluation and laboratory testing

The main features of each patient were recorded on the day of the procedure by MOC and included mast cell activation symptoms (fatigue, pruritus, flushing, anaphylactic reactions, angioedema, diarrhea and/or gastrointestinal pains, pollakiuria (frequent urination), clinical examination with neurological testing, B- and C-findings (that is, signs of aggressiveness) according to the validated classification criteria, serum tryptase level, past and present treatment history of mastocytosis (symptomatic as well as cytoeductive therapies) and all other drugs, notably psychoactive substances. Cardiovascular risk factors including tobacco consumption, hypertension, overweight, diabetes and cannabis use were recorded. The mental state of patients was assessed in all but one patient by a psychiatrist (RG) using the French version of the Mini International Neuropsychiatric Interview10 to diagnose psychiatric conditions according to DSM-IV-TR criteria and auto-questionnaires, including the Symptom Check List 90R11 and the Modified Fatigue Impact Scale.

Laboratory tests included serum tryptase level, skin and/or bone marrow histological analysis and/or bone marrow aspirate analysis, C-KIT muta-tional status obtained from skin and/or bone marrow molecular analysis.

Brain imaging

All the subjects were scanned on a 1.5 T Signa General Electric scanner to obtain both morphological and perfusion sequences. The protocol included a three-dimensional T1-weighted FSPGR (Fast Spoiled Gradient echo) sequence (repetition time (TR): 16.4 ms, echo time (TE): 7.2 ms, bandwidth: 11.9 Khz, inversion time (TI): 550 ms, field of view (FOV): 22 × 22 cm², slice thickness: 1.2 mm, acquisition matrix: 288 × 224, NEX: 0.75) without injection, a three-dimensional T1-weighted sequence with injection of Gadolinium (TR: 7000 ms, TE: 97.2 ms, EC: 1/1, bandwidth: 35.7 Khz, FOV: 24 × 24 cm², slice thickness: 4.0 mm, acquisition matrix: 320 × 320, NEX: 1.50), an axial T2-weighted sequence (TR: 12 ms, TE: 3.6 ms, EC: 1/1, bandwidth: 15.6 Khz, TI: 550 ms, FOV: 24/L8 cm², slice thickness: 1.6 mm, acquisition matrix: 320 × 256, NEX: 1.00) and an Axial FLAIR (Fluid Attenuation Inversion Recovery) sequence (TR: 9002 ms, TE: 154.3 ms, EC: 1/1, bandwidth: 31.2 Khz, TI: 2250 ms, FOV: 22 × 22 cm², slice thickness: 4 mm, NEX: 1.00, acquisition matrix: 320 × 224). ASL (arterial spin labeling) sequence was performed to measure the cerebral blood flow using pulsed continuous ASL (pseudo-continuous) in the axial scan plane with post-label delay of 1025 s with 40 slices of 4 mm (TR: 4554 ms, TE: 10.5 ms, EC: 1/1, TI: 1025 ms, FOV: 24 × 24 cm³, NEX: 3.00, acquisition matrix: 512 × 8). The MRI images were pre-processed using Statistical Parametric Mapping (SPM8 software from the Wellcome Department of Cognitive Neurology London www.fil.ion.ucl.ac.uk/spm/software/spm8) implemented in Matlab (Mathworks, Sherborn, MA, USA) and analyzed using a voxel-based approach. Several steps were required regarding the pre-processing part of the analysis. A DICOM to NIFTI conversion was necessary before these steps. First, native T1 images were segmented into gray matter, white matter and cerebrospinal fluid using the segmentation tool of SPM8. Then, the gray matter resulting from that segmentation was normalized to MN152 space using the SPM default template. Because patients may have moved between the different acquisitions causing possible geometric changes such as rotations, ASL images were coregistered to the native gray matter images. Consequently, the ASL images were normalized by applying the deformation matrices from the gray matter normalization process. The resulting images were smoothed using a 10 mm isotropic Gaussian filter.

Visual inspection of the MRI

The MRI scans were interpreted independently by two board-certified radiologists experienced in neuroradiology (NB, ON). Structural malformations or signal abnormalities of gray and white matter were rated for each examination. The white matter abnormalities (WMA) were classified as multiple punctate or plaque-like confluent hypersignals on T2 and FLAIR.
sequences. Multiple punctate WMA were further classified as periventricular, deep or subcortical abnormalities.

Statistical analysis
Statistical analyses of clinical data were performed using the R statistics software (www.r-project.org). A detailed description of clinical features of each group is provided as a Supplementary Table; individual data are available upon request. The differences between subgroups (diagnostic subgroups or WMA versus non-WMA subgroups) were assessed through uncorrected two-tailed t-tests when the independent variable was continuous (Symptoms check list SCL score, age and typtase level) and through chi-squared tests when the independent variable was categorical (depression diagnostic, presence of WMA, presence of neurological signs and migraine) or through Fisher’s exact test when required (one or more expected count below 5). The assumptions of each statistical test used were checked, including equality of variances, and statistical significance was set at 0.05. The SCL scores were analyzed with an ANOVA (analysis of variance) with SCL dimension as a factor, and subsequent uncorrected pairwise t-tests to identify specific dimensions of symptoms in patients. A specific analysis of the depression dimension was performed with a factor analysis to determine factors that best explained interindividual differences (the details of the method used are described with the results).

Principal component analysis with Varimax rotation was used for data analysis. Voxel-based analyses were performed with SPM8 on smoothed and normalized ASL images to compare different groups within a mask encompassing all coronal slices with y = −30 mm.

RESULTS
A total of 72 subjects were enrolled in the study: 39 patients (referred to hereafter as the test cohort, mean age: 44.2 ± 11.8 years, age range: 15–65 years, 6 men) and 33 healthy controls (mean age: 39.2 ± 12.8 years, age range: 23–60 years, 11 men), with no significant difference between patients’ age and controls’ age (P-value > 0.1).

Main clinical features
In the test cohort, 12/39 patients (30.8%) had CM, 26/39 patients (66.7%) had ISM and 1/39 patient (2.6%) had SSM. The mean length of time for the first mastocytosis-related symptom was 17 years and that of diagnosis confirmation was 13.9 years. Skin involvement was reported for all the patients in the test cohort with a vast majority of maculopapular CM skin lesions (previously denominated urticaria pigmentosa) in 92.3% of patients. Although variable in type and intensity, with acute exacerbations, were identified in all patients. The most prevalent symptoms were asthma (97.4%), gastrointestinal disorders (94.8%) and musculoskeletal pains, notably headaches (84.6%), flushing (82%), pruritus (74.3%) and pellagria (59%). The evaluation of symptoms following the grading introduced by Valenti et al. showed that MCA symptoms in all the patients were graded 2 or 3, with frequent mild-to-severe symptoms requiring daily therapy resulting in satisfactory (grade 2) or unsatisfactory (grade 3) control. None had severe adverse events requiring immediate therapy and hospitalization (grade 4). Symptomatic treatment consisted mainly of antihistamines (87%). Approximately 41% of patients from the test cohort had received one to five previous lines of cytoreductive treatment, mainly tyrosine kinase inhibitor, due to refractory and disabling MCA. Moreover, at the time of this study, 20/39 patients (51.3%) from the test cohort were in need of a first or new line of cytoreductive therapy, stressing the burden of MCA in this cohort.

Neuroimaging evidence of brain abnormalities in mastocytosis
N Boddaert et al

Visual inspection of MRI. MRI was rated as abnormal in 19/39 patients (49%), and three main types of abnormalities were found: WMA (n = 16), plaque-like areas (n = 2), meningoisias (n = 2) and cerebellar atrophy (n = 1). These abnormalities occurred in combination in two patients.
In the group of CM patients, we found five patients with WMA and one plaque-like area and six normal MRIs. The WMA involved the periventricular white matter fibers (n = 2/5), the deep juxta-ventricular white matter (n = 3/5) and the subcortical U fibers (n = 5/5). In the group of ISM/SSM patients, we found 11 patients with WMA, 1 plaque-like area, 2 meningiomas and 16 normal MRI. The WMA involved the periventricular white matter fibers (n = 6 - 11), the deep juxta-ventricular white matter (n = 7/11) and/or the subcortical U fibers (n = 8/11).

The WMA were small (< 2 mm), asymmetric and homogeneous, and they were very intense compared with the adjacent white matter on T2 and FLAIR sequences. No findings suggested that necrosis was present. Their localizations showed inter-patient variability. They could involve the periventricular white matter fibers (n = 8/16), the deep juxta-ventricular white matter (n = 8/16) and/or the subcortical U fibers (n = 13/16; Figure 1). The WMA were equally distributed in the CM and ISM/SSM groups (5 patients among 12 CM and 11 patients among 27 ISM/SSM, respectively, P = 1, two-sided Fisher’s exact test of independence). The overall frequency of neurological complaints was comparable in the CM and ISM/SSM groups (24 and 34, respectively, Chi-square P = 0.40). Neurological complaints frequency was also comparable by type of symptom: migraine (9/12 and 16/27, Chi-square P = 0.87), symptoms suggesting peripheral neuropathy (6/12 and 10/27, Chi-square P = 0.87), dizziness (6/12 and 5/27, Fisher’s P = 0.17), numbness of one or more limbs (1/12 and 1/27, Fisher’s P = 0.54), movement control complaints suggesting dyskinesia (0/12 and 2/27, Fisher’s P = 1), speech disorder (1/12 and 0/27, Fisher’s P = 0.32) and visual complaints (1/12 and 0/27, Fisher’s P = 0.32). The SCL depression subscale was lower in the CM than in the ISM/SSM group (1.04 versus 1.77 raw score, t-test P = 0.035), but the total SCL score was not different (0.86 versus 1.32 raw score, t-test P = 0.12) and the frequency of depression diagnostic was not significantly different (2/12 and 10/27, Fisher’s P = 0.27).

Plaques-like areas with hyperintensity on T2 and FLAIR were present in two patients. One patient had two plaques-like areas: one plaque-like area was localized in the right temporal pole/amygdalian region and the hyperintensity on FLAIR decreased over 2 months (Figure 2a); the second plaque-like area was localized in the right periventricular region with a contrast enhancement, which decreased in 7 months. (b) The second plaque-like area was localized in the right periventricular region as shown by the axial FLAIR sequence (up) with an important contrast enhancement (axial T1 with injection on bottom row) that also decreased at 6 months.
enhancement that disappeared over 6 months (Figure 2b). For the second patient, one plaque-like area was localized in the frontal superior lobe and was mimicking a low-grade oligodendroglioma without any mass effect or contrast enhancement (Figure 3).

When looking for clinical features that could explain these morphological brain abnormalities, the comparison of subgroups with or without WMA (n = 16 and 23, respectively) revealed no significant differences: the mean age in the WMA subgroup was 49 years (range 15–65) versus 40.8 years (range 21–57) in the subgroup without WMA; the sex ratio was 4/12 versus 3/20, respectively; tobacco (in 4/16 patients, 25% versus 8/23 patients, 8.7%); cannabis abuse (in 1/16 patient, 6.3% versus 2/23 patients, 8.7%); putamen perfusion changes, with a less significant effect that did not survive our whole-brain threshold (22, 18, −15; z = 3.51, 140 voxels, P < 0.001 uncorrected, P = 0.678 corrected). In the between-group analyses (Figure 4b), WMA mastocytosis patients showed a significant hyperperfusion in the left putamen compared with both healthy control subjects and non-WMA mastocytosis patients (P < 0.001 uncorrected, P = 2.3 × 10⁻⁵ corrected, z = 5.01 and P < 0.001 uncorrected, P = 0.0013 corrected, z = 4.05, respectively). At a more lenient threshold, WMA mastocytosis patients also had an increase of cerebral blood flow in the right putamen compared with both non-WMA mastocytosis patients and control subjects (P = 0.002 uncorrected, z = 2.93 and P = 2.1 × 10⁻⁵ uncorrected, z = 4.08, respectively). Non-WMA mastocytosis patients did not differ from controls in the left or right putamen (P = 0.13 uncorrected, z = 1.09 and P = 0.07 uncorrected, z = 1.48, respectively).

Finally, we tested whether brain activity correlated with clinical scores using the factors found to best explain interindividual differences in depression scores, factors 1 through 3 of the factor analysis. Putamen perfusion correlated strongly with the lack of motivation dimension (factor 3, item 71, Pearson’s correlation r = 0.60, P < 0.001, Figure 4c). There was no correlation with the main symptoms dimension (factor 1, r = −0.31, P = 0.06) and a marginal correlation with the severity dimension (factor 2, r = −0.08, P = 0.63).

Based on the depression diagnosis on a small subset of patients, we compared cerebral blood flow in depressed versus non-depressed mastocytosis patients but found no difference in cerebral blood flow in a whole-brain analysis (P > 0.1). For exploratory purposes, mean ASL perfusion was calculated within the subgenual cingulate cortex defined a priori following previous publications in depression, as detailed in the ‘Materials and methods’ section. The region of interest was a 5 mm radius sphere centered on x = −10; y = 28; z = −12. This analysis yielded a significant decrease in cerebral blood flow (hyperperfusion) in the subgenual cingulate cortex in depressed compared with non-depressed mastocytosis patients (P = 0.002 uncorrected, P = 0.012 corrected, T = 3.06 and z = 2.96, Figures 5a and b). Again, perfusion in this region correlated strongly with the lack of motivation dimension of the depression subscale of the SCL90 (factor 3, item 71, Pearson’s correlation r = −0.460, P = 0.003, Figure 5c).

DISCUSSION

The aim of this study was to determine the neural basis of psychiatric and cognitive complaints in indolent forms of mastocytosis through systematic MRI and psychiatric evaluations. In the test cohort of 39 mastocytosis patients with a neuropsychiatric complaint, we found that (i) 49% of patients had morphological brain abnormalities, mainly abnormal punctuated white matter hypersignals (that is, WMA); (ii) an increased perfusion was demonstrated in the putamen in mastocytosis patients compared with control subjects, an increase that was demonstrated to be specific to those mastocytosis patients with WMA; (iii) putamen perfusion was negatively correlated with the motivation dimension of the depression subscore of the SCL90; and (iv) an exploratory analysis showed a decreased perfusion in the subgenual cingulate cortex in depressed compared with non-depressed mastocytosis patients.

Among the test cohort of mastocytosis patients with psychocognitive complaints (n = 39), 41% had punctuated WMA. The pathological character for isolated periventricular hypersignals could be confounded by age because such signals are seen in patients over the age of 40 years with leukoaraiosis. However, only 1/16 patients (6.3%) from the WMA subgroup with isolated periventricular hypersignals was over 40 years old. Furthermore,
the WMA and non-WMA subgroups were well-matched for age and cardiovascular risk factors. Moreover, in 14/16 patients (87.5%) these periventricular hypersignals were not isolated but associated with deep white matter hypersignals (4/16) or subcortical hypersignals (5/16). Of the 16 WMA patients, 13 also presented with an association of abnormal deep and subcortical white matter hypersignals, 8 presented with deep white matter hypersignals similar to what is seen in inflammatory disease such as multiple sclerosis. These morphological abnormalities were not related to any features of mastocytosis such as the sex ratio, mean duration of illness or history of treatments. An inflammatory (notably multiple sclerosis), infectious or tumoral disease could be stringently eliminated through extensive explorations in three patients.

In two of the three extensively explored patients, we also found hyperintensity ‘plaque-like areas’ on FLAIR sequences. One plaque-like area was localized in the frontal superior lobe and was mimicking a low-grade oligodendroglioma. A biopsy of the lesion was not very contributive as it was not possible to distinguish between oligodendroglioma tumor and inflammatory disease. The fact that no definite histological diagnosis was done in this patient, including the absence of mast cell infiltrate, does not exclude the role of mastocytosis in this lesion. Indeed, the recruitment and proliferation of inflammatory and glial cells could have occurred due to multiple sclerosis. These inflammatory and glial cells could have been seen in vasculitis diseases. Among the 16 patients, 7 presented with an association of abnormal deep and subcortical white matter hypersignals, 8 presented with deep white matter hypersignals similar to what is seen in inflammatory disease such as multiple sclerosis. These morphological abnormalities were not related to any features of mastocytosis such as the sex ratio, mean duration of illness or history of treatments. An inflammatory (notably multiple sclerosis), infectious or tumoral disease could be stringently eliminated through extensive explorations in three patients.

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interest, this patient received a diagnosis of panic disorder, a condition that resolved with antidepressant treatment (escitalopram 10 mg per day) and coincided with the disappearance of the right amygdalian lesion. This pattern is consistent with the potential involvement of amygdala dysfunction in panic disorder pathophysiology, with mast cells promoting anxiety through a direct anatomical relationship.

Increased perfusion in the putamen was specific to WMA mastocytosis patients. Both the WMA and putamen hyperperfusion might be related to a common mechanism such as inflammation and/or ischemia through mast cell activation. WMA might also disrupt the prefrontal and basal ganglia networks, linking cortical impairment in the prefrontal cortex by WMA and increased perfusion in the basal ganglia. In another...
dysconnectivity hypothesis, WMA might impair cortico-cortical connectivity, including long-range connectivity, resulting in working memory and attention impairment\(^{31,32}\) and eventually in cognitive efforts that basal ganglia perfusion would translate.\(^{33,34}\) Such a cortico-cortical impairment would be reminiscent of multiple sclerosis,\(^{35,36}\) in which cognitive symptoms and fatigue have a huge burden.\(^{36–38}\) We might also draw a link with another condition with high prevalence of fatigue, systemic lupus erythematosus, in which increased basal ganglia metabolism has been recently demonstrated in a cognitive paradigm,\(^{39}\) as well as with a similar pattern demonstrated in patients treated with interferon alpha.\(^{40,41}\) However, in contrast with observations in interferon alpha-treated patients, we found a negative correlation between putamen hyperperfusion and fatigue, as approximated by the motivation factor from the SCL90 depression dimension.\(^{33,34}\) This discrepancy might be related to chronic brain inflammation in mastocytosis patients, in contrast with early observations after only 4 to 6 weeks of interferon alpha treatment.\(^{40,41}\) If putamen activation in an inflammatory context initially correlates with fatigue, a persistent activation with chronic inflammation might conversely allow compensating the sickness behavior related to the inflammation.

Consistent with the inflammation hypothesis, we have recently shown that in mastocytosis, tryptophan catabolism is disturbed.\(^{32}\) Indeed, patients display a low level of tryptophane and serotonin associated with a higher IDO1 activity resulting in higher kynurenic and mostly quinolinic acid levels. These alterations correlate with perceived stress and depression, demonstrating mast cell involvement in inflammation pathways associated with depression. It remains to be determined whether or not these metabolic changes are correlated and/or responsible for the MRI abnormalities.

Although exploratory, the region of interest analysis hints at decreased perfusion in the sgACC of depressed versus non-depressed mastocytosis patients, consistent with the key role attributed to the sgACC in the pathophysiology of depression in the literature (for reviews, see refs 21–23; and for a causal role demonstration through deep brain stimulation, see ref. 24). However, it is noteworthy that despite early demonstrations of decreased activity or perfusion, as in our results, most neuroimaging studies demonstrated an increased activity. This result might be related to the clinical characteristics of depression in mastocytosis patients that further studies with a larger sample could determine. Reduced cingulate activity following infarcts or surgery is known to contribute to behavioral disorders including akinetic mutism, diminished self-awareness and depression, motor neglect and impaired motor initiation.\(^{23}\) Indeed, the strong negative correlation between sgACC perfusion and the motivation factor from the SCL90 depression dimension (everything seems to be an effort) argue for a relation between sgACC hypoperfusion and lack of motivation or energy, consistent with the crucial involvement of the cingulate cortex in motivating and ‘energizing’ behavior.\(^{45}\)

In conclusion, we found certain morphological and functional brain abnormalities to be associated with mastocytosis. It remains to be elucidated whether and how mastocytosis causes these abnormalities and whether these abnormalities are specific to mastocytosis patients featuring these neuropsychiatric symptoms. Further studies with larger groups of patients are warranted to confirm these results, along with therapeutic studies to evaluate the correlation between clinical/biological and morphological/ perfusion brain changes.

**CONFLICT OF INTEREST**

RG has received compensation as a member of the scientific advisory board of Janssen, Lundbeck, Roche and Takeda. He has served as a consultant and/or speaker for Astra Zeneca, Pierre Fabre, Lilly, Otsuka, SANOFI, Servier and received compensation, and he has received research support from Servier. OH received research funding and honorarium from AB Science, and research grant from Novartis, Celgene, Hybirogenics, Inatheys Bristol Myer Squibb and Takeda. The remaining authors declare no conflict of interest.

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