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HOMA-IR increase after antidepressant treatment in depressed patients with the Met allele of the Val66Met BDNF genetic polymorphism

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Abstract

Background. The brain-derived neurotrophic factor (BDNF) Val66Met polymorphism is associated with response to antidepressant drugs in depressed patients and with metabolic side effects after antipsychotic treatment. This study aims to assess the association between this polymorphism and insulin resistance after antidepressant treatment in depressed patients.

Methods. One hundred forty-eight Caucasian patients with a current unipolar major depressive episode (DSM IV-TR) were genotyped for the BDNF Val66Met polymorphism and assessed at baseline and after 3 and 6 months of antidepressant treatment for the 'Homoeostasis model assessment of insulin resistance' (HOMA-IR) index, a valid measure of insulin resistance based on fasting plasma insulinaemia and glycaemia. Because validity assumptions were fulfilled, data were analysed using analysis of variance for repeated measures.

Results. The 52 (35%) Met carriers and 96 (65%) Val/Val patients were not different at baseline for clinical characteristics and HOMA-IR. A significant Val66Met × time interaction ($p = 0.02$), a significant time effect ($p = 0.03$) and a significant Val66Met effect ($p = 0.0497$) were shown for HOMA-IR. A significant Val66Met × time interaction ($p = 0.01$) and a significant time effect ($p = 0.003$) were shown for fasting glycaemia. HOMA-IR and fasting glycaemia changes after antidepressant treatment were significantly higher in Met carrier than in Val/Val patients (HOMA-IR changes: Met: 0.71 ± 3.29 *v.* Val/Val: -0.16 ± 1.34, $t = 2.3$, df = 146, $p = 0.02$, glycaemia changes: Met: 0.09 ± 0.30 *v.* Val/Val: 0.02 ± 0.16, $t = -2.0$, df = 146, $p = 0.045$).

Conclusions. The Met allele of the Val66Met BDNF polymorphism confers to depressed patients a higher risk of insulin-resistance after antidepressant treatment. These patients could benefit from specific monitoring of metabolism and preventive measures.

Introduction

Major depressive disorder (MDD) is the second worldwide cause of disability (Global Burden of Disease Study, 2015) and is associated with insulin resistance (Alberti *et al.*, 2005; Nicholson *et al.*, 2006; Lee *et al.*, 2017; Penninx, 2017). Insulin-resistance, the physiopathological phenomenon in which cells fail to respond normally to insulin, is associated with diabetes, metabolic syndrome and cardiovascular events (Laakso and Kuusisto, 2014). In clinical samples, insulin-resistance can be easily measured using the homoeostasis model assessment of insulin resistance index (HOMA-IR) (Matthews *et al.*, 1985), using fasting plasma glucose level and fasting plasma insulin level (Matthews *et al.*, 1985).

Antidepressant drugs, the main treatments for MDD, may increase insulin-resistance (Serodio *et al.*, 2014; Corruble *et al.*, 2015). Indeed, in the general population, Serodio *et al.* (2014) showed a higher HOMA-IR in individuals receiving tricyclic antidepressants (TCAs). Our team has shown that, in depressed patients, antidepressants could induce an increase

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of fasting plasma glucose levels (Corruble *et al.*, 2015). However, the predictive factors of insulin-resistance after antidepressant initiation remain unknown. Thus, identifying predictive biomarkers of insulin-resistance after antidepressant treatment is an important challenge to prevent insulin-resistance after antidepressant treatment.

The brain-derived neurotrophic factor (BDNF) pathway is a key factor for antidepressant treatment effects. Its expression is increased by antidepressant drug treatments (Nibuya *et al.*, 1995; Duman and Monteggia, 2006; Castren and Rantamaki, 2010). Furthermore, BDNF treatment decreases glucose levels and insulin resistance in obese and diabetic rodents (Nakagawa *et al.*, 2000; Nakagawa *et al.*, 2002; Xu *et al.*, 2003; Unger *et al.*, 2007; Noble *et al.*, 2011; Eyileten *et al.*, 2017). And lower BDNF gene expression induces insulin resistance in mice (Kernie *et al.*, 2000). In humans, a biological and clinical impact has been described for a functional single-nucleotide polymorphism of the BDNF gene, the Val66Met polymorphism (rs6265). It results in a valine substitution instead of a methionine residue, affecting cellular trafficking and secretion of BDNF, and resulting in an alteration of neurogenesis and synaptogenesis (Egan *et al.*, 2003; Castren and Rantamaki, 2010). In the general population, the association of the Val66Met BDNF polymorphism with metabolic syndrome, and regulation of appetite, depends on sex and ethnicity (Gunstad *et al.*, 2006; Thorleifsson *et al.*, 2009; Wu *et al.*, 2010; Takeuchi *et al.*, 2011; Delahanty *et al.*, 2012; Hong *et al.*, 2012; Ma *et al.*, 2012; Xi *et al.*, 2013; Liu *et al.*, 2016). Of note, the Met allele may be associated with metabolic effects of antipsychotic drugs. Indeed, in 199 men with schizophrenia treated with clozapine, Zhang *et al.* (2013) found higher blood glucose levels in Met homozygous than in Val carriers patients (Zhang *et al.*, 2013). However, in depressed patients, we were unable to find studies assessing the association between the Val66Met BDNF polymorphism and insulin-resistance changes after antidepressant treatment.

The aim of this study was to assess the association between the BDNF Val66Met polymorphism and insulin-resistance after antidepressant treatment in depressed patients.

Materials and methods

Design

In a 6-month prospective, real-world setting, treatment study, Caucasian patients with a current unipolar major depressive episode (MDE) were assessed for insulin resistance at the beginning of antidepressant treatment (M0), and 3 (M3) and 6 months (M6) later.

Patients

One hundred forty-eight depressed patients from the METADAP cohort (ClinicalTrials.gov NCT00526383), aged 18–65 years, Caucasian, with a current MDE in a context of unipolar MDD (DSM-IV-TR), based on the Mini International Psychiatric Interview (MINI), with a minimum depression score of 18 on the Hamilton Depression rating Scale (HAMD) (Hamilton, 1960), and requiring an antidepressant treatment were included in this analysis. The Quick Inventory for Depressive Symptomatology, Clinician-Rated (QIDS-C) (Rush *et al.*, 2003) was used to assess atypical depression. It was defined by at least two features among the following: significant weight gain (item '9', score $\geqslant$1), significant increase in appetite (item '7', score$\geqslant$1) and hypersomnia (item '4', score $\geqslant$2).

Patients with diagnoses of bipolar disorder or psychotic disorder according to the DSM-IV-TR, with current substance dependence, eating disorder, unstable medical condition, pregnancy or breast feeding, were excluded.

Patients provided written informed consent for study participation and for genetic analyses.

They were treated with a monotherapy of antidepressant, from one of the following class of antidepressants: serotonin selective reuptake inhibitor, serotonin and norepinephrine reuptake inhibitor, TCA, or other antidepressants. The drug and the dose were chosen by the prescribing psychiatrist in naturalistic conditions, using 'real world' treatment options. Patients were not allowed to receive other antidepressants, antipsychotics, or mood stabilisers. Benzodiazepines were allowed at the minimum effective dose and for the minimum duration to treat symptoms like anxiety or insomnia.

Genotype

Genomic DNA was extracted from circulating blood leukocytes by using Gentra Puregene Blood Kits according to the manufacturer's protocol (Qiagen) and was stored at −20 °C. The Val66Met BDNF polymorphism (rs6265) was genotyped using TaqMan allelic discrimination (Coulbault *et al.*, 2006), with the ABI Prisms 7900HT Sequence Detection System (Life Technologies). The sequence of interest was amplified using the following primers: 5′-CTGTCTTGTTTCTGCTTTCTCCCT-3′ and reverse primer 5′-ACCCTCATGGACATGTTTGCA-3′. Wild type allele (Val) was detected using a 5′-CTTTCGAACACGTGATAG-3′ VIC-fluorescent probe. Mutant allele (Met) was detected using the 5′-ACTTTCGAACACATGATAGA-3′ FAM-fluorescent probe. For both genes reverse transcription-polymerase chain reaction was performed on a TaqMan ABI PRISMs 7000 sequence detection system (Applied Biosystems) for allelic discrimination.

Genotypic analyses were run blind to clinical evaluations.

Participants were classified into two groups: Val/Val and Met (Met/Met and Met/Val genotypes), on account of the dominant nature of the Met allele (Frodl *et al.*, 2007).

HOMA-IR

Fasting blood samples were collected for each participant at the beginning of the study, and after 3 and 6 months of antidepressant treatment, for assessment of fasting plasma glucose and insulin levels.

The HOMA-IR Index was the main end-point. It is a non-invasive and validated method for estimation of insulin resistance values assessed by reference methods (Matthews *et al.*, 1985; Serodio *et al.*, 2014). It is calculated based on the following formula:

HOMA-IR = fasting blood glucose levels (mM) × fasting blood insulin levels (mUI/L)/22.5 (Matthews *et al.*, 1985).

Statistical analysis

The statistical analyses were performed using R 3.4.2 and Statview 5.0.

The Val66Met BDNF polymorphism was the independent variable, Met patients being compared with Val/Val patients. The HOMA-IR was the main dependent variable.

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Table 1. Sample characteristics at baseline for the whole sample, Val/Val and Met subgroups

	Whole sample ($n = 148$)	Val/Val ($n = 96$)	Met ($n = 52$)	Comparison of Val/Val and Met P
Age (m ± s.d.)	47.2 ± 12.0	46.5 ± 12.2	48.4 ± 11.5	0.37
Women (%) (*n*)	63.5 (94)	65.6 (63)	59.6 (31)	0.47
Recurrent MDD (%) (*n*)	68.2 (101)	67.7 (65)	69.2 (36)	0.85
Previous antidepressant treatment (%) (*n*)	81.8 (121)	81.2 (78)	82.7 (43)	0.83
Inpatients (%) (*n*)	83.8 (124)	87.5 (84)	76.9 (40)	0.10
HAMD M0 (m ± s.d.)	23.2 ± 4.0	23.7 ± 4.3	22.4 ± 3.4	0.08
MDD duration years (m ± s.d.)	10.6 ± 12.6	10.9 ± 12.9	10.0 ± 12.2	0.66
Atypical depression (%) (*n*)	9.5 (14)	6.2 (6)	15.4 (8)	0.08
Remission M3 (%) (*n*)	32.4 (48)	30.2 (29)	36.5 (19)	0.43
Remission M6 (%) (*n*)	41.2 (61)	41.7 (40)	40.4 (21)	0.88
Antidepressant class (%) (*n*)				0.76
SSRI	37.2 (55)	39.6 (38)	32.7 (17)	
SNRI	42.6 (63)	44.2 (40)	44.2 (23)	
TCA	9.5 (14)	9.4 (9)	9.6 (5)	
Others	8.8 (12)	8.3 (8.3)	9.6 (5)	
HOMA-IR (m ± s.d.)	1.65 ± 1.54	1.63 ± 1.72	1.69 ± 1.16	0.83
Fasting plasma glucose (g/L) (m ± s.d.)	0.90 ± 0.17	0.90 ± 0.19	0.89 ± 0.12	0.67
Fasting plasma insulin (pg/mL) (m ± s.d.)	297.8 ± 237.0	287.2 ± 247.9	317.2 ± 216.3	0.47

m, mean; s.d., standard deviation; MDD, major depressive disorder; HAMD, Hamilton Depression Rating Scale 17 items; TCA, tricyclic antidepressants; SNRI, serotonin and norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; HOMA-IR, homoeostasis model assessment of insulin resistance index.

Bivariate analyses were performed to compare Met and Val/Val patients for socio-demographical and MDD characteristics at baseline.

The main criterion (HOMA-IR), and the secondary criteria (insulinaemia and glycaemia) are continuous repeated variables, which are measured at baseline before treatment and 3 and 6 months after treatment. Since data are continuous and repeated, they were analysed using mixed effect models (with Val66 Met polymorphism and time effects, and interactions between these two effects) and analysis of variances (ANOVAs) for repeated measures (with Val66 Met polymorphism and time effects, and interactions between these two effects), ANOVAs for repeated measure being a subtype of mixed effect models, which require specific validity conditions (independence of cases, normality of the residuals and equality or homogeneity of variances). Indeed, validity assumptions for ANOVAs for repeated measures (independence of cases, normality of the residuals and equality or homogeneity of variances) are fulfilled for the three criteria (HOMA-IR, insulinaemia and glycaemia). Accordingly, both mixed effect models and ANOVAs led to similar results and only results of ANOVAs for repeated measures are shown. In case of significant results for ANOVAs for repeated measures, changes from baseline after antidepressant treatment were compared between Met and Val/Val patients using *t* tests. The *p* values lower than 0.05 were considered significant.

Results

Sample characteristics

One hundred forty-eight patients were assessed for the HOMA-IR. Ninety-six (65%) were homozygous Val/Val, 52 (35%) were Met carriers [8 (5.5%) homozygous Met and 44 (29.5%) Val/Met]. No significant deviation from Hardy–Weinberg equilibrium was reported.

Characteristics of these patients are summarised in Table 1. Met and Val/Val groups did not differ for age, gender, socio-demographic characteristics, MDD clinical characteristics, antidepressant drug or remission rate (Table 1).

HOMA-IR

HOMA-IR, fasting blood glucose and fasting blood insulin levels at each time of the study are shown in Fig. 1.

The repeated measures ANOVA for HOMA-IR showed a significant Val66Met × time interaction ($F = 4.0$, df = 2, $p = 0.02$), a significant time effect ($F = 3.4$, df = 2, $p = 0.03$) and a significant Val66Met effect ($F = 3.9$, df = 1, $p = 0.0497$). Accordingly, the HOMA-IR change from baseline was significantly higher in Met carrier than in Val/Val patients (Met: 0.71 ± 3.29 *v.* Val/Val: −0.16 ± 1.34, $t = 2.3$, df = 146, $p = 0.02$).

The repeated measures ANOVA for fasting blood glucose levels showed a significant Val66Met × time interaction ($F = 4.4$, df = 2, $p = 0.01$), a significant time effect ($F = 5.8$, df = 2, $p = 0.003$), and no Val66Met effect ($F = 0.1$, df = 1, $p = 0.78$). Accordingly, the fasting blood glucose levels change from baseline was significantly higher in Met carrier than in Val/Val patients (Met: 0.09 ± 0.30 *v.* Val/Val: 0.02 ± 0.16, $t = -2.0$, df = 146, $p = 0.045$).

The repeated measures ANOVA for fasting blood insulin levels showed a significant Val66Met effect ($F = 4.7$, df = 1, $p = 0.03$), but no significant Val66Met × time interaction ($F = 1.6$, df = 2, $p = 0.21$) and no significant time effect ($F = 2.0$, df = 2, $p = 0.13$).

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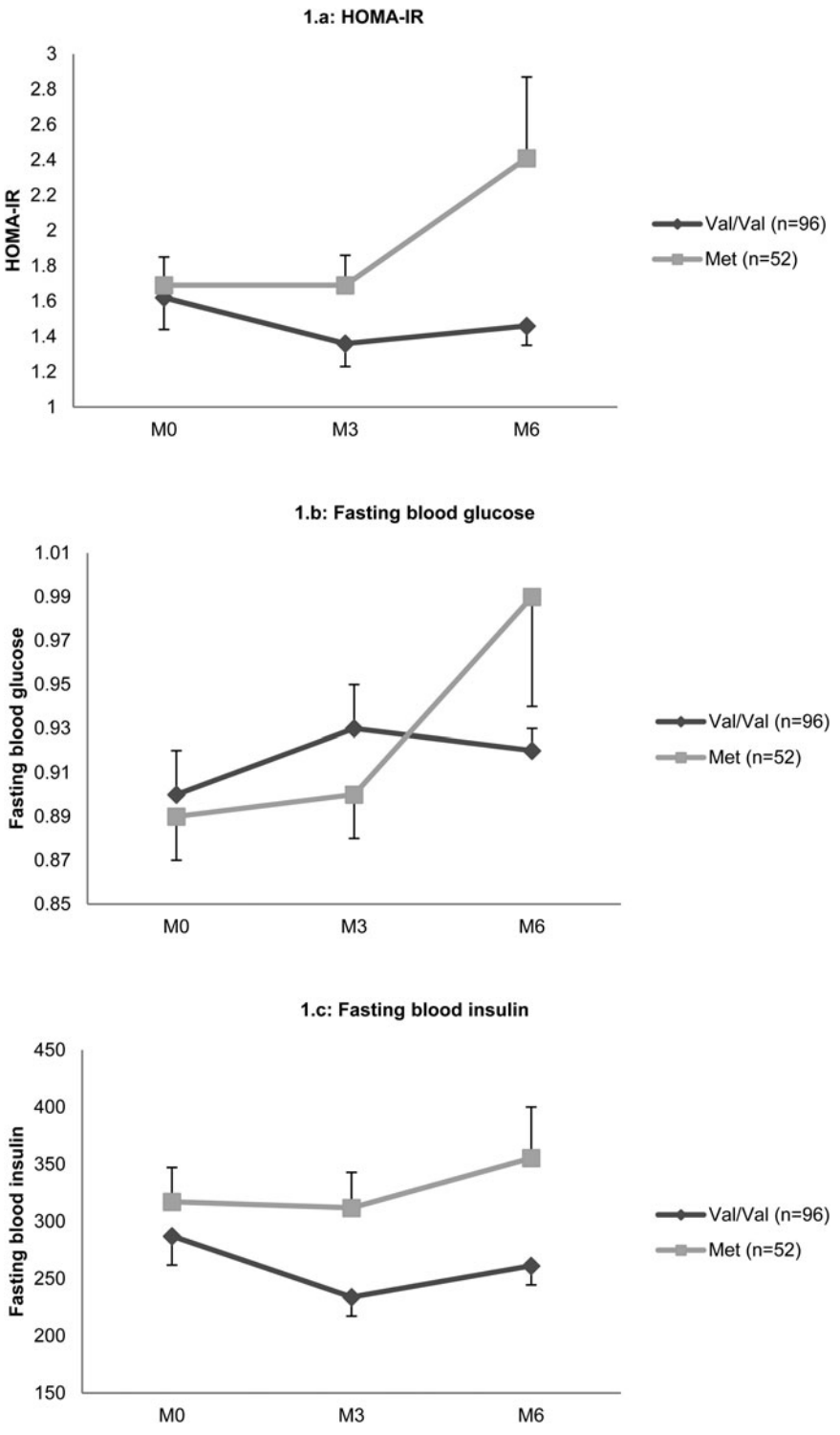

Fig. 1. Insulin resistance change over time. HOMA-IR, homoeostasis model assessment of insulin resistance index (m ± S.E.M.); fasting blood glucose level (m ± S.E.M.) (g/L); fasting blood insulin level (m ± S.E.M.) (pg/mL); M0, baseline; M3, after 3 months of antidepressant treatment; M6; after 6 months of antidepressant treatment.

This means that Met patients had higher plasma insulin levels than Val/Val, but that insulinaemia did not change significantly after treatment.

Discussion

The BDNF Val66Met polymorphism was investigated because it could affect both insulin resistance and response to antidepressant treatment. We show for the first time that the Met allele of the Val66Met BDNF polymorphism confers to depressed patients a higher risk of insulin resistance after antidepressant treatment. Indeed, as compared with Val/Val patients, Met carriers have higher plasma insulin levels and higher fasting blood glucose levels change after antidepressant treatment. Accordingly, HOMA-IR changes, reflecting insulin resistance changes after antidepressant treatment, are significantly higher in Met carrier than in Val/Val patients.

Our results are coherent with those of Serodio *et al.* (2014) who showed that individuals treated with TCAs have higher

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HOMA-IR scores (Serodio *et al.*, 2014). But our results go beyond these results since they highlight the impact of the Val66Met BDNF genetic polymorphism on HOMA-IR in depressed patients treated with antidepressant drugs.

Our results are also consistent with some data about antipsychotic drugs, which show that the Met allele (associated with an altered BDNF signalling) is a risk factor for development of metabolic abnormalities. Accordingly, in a transversal study of 199 Han Chinese schizophrenic patients treated with clozapine, Zhang *et al.* (2013) find that homozygous Met/Met males have 1.16 higher blood glucose levels than other genotypes (0.16 g/L, MetMet: 1.17 ± 0.27 g/L, ValMet: 1.01 ± 0.20 g/L, ValVal: 1.01 ± 0.27 g/L).Our study was prospective and reported a change of blood glucose level 4.5-fold higher in Met carriers as compared with Val/Val (Met: 0.09 ± 0.30 g/L *v.* Val/Val: 0.02 ± 0.16 g/L).

In this sample of depressed patients, the Met allele is a risk factor for insulin resistance after antidepressant treatment. Interestingly, the Met allele has been associated with altered BDNF signalling pathway, both in preclinical studies with BDNF functional loss in neurons (Castren and Rantamaki, 2010), and in depressed patients with lower BDNF plasma levels (Colle *et al.*, 2017). Besides, altered BDNF signalling pathway has been associated with insulin resistance and higher glucose levels in experimental investigations (Eyileten *et al.*, 2017). In rodents, alterations in the BDNF signalling pathway result in hyperglycaemia (Rios *et al.*, 2001) and BDNF effects may act by increasing insulin sensitivity in peripheral tissues (Tsuchida *et al.*, 2001; Nakagawa *et al.*, 2002). Our findings in depressed patients are consistent with preclinical studies in terms of the negative impact of altered BDNF signalling pathway (here the Met allele) on insulin sensitivity and on worse blood glucose control (Nakagawa *et al.*, 2000; Nakagawa *et al.*, 2002).

It is important to notice that depression itself is associated with a significantly increased risk of metabolic syndrome, type-2 diabetes and cardiovascular disease (Ossola *et al.*, 2015). Thus, improvement of major depression after treatment should lead to an insulin resistance decrease. But we show that insulin resistance worsens after antidepressant treatment despite depression score decrease. And our results are coherent with those of Penninx *et al.* (2013), who show that a MDE could induce a metabolic dysregulation, that persists after its remission. Consequently, our results, in line with those of Penninx *et al.* (2013), might be explained by the potential metabolic effects of antidepressant drugs prescribed to treat major depression.

This study has some limitations. First, the sample size, in particular for the Met subgroup, is rather small for a genetic study. Second, the results of a cohort study do not allow to conclude to a causal connection between antidepressants and insulin resistance. Thus, a randomised, double-blind, controlled study *v.* placebo should confirm these results. Besides, our study was performed in naturalistic conditions of prescription, in which physicians could choose the antidepressant drug according to several criteria, including metabolic ones. However, our main criterion was biological and assessed independently from the treating psychiatrists. Third, the study of Lee *et al.* (2013) reported a significant dose-effect of the Met allele on chronicity of depression in Asian patients. We failed to show this association in Caucasian patients. Fourth, an association between atypical features of major depression (increased appetite or weight gain, increased sleep) (Stewart *et al.*, 2007) at baseline and the Met allele of the Val66Met polymorphism may have explained our results. However, the lack of statistical significant association between the Met allele and atypical features on the one hand and the lack of difference of fasting glycaemia at baseline between Met and Val/Val patients do not favour this hypothesis. Nonetheless, further studies are needed in this field.

The main strength of this study is that it assesses for the first time insulin-resistance in depressed patients prospectively treated with antidepressants in association with the Val66Met BDNF polymorphism assessment. Met carriers of the Val66Met polymorphism treated with antidepressant drugs for a MDE have a higher risk to develop insulin resistance after antidepressant treatment. If these results could be confirmed, these subjects should benefit from intensified metabolic monitoring, and strategies for cardiometabolic prevention, including specific dietary strategies, systematic interventions of nutritionists and/or physical activity programmes.

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Conflict of interest. Severine Martin, Romain Colle, Céline Verstuyft and Emmanuelle Corruble have no conflict of interest.

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