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ORIGINAL ARTICLE

Sex differences in imaging and clinical characteristics of patients from the WAKE-UP trial

Anke Wouters[1,2,3] | Lauranne Scheldeman[2,3,4] | Hannelore Liessens[4] | Patrick Dupont[5,6] | Florent Boutitie[7] | Bastian Cheng[8] | Martin Ebinger[9,10] | Matthias Endres[9,11,12,13,14] | Jochen B. Fiebach[9] | Christian Gerloff[8] | Keith W. Muir[15] | Norbert Nighoghossian[16] | Salvador Pedraza[17] | Claus Z. Simonsen[18] | Vincent Thijs[19,20] | Götz Thomalla[8] | Robin Lemmens[2,3,4]

[1]Neurology, Amsterdam University Medical Centers location AMC, Amsterdam, the Netherlands

[2]Department of Neurosciences, Experimental Neurology, KU Leuven – University of Leuven, Leuven, Belgium

[3]Center for Brain & Disease Research, Laboratory of Neurobiology, VIB, Leuven, Belgium

[4]Department of Neurology, University Hospitals Leuven, Leuven, Belgium

[5]Department of Neurosciences, Laboratory for Cognitive Neurology, KU Leuven – University of Leuven, Leuven, Belgium

[6]Leuven Brain Institute, Leuven, Belgium

[7]Hospices Civils de Lyon, Service de Biostatistique, Université Lyon, Lyon, France

[8]Klinik und Poliklinik für Neurologie, Kopf- und Neurozentrum, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany

[9]Center for Stroke Research Berlin (CSB), Charité – Universitätsmedizin Berlin, Berlin, Germany

[10]Klinik für Neurologie, Medical Park Berlin Humboldtmühle, Berlin, Germany

[11]Klinik und Hochschulambulanz für Neurologie, Charité– Universitätsmedizin Berlin, Berlin, Germany

[12]German Center for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany

[13]German Center for Neurodegenerative Diseases (DZNE), partner site Berlin, Berlin, Germany

[14]ExcellenceCluster NeuroCure, Berlin, Germany

[15]Institute of Neuroscience & Psychology, University of Glasgow, Glasgow, UK

[16]Department of Stroke Medicine, Université Claude Bernard Lyon 1; Hospices Civils de Lyon, Lyon, France

[17]Department of Radiology, Institut de Diagnostic per la Image (IDI), Hospital Dr Josep Trueta, Institut d'Investigació Biomedica de Girona (IDIBGI), Parc Hospitalari Marti i Julia de Salt – Edifici M2, Girona, Spain

[18]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

[19]Stroke Theme, Florey Institute of Neuroscience and Mental Health, University of Melbourne, Heidelberg, Victoria, Australia

[20]Department of Neurology, Austin Health, Heidelberg, Victoria, Australia

Correspondence
Anke Wouters, Herestraat 49, 3000 Leuven, Belgium.
Email: anke.wouters@kuleuven.be

Abstract

Background and purpose: Sex-based differences in acute ischemic stroke are a well-known phenomenon. We aimed to explore these differences between women and men in the Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial.

Methods: We compared baseline demographic and imaging characteristics (visual fluid-attenuated inversion recovery [FLAIR] positivity, relative FLAIR signal intensity, collateral status) between women and men in all screened patients. In randomized patients (i.e., those with

Anke Wouters and Lauranne Scheldeman contributed equally.

diffusion-weighted imaging (DWI)–FLAIR mismatch), we evaluated a modifying role of sex on the treatment effect of alteplase in multivariable logistic regression, with treatment adjusted for National Institute of Health Stroke Scale (NIHSS) score and age. Dependent variables were modified Rankin Scale (mRS) score of 0–1 at 90 days and distribution of mRS scores at 90 days.

Results: Of 1362 screened patients, 529 (38.8%) were women. Women were older than men, had higher baseline NIHSS scores and smoked less frequently. FLAIR positivity of the DWI lesion was equally present in women (174/529, 33.1%) and men (273/833, 33.3%; $p = 1.00$) and other imaging variables also did not differ between the sexes. In a total of 503 randomized patients, of whom 178 were women (35.4%), sex did not modify the treatment effect of alteplase on mRS score 0–1 or on the total distribution of mRS scores.

Conclusion: As in many other stroke trials, more men than women were included in the WAKE-UP trial, but the presence of a visual DWI–FLAIR mismatch and the relative FLAIR signal intensity did not differ between the sexes. The treatment effect of alteplase was not modified by sex.

KEYWORDS
ischemic stroke, sex, MRI, wake-up

INTRODUCTION

Sex-based differences in the acute stroke setting have been described. Women more often present with non-typical and more severe stroke symptoms and with stroke mimics [1–4]. Furthermore, they may have longer delays from stroke onset to emergency department arrival as well as longer door-to-imaging times, and receive treatment with alteplase less often, despite having no difference in overall treatment eligibility [5–15]. Visual fluid-attenuated inversion recovery (FLAIR) positivity and the relative FLAIR (rFLAIR) signal intensity within the area of a diffusion-weighted imaging (DWI) lesion are related to the time from symptom onset [16, 17]. Therefore differences between men and women with regard to these imaging variables in unknown stroke onset patients could be assumed but are unknown. Furthermore, men and women have similar outcomes after treatment with intravenous recombinant tissue plasminogen activator, but a stronger treatment effect may exist in women and they might have worse outcomes if acute stoke is untreated [18–21]. However, there is substantial between-study variability and more recent studies suggest that the gap between men and women has narrowed over recent years [6, 10]. In this post hoc analysis of the Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial [22], we explored sex-based differences in baseline imaging (FLAIR lesion, DWI lesion, rFLAIR signal intensity and quality of collateral circulation) and clinical characteristics in screened patients, and outcome in randomized women versus men.

PATIENTS AND METHODS

Study design and patient population

In this post hoc analysis, we studied sex-based differences in demographic, clinical, and imaging baseline characteristics and clinical outcome in patients screened and randomized in the WAKE-UP trial. The WAKE-UP trial was a multicenter, randomized, double-blind, placebo-controlled trial, designed to investigate if patients with an unknown time of stroke onset benefit from thrombolysis in the presence of a DWI–FLAIR mismatch [22]. Patients or their legal representatives provided written informed consent according to national and local regulations. The trial was approved for each study site by the competent authorities and the corresponding ethics committee. Patients were screened for the presence of a DWI–FLAIR mismatch with magnetic resonance imaging (MRI; screened patients) and randomized to placebo or alteplase if this mismatch was present (randomized patients). Only randomized patients received follow-up with imaging at 24–36 hours and documentation of clinical outcome.

Analysis of imaging characteristics

As in the original WAKE-UP trial, acute MRI images of the screened patients were visually rated for the presence of a DWI-positive lesion on the B1000 images and for a FLAIR hyperintense signal (i.e., FLAIR-positive) within the region of the acute stroke. The DWI–FLAIR mismatch was defined as a DWI-positive lesion with no signal alterations on the FLAIR [22]. Furthermore, we investigated the maturation of the FLAIR lesion in men versus women in screened patients in the WAKE-UP trial who had FLAIR of sufficient quality at baseline available. The rFLAIR signal intensity was calculated as described previously [23]. To summarize, the rFLAIR signal intensity was calculated as the ratio of the FLAIR signal intensity in one voxel and median FLAIR signal intensity of all voxels within a sphere with radius of 15 mm around a homologue voxel in the contralateral hemisphere. We defined the ischemic core lesion and its volume using RAPID software, which calculates the ischemic core lesion based on the apparent diffusion coefficient threshold $<620\times10^{-6}\text{mm}^2/\text{s}$.

Only patients with a core lesion volume >10 ml were included for further analysis.

To investigate sex-based differences in the quality of the collateral circulation, we studied the hypoperfusion intensity ratio (HIR) in patients screened in the WAKE-UP trial who also underwent perfusion-weighted imaging [24, 25]. We used RAPID software (iSchemaView) to calculate the perfusion lesion, defined as tissue with a time to the maximum of the residue function (Tmax) of >6 s. For patients with a minimal perfusion lesion of 10 ml, we calculated the HIR as the ratio of the lesion volume with Tmax >10 s and the lesion volume with a Tmax >6 s. We dichotomized the HIR at a threshold of 0.5 to define collateral status: <0.5 as an indicator of good and ≥0.5 of poor collaterals [25].

Statistical analysis

The baseline characteristics were compared between men and women in the screened and randomized population using two-sample *t*-tests for parametric data, Wilcoxon rank-sum tests for non-parametric data, and chi-squared tests for categorical data.

In randomized patients (i.e., those with the DWI–FLAIR mismatch), we evaluated the influence of sex on treatment effect of alteplase in multivariable logistic regression with treatment, sex and their interaction term as independent variables (adjusted for NIHSS score >10 and age >60 years, as in the original trial) [22] to predict good outcome, defined as a score on the modified Rankin Scale (mRS) of 0–1 at 90 days, and mortality at 90 days. The categorical shift in distribution of the mRS scores was studied with proportional odds logistic regression analysis, adjusted for the same variables. *p* values < 0.05 were taken to indicate statistical significance. All the analyses were conducted in R.

RESULTS

Baseline demographic, clinical and imaging characteristics in screened patients

In the population of 1,362 screened patients, more men (833; 61.2%) were screened than women ($p < 0.01$). Women were older, had higher baseline NIHSS score, higher baseline mRS score and smoked less frequently (Table 1). Furthermore, they presented more often with aphasia compared to men (9.3% vs. 5.3%; $p = 0.01$). A trend towards a lower proportion of women being randomized compared to men was not statistically significant (178/529 women, 33.6% vs. 325/833 men, 39.0%; $p = 0.05$). The presence of a hyperintense FLAIR signal within the DWI lesion did not differ between women (174/529, 33.1%) and men (273/833, 33.3%; $p = 1.00$). Also, the proportion of screened patients without a DWI-positive lesion was similar between the sexes (27.6% of women vs. 24.6% of men; $p = 0.52$; Table 1).

TABLE 1 Baseline characteristics of the screened patients.

	Women ($n = 529$)	Men ($n = 833$)	*p* value
Age, years	70 (61–76)	67 (57–74)	<0.01
Arterial hypertension	288 (54.9%)	421 (50.9%)	0.30
Atrial fibrillation	47 (9.0%)	60 (7.3%)	0.53
Hypercholesterolemia	157 (29.9%)	272 (32.9%)	0.52
Type 2 diabetes	75 (14.3%)	149 (18.3%)	0.20
Smoking	89 (18.4%)	223 (29.6%)	<0.01
Pre-stroke mRS score			0.04
0	422 (80.1%)	698 (84.9%)	
1	99 (18.8%)	112 (13.6%)	
2	2 (0.4%)	7 (0.9%)	
3	3 (0.6%)	1 (0.1%)	
4	1 (0.2%)	4 (0.5%)	
Median NIHSS score	7 (4–12)	5 (3–9)	<0.01
Reason for unknown time of symptom onset			0.03
Night-sleep	445 (85.1%)	734 (88.9%)	
Day-sleep	20 (3.8%)	24 (2.9%)	
Aphasia	49 (9.3%)	44 (5.3%)	
Other	5 (1.0%)	16 (1.9%)	
Randomization rate	178 (33.6%)	325 (39.0%)	0.05
FLAIR positivity	174 (33.1%)	273 (33.3%)	1.00
DWI negativity	97 (27.6%)	125 (24.6%)	0.52

Note: Data are median (IQR) or *n* (%).

Abbreviations: DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; IQR, interquartile range; mRS, Modified Rankin Scale; NIHSS, National Institute Health Stroke Scale.

Analysis of the rFLAIR signal intensity (as a proxy of time from symptom onset to imaging) was successful in 307 patients with minimal core lesion of 10 ml. The mean rFLAIR signal intensity did not differ in women (ratio 1.08, interquartile range [IQR] 1.05–1.13) versus men (ratio 1.07, IQR 1.03–1.12; $p = 0.31$).

Of 1,362 screened patients, 186 had successful RAPID analysis of perfusion-weighted imaging and a minimal Tmax >6 s lesion of 10 ml. An HIR ≥0.5 suggestive of poorer collateral status did not differ significantly between men and women (40/110 women, 36.3%, vs. 22/76 men, 28.9%; $p = 0.37$).

Patient characteristics, outcome and treatment effect in randomized patients

Of 503 randomized patients, 178 were female (35.4%). Baseline and outcome characteristics for men and women are presented in Table 2. Similarly to the screened population, women were older, had higher baseline NIHSS scores and smoked less frequently. Of all

TABLE 2 Baseline and outcome characteristics of the randomized patients.

	Women (n = 178)	Men (n = 325)	p value
Age, years	70 (63–76)	67 (58–73)	0.02
Arterial hypertension	101 (56.7%)	165 (50.8%)	0.20
Atrial fibrillation	29 (16.3%)	30 (9.2%)	0.06
Hypercholesterolemia	67 (37.6%)	111 (34.2%)	0.38
Type 2 diabetes	24 (13.5%)	58 (17.8%)	0.13
Smoking	42 (24.1%)	91 (29.2%)	0.01
Median NIHSS score	7 (4–11)	5 (3–9)	0.01
Reason for unknown time of symptom onset			0.67
Night-sleep	156 (87.6%)	293 (90.2%)	
Day-sleep	10 (5.6%)	13 (4.0%)	
Aphasia	9 (5.1%)	12 (3.7%)	
Other	3 (1.7%)	7 (2.1%)	
Treatment with IV rtPA	89 (50.0%)	165 (50.8%)	0.94
Core volume at baseline, ml[a]	2.5 (0.96–11)	2.1 (0.73–7.5)	0.14
mRS score[b]	2 (1–3)	2 (1–3)	0.69
mRS score 0–1[b]	76 (44.2%)	157 (49.4%)	0.32
Mortality[b]	5 (2.9%)	8 (2.5%)	1.00
Hemorrhage type PH1[c]			
Overall	6 (3.4%)	7 (2.2%)	0.36
Group with IV rtPA	3 (3.4%)	4 (2.4%)	0.83
Hemorrhage type PH2[c]			
Overall	2 (1.1%)	8 (2.5%)	0.29
Group with IV rtPA	1 (1.1%)	8 (4.8%)	0.28

Note: Data are median (IQR) or *n* (%).

Abbreviations: IQR, interquartile range; IV rtPA, intravenous recombinant tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institute Health Stroke Scale.

[a]Fourteen patients had missing data.

[b]Thirteen patients were lost to follow-up. Outcome parameters were assessed at Day 90.

[c]Seven patients had missing data.

randomized patients, 249 received placebo (35.7% women, 64.3% men) and 254 received recombinant tissue plasminogen activator (35.0% women, 65.0% men). No day 90 outcome was available for 13 patients lost to follow-up. There was no difference between women and men in the rate of good outcome (44.2% vs. 49.4%; $p = 0.32$), in mortality (2.9% vs. 2.5%; $p = 1.00$) or in the distribution of mRS scores at 90 days (adjusted odds ratio [aOR] 1.14, 95% confidence interval [CI] 0.82–1.60; Figure 1). Although the effect of thrombolysis on mRS score 0–1 was significant in men (aOR 1.79 95% CI 1.10–2.91; $p = 0.02$) but not in women (aOR 1.36, 95% CI 0.74–2.59; $p = 0.35$), sex did not modify the treatment effect of alteplase on mRS score 0–1 ($p = 0.57$ for interaction) or on the total distribution of the mRS scores ($p = 0.75$ for interaction; Figure 2).

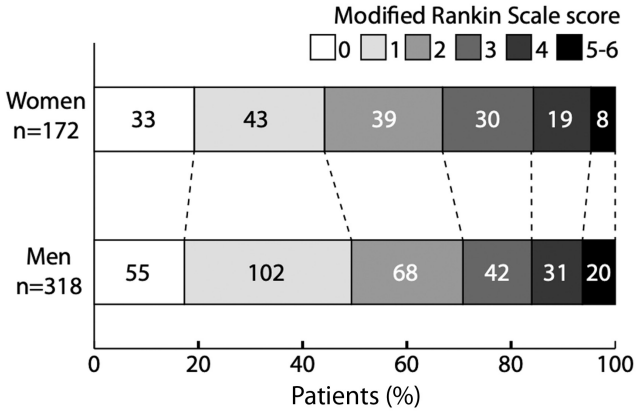

FIGURE 1 Distribution of scores on the modified Rankin Scale (mRS) at 90 days. Differences in mRS scores at 90 days among women versus men randomized in the WAKE-UP trial. Numbers indicate the absolute numbers of patients. There was no significant difference between the two groups when adjusted for age, National Institute of Health Stroke Scale score and treatment with alteplase (adjusted odds ratio 1.14, 95% confidence interval 0.82–1.60).

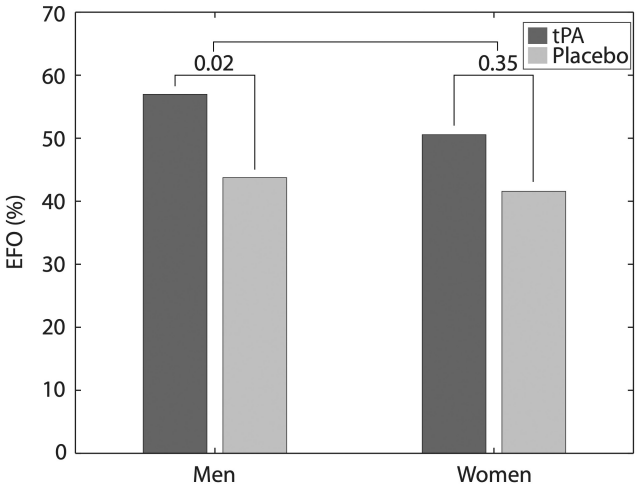

FIGURE 2 Excellent functional outcome (EFO) and effect of thrombolysis. Percentage of patients with an EFO (modified Rankin Scale [mRS] score 0–1) for men versus women treated or not treated with intravenous thrombolysis (tissue plasminogen activator [tPA]). The effect of tPA on excellent functional outcome was not significantly different between the sexes (adjusted odds ratio [aOR] for women 1.36, 95% confidence interval [CI] 0.74–2.59 [$p = 0.35$]; aOR for men 1.79, 95% CI 1.10–2.91 [$p = 0.02$, p-value for interaction = 0.57]).

DISCUSSION

In this post hoc analysis of the WAKE-UP trial, we found that the proportion of women screened for inclusion in the trial was lower compared to men. Moreover, women were older, had increased stroke severity at admission and smoked less often than men. Presence of DWI–FLAIR mismatch was similar in women and men and there

were similar proportions of patients that had no DWI lesion on baseline imaging. Also, we found no difference in other imaging variables, such as rFLAIR signal intensity and quality of the collateral circulation. Outcomes were similar between men and women, and sex did not modify the treatment effect of alteplase on clinical outcome.

The literature consistently reports that women are older at stroke onset [2, 4, 26]. The most obvious explanation is that women live longer than men, in concert with a higher incidence of stroke with aging. The higher severity of stroke on admission has been attributed to women more often presenting with proximal occlusions, anterior circulation stroke and cardio-embolic strokes, which are more frequently severe compared to other stroke mechanisms [13, 27, 28]. Another explanation might be older age and women more often having worse premorbid functional status [8, 28]. In our population of screened patients, women were indeed older and presented with a higher pre-stroke mRS score. Furthermore, women presented more often with aphasia, possibly reflected in the higher NIHSS score. This sex disparity regarding language disturbance at presentation has been described previously [29, 30]. A smaller stroke lesion volume threshold to cause aphasia for women as compared to men has been postulated as a potential cause [31]. The lower incidence of smoking in female WAKE-UP patients is also consistent with previous literature [32]. Despite the non-significant results in our study, there was also a trend towards a higher frequency of hypertension and atrial fibrillation in women, as described in the literature [5, 8].

Collateral circulation as assessed by the HIR was not different between women and men. A recent study showed better collaterals in women, associated with better functional outcome. Women had smaller perfusion lesions, less ischemic growth, and smaller final infarct volumes [33]. Similar results of better collateral circulation, smaller baseline core volumes, and slower ischemic core growth among women were reported in DEFUSE 3 [34]. In WAKE-UP, we included a more heterogeneous population. Many patients had small DWI and perfusion lesions and only approximately one-third of patients presented with large vessel occlusions, hampering a robust analysis of collateral status by sex [22].

Fewer women than men were screened with MRI for the presence of a DWI–FLAIR mismatch. One explanation for this could be that women are older when presenting with stroke, exceeding the upper age limit of 80 years as defined by the inclusion criteria in the original WAKE-UP trial. Furthermore, poorer premorbid functionality similarly could have led to exclusion of more women than men because WAKE-UP excluded patients with an mRS score >1 [28]. Also the number of women presenting with a wake-up stroke could have been lower compared to men due to different stroke mechanisms. However, because data are lacking on the total number of women presenting to the sites during the trial, this remains speculative. Since sites did not document reasons for not screening patients with unknown stroke onset, the possibility of more atypical symptoms and more risk averseness in women compared to men, although reported by others, could not be assessed [26, 35]. A higher frequency of stroke mimics could be a possible explanation for fewer women being randomized in an MRI-based stroke study. However, in our analysis, lack of DWI lesion as a reason for exclusion was equal between the sexes, which suggests similar presentation of stroke mimics (although some of these patients could have had transient ischemic attacks without a DWI lesion). An overview of sex representation in different fields of stroke research found a similar under-representation of women [36]. The average percentage of female participants is approximately 40% but the reasons for this under-representation in randomized controlled stroke trials has not been extensively investigated [32]. More equal sex representation in randomized controlled trials is desirable but in order to achieve this, better understanding of the factors that limit participation of women is needed. Our data indicate no difference in eligibility based on imaging features.

The presence of a DWI–FLAIR mismatch was equal in women and men. As reports exist on longer times from stroke onset to emergency department arrival in women, we explored the visual FLAIR positivity and rFLAIR signal intensity within the DWI lesion because this is known to increase with time after symptom onset [9, 17]. However, we did not identify more FLAIR-positive lesions, neither did we identify an increase in the rFLAIR signal intensity in women, arguing against a delay between stroke onset to time of imaging in women with wake-up stroke.

The treatment effect of alteplase on clinical outcome in patients with unknown onset of stroke and a DWI–FLAIR mismatch was not modified by sex. The rate of excellent functional outcome and mortality was comparable between men and women. There is heterogeneity in the literature about the differences in outcome or effect of alteplase between men and women. Some authors report similar outcomes at hospital discharge and 90-day survival [4, 19], whereas others report worse functional outcome [27] and higher mortality rate in women [5], or even a more favourable in-hospital recovery in women compared to men and higher likeliness of favourable functional outcome at discharge [13]. Different pathophysiological and hormonal-based theories are described to explain the sex differences [19, 20, 27]. Interestingly, sex differences were no longer present in many studies after correction for age, stroke severity and premorbid function [28]. In the WAKE-UP trial, an upper age limit of 80 years and minimal premorbid functionality state were predefined inclusion criteria, possibly reducing the confounding effect of these variables. Furthermore, the analysis of the interaction between sex and treatment effect was adjusted for age and NIHSS score. This revealed the lack of a modifying effect of sex on clinical outcomes in this population.

Our study has some limitations. First of all, we had no insights into the rationale of each local investigator to decide not to screen patients with unknown stroke onset time with MRI, nor on the total number of female stroke patients presenting to the different study sites. Furthermore, we only had outcome data from the population of randomized patients because screened patients had no follow-up after documentation of the absence of a DWI–FLAIR mismatch. Therefore, we cannot exclude sex-based variation in outcome for wake-up stroke patients without the DWI–FLAIR mismatch at

admission. In the population of randomized patients, subgroups may have been too small to study the treatment effect of alteplase in men and women separately.

In conclusion, in the WAKE-UP trial, fewer women than men were included in MRI screening. Women were older, had higher pre-stroke mRS scores, higher NIHSS scores at admission, and smoked less frequently. Imaging characteristics did not differ between the sexes. In this post hoc analysis, there was no effect of sex on the clinical outcome after treatment with alteplase.

AUTHOR CONTRIBUTIONS

Anke Wouters: Conceptualization; Investigation; Writing—original draft; Methodology; Visualization. Lauranne Scheldeman: Investigation; Writing—original draft; Methodology; Conceptualization; Visualization. Hannelore Liessens: Writing—original draft; Conceptualization. Patrick Dupont: Writing—review and editing; Methodology. Florent Boutitie: Writing—review and editing; Methodology. Bastian Cheng: Writing—review and editing; Data curation. Martin Ebinger: Writing—review and editing. Matthias Endres: Writing—review and editing. Jochen B Fiebach: Writing—review and editing. Christian Gerloff: Writing—review and editing. Keith W Muir: Writing—review and editing. Norbert Nighoghossian: Writing—review and editing. Salvador Pedraza: Writing—review and editing. Claus Z Simonsen: Writing—review and editing. Vincent Thijs: Writing—review and editing. Götz Thomalla: Writing—review and editing. Robin Lemmens: Writing—review and editing; Supervision; Methodology; Conceptualization; Investigation.

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CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Anke Wouters https://orcid.org/0000-0001-5229-2699
Lauranne Scheldeman https://orcid.org/0000-0002-5263-3550
Keith W. Muir https://orcid.org/0000-0001-9535-022X
Norbert Nighoghossian https://orcid.org/0000-0003-0594-4409

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