



ORIGINAL ARTICLE

Clinical predictors of incident somatic morbidity in a sample of depressed patients: A 16–30 years follow-up study



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KEYWORDS

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Abstract

Background and objectives: We investigated the independent associations between various characteristics at trial entrance and subsequent development of somatic morbidity in patients participating trials on antidepressants.

Methods: 338 in-patients diagnosed with major depression who had participated in trials on antidepressants conducted between 1983 and 1994 were followed for up to 30 years in Danish registers. By applying a Cox regression model with incident diagnoses of somatic disease as outcome, explanatory variables such as age at first episode, duration of index episode, bipolarity and scores on the Hamilton Depression Scale and subscales hereof, were investigated.

Results: Cardiovascular diseases were associated with increasing number of previous depressive episodes at baseline (HR 1.06, 95% CI (1.00–1.11)). The risk of diabetes was associated with increasing duration of index episode (HR 1.01, 95% CI (1.00–1.01) as was respiratory disease (HR 1.00, 95% CI (1.00–1.01)). Diagnoses of infection were associated with increasing score on HAM-D₆ (HR 1.11, CI 95 % (1.01–1.22)).

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Conclusions: The association between number of previous depressive episodes and CVD is in line with previous results. The findings of associations between the psychometric measures and specific diseases should be interpreted with caution, as well as the associations between duration of episodes, higher severity and higher number of previous episodes, and increased risks of somatic morbidity, albeit these are in line with previous evidence.

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Introduction

Patients suffering from unipolar depression (UD) or bipolar disorder (BD) have an increased mortality rate compared to the general population, with the standardized mortality ratios (SMRs) being highest for unnatural causes of death, but with overall excess of deaths due to natural causes.^{1–4}

Sedentary lifestyle including lack of exercise has been associated with UD and BD^{5,6} and influences the development of cardiovascular disease (CVD), metabolic syndrome, and diabetes mellitus (DM).⁷ These risk factors might be resulting in the 20–30% increased risk of CVD in patients diagnosed with BD.⁸ Furthermore, patients diagnosed with BD have an increased prevalence of general medical diseases^{9,10} with onset being 4–7 years earlier than those in the general population.¹⁰ Crump et al. and Wu et al. have both shown increased rates of stroke in patients with BD as compared to the general population.^{8,11} A side from CVD, Crump et al. found that BD patients had an increased risk of influenza,⁸ while Davydow et al. found an association between UD and hospitalization for pneumonia.¹² Additionally, Crump et al. showed that patients diagnosed with BD had an increased risk of chronic obstructive pulmonary disease (COPD) as compared to the general population.⁸ These findings were further supported by Rapsey et al.¹³ who showed an increased risk of subsequent diagnosis of COPD in both patients diagnosed with UD and in patients diagnosed with BD. The associations between asthma and mood disorders have been investigated, and Alonso et al. found an increased risk in patients diagnosed with BD for developing asthma.¹⁴ Finally, Caporamos et al. showed an inverse correlation between mood disorders and lung cancer¹⁵ similar to the findings by Boyko et al.,¹⁶ although competing risk, and lack of proper diagnostic practice in patients with SMI may have biased the result.

Previous studies have focused on associations between UD/BD per se and somatic morbidity as outlined above, but studies addressing potential associations between specific clinical characteristics of depression and later development of somatic morbidity are lacking. Therefore, in a sample of hospitalized patients with depression irrespectively of presence or no presence of bipolarity participating in trials on antidepressants, we aimed at investigating independent associations between various clinical characteristics at trial entrance and the risk of later development of somatic morbidities.

Material and methods

Design and study subjects

A follow-up study of 360 in-patients who participated in one of three clinical trials on antidepressants conducted by the Danish University Antidepressant Group (DUAG) 1985–1994.^{17–19} The three DUAG trials investigated antidepressant effects and adverse effects of paroxetine versus clomipramine (DUAG-2),¹⁷ moclobemide versus clomipramine (DUAG-3),¹⁸ and dose-effect and plasma concentration-effects of antidepressant therapy with clomipramine (DUAG-4),¹⁹ respectively. The inclusion criteria of the trials were a depressive episode (in DUAG-2 and in DUAG-4 specified as a major depression according to the DSM-III-R²⁰) and a score ≥ 18 on the 17-item version of the Hamilton Depression Scale (HAM-D)²¹ or a score ≥ 9 on the 6-item subscale (HAM-D₆)²² of the HAM-D. None of the trials contained specification of presence or no presence of bipolarity in accordance with the ICD-8²³ which was used in clinical practice in Denmark during the years when the trials were planned and executed. Exclusion criteria in all studies were organic brain syndrome, chronic alcohol abuse, drug abuse, and serious disease such as myocardial infarction within the past 5 months, heart failure, acute glaucoma, severe liver disease, drug-treated arterial hypertension, endocrine disorder being treated. Patients diagnosed with a previous somatic disorder as defined by a diagnosis in the Danish healthcare registers before inclusion in the original studies was excluded from analysis.

Data were obtained utilizing the Danish nationwide healthcare registers' complete information about all psychiatric and somatic admissions and hospitalizations from 1985, when DUAG-2 was initiated, until 1995 since when all out-patient hospital-based contacts have been included.²⁴ Patients were followed from index, defined as inclusion into the original antidepressant trial to end of the follow-up period December 31, 2011 or death, whichever came first. The follow-up data collection ended ultimo 2011.

Explanatory variables

Participants were psychometrically evaluated utilizing the Newcastle Scales which define depression as endogenous or non-endogenous,^{25,26} and the Bech-Rafaelsen Melancholia Scale (MES).²⁷ Furthermore, all patients underwent ratings

with the HAM-D from which subscale scores according to the HAM-D ABC model proposed by Bech,²⁸ comprising the HAM-D₆²² (HAM-D items 1, 2, 7, 8, 10 and 13), stress-related arousal (HAM-D items 4, 5, 6, 9, 11, 12, 14, 15 and 17), and suicide risk behavior (HAM-D items 3 and 16), the Maier-Philipp Severity subscale (HAM-D items 1, 2, 7, 8, 9 and 10),²⁹ and the Gibbons Global Depression Severity (HAM-D items 1, 2, 3, 7, 9, 10, 11 and 14) were extracted.³⁰

Age at first mood episode, number of previous depressive episodes and duration of index episode were defined as additional explanatory variables.

Based on available register data prior to the patients' trial entrance and on register data from the follow-up period, a subgroup of patients was identified as suffering from BD at index and a subgroup of patients were identified as developing BD during the follow-up study (see details in Reference 31). As a result, we entered BD as a time-varying explanatory variable, with each participant contributing time at risk in the UD group, until the first register-based ICD-10 diagnosis of single manic episode or bipolar affective disorder was given. Participants identified as suffering from BD at trial entrance were coded as BD from that point in time in the model.

Outcome measures

Somatic diseases were grouped into seven different clusters: cancer, CVD (including cerebrovascular disease), diabetes, infections, respiratory diseases, epilepsy, and self-harm, as defined as intentional self-harm and event of undetermined intent (see appendix). Self-harm was included as a somatic morbidity due the somatic nature that self-harm causes. Patients were excluded from the respective analysis if the respective outcome event occurred prior to index.

Statistical analysis

Initially, we conducted descriptive analyses of baseline characteristics utilizing t-test for normally distributed data and Mann–Whitney test for data not normally distributed. Secondly, we applied a Cox multievent regression model with each of the defined somatic disease clusters as outcome entering the explanatory variables as described below.

Due to high correlation between the five HAM-D subscale scores, the initial Cox regression analysis was conducted without subscales included as explanatory variables, after which the subscales were entered separately, utilizing a total of six regression analyses per outcome.

Since the age at first depressive episode was rather late (40.81) we performed a post-hoc sensitivity analysis stratifying patients experiencing first depressive episode before and after age 40 years.

In case of missing data, we imputed these using linear, logistic or negative binomial regression techniques depending on the nature of the covariate. The input variables for the imputation were gender and age at inclusion.

Hazard ratios (HR) were computed, and a p-value <0.05 was considered statistically significant. All analyses were carried out in Stata 15.³² In the present study we decided not to test for multiple comparisons.^{33,34}

Results

Out of 360 patients originally included in DUAG trials 2, 3, and 4, we were able to identify 338 patients for follow-up. Patients were identified from case report files from the original studies and we were unable to identify the remaining 22 patients due to insufficient data. Forty-eight of these were identified as having a bipolar diagnosis at baseline, and during the follow-up, 60 patients converted from UD to BD. No significant differences were observed between female and male participants, as shown in Table 1. No patients were excluded on the basis of somatic disease diagnosed in the Danish registers before inclusion. Baseline characteristics are displayed in Table 1.

An increased number of previous depressive episodes was associated with an increased risk of CVD (HR 1.06, 95% CI (1.03–1.08), $P < 0.05$).

Increased duration of the index depressive episode was associated with an increased risk of DM (HR 1.01, 95% CI (1.00–1.01), $P < 0.05$) and with an increased risk of any respiratory disease (HR 1.00, 95% CI (1.00–1.01), $P < 0.03$). Increased depression severity, as measured on the HAM-D₆, was associated with an increased risk of any infection (HR 1.11, CI 95 % (1.01–1.22), $P < 0.05$), and an increase on the Maier Philipp severity subscale score was associated with a decreased risk of CVD (HR 0.90, 95 % CI (0.83–0.99), $P < 0.05$). The values of the HRs refer to each HR per relevant units of the explanatory variables, i.e. respectively number of previous episodes, months of duration and the absolute change in integer scoring values on the mentioned rating scales.

Bipolarity (versus non-bipolarity) was not associated with an increased risk of any somatic morbidity.

The Cox regression analysis showed that increasing age at inclusion was associated with an increased risk of cancer (HR 1.06, 95% CI (1.02–1.10), $P < 0.005$), CVD (HR 1.06, 95% CI (1.03–1.08), $P < 0.001$), respiratory disease (HR 1.00, CI 95% (1.00–1.01), $P < 0.05$) and infection (HR 1.05, CI 95% (1.02–1.07), $P < 0.001$). Baseline predictors are shown in Table 2.

The post-hoc sensitivity analysis investigating patients experiencing first depressive episode before age 40 years as compared to patients experiencing first depressive episode after age 40 years did not reveal any changes in results for cancer, cardiovascular disease, self-harm, epilepsy, and respiratory disease categories. The effect on HAM-D₆ baseline on infection and the effect on duration of baseline episode in days on diabetes is no longer significant, most likely due to loss of power as a result of diminishing sample size.

Discussion

We investigated independent associations between various characteristics of the sample at trial inclusion and the risk of subsequent somatic morbidity in a well-defined sample of initially hospitalized, severely depressed patients participating in trials on antidepressants. We found that an increased number of previous depressive episodes was associated with an increased risk of CVD. Increased duration of the index depressive episode was associated with an increased risk of DM and with an increased risk of any respi-

Table 1 Demographic variables.

Variables	Total	Female	Male	P (gender)
# of patients	338	224	114	
Age at inclusion (SD)	50.31 (11.77)	51.19 (11.64)	48.57 (11.88)	0.053
Age at first depressive episode in years (SD)	40.81 (13.73)	40.46 (13.84)	41.51 (13.55)	0.507
# of previous depressive episodes at baseline (SD)	2.53 (4.09)	2.86 (4.55)	1.89 (2.88)	0.081
Duration of baseline episode in days (SD)	110.72 (85.79)	114.23 (86.16)	103.79 (85.00)	0.293
HAM-D6 (SD)	12.82 (2.08)	12.82 (2.04)	12.81 (2.17)	0.984
Stress-related arousal (SD)	9.17 (3.05)	9.20 (3.00)	9.11 (3.17)	0.793
HAM suicide risk (SD)	1.55 (1.16)	1.57 (1.17)	1.51 (1.15)	0.648
Maier-Phillipp severity subscale (SD)	12.46 (2.20)	12.43 (2.17)	12.52 (2.26)	0.731
Gibbons global depression severity (SD)	14.15 (2.83)	14.24 (2.88)	13.96 (2.72)	0.379

SD = standard deviation. HAM-D6 = Hamilton depression scale – 6 items. HAM = Hamilton depression scale.

ratory disease. Increased depression severity, as measured on the HAM-D₆, was associated with an increased risk of any infection, and an increase on the Maier Philipp severity subscale score was associated with a decreased risk of CVD. Bipolarity (versus non-bipolarity) was not associated with an increased risk of any somatic morbidity.

The Cox regression analysis showed that increasing age at inclusion was associated with an increased risk of cancer, respiratory disease and infection.

The association between increasing age and increased risk of various somatic diseases was expected and is concordant with previous studies.^{35–37}

Our finding that previous number of depressive episodes was associated with an increased risk of any CVD is in line with Gan et al., who have shown that depression is independently associated with coronary heart disease and with myocardial infarction.³⁸ Furthermore, in a meta-analysis, Dong et al. showed an association between depression and the risk of stroke.

The association between an increased score on the Maier Philipp subscale and a decreased risk of CVD is puzzling; however, we deem this observation a result of comparing patients with similar levels of melancholia and endogenousness as well as the remaining covariates.

Winokur suggested in 1988 a state of functional insulin resistance during depression,³⁹ proposing a causal relationship between UD and DM possible. In our study, we showed an association between duration of the index depressive episode and an risk of DM supporting this previous finding, also substantiated by Knol et al. finding depression as a risk factor for developing type 2 diabetes.⁴⁰

Over the recent years, inflammation and disturbances of the immune system have been investigated as a possible etiological cause of depressive disorders and as a possible target for treatment in both UD and BD.^{41–45} A large study by Andersson et al. has shown associations between depression and risk of infections, with risks increasing with the number of previous depressions.⁴⁶ The latter finding could not be replicated in our study. Since the Andersson study consisted of more than 142,000 patients with depression and our study had 338 patients, it is possible that the lack of an association between number of depressive episodes and subsequent risk of infection is missed due to a type II error. However, our finding that an increased risk of infection was associated with increased severity

of depression as measured by HAM-D₆ might support the hypothesis of inflammation or disturbances in the immune system being the link between depression and infections. Furthermore, this link is supported by our data showing an association between the duration of the index episode and the risk of pulmonary disease. Previous studies have also demonstrated an association between depression and pulmonary disease¹³ including asthma.^{14,47} Besides inflammation, the link between depression and pulmonary diseases obviously may also be attributed to smoking during depressive episodes.⁴⁸

In the current study, we did not find any difference between patients with bipolarity and patients without in terms of risk of any subsequent somatic morbidity, which was contrary to previous findings of increased mortality, especially CVD, and increased risk of self-harm.^{1,4,49,50} These findings may be a consequence of the small sample with few events or a selected population of patients included in randomized controlled trials.

Strengths and limitations

The study population consists of severely depressed, hospitalized patients treated with an antidepressant during clinical trials. Therefore, the generalizability of our findings is restricted to patients with depression receiving antidepressants in hospital-based psychiatric settings irrespective of the depressive episode being part of a UD or BD. On the other hand, since both primary and secondary care in Denmark is free of charge, and no private health insurance is needed, the generalizability of our results is not limited by some subgroups having easier access to treatment than others. The follow-up was performed utilizing the extensive Danish healthcare registers, which results in some inherent limitations.⁵¹ In particular, the somatic diagnoses were those reported to the registers, which will most likely have biased the associations in a conservative direction, as only somatic morbidities reaching the need of hospital-based treatment would be identified. Somatic diseases diagnosed and treated by general practitioners will not have resulted in a register diagnosis and are as such not counted in this study, resulting in an underreporting of somatic disease. Furthermore, we are testing a large number of hypothesis utilizing a moderate sized datasample which is unique due to the psychometric

Table 2 Independent effects on diagnostic groups of explanatory variables (N = 321).

Cancers	Bipolar	0.58	0.27	0.17
			1.26	
	Gender	0.89	0.48	0.72
			1.65	
	Age at inclusion	1.06	1.02	<0.002
			1.10	
	Age at first depressive episode (years)	1.01	0.98	0.70
			1.04	
	Number of previous depressive episodes	0.99	0.89	0.82
			1.10	
	Duration of baseline episode (days)	1.00	1.00	0.55
			1.01	
	Is the patient endogeneous? (above 6 on the Newcastle I scale)	1.08	0.61	0.79
			1.90	
	Melancholic depression	1.34	0.74	0.34
			2.43	
	HAM-D6	1.01	0.88	0.92
			1.15	
	HAM stress-related arousal	1.02	0.92	0.72
			1.14	
Cardiovascular diseases	HAM suicide-risk behaviour	0.93	0.72	0.58
			1.20	
	Maier Phillipp severity subscale	0.95	0.83	0.46
			1.09	
	Gibbons global depression severity	1.01	0.91	0.90
			1.12	
	Bipolar	1.40	0.90	0.14
			2.17	
	Gender	1.32	0.88	0.18
			1.99	
	Age at inclusion	1.06	1.03	<0.001
			1.08	
	Age at first depressive episode (years)	1.02	1.00	0.13
			1.04	
	Number of previous depressive episodes	1.06	1.00	<0.05
			1.11	
	Duration of baseline episode (days)	1.00	1.00	0.84
			1.00	
	Is the patient endogeneous? (above 6 on the Newcastle I scale)	0.93	0.63	0.73
			1.38	
Diabetes	Melancholic depression	1.19	0.80	0.40
			1.78	
	HAM-D6	0.95	0.86	0.22
			1.04	
	HAM stress-related arousal	0.99	0.92	0.80
			1.06	
	HAM suicide-risk behaviour	0.99	0.85	0.90
			1.16	
	Maier Phillipp severity subscale	0.90	0.83	<0.03
			0.99	
	Gibbons global depression severity	0.94	0.88	0.06
			1.00	
	Bipolar	1.81	0.67	0.24
			4.90	
	Gender	0.96	0.39	0.93
			2.39	
	Age at inclusion	1.00	0.94	0.97

Table 2 (Continued)

			1.06	
	Age at first depressive episode (years)	1.03	0.98	0.22
			1.09	
	Number of previous depressive episodes	1.05	0.94	0.37
			1.17	
	Duration of baseline episode (days)	1.01	1.00	<0.03
			1.01	
	Is the patient endogeneous? (above 6 on the Newcastle I scale)	0.69	0.30	0.39
			1.62	
	Melancholic depression	1.47	0.58	0.42
			3.77	
	HAM-D6	0.94	0.76	0.60
			1.17	
	HAM stress-related arousal	1.07	0.90	0.44
			1.27	
	HAM suicide-risk behaviour	0.91	0.62	0.63
			1.34	
	Maier Phillipp severity subscale	0.99	0.81	0.89
			1.20	
	Gibbons global depression severity	0.97	0.83	0.74
			1.14	
Infections	Bipolar	1.16	0.73	0.54
			1.84	
	Gender	1.01	0.66	0.96
			1.55	
	Age at inclusion	1.05	1.02	<0.001
			1.07	
	Age at first depressive episode (years)	1.00	0.98	0.68
			1.02	
	Number of previous depressive episodes	1.00	0.94	0.93
			1.07	
	Duration of baseline episode (days)	1.00	1.00	0.14
			1.00	
	Is the patient endogeneous? (above 6 on the Newcastle I scale)	1.05	0.70	0.83
			1.56	
	Melancholic depression	1.10	0.72	0.66
			1.68	
	HAM-D6	1.11	1.01	<0.03
			1.22	
	HAM stress-related arousal	1.03	0.96	0.38
			1.12	
	HAM suicide-risk behaviour	1.00	0.85	0.96
			1.17	
	Maier Phillipp severity subscale	1.04	0.95	0.41
			1.13	
	Gibbons global depression severity	1.02	0.96	0.50
			1.10	
Respiratory diseases	Bipolar	1.13	0.58	0.72
			2.21	
	Gender	1.21	0.68	0.53
			2.15	
	Age at inclusion	1.01	0.97	0.65
			1.04	
	Age at first depressive episode (years)	1.01	0.98	0.37
			1.05	
	Number of previous depressive episodes	1.05	0.97	0.20

Table 2 (Continued)

Epilepsy			1.13	
	Duration of baseline episode (days)	1.003	1.00	<0.03
	Is the patient endogeneous? (above 6 on the Newcastle I scale)	0.97	1.01	0.91
	Melancholic depression	1.64	0.55	1.70
	HAM-D6	1.02	0.91	0.10
			2.98	
	HAM stress-related arousal	0.92	0.89	0.78
			1.16	
	HAM suicide-risk behaviour	1.05	0.83	0.15
			1.03	
	Maier Phillipp severity subscale	1.03	0.84	0.68
			1.31	
	Gibbons global depression severity	0.99	0.91	0.63
			1.16	
	Bipolar	−0.34	0.90	0.82
			1.09	
	Gender	−0.05	−1.90	0.67
			1.22	
	Age at inclusion	0.03	−1.43	0.94
			1.32	
	Age at first depressive episode (years)	−0.03	−0.04	0.39
			0.09	
	Number of previous depressive episodes	0.04	−0.10	0.28
			0.03	
Self-harm	Duration of baseline episode (days)	<0.004	−0.11	0.58
	Is the patient endogeneous? (above 6 on the Newcastle I scale)	−0.19	0.20	
			−0.002	0.21
	Melancholic depression	−0.89	0.010	
	HAM-D6	0.10	−1.41	0.77
			1.02	
	HAM stress-related arousal	−0.02	−2.70	0.34
			0.93	
	HAM suicide-risk behaviour	0.21	−0.19	0.51
			0.39	
	Maier Phillipp severity subscale	0.06	−0.26	0.85
			0.21	
	Gibbons global depression severity	0.03	−0.29	0.42
			0.71	
	Bipolar	0.45	−0.23	0.67
			0.35	
	Gender	−1.15	−0.20	0.83
			0.25	
	Age at inclusion	0.01	−0.83	0.49
			1.73	
	Age at first depressive episode (years)	0.01	−2.68	0.14
			0.38	
	Number of previous depressive episodes	0.01	−0.05	0.72
			0.07	
	Duration of baseline episode (days)	<−0.01	−0.05	0.82
			0.06	
			−0.11	0.84
			0.14	
			−0.01	0.86
			0.01	

Table 2 (Continued)

Is the patient endogeneous? (above 6 on the Newcastle I scale)	0.07	−1.06 1.19	0.91
Melancholic depression	0.65	−0.51 1.81	0.27
HAM-D6	0.04	−0.23 0.31	0.79
HAM stress-related arousal	0.09	−0.11 0.29	0.37
HAM suicide-risk behaviour	0.05	−0.41 0.50	0.85
Maier Phillipp severity subscale	0.14	−0.10 0.38	0.25
Gibbons global depression severity	0.16	−0.01 0.34	0.07

HR = hazard rate ratio. CI = confidence interval. HAM-D6 = Hamilton depression scale – 6 items). HAM = Hamilton depression scale.

description. There is an inherent risk of type 1 error, in which associations are significant by chance and as such do not represent true associations. Further studies in other populations are needed to confirm the findings in the present study.

Unfortunately, the data set did not allow adjustment for potential confounders such as social factors and lifestyle factors including smoking.

Conclusion

The associations between higher degrees of depression, i.e. longer duration of episodes, higher severity of symptoms and higher number of previous episodes, and increased risks of various somatic morbidity add to the evidence that depression and somatic disease are linked.

Ethical considerations

The Danish Data Protection Agency and Statistics Denmark approved identification of the patients utilizing data from the original case report forms and data from the Danish registers. Original data were anonymized according to the Danish law on data protection.

The study was approved by the Regional Scientific Ethical Committees for Southern Denmark.

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Conflicts of interest

J Holmskov has speaker honorarium from Lundbeck Pharma.

K Andersen has received research grant from the Lundbeck Foundation and a travel grant from H. Lundbeck.

RW Licht has within the preceding three years served on advisory board of Janssen Cilag and Sage and has received speaker honorarium from Astra Zeneca, Janssen-Cilag, Servier and Lundbeck.

FM Nilsson has reported no conflicts of interest.

JV Brink has reported no conflicts of interest.

KB Stage has reported no conflicts of interest.

RE Nielsen has received research grants from H. Lundbeck for clinical trials, received speaking fees from Bristol-Myers Squibb, Astra Zeneca, Janssen & Cilag, Lundbeck, Servier, Otsuka Pharmaceuticals, Eli Lilly and has acted as advisor to Astra Zeneca, Eli Lilly, Lundbeck, Otsuka Pharmaceuticals, Takeda and Medivir.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ejpsy.2021.04.001>.

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