Mood Homeostasis, Low Mood, and History of Depression in 2 Large Population Samples

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**IMPORTANCE** Existing therapeutic options are insufficient to tackle the disease burden of depression, and new treatments are sorely needed. Defining new psychotherapeutic targets is challenging given the paucity of coherent mechanistic explanations for depression.

**OBJECTIVE** To assess whether mood homeostasis (ie, the stabilization of one’s mood by engaging in mood-modifying activities) is a possible new therapeutic target by testing the hypothesis that people with low (vs high) mean mood and people with (vs without) a history of depression have impaired mood homeostasis.

**DESIGN, SETTING, AND PARTICIPANTS** The quantitative association between mood and daily activities was computed in 2 large case-control studies based on the 58sec data set (collected from December 1, 2012, to May 31, 2014, and analyzed from April 1 to 30, 2019), and the World Health Organization Study on Global Aging and Adult Health (WHO SAGE) data set (collected from January 1, 2007, to December 31, 2010, and analyzed from June 1 to 30, 2019). The 58sec data set consists of self-enrolled participants from high-income countries. The WHO SAGE data set consists of nationally representative participants in low- and middle-income countries recruited via cluster sampling.

**MAIN OUTCOMES AND MEASURES** The main outcome (defined before data analysis) was the difference in mood homeostasis between people with high vs low mean mood (58sec data) and between people with vs without a history of depression (WHO SAGE data).

**RESULTS** A total of 28 212 participants from the 58sec data set (65.8% female; mean [SD] age, 28.1 [9.0] years) and 30 116 from the WHO SAGE data set (57.0% female; mean [SD] age, 57.8 [14.7] years) were included, for an overall study population of 58 328 participants. Mood homeostasis was significantly lower in people with low (vs high) mean mood (0.63 [95% CI, 0.45 to 0.79] vs 0.96 [95% CI, 0.96 to 0.98]; P < .001) and in people with (vs without) a history of depression (0.03 [95% CI, −0.26 to 0.24] vs 0.68 [95% CI, 0.55 to 0.75]; P < .001). In dynamic simulations, lower mood homeostasis led to more depressive episodes (11.8% vs 3.8% yearly risk; P < .001) that lasted longer (4.19 vs 2.90 weeks; P = .006).

**CONCLUSIONS AND RELEVANCE** In this study, mood homeostasis appeared to have been impaired in people with low mood and in those with a history of depression. Mood homeostasis may therefore provide new insights to guide the development of treatments for depression.
Majordepressivedisorderistheleadingcauseofdisabilityworldwide.1 Existingpharmacological2 and nonpharmacological3,4 treatmentoptionsfordepressionachievesresponse ratesofabout50%—areslatively modestcontributiontothereductionofthediseaseburden.5 The developmentoftreatmentswithnoveloroptimized mechanismsofactionhasthereforebecomeakyeystrategic objectiveofresearchinpsychiatry.6

Weproposethatifundamental—yetunexplored—underlyingmechanismofdepressionmaylieinsomepeople's inabilitytostabilizemoodthroughtheirchoiceofeveryday activities. This idea was inspired by recent largescale studies showingarobustpatternofassociationsbetweenmood andchoicesofactivitiesinthegeneralpopulation,7,8 termed the hedonic flexibility principle. According to this principle,people haveahigherpropensitytoengageinmood-increasingactivitieswhentheirmoodislowandtostayusefulbutmooddecreasingactivitieswhentheirmoodishigh. Whypothesizedthatthisprinciplereflectsahomeostaticmechanismthat helpsstabilizemoodinhealthypeople. Conversely,ifweak orabsent,themechanismcouldincreasetheriskofaspiral down to depression.

Wefirsttestedthishypothesisbyassessingtheassociation betweenmoodhomeostasisandindividuals'meann mood among 28,212 people whose moods and activities were tracked in realtime. We thensoughttoconfirmthishypothesisbycomparing moodhomeostasisbetweenpeoplewithandwithout ahistoryofdepressioninanindependentdatasetof30,116 peopleacross6countriesobtainedfromtheWorldHealth OrganizationStudyonGlobalAgingandAdultHealth(WHO SAGE).10

Method

Participants and Data
Weused2independentandcomplementarycase-control datasets.Demographicdataforbothstudiesarepresentedin the eTable in the Supplement. This study was approved by the EthicsCommitteeofESADE(EscuelaSuperiordeAdministraciónyDireccióndeEmpresas)BusinessSchool,Barce lonaspain.Participantsprovidedwritteninformedconsent. ThisstudyfollowedtheStrengtheningtheReportingof Observational Studies in Epidemiology (STROBE) reporting guideline.

Thefirstdataset(referredtoasthe58secdataset)was acquiredinyoungadults(mean[SD]age:28.1[9.0]years)living inhigh-incomefrancophonecountries.Participantsvolun teeredbydownloadingamobileapplicationforecologicalmoment aryassessmentofmoodandbehaviorviashortquestionnairespresentedarandomtimes throughouttheday.Thetwoquestionsofinterestwere“Howareyou currentlyfeeling?”(onaslidingscalefrom0[veryunhappy]to100[veryhappy]) and“Whatareyoucurrentlydoing?”(fromanonnmutually exclusive list of 25 activities, eg, exercising, chatting, working) (eMethods1inthSupplement). Weselectedallparticipants whoanswered2consecutivequestionnairesormorewithin 12 hours. Thisresultedin28,212participantsand216,794pairs of observations. Details on the working of the app have been published previously10 (eMethods2intheSupplement). Data were collected from December 1, 2012, to May 31, 2014, and analyzed from April 1 to 30, 2019.

Theseconddataset(WHO SAGEdataset)formspartofthe WHO SAGE study (wave 1),10 which consists of questionnaires administered to nationally representative samples in China, Ghana, India, Mexico, Russia, and South Africa. The participants were asked to name, in chronological order, the activities that they engaged in during the day11(eg,religion, subsistence farming),theirmood(eMethods1intheSupplement),and whetherytheywereeverdepressed;30,116participants recordeleast2activities(mean[SD],4.4[1.6])corresponding mood. Data were collected from January 1, 2007, to December 31, 2010, and analyzed from June 1 to 30, 2019.

Mood Homeostasis
Wedefinemoodhomeostasisasthextenttowhichaperson preferentially engages in mood-increasing activities such as exercising when their mood is low and saves the mooddecreasingactivitiessuchashouseworkforwhentheirmood ishigher. Thus,individualswhopreferentiallyengageinmoodincreasingactivitieswhentheirmoodisalreadyhigh andunpleasantactivitieswhentheirmoodisalreadylowwould havealowmoodhomeostasis.

Mood homeostasisrepresents the extent to which people demonstrahedonic flexibility.7 Mood homeostasisisan aspectofthebroaderconceptofmoodregulation,12 butitspecificallyrefertothemoment-to-momentregulationofmood states viachoicesofactivities.Detaillsonmoodhomeostasis anditscomputationarepresentedin eMethods3to5andeFig urers1and2intheSupplement.

Statistical Analysis
Mood homeostasisispositiveiftheprobabilityofnextengag inginanactivitywhencurrentmoodislow(estimatedwithalogisticregression)isperativelycorrelatedwiththechange in moodresultingfromthisactivity(estimatedwithlinearregression).Inthe58secdataset,weletthecoefficientsofinterest(iet,thearrangementbetweencurrentmoodandthe probabilityoflaterengaginginaparticularactivityfromthelogistic regression model, and the resulting change in mood from the
linear regression model) vary as a function of a participant's mean mood. We evaluated mood homeostasis for mean moods ranging from 2 SDs below the population mean to 2 SDs above (ie, from 25 to 97 on a sliding scale of 0 to 100). We first tested the null hypothesis that mood homeostasis at any level of mean mood is equal to zero. We then tested the null hypothesis that mood homeostasis is identical between a mean mood equal to the mean in the top half of the population (75.2) and that in the bottom half of the population (46.9). Similarly, in the WHO SAGE data set, we calculated the coefficients of interest separately for people with and without a history of depression. We first tested the null hypotheses that mood homeostasis is equal to zero in each group (people with and people without a history of depression) and then the null hypothesis that there is no difference between the groups.

As in previous studies,7–9 the time of day and day of the week (only available for the 58sec data set) were included as potential confounders in the 2 regressions. The regression used to assess the association between current mood and the probability of later engaging in a particular activity also included a latency effect (ie, whether an individual was already engaged in that activity before), and the daily mean mood as potential covariates. Details on covariates are provided in eMethods 6 in the Supplement. Full details on the statistical analysis are presented in eMethods 7 and eFigure 3 in the Supplement, and robustness analysis is presented in eMethods 8 in the Supplement. Significance level was set at \( P < .05 \), and all statistical tests were 2-sided. Statistical tests were achieved using the nonparametric bootstrap method.

Dynamic Simulations
To further assess the association of low mood homeostasis with depressive episodes, we developed a generative model to simulate mood and activity timelines for a 5-year period for 200 simulated individuals: 100 with high and 100 with low mood homeostasis. This simulation is further described in eMethods 9 in the Supplement.

Results
A total of 28,212 participants from the 58sec data set (18,504 [65.8%] female and 9,621 [34.2%] male, among those who reported sex; mean [SD] age, 28.1 [9.0] years) and 30,116 from the WHO SAGE data set (17,175 [57.0%] female and 12,939 [43.0%] male, among those who reported sex; mean [SD] age, 57.8 [14.7] years) were included in the analysis, for a total study population of 58,328 participants. Mood homeostasis as a function of an individual's mean mood in the 58sec data set is shown in Figure 1. For individuals' mean moods below the population mean \((\mu = 61)\), mood homeostasis decreased monotonically. Its value fell to a range that included zero for mean moods below 33. Mood homeostasis for a high mean mood (taken as 75.2, which is the mean in the top half of the population) was significantly higher than mood homeostasis for a low mean mood (taken as 46.9, which is the mean in the bottom half of the population): 0.96 (95% CI, 0.96–0.98) vs 0.63 (95% CI, 0.45–0.79) \((P < .001)\) (Figure 2A). Both values were significantly larger than zero \((P < .001)\).

In the WHO SAGE data set, mood homeostasis among people without a history of depression was 0.68 (95% CI, 0.55–0.75) and significantly different from zero \((P < .001)\) (Figure 3A). Among people with a history of depression, mood homeostasis was 0.03 (95% CI, −0.26 to 0.24) and not significantly different from zero \((P = .68)\) (Figure 3A). The difference between the 2 was statistically significant (difference, 0.65; 95% CI, 0.46–0.93; \( P < .001 \)), which implies that people with a history of depression had a disrupted mood homeostasis (which may even be effectively absent) compared with people without a history of depression. These findings were found to be robust when the data were randomly split in 2 independent subsets, when using parametric tests, when using multilevel regression models, and when adjusting for the country of origin (eFigure 4 in the Supplement).

Factors Associated With Group Differences in Mood Homeostasis
In the 58sec data set, thinking was associated with a reduction in mood homeostasis in participants with low mean mood (Figure 2B and C). These participants tended to think more when their mood was low, although this was associated with a further decrease in their mood—the opposite of mood homeostasis. However, the group difference in mood homeostasis in terms of all other activities was also statistically significant (difference, 0.15; 95% CI, 0.04–0.26; \( P < .001 \)) (eFigure 5 in the Supplement), suggesting that it must also be associated with other factors. No specific activity was found to be associated with the group difference in mood homeostasis in the WHO SAGE data set (Figure 3B and C and eFigure 6 in the Supplement).

The group differences in mood homeostasis were more closely associated with when people engage in mood-modifying activities than with how activities modify mood.
In the 58sec data set, the change in mood resulting from engaging in different activities was virtually identical for people with high and low mean mood (correlation between the horizontal spread of activities, in Figure 2 Band C, within the group with high mean mood and the horizontal spread of activities within the group with low mean mood: 0.955). For example, exercising was the activity that was associated with the largest boost in participants’ mood regardless of mean mood levels. In contrast, the 2 groups were less similar in their propensity to engage in different activities as a function of their current mood (correlation between vertical spreads in Figure 2B and C: 0.787). The difference between these 2 correlations was statistically significant (difference, 0.17; 95% CI, 0.07-0.32; P < .001). Similarly, in the WHO SAGE data set, people with and without a history of depression were relatively similar in the change in mood associated with different activities (correlation between horizontal spreads in Figure 3B and C: 0.782) but less similar in their propensity to engage in different activities as a function of their current mood (correlation between vertical spreads in Figure 3B and C: 0.135). The difference between these 2 correlations was statistically significant (difference, 0.65; 95% CI, 0.41-1.03; P < .001).

When people experience low mood, mood homeostasis can be achieved in 2 ways: individuals can refrain from engaging...
in mood-decreasing activities (negative valence; eg, postponing housework), or they can engage in mood-increasing activities (positive valence; eg, exercising). In the 58sec data set, activities with negative valence contributed more to the group difference in mood homeostasis than activities with positive valence. Specifically, the group difference in mood homeostasis between people with high and low mean mood for negative activities was 1.27 (0.76 vs −0.51 [95% CI, 1.07-1.59]; P < .001), whereas the group difference in mood homeostasis for positive activities was 0.22 (0.94 vs 0.72 [95% CI, 0.08-0.47]; P < .001), and the difference between the 2 was statistically significant (1.05 [95% CI, 0.81-1.41]; P < .001). A similar trend was observed in the WHO SAGE data set. The group difference in mood homeostasis between people with and without a history of depression was 0.860 for negative activities (0.559 vs −0.301 [95% CI, 0.314-1.456]; P = .003) and 0.285 for positive activities (0.383 vs 0.098 [95% CI, −0.002 to 0.937]; P = .054), although the difference between the 2 did not reach statistical significance (0.575 [95% CI, −0.320 to 1.226]; P = .24).

**Dynamic Simulations**

In simulations of mood and activity timelines (Figure 4), low mood homeostasis was associated with 3 times more depressive episodes than high mood homeostasis (11.8% vs 3.8% annual incidence of depressive episodes; P < .001) (Figure 5). When they occurred, these depressive episodes lasted significantly
mood-decreasing activities (blue dots) in higher proportion than mood homeostasis may have been more likely to engage in activities that are more clinically interpretable. The finding that the simulated difference in mood homeostasis was associated with a 3-fold increase in the incidence of depressive episodes and a 44% increase in their duration thus also supports clinically significant associations between low mood homeostasis and depression.

The 2 data sets used in this study differed on many important aspects, including age, socioeconomic background, and data acquisition methods. The convergence of the findings from these data sets as well as in sensitivity analyses testify to their robustness. In addition, the consistency of the findings for high-income and low- and middle-income countries contributes to filling the gap between the burden of psychiatric disorders in low- and middle-income countries and the scarcity of research performed in them. Although findings converge in the 2 data sets, the strength of the association with mood homeostasis was substantially lower in people without a history of depression (WHO SAGE data set) than in people with high mean mood (58sec data set). This gap might be entirely accounted for by differences in sampling duration and mean mood level between the data sets (as shown in eResults 2 and eFigure 7 in the Supplement). Differences in age and income between data sets might also have been a factor: older adults and people with lower income might have daily activities that are less driven by their mood and more driven by external factors such as the time of day, day of the week, or immediate needs of the person or family. However, in eResults 2 and eFigure 8 in the Supplement, we show these were unlikely to have played significant roles. Finally, this gap in mood homeostasis may result from underreporting of depression by participants in the WHO SAGE data set (some of the control individuals would then have a history of depression, effectively lowering mood homeostasis in that group). This underreporting would explain why the prevalence of depression in that data set was lower than in the corresponding countries. Alternatively, the survey might have failed to reach a fully representative sample. Reliably establishing cross-cultural differences in mood homeostasis remains for future work.

The association between mood homeostasis and depression may provide important insights into the treatment of depression. Most treatments are developed in pragmatic ways poorly informed by mechanistic understandings of mood regulation, hampering their refinement and optimization. For example, activity scheduling—a therapeutic technique in which patients elaborate activity charts, predict their resulting pleasure, and actively evaluate with the therapist whether they have had the anticipated effect—is part of a wide range of psychotherapies for depression, such as cognitive-behavioral therapy and behavioral activation. However, its mechanism of action remains largely unknown. Activity scheduling avoids situations in which many unpleasant activities are...
scheduled consecutively, which is critical for achieving mood homeostasis. This may be an important determinant of its therapeutic benefit, in which case focusing explicitly on mood homeostasis might further increase its efficacy. Moreover, measuring mood homeostasis at baseline might help to predict which patients will most benefit from such treatments or from antidepressants. Similar to the early effect of antidepressants on emotional processing, a gain of mood homeostasis could also be an early biomarker of drug action.

A question for future investigation is the extent to which behavior is driven primarily by conscious recognition of mood states and active choice of subsequent activities, or whether behavior is driven primarily by unconscious mood. By monitoring mood in real time, intelligent systems might be able to make activity recommendations to increase mood homeostasis. Such an intervention could be delivered remotely, improving access to treatment for patients for whom face-to-face care is unavailable, including in low- and middle-income countries. Importantly, some associations between activities and mood were highly culture specific. For instance, exercise led to the highest increase in mood in high-income countries, whereas religion did so in low- and middle-income countries. Therefore, it seems that interventions aimed at increasing mood homeostasis will need to be culture specific— or even individual specific—and account for people's constraints and preferences. If a gap in mood homeostasis is found to be driven by a few specific activities, then interventions could directly target them. For instance, the effect of thinking on mood homeostasis in the 58sec data set might reflect the tendency for some people to ruminate when feeling depressed. In those people, an intervention that targets rumination could restore mood homeostasis. Using the concept of mood homeostasis might therefore unify different therapeutic approaches by expressing their outcome as a quantifiable measurement of mood stability.

Limitations
Although our hypothesis is that weak or absent mood homeostasis may lead to depression, it is possible that low mood itself drives this association because this study was cross-sectional. Using simulations, we have explored the possibility of a direct link between the two. However, additional studies are needed to establish whether impaired mood homeostasis may indeed cause depression. The large number of participants guards against extreme unrepresentativeness, but we know relatively little about their medical and social histories. Hence, it is difficult to exclude various forms of selection bias resulting, for example, from access to mobile technologies (58sec cohort) or recruitment in different countries (WHO SAGE study). Finally, measuring mood with a sliding scale in the 58sec data set was motivated by the need for simplicity (to be used multiple times a day within a mobile application) while preserving a degree of granularity. However, clinically validated mood scales could be used in future studies, or the sliding scale could be validated against them.

Conclusions
This study found that lower mood homeostasis was associated with low mood and a history of depression, and dynamic simulations showed a plausible causal association linking the two. These mechanistically informed findings may prompt the development of new treatments for depression or the optimization of existing ones, such as activity scheduling. As a quantitative approach, measuring mood homeostasis may play a role in personalized psychiatry by identifying the patients most likely to benefit from a variety of treatments. Additional studies are needed to demonstrate a causal link between mood homeostasis and depression. We believe our findings thus open the door to new research avenues that may ultimately help reduce the disease burden of depression.

ARTICLE INFORMATION
Accepted for Publication: February 11, 2020.
Published Online: April 22, 2020.

Author Contributions: Dr Taquet had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Taquet, Quoidbach, Saunders. Acquisition, analysis, or interpretation of data: Taquet, Quoidbach, Gross, Goodwin.

Drafting of the manuscript: Taquet, Saunders, Goodwin.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Taquet, Quoidbach.

Obtained funding: Taquet.

Administrative, technical, or material support: Taquet, Goodwin.

Supervision: Gross, Saunders.

Conflict of Interest Disclosures: Dr Taquet reported receiving grants from the Royal College of Psychiatrists and the Foulkes Foundation during the conduct of the study. Dr Saunders reported receiving grant BRC-1215-20005 from the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre during the conduct of the study. Dr Goodwin reported receiving personal fees from Allergan, Inc, Angelini Pharma, COMPASS Pathways, Merck & Co, Johnson & Johnson, Lundbeck, Inc, Medscape, Minerva Neurosciences, Inc, Pliivital, Pfizer, Inc, Sage Therapeutics, Inc, Servier Laboratories, Shire PLC, and Sun Pharmaceutical Industries, Inc, outside the submitted work and holding an equity stake in Pliivital and Pliivital products. No other disclosures were reported.

Funding/Support: This study was supported by fellowships with financial support from the Foulkes Foundation and the Royal College of Psychiatrists (Dr Taquet) and grant RYC-2016-21020 from the Ministerio de Economía, Industria y Competitividad, Gobierno de España (Dr Quoidbach).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, or the Department of Health.

REFERENCES
3. Leichsenring F. Comparative effects of short-term psychodynamic psychotherapy and
Research Original Investigation

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