The World Journal of Biological Psychiatry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iwbp20

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To cite this article: Dimitris Dikeos, Adam Wichniak, Periklis Y. Ktonas, Thorsten Mikoteit, Tatjana Crönlein, Anne Eckert, Jana Kopřivová, Maria Ntafouli, Kai Spiegelhalder, Martin Hatzinger, Dieter Riemann & Constantin Soldatos (2023): The potential of biomarkers for diagnosing insomnia: Consensus statement of the WFSBP Task Force on Sleep Disorders, The World Journal of Biological Psychiatry, DOI: 10.1080/15622975.2023.2171479

To link to this article: https://doi.org/10.1080/15622975.2023.2171479

THE WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY
https://doi.org/10.1080/15622975.2023.2171479

REVIEW ARTICLE

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The potential of biomarkers for diagnosing insomnia: Consensus statement of the WFSBP Task Force on Sleep Disorders

Dimitris Dikeos[a], Adam Wichniak[b], Periklis Y. Ktonas[a,c], Thorsten Mikoteit[d], Tatjana Crönlein[e], Anne Eckert[f], Jana Kopřivová[g,h], Maria Ntafouli[a], Kai Spiegelhalder[i], Martin Hatzinger[d], Dieter Riemann[i] and Constantin Soldatos[a]

[a]First Department of Psychiatry, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece; [b]Third Department of Psychiatry, Sleep Medicine Center, Institute of Psychiatry and Neurology, Warsaw, Poland; [c]Department of Electrical and Computer Engineering, University of Houston, Houston, TX, USA; [d]Psychiatric Services Solothurn, Faculty of Medicine, University of Basel, Solothurn, Switzerland; [e]Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany; [f]Neurobiology Lab for Brain Aging and Mental Health, Transfaculty Research Platform Molecular & Cognitive Neuroscience (MCN), University of Basel, Basel, Switzerland; [g]National Institute of Mental Health, Klecany, Czechia; [h]Third Faculty of Medicine, Charles University, Prague, Czechia; [i]Department of Psychiatry and Psychotherapy, Faculty of Medicine, Medical Centre, University of Freiburg, Freiburg, Germany

ABSTRACT

Objectives: Thus far, the diagnosis of insomnia is based on purely clinical criteria. Although a broad range of altered physiological parameters has been identified in insomniacs, the evidence to establish their diagnostic usefulness is very limited. Purpose of this WFSBP Task Force consensus paper is to systematically evaluate a series of biomarkers as potential diagnostic tools for insomnia.

Methods: A newly created grading system was used for assessing the validity of various measurements in establishing the diagnosis of insomnia; these measurements originated from relevant studies selected and reviewed by experts.

Results: The measurements with the highest diagnostic performance were those derived from psychometric instruments. Biological measurements which emerged as potentially useful diagnostic instruments were polysomnography-derived cyclic alternating pattern, actigraphy, and BDNF levels, followed by heart rate around sleep onset, deficient melatonin rhythm, and certain neuroimaging patterns (mainly for the activity of frontal and pre-frontal cortex, hippocampus and basal ganglia); yet, these findings need replication, as well as establishment of commonly accepted methodology and diagnostic cut-off points. Routine polysomnography, EEG spectral analysis, heart rate variability, skin conductance, thermoregulation, oxygen consumption, HPA axis, and inflammation indices were not shown to be of satisfactory diagnostic value.

Conclusions: Apart from psychometric instruments which are confirmed to be the gold standard in diagnosing insomnia, six biomarkers emerge as being potentially useful for this purpose.

ARTICLE HISTORY
Received 21 October 2022
Revised 30 December 2022
Accepted 17 January 2023

KEYWORDS
Insomnia; biomarkers; psychometrics; diagnostic accuracy; grading system

Introduction

Insomnia is regarded as one of the major health challenges, deserving accuracy in its diagnosis considering its global burden related to mental and physical health (Collins et al. 2011). The diagnosis of insomnia, as defined in the major diagnostic classification systems published by the World Health Organisation (ICD-11; WHO 2019), the American Psychiatric Association (DSM-5; APA 2013), and the American Academy of Sleep Medicine (ICSD-3; AASM 2014), is based on a number of clinical criteria referring to subjective complaints, i.e. difficulty in initiating or maintaining sleep, dissatisfaction with quantity and/or quality of sleep, as well as psychological and other negative consequences of sleep disturbance. In both the 'Practice Parameters for the Evaluation of Chronic Insomnia' developed by the American Academy of Sleep Medicine (Chesson et al. 2000) and the most recently published European Guideline for the Diagnosis and Treatment of Insomnia developed by

CONTACT Dimitris Dikeos ddikeos@med.uoa.gr First Department of Psychiatry, Eginition Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece

Supplemental data for this article can be accessed online at https://doi.org/10.1080/15622975.2023.2171479

the European Sleep Research Society—ESRS (Riemann et al. 2017) the diagnosis of insomnia is established through the use of the above mentioned criteria. In spite of the fact that these universally accepted criteria are purely clinical, certain biological measurements are being considered for the diagnosis of insomnia in both the above guideline papers, as well as in an AASM companion paper for the evaluation of insomnia (Sateia et al. 2000).

Since the diagnosis of insomnia is based on subjective complaints (ICD-11, DSM5, ICSD-3), rating scales and other means of psychometric assessment are expected to show considerable diagnostic validity. On the other hand, biological research has identified a broad range of altered physiological parameters among insomnia patients, which could be considered as appropriate biomarkers (Califf 2018). However, as yet, there has been very limited evidence on sensitivity, specificity, and/or other appropriate measures of diagnostic accuracy of these parameters to establish their usefulness as diagnostically valid biomarkers for insomnia. Both the American (Chesson et al. 2000) and the European (Riemann et al. 2017) guidelines mainly rely on expert evaluation of the existing literature to generate the respective recommendations for the diagnosis of insomnia. In the extensive review of studies for the diagnosis of insomnia by Sateia et al. (2000), on which the American guidelines are based, the approach to detect the diagnostic potential of the methods examined relies primarily on the value of alpha and beta errors, indices which denote statistical significance but do not necessarily correspond to specific measures reflecting diagnostic accuracy *per se*.

The present consensus paper consists of a systematic evaluation of biomarkers as potential diagnostic tools for insomnia based on measures of diagnostic accuracy, following an identical assessment of the diagnostic accuracy of psychometric instruments in diagnosing insomnia. For this purpose, we created a novel grading system for assessing the studies which are reviewed herein regarding the degree of pertinence of their reported data and the level of accuracy of their method approach in establishing the diagnosis of insomnia. It is noteworthy that the diagnostic usefulness of the biological parameters for insomnia has not been previously compared among themselves, neither *vs.* psychometric measurements.

Methods

In a business meeting of the WFSBP Task Force on Sleep Disorders, it was decided to create a consensus statement on the value of biomarkers and other means of assessment for the diagnosis of insomnia. To this effect, a steering group consisting of Adam Wichniak, Dimitris Dikeos, and Constantin Soldatos took the initiative to invite several colleagues, each having expertise in a specific research/clinical domain for the study of insomnia. Those who contributed to the consensus statement and their respective specific fields of expertise are as follows: Dieter Riemann (DR) and Periklis Ktonas (PK) on polysomnography and sleep EEG spectral analysis; Adam Wichniak (AW) on actigraphy; Kai Spiegelhalder (KS) on neuroimaging; Thorsten Mikoteit (TM) and Martin Hatzinger (MH) on psychophysiology (heart rate, skin conductance, thermoregulation, oxygen consumption rate); TM, MH, and Anne Eckert (AE) on neuroendocrinology (HPA axis and melatonin), inflammation and neuroplasticity; Dimitris Dikeos (DD) and Constantin Soldatos (CS) on psychometrics through scales and questionnaires for assessing insomnia; Jana Kopřivová (JK) on psychometrics through scales and questionnaires for assessing dysfunctional beliefs and attitudes about sleep; and Tatiana Crönlein (TC) on inventories for assessing personality patterns. Maria Ntafouli (MN) contributed to data handling, preparation of tables, and the procedure of composing the paper.

The contributors provided their respective parts of the manuscript, each accompanied by a table presenting the studies on which their specific reports were based. The text provided by each contributor appears in part as an appropriate section of the review of studies and in part in the discussion; the unified text of the entire paper was based on the integration of the parts provided by the contributors implemented by DD and CS.

In their tables, the contributors included summarised information for each study as follows: Citation, Type of Study, Type and Number of Subjects, Instruments and Methods, Results, Main Conclusions, and Comments. The tables provided by the contributors were then homogenised by DD and CS through (a) presenting all data included in them in a similar way, (b) adding appropriate data to the individual entries (whenever those were not included in the tables originally provided by the contributors) after scrutinising the papers on which the entries were based, (c) calculating appropriate values of Cohen's d or Hedge's g based on the data available in each study (see Supplementary Table S1), and (d) adding/restructuring conclusions and comments by using information originating from the texts provided by the contributors and/or from the original papers cited by them. Moreover, the selection of entries which were to appear in the main tables of the paper was based

Table 1. Grading system for establishing diagnosis.

Grade of diagnostic pertinence				
Grade	Data reported or extracted			
A (high)	Sensitivity and Specificity or AUC of the Receiver Operating Characteristic (ROC) curve			
B (moderate)	Cohen's d or Hedge's g (provided or extracted from available data as shown in Supplementary Table S1)			
C (low)	Correlation coefficient (*r*)* or data from review studies relevant for the assessment of diagnostic validity			
D (inadequate)	Data inadequate for the establishment of diagnostic accuracy (*p*-values, mean values without available standard deviations, geometric mean values)			
Grade of diagnostic accuracy				
Grade	Sensitivity and specificity	AUC of ROC	Cohen's *d* or Hedge's *g*	Correlation coefficient (*r*)
1 (high)	≥0.80	≥0.80	≥1.50	≥0.80
2 (moderate)	0.70–0.79	0.70–0.79	1.00–1.49	0.60–0.79
3 (low)	0.60–0.69	0.50–0.69	0.70–0.99	0.40–0.59
4 (virtually absent)	<0.60	<0.50	<0.70	<0.40

*Between the diagnostic method under examination and another well-established method for diagnosing insomnia.

on the following criteria: (a) study samples included well defined groups of insomniacs and control subjects, (b) study samples were not based only on special populations (e.g. elderly, children, patients with somatic disorders, etc.), and (c) respective papers were either reviews/meta-analyses or provided precise numerical values for diagnostic accuracy, effect size or other values reflecting the strength of differences between compared groups. Data of other studies which were referred to by the contributors but did not meet any of the above mentioned requirements were placed in the online Supplementary Tables S2 and S3. It should be noted that, based on each original study's description, it was not always possible to specify whether patients included were diagnosed with any type of insomnia (INS) or specifically with primary insomnia (PI). Thus, we resorted to include in the tables the rubric used by the respective authors (e.g. INS, PI, etc.) and to base our analysis on patients with PI only whenever this was specifically mentioned or, otherwise, on unspecified insomnia patients.

The review section contains two main parts: one on Psychometric Measurements and another on Biological Measurements. Each of these parts is accompanied by its respective main table and the corresponding Supplementary Table in the online material. The two main tables are subdivided into several sections, each corresponding to a specific scientific area (psychometric or biological approach for the diagnosis of insomnia) and are organised in a chronological order based on the year of publication, whereas the entries in the Supplementary Tables are listed in alphabetical order based on first author's surname.

A grading system for establishing the quality of diagnosis was created as follows: data provided in the individual studies which are included in the main tables were categorised in four levels (A to D) based on the degree of pertinence of their reported indices to diagnose insomnia (Grade of Diagnostic Pertinence, see Table 1). Thus, 'A' is for studies directly assessing the data in a detection framework (e.g. ROC) while 'B' is for studies using only general distribution parameters like effect sizes or means and variances. The Diagnostic Accuracy potential of the psychometric or biological approach examined in each study was graded in four levels (1–4), as also shown in Table 1. Thus, a diagnostic grading index could be attributed to each study based on the combination of the grades of diagnostic pertinence and diagnostic accuracy. For example, a diagnostic grading index of A1 corresponds to a study whose results show high diagnostic accuracy which is based on measures of high pertinence (i.e. Sensitivity, Specificity, or ROC-AUC higher than 0.80), A3 corresponds to high quality diagnostic measures showing low diagnostic accuracy, while C1 corresponds to a study showing high diagnostic accuracy which is, however, based on measures of low pertinence. The cut-off scores used for establishing the level of diagnostic accuracy were based on relevant literature (Hosmer and Lemeshow 2000; Ferguson 2009; Sawilowsky 2009). In case a study reported several measures, the diagnostically pertinent index which was chosen was the most accurate one among these measures. Grade D of diagnostic pertinence corresponds to a study reporting possibly useful information on differences between insomniacs and controls, but the data provided are not adequate to assess the diagnostic validity of the existing differences; therefore, no level of diagnostic accuracy can be established.

Review of studies on psychometric measurements

Rating scales and questionnaires for assessing insomnia

There is a very large number of scales and questionnaires for diagnosing insomnia; therefore, a search

based on Pubmed and secondary citations was performed for original papers, each having being cited at least ten times in 'Web of Science' or Google Scholar. The papers produced through this search had to report on suitable measures of diagnostic validity for insomnia, based on a well-defined population of insomniacs *vs.* a sample of non-insomniac controls. Consequently, five studies reporting on an equal number of psychometric instruments (Pittsburgh Sleep Quality Index, Buysse et al. 1989; Athens Insomnia Scale, Soldatos et al. 2000; Global Sleep Assessment Questionnaire, Roth et al. 2002; Sleep-50 Questionnaire, Spoormaker et al. 2005; Brief Insomnia Questionnaire, Kessler et al. 2010) were finally selected for presentation herein.

As presented in Table 2(a), the diagnostic validity of all five psychometric instruments was quite satisfactory, based on measures of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristic curve (ROC-AUC). The values corresponding to these measures indicate that scales and questionnaires for assessing insomnia are indeed useful psychometric tools (diagnostic grading A1 for three of the above scales and A2 for two of them).

Further to their diagnostic validity, Cronbach's alphas were invariably high (0.77–0.90), indicating the strong internal consistency of the five instruments presented above. In studies of other well-known scales and questionnaires for assessing insomnia, which are not presented here as they do not meet the inclusion criteria mentioned above, similarly high values of Cronbach coefficients were also observed (Parrott and Hindmarch 1980; Ellis et al. 1981; Jenkins et al. 1988; Bastien et al. 2001; Pallesen et al. 2008; Okun et al. 2009; Drake et al. 2014; Espie et al. 2014). Test-retest reliability, in the four studies in which it was assessed (Table 2(a)), was found to range from 0.78 to 0.90 (for periods of 1–3 weeks). The high values of both Cronbach's alpha and test-retest reliability show that the psychometric instruments (scales and questionnaires) focussing on the assessment of the subjective complaints of insomnia are indeed robust and retain their ability to record sleep disturbance consistently over repeated administration.

Scales and questionnaires for assessing dysfunctional beliefs and attitudes about sleep

Cognitive processes play an important role in insomnia (Harvey 2002). To quantify sleep-related cognitions, the Dysfunctional Beliefs and Attitudes about Sleep scale (DBAS) has been developed by Morin et al. (1993, see Supplementary Table S2), containing 30-items. More recently, however, shorter versions have been published (DBAS-16 by Morin et al. 2007, see Supplementary Table S2; DBAS-10 by Espie et al. 2000 and by Edinger and Wohlgemuth 2001, see Supplementary Table S2). Psychometric and clinical studies reported satisfactory internal consistency of all DBAS versions (e.g. Smith and Trinder 2001, see Table 2(b); Carney and Edinger 2006; Morin et al. 2007, see Supplementary Table S2; Carney et al. 2010, see Table 2(b); Fortier-Brochu and Morin 2014; Hertenstein et al. 2015, see Table 2(b); Palagini et al. 2016).

Four studies demonstrated that DBAS adequately differentiates between insomnia patients and good sleepers (Smith and Trinder 2001, diagnostic grading A1; Carney et al. 2010, diagnostic grading A2 for the primary insomnia group; Hertenstein et al. 2015, diagnostic grading B1; Crönlein et al. 2014, diagnostic grading B2; see Table 2(b)). DBAS score is also positively correlated with insomnia severity (Bluestein et al. 2010; Crönlein et al. 2014, see Table 2(b); Seow et al. 2018), although increased DBAS scores have been also reported in other sleep disorders, such as restless leg syndrome or restless leg syndrome with sleep apnoea (Crönlein et al. 2014).

Besides DBAS, other scales focussing on cognitive processes have also been found to be useful in diagnosing insomnia: the Glasgow Content of Thoughts Inventory (Harvey and Espie 2004, diagnostic grading A1, see Table 2(b)) and the Glasgow Sleep Effort Scale (Broomfield and Espie 2005, diagnostic grading A1; Hertenstein et al. 2015, diagnostic grading B1; see Table 2(b)).

Inventories of assessing personality patterns

In the early eighties, a study of insomniacs *vs.* good sleepers based on the Minnesota Multiphasic Personality Inventory (MMPI) found more frequently at least one pathologically elevated scale (79 *vs.* 29%) and higher scores of clinical scales D (depression), Pt (psychasthenia), Hy (hysteria), Hs (hypochondriasis) in insomniacs, denoting a personality profile characterised by depression, rumination, anxiety and inhibition of emotions in insomnia (Kales et al. 1983, diagnostic grading A2, see Table 2(c)). Subsequent studies have produced similar findings, as reviewed by Van de Laar et al. (2010, diagnostic grading C2, see Table 2(c)) showing that, in the majority of studies, the scales which were pathologically elevated were indeed D, Hy, Hs, and Pt.

Table 2. Studies of psychometric measurements in diagnosing insomnia.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
(a) Rating scales and questionnaires for the assessment of insomnia						
Buysse et al. (1989)	Case-control; psychometric instrument development (Pittsburg Sleep Quality Index—PSQI)	45 INS; 17 OSD; 34 Psy; 52 HS	**PSQI**; CBDI; PSG	Sens 84.4% (for INS)*, 89.6% (for all study pts); Spec 86.5% (all study pts); $\alpha = 0.83$; T-R = 0.85; Ext val: $r = 0.20$ (only for SOL) to PSG	The PSQI covers a multitude of sleep complaints/disorders with high scores of reliability and validity. Regarding external validity, correlation to PSG was very low or non-existent. Diagnostic Grading: **A1**	The PSQI is quite lengthy and its rating procedure is rather complicated; yet, it is widely used in research projects, evidently due to its comprehensiveness and its satisfactory psychometric properties.
Soldatos et al. (2000)	Case-control; psychometric instrument development (Athens Insomnia Scale—AIS)	105 INS; 144 Psy; 50 HS	**AIS**; CBDI; SPS	Sens 93%; Spec 85%; PPV 86%; NPV 92%; $\alpha = 0.90$; T-R = 0.89 (1 week); Ext val: $r = 0.90$ to SPS, $r = 0.76$ to PSQI**	The AIS, based on ICD-10 criteria for insomnia, presents with high scores of reliability and validity. Diagnostic Grading: **A1**	The AIS consists of 8 items and is easy to use and to rate. While not providing information on other sleep disorders apart from insomnia, it is being widely used by clinicians and researchers presumably due to its simplicity and its diagnostic usefulness.
Roth et al. (2002)	Case-control; psychometric instrument development (Global Sleep Assessment Questionnaire—GSAQ)	104 INS; 95 OSD; 13 HS	**GSAQ**; CBDI; SF-36; MOS-SPI	Sens 79%; Spec 57%; ROC-AUC = 0.72; T-R = 0.86 (2 weeks)	The GSAQ is a screening tool, especially useful in sleep centres and primary care settings for distinguishing among primary insomnia, insomnia associated with a mental disorder, OSA, PLM and parasomnias. Diagnostic Grading: **A2**	Sensitivity, specificity and AUC of the GSAQ were relatively low for primary insomnia, while they were generally higher for sleep disorders other than insomnia. A limitation of the study is the small sample size of HS.
Spoormaker et al. (2005)	Case-control; psychometric instrument validation (Sleep—50 Questionnaire)	65 INS; 213 OSD; 380 HS	**Sleep-50 Questionnaire**; CBDI; sleep log	Sens 71%; Spec 75%; $\alpha = 0.85$; T-R = 0.78 (3 weeks)	Sensitivity and specificity of the SLEEP-50 Questionnaire for diagnosing insomnia, although quite satisfactory, are generally lower than relevant measures for diagnosing other sleep disorders. Diagnostic Grading: **A2**	The SLEEP-50 Questionnaire is a valid psychometric tool, designed to detect many sleep disorders with 8 out of 50 items pertaining to insomnia. Its length limits its use for population studies which focus only on insomnia.
Kessler et al. (2010)	Case-control; psychometric instrument development (Brief Insomnia Questionnaire—BIQ)	83 INS and 120 HS, derived from the America Insomnia Survey's 10.094 individuals.	**BIQ**; CBDI	Sens 72.6%; Spec 98.9%; PPV 96.7%; NPV 88.7%; ROC-AUC = 0.86***	The reliability and validity of BIQ are very satisfactory. Diagnostic Grading: **A1**	The BIQ is quite lengthy and somewhat difficult to rate but its sophisticated design makes it a valuable tool, particularly for large epidemiological studies.
(b) Rating scales and questionnaires for assessing beliefs and attitudes about sleep						
Smith and Trinder (2001)	Case-control	19 INS; 19 HC	**DBAS**; CBDI; SII; SDQ; SWAI	ROC-AUC = 0.92; Sens 89%, Spec 78% (for cut-off 34.9)	Validity measures were quite satisfactory for DBAS; similar discrimination accuracy was also shown by SII and a psychiatric subscale of SDQ. Diagnostic Grading: **A1**	DBAS showed high accuracy in discriminating between INS and HC.
Harvey and Espie (2004)	Case-control; psychometric instrument validation (Glasgow Content of Thoughts Inventory—GCTI)	29 INS; 29 HS	**GCTI**	Sens 100%; Spec 83%; $\alpha = 0.87$; T-R = 0.88 (3 weeks); Ext val: $r = 0.65$ to a sleep diary, $r = 0.48$ to actigraphy.	The GCTI is a scale for reporting pre-sleep thought content; it has been found to distinguish satisfactorily between insomniacs and good sleepers. External validity to actigraphy was quite low, in contrast to the same measure *vs.* a sleep diary. Diagnostic Grading: **A1**	The GCTI scale is intended to be used mainly in the field of cognitive psychology, focussing on the assessment of pre-sleep cognitive activity, and it is not designed to measure insomnia *per se*; thus it seems to have a rather limited usefulness for wide application in every-day clinical practice. The stronger correlation of the GCTI to the sleep diary than to actigraphy highlights the subjective nature of insomnia.

(*continued*)

Table 2. Continued.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
Broomfield and Espie (2005)	Case-control; psychometric Instrument development (Glasgow Sleep Effort Scale—GSES)	89 INS;102 HS	**GSES**; CBDI; PSQI; HADS; DBAS	Sens 93%; Spec 87%; PPV 87%; NPV 94%; $\alpha = 0.77$; Ext val: high to PSQI.	The GSES can distinguish satisfactorily between insomniacs and good sleepers. Diagnostic Grading: **A1**	The GSES scale has not been developed to measure the condition insomnia *per se*, but it is rather devised as a measure of the voluntary attempt to control sleep which leads to psychophysiological insomnia.
Carney et al. (2010)	Case-control	Four INS groups (329 PI, 76 PBUI, 114 IMC, 530 CIMS); 335 HC	**DBAS-16**; CBDI; sleep log	$\alpha = 0.82$; for all groups of insomniacs: ROC-AUC = 0.86 Sens 80% Spec 76% (for cut-off 3.8); for PI only: AUC = 0.78 Sens 66% Spec 76%.	DBAS-16 shows a moderately high discrimination accuracy and good sensitivity and specificity. A slightly lower cut-off (3.5) may be useful in highly screened INS patients (e.g. PI and IMC) to increase the sensitivity of the measure. Diagnostic Grading: **A2**	DBAS-16 is a reliable and valid tool for use across a range of insomnia patient groups.
Crönlein et al. (2014)	Case-control	34 INS; 30 SAS; 31 RLS; 26 SAS + RLS; 24 HYP; 84 HC	**DBAS-16**; CBDI; RIS; PSQI; PSG	DBAS-16 (92.2 ± 22.8 INS *vs.* 56.5 ± 25.5 HC, $d = 1.47$, $p < 0.001$) Ext val: $r = 0.603$ to RIS; $r = 0.346$, −0.300, 0.470 (to subjective SOL, TST, WASO, resp.); $r = -0.218$, 0.238, −0.253, −0.218 (to PSG determined TST, WASO, N2%, SE%, respectively).	DBAS-16 score was moderately correlated with RIS in the whole sample; it showed low correlation with several subjective sleep measures and with PSG variables in patients. Diagnostic Grading: **B2**	Increased DBAS scores were found not only in primary insomnia, but also in other sleep disorders.
Hertenstein et al. (2015)	Case-control	47 INS; 52 GSC	**DBAS-16**; CBDI; GSES; ISI; PSG; sleep log	DBAS-16 (4.9 ± 1.8 INS *vs.* 2.3 ± 1.1 GSC, $d = 1.76$) GSES (6.7 ± 3.2 INS *vs.* 1.0 ± 1.4 GSC, $d = 2.31$) Ext val: $\beta = -0.41$ to PSG-determined total sleep time Correlation of ISI to GSES $r = 0.35$ and to DBAS $r = 0.32$ (both $p < 0.05$).	DBAS-16 score was negatively related to PSG-determined total sleep time with a medium effect size. Diagnostic Grading: **B1**	DBAS was not related to ISI in this study.
(c) Inventories for the assessment of personality patterns						
Kales et al. (1983)	Case-control	279 INS; 97 GS	Minnesota Multiphasic Personality Inventory (**MMPI**); CBDI	MMPI clinical scales**** differed between INS and GS as follows (mean ± *SD*, Cohen's *d*): *D* (71.6 ± 10.8 *vs.* 52.8 ± 16.7, $d = 1.22$), Pt (67.7 ± 8.9 *vs.* 53.7 ± 13.4, $d = 1.13$), Hy (66.8 ± 7.9 *vs.* 54.8 ± 11.7, $d = 1.11$), Hs (63.2 ± 7.9 *vs.* 50.2 ± 13.4, $d = 1.07$), Sc (66.4 ± 9.8 *vs.* 54.5 ± 15.0, $d = 0.86$), Pd (65.0 ± 10.8 *vs.* 56.2 ± 11.7, $d = 0.77$), Pa (60.7 ± 8.9 *vs.* 55.4 ± 10.0, $d = 0.54$), Ma (57.2 ± 9.8 *vs.* 55.0 ± 11.7, $d = 0.20$). At least one pathologically elevated scale in 76% of INS *vs.* 29% of GS (Sens 76%, Spec 88.3%); mean number of elevated scales per subject 2.6 in INS *vs.* 0.5 in GS.	Pathologically elevated MMPI scales in INS; profiles of INS were consistent with the presence of neurotic depression, rumination, chronic anxiety and inhibition of emotions, in particular anger. Diagnostic Grading: **A2**	Predominant personality style in insomnia is indicative of internalisation of negative emotions and other psychological disturbances; this pattern leads to psychophysiological activation and to the vicious cycle of generation and perpetuation of insomnia.

(*continued*)

Table 2. Continued.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
Stephan et al. (2018)	Longitudinal	4 general population samples; $N > 22.000$	**Midlife Development Inventory**; **Big Five Inventory**; self-administered questionnaire to measure sleep quality, follow-up after a 4–12 year period	Correlation coefficients (based on random effect metaanalysis) were generally low: impaired sleep quality at baseline with neuroticism (0.23) and extraversion (−0.06); decline in sleep quality at follow-up with neuroticism (0.10), extraversion (−0.03) and conscientiousness (−0.02).	Low neuroticism and high extraversion were related to better sleep quality at baseline and over time, and low conscientiousness was associated with a decrease of sleep quality over time, although the strength of the associations was weak. Diagnostic Grading: **C4**	Longitudinal relations were found between personality traits and poor and worsening sleep quality.
Van de Laar et al. (2010)	Review	38 articles on insomnia and personality; MMPI: 8 studies with a total of 857 INS	PubMed Search for **MMPI** in INS	Four MMPI clinical scales were pathologically elevated in INS: D (8/8 studies), Hy (7/8), Hs (6/8), Pt (6/8); two scales less frequently found to be elevated were Pd (2/8), Sc (1/8); no elevation for Mf, Pa, Ma, Si.	Neuroticism, internalisation, anxiety and perfectionism are commonly associated with insomnia. Diagnostic Grading: **C2**	Further longitudinal studies are needed to explore the relationship between personality and insomnia, particularly in relation to whether the persistence of chronic insomnia leads to changes in personality.

α: Cronbach's alpha; AIS: Athens Insomnia Scale; β: regression coefficient beta; BIQ: Brief Insomnia Questionnaire; CBDI: clinically-based diagnosis of insomnia; CIMS: complains of initiating maintaining sleep; *d*: Cohen's *d*; DBAS: Dysfunctional Beliefs and Attitudes about Sleep scale; DBAS-10: 10-item version of DBAS; DBAS-16: 16-item version of DBAS; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; Ext val: external validity; *g*: Hedge's *g*; GCTI: Glasgow Control of Thoughts inventory; GS: good sleepers; GSAQ: Global Sleep Assessment Questionnaire; GSC: good sleeper controls; GSES: Glasgow Sleep Effort Scale; HADS: Hospital Anxiety and Depression Scale; HC: healthy controls; HYP: hypersomnia; HS: healthy subjects; ICD-10: International Classification of Diseases,10th Revision; IMC: insomnia and medical condition; INS: insomniacs; ISI: Insomnia Severity Index; *k*: Cohen's kappa; MMPI: Minnesota Multiphasic Personality Inventory; MOS-SPI: Medical Outcome Study Sleep Problems Index I; N2: non-rapid eye movement sleep, stage 2; NPV: negative predictive value; OSA: obstructive sleep apnoea; OSD: other sleep disorders patients; PBUI: prolonged benzodiazepine users for insomnia; PI: primary insomniacs; PPV: positive predictive value; PSG: polysomnography; PSQI: Pittsburgh Sleep Quality Index; Psy: psychiatric patients; pts: patients; RIS: Regensburg Insomnia Scale; RLS: restless leg syndrome; ROC-AUC: receiver operating characteristic-area under the curve; SAS: sleep apnoea syndrome; SDQ: Sleep Disorders Questionnaire; SE: sleep efficiency; Sens: sensitivity; SF-36: Short Form Health Survey; SII: Sleep Impairment Index; SOL: sleep onset latency; sl lat: sleep latency; Spec: specificity; SPS: Sleep Problems Scale; SRBD: sleep related breathing disorders; SWAI: Sleep-Wake Activity Inventory; TST: total sleep time; T-R: test-retest reliability (week interval in brackets); WASO: wake after sleep onset.

Primary measure(s) assessed in each study are highlighted by the use of bold characters in the Instruments and Methods column.

*All values presented on this table pertain only to the sample of insomniacs of each study, unless otherwise specified.

**As shown by Pallesen et al. (2008).

***The psychometric characteristics of the BIQ provided in the paper are examined based on various diagnostic criteria (DSM -IV-TR, ICD-10, RDC); herewith we report the values pertaining to the diagnosis of insomnia when any of the above criteria are met.

****MMPI clinical scales: Hs: hypochondriasis; D: depression; Hy: hysteria; Pd: psychopathic deviate; Mf: masculinity/femininity; Pa: paranoia; Pt: psychasthenia; Sc: schizophrenia; Ma: hypomania, Si: social introversion.

In studies examining personality traits (such as the Big Five, Costa and McCrae 1992) in insomniacs, a high score on neuroticism was found to be the strongest predictor of insomnia, when poor sleep was assessed either subjectively or objectively (Williams and Moroz 2009; Duggan et al. 2014; Hintsanen et al. 2014; Stephan et al. 2018; Križan and Hisler 2019); however, the association of neuroticism with insomnia was not found to be diagnostically useful (Stephan et al. 2018, diagnostic grading C4, see Table 2(c)). On the other hand, extraversion and positive affectivity were associated with subjectively reported good sleep quality in studies that did not meet the criteria to be included herein (Gray and Watson 2002; Williams and Moroz 2009; Duggan et al. 2014).

Studies evaluating other personality characteristics beyond those assessed through the MMPI and the Big Five have shown that patients with chronic insomnia were more perfectionistic than healthy controls (Lundh et al. 1994; Vincent and Walker 2000). Cross-sectional studies, as well as longitudinal studies, confirmed significant associations between perfectionism and poor sleep even when measured with polysomnography (Vincent and Walker 2000; Azevedo et al. 2010; Jansson-Fröjmark et al. 2011; Johann et al. 2017, see Supplementary Table S2), although the available data did not allow to establish the diagnostic usefulness of measures of perfectionism in insomnia.

Review of studies on biological measurements

Polysomnography and sleep EEG analysis

To clarify the clinical value of polysomnography for diagnosing insomnia Baglioni, Regen, et al. (2014, see Table 3(a)) conducted a meta-analysis including all polysomnographic studies published up to that time in 582 patients with chronic primary insomnia and 485 good sleeper controls. Many significant differences were found between insomniacs and good sleepers as reflected in reduced sleep efficiency, increased sleep onset latency, reduced total sleep time, increased number of awakenings, reduced slow wave sleep and REM sleep, and increased wake time. However, the between groups difference for total sleep time was only 25 min (Cohen's $d = -0.6$); also the d-values for all PSG measures indicating reduced sleep quantity were generally low, the highest being for Sleep Efficiency and Slow Wave Sleep duration (-0.7 and -0.8, respectively), which correspond to a weak level of evidence for diagnostic accuracy (diagnostic grading B3). Interestingly, based on sleep diary data, the effect between groups was much stronger, with an average difference of $\sim$2 h for subjectively estimated total sleep time.

Through spectral analysis of sleep EEG, Spiegelhalder et al. (2012, see Table 3(a)) were able to demonstrate increased amounts of fast frequencies (in the sigma and beta bands), although the level of diagnostic accuracy at this finding was weak (diagnostic grading B3). It should also be noted that Colombo et al. (2016), based on high-density EEG, demonstrated that increased amounts of beta waves can also be detected in the resting-state EEG of patients with insomnia during wakefulness.

Riedner et al. (2016, see Table 3(a)) analysing all-night NREM sleep EEG found more power in high frequency EEG activity ($>$16 Hz) in chronic insomnia subjects *vs.* controls widespread across the scalp, indicating a possible hyperarousal state in chronic insomnia, even during the deepest stage of sleep. Buysse et al. (2008, see Table 3(a)) found evidence of hyperarousal (elevated EEG power in 18–40 Hz) only in the first NREM sleep period of insomniacs *vs.* controls. However, the results of this study as well as those of the study by Svetnik et al. (2017, see Table 3(a)) indicate that hyperarousal during sleep in insomnia may relate to female subjects only. Nonetheless, data provided in the above three studies were insufficient for establishing diagnostic validity (grade D for all of them). Moreover, Schwabedal et al. (2016, see Supplementary Table S3) found that the alpha wave frequency during sleep arousals in male insomniacs is similar to that during wake, while it is less than wake levels in controls, indicating a possible presence of hyperarousal during sleep also in male insomnia subjects.

Another possibility to analyse polysomnography is the so-called cyclic alternating pattern (Terzano et al. 2001). This is a phenomenon of NREM sleep and shows some overlap with certain Rechtschaffen and Kales events (mostly arousals). The cyclic alternating pattern (CAP) is based on the observation that certain EEG elements, distinct from background EEG, recur with a periodicity of 20–40 s. It marks an arousal fluctuation, containing unstable or aroused parts of sleep alternating with consolidated sleep. A large CAP rate marks disturbed sleep with poor sleep quality. Chouvarda et al. (2012, see Table 3(a)) showed that altered CAP patterns differentiate insomniacs from good sleepers, with satisfactory diagnostic accuracy (diagnostic grading A1) arguing for a destabilisation of sleep in insomnia.

When considering the diagnostic validity of sleep EEG-derived measures based on the grading system

Table 3. Studies of biological measurements in diagnosing insomnia.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
(a) Polysomnography and sleep EEG analysis						
Buysse et al. (2008)	Case-control	48 PI (29 women), 25 GSC (15 women)	**PSG power spectral analysis** (1–50 Hz) of EEG in NREM sleep with central EEG leads referenced to A1 + A2	No group difference in EEG power for whole-night NREM sleep; PI had higher power than GSC in 18–40 Hz in the first NREMP ($p < 0.05$); PI women *vs.* GSC women had higher power in 16–44 Hz (first three NREMPs) and in 3–6 Hz (all NREMPs) ($p < 0.05$); PI men *vs.* GSC men showed no power differences.	Women with PI showed increased high-frequency and low-frequency EEG power in NREM sleep compared to controls, particularly in early NREMPs; men with PI showed no EEG power differences *vs.* controls. Diagnostic Grading: **D**	Sex and NREMP rank may affect quantitative EEG differences between PI and controls; hyper-arousal and 'deep' sleep may coexist in women with PI.
Chouvarda et al. (2012)	Case-control	10 PI, 11 GSC	**CAP rate** based on PSG	Diagnostic potential of increased CAP rate: Sens 81.8% Spec 100% Diag Acc 90.5%.	Increase in CAP rate differentiates INS from GSC. Diagnostic Grading: **A1**	Increased CAP reflects sleep instability; promising tool in the diagnosis of insomnia; proof for the hyperarousal concept of insomnia.
Spiegelhalder et al. (2012)	Case-control	25 PI, 29 GSC	**PSG power spectral analysis**	Differences between power EEG frequency spectra in PI *vs.* GSC regarding wave bands: sigma (12–16 Hz; 1.89 ± 0.46 *vs.* 1.49 ± 0.43, $d = 0.90$), beta 1 (16–24 Hz; 0.51 ± 0.50 *vs.* 0.19 ± 0.36, $d = 0.74$), beta 2 (24–32 Hz; -0.63 ± 0.45 *vs.* -0.93 ± 0.39, $d = 0.72$).	Spectral power values for beta and sigma frequency bands are elevated during NREM in PI. Diagnostic Grading: **B3**	Spectral analysis data reflect a marker of cortical arousal; proof for hyperarousal theory.
Baglioni, Regen, et al. (2014)	Meta-analysis of 23 PSG studies	582 PI, 485 GSC	**PSG**; self-ratings	Based on studies with subjectively defined insomnia, PI differed from GSC regarding sleep continuity measures: SE ($d = -0.7$), TST ($d = -0.6$), SOL ($d = 0.4$), NA ($d = 0.6$), and WASO ($d = 0.6$). Also they differed in terms of duration of SWS ($d = -0.8$) and REM ($d = -0.6$).	Disturbed sleep continuity and reduced SWS and REM in PI. Diagnostic Grading: **B3**	Significant differences of PSG measures between PI and GSC (for TST about 25 min). Yet, subjective TST difference is much larger (about 2 h).
Riedner et al. (2016)	Case-control	8 CI, 8 GSC (sex and age-matched)	Sleep diaries; single-night PSG with 256-channel high-density EEG recording **power spectral analysis** and **sLORETA** (for cortical source imaging) of NREM sleep	CI *vs.* GSC had more power in high-frequency EEG activity (>16 Hz: for beta $p < 0.02$, for low gamma $p < 0.004$), widespread across the scalp; more power in alpha EEG activity (8–12 Hz, $p < 0.03$), even in sleep stage N3 ($p < 0.04$); in source imaging analysis CI *vs.* GSC showed elevated alpha EEG activity during sleep stage N3 in sensory and sensorimotor cortical areas ($p < 0.06$).	Possible hyperarousal, even in the deepest stage of sleep, in chronic insomnia subjects *vs.* controls. Sensory and sensorimotor cortical areas may be relatively more active, even in sleep stage 3, in CI *vs.* GSC. Diagnostic Grading: **D**	Possible sleep dysregulation in insomnia, denoting hyperarousal, seems to be localised in certain brain areas.
Svetnik et al. (2017)	Case-control	803 INS (509 women), 811 GSC (502 women)	Single-night **PSG power spectral analysis** (1–32 Hz) of NREM sleep EEG data, for each of three equal (one-third) parts of the night	INS *vs.* GSC under 40–45 years old had reduced power in the delta band (1–4 Hz) during Part 1 of the night ($p < 0.01$); male INS under 40 years old had reduced power in the theta band in Part 1 of the night ($p < 0.05$); female INS had increased power in the	Evidence for hyperarousal in INS, based on EEG spectral analysis; there may be an influence of age, sex and part of the night. Diagnostic Grading: **D**	Sleep hyperarousal in insomnia, possibly more pronounced among female subjects.

(*continued*)

Table 3. Continued.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
				beta2 band (25–32 Hz) in all parts of the night (ratio INS/GSC power from 1.11 to 1.16; $p < 0.05$); male INS had reduced power in the alpha band (9–12 Hz) during all parts of the night (ratio INS/GSC power from 0.82 to 0.92; $p < 0.01$).		
(b) Actigraphy						
Natale et al. (2009)	Case-control	126 INS, 282 NS	**ACT** (Mini-Motionlogger) for $\geq$7 consecutive nights (mean 8.4 nights)	Diagnostic potential of ACT: (a) SOL (12 min cut-off): ROC-AUC 0.68, Sens 0.55, Spec 0.81, PPV 0.56, NPV 0.80; (b) TST (440 min cut-off): ROC-AUC 0.68, Sens 0.66, Spec 0.61, PPV 0.43, NPV 0.80; (c) WASO (25 min. cut-off): ROC-AUC 0.75, Sens 0.66, Spec 0.75, PPV 0.54, NPV 0.83; (d) SE (92% cut-off): ROC-AUC 0.83, Sens 0.71, Spec 0.78, PPV 0.58, NPV 0.86. Discriminant score (based on combination of actigraphy-based TST, SOL and NA > 5): ROC-AUC 0.87, Sens 0.64, Spec 0.92, PPV 0.81, NPV 0.83	Actigraphy-based sleep parameters (each alone or in combination) differentiated INS from NS. Diagnostic Grading: **A1**	One of the few large studies providing quantitative criteria for identifying INS using Mini-Motionlogger
Natale et al. (2009)	Case-control	151 INS, 342 HC	**ACT** (Actiwatch 64) for one week	Diagnostic accuracy: (a) SOL (14 min cut-off): ROC-AUC 0.64, Sens 0.42, Spec 0.82, PPV 0.50, NPV 0.76; (b) WASO (40 min cut-off): ROC-AUC 0.74, Sens 0.68, Spec 0.55, PPV 0.40, NPV 0.79; (c) SE (87% cut-off): ROC-AUC 0.72, Sens 0.50, Spec 0.74, PPV 0.47, NPV 0.77.	ACT can differentiate INS from NS. Diagnostic Grading: **A2**	One of the few large studies providing quantitative criteria for identifying INS using Actiwatch 64. The quantitative criteria were not the same as those obtained by the same group with a different device denoting the need to adopt shared technical solutions.
(c) Heart rate (HR) and heart rate variability (HRV)						
Bonnet and Arand (1998)	Case-control	12 INS, 12 HC	ECG for **HR**; PSG over a 36-h sleep laboratory stay	Heart period (beat-to-beat interval) and its *SD* were lower in all stages of sleep in insomniacs *vs.* HC ($p < 0.001$ for both comparisons). Heart period in SWS was shorter in INS *vs.* HC (0.84 *vs.* 1.095, $p = 0.02$, $d = -0.91$–1.19*).	HR is increased and its variability (HRV) is decreased in INS *vs.* HC. Diagnostic Grading for HR: **B2**	HR and HRV changes indicate increased sympathetic nervous system activity in insomniacs during sleep.
Fang et al. (2008)	Case-control	18 INS, 21 NS	Resting **HRV** under paced breathing (resting wakefulness); neuropsychological evaluation.	No statistically significant differences between groups for HRV. Trend for lower resting HRV in INS *vs.* NS (HF of HRV 6.31 ± 0.93 in INS, *vs.* 6.91 ± 1.15 in NS; $d = -0.57$).	Heart rate variability may be decreased in insomniacs even during wakefulness. Diagnostic Grading for HRV: **B4**	Weak evidence of autonomic system dysregulation in insomnia.
Spiegelhalder et al. (2011)	Case-control	58 INS, 46 HC	**HRV** assessments in PSG-derived 5-min periods during waketime, stage 2 NREM, and REM.	INS *vs.* HC: lower wake-to-sleep HR reduction and lower variability of R-R intervals. Nocturnal HF of HRV (as indicator of parasympathetic activity) was in INS-SSD *vs.*	Based on HF of HRV values, INS with SSD showed the lowest parasympathetic activity, HC the highest; INS without SSD had values between the above	Alterations in HRV associated with sympathovagal disbalance may depend on sleep duration in insomniacs.

(*continued*)

Table 3. Continued.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
				INS-NSD *vs.* HC 522 ± 116 *vs.* 902 ± 224 *vs.* 1054 ± 179 for NREM and 497 ± 121 *vs.* 684 ± 169 *vs.* 1002 ± 203 for REM (values in ms^2 ± SEM); *d*-values for INS-SSD *vs.* HC, INS-SSD *vs.* HC and INS-SSD *vs.* INS-NSD were respectively, −0.52, −0.13, −0.40 for NREM and −0.44, −0.26, −0.24 for REM sleep.	two groups. Diagnostic Grading for HRV: **B4**	
de Zambotti et al. (2013)	Case-control	9 INS, 9 NS	Assessment of impedance cardiography for **HR** and **HRV** during a night of PSG; PSQI; AIS	(a) HR in bpm was 71.10 ± 7.24 in INS *vs.* 61.92 ± 12.01 in NS during time awake ($g = 0.88$); the difference between stage awake and sleep stages was much smaller in NS *vs.* INS (group by stage interaction $p < 0.001$). (b) HRV spectral analysis: reduction from wake to sleep of LF/HF ratio and increase in HF; no difference between groups. (c) PEP (inversely related to β-adrenergic activity) was shorter in INS *vs.* NS ($p < 0.05$). (d) PEP was correlated with AIS ($r = 0.53$) and PSQI ($r = 0.58$); both $p < 0.05$.	(a) Strong reduction in HR from wake to sleep in INS. (b) No differences between groups in spectral analysis findings. (c) Constant hyperactivation of the sympathetic nervous system throughout the whole night in INS *vs.* NS. (d) Correlation between high physiological sympathetic activation and low score in subjective sleep assessment measurements. Diagnostic Grading for HR: **B3**	Sympathetic hyper-activation is a feature of INS.
Farina et al. (2014)	Case-control	85 INS, 55 HC	**HR** based on home-based PSG; subjective sleep evaluation	HR (in bpm) in INS *vs.* HC was increased in wake before sleep (67.8 ± 8.7 *vs.* 59.0 ± 7.3; $p < 0.001$, $d = 1.08$), in early stage N2 sleep (64.8 ± 7.6 *vs.* 49.0 ± 5.4; $p < 0.001$, $d = 2.32$) and late-stage N2 sleep (60.9 ± 8.0 *vs.* 53.5 ± 10.4; $p < 0.001$, $d = 0.82$); no significant differences for stages N3, REM and wake state after final awaking. HRV was lower in INS *vs.* HC across periods of wakefulness and the various sleep stages.	Modifications of heart rate and HRV were consistent with increased sympathetic activity while being awake before sleep and in Stage-2 NREM sleep; no differences during slow-wave sleep, REM sleep and post-sleep awake. Diagnostic Grading for HR: **B1**	Autonomic hyperarousal is a feature of insomnia, both before and during sleep.
(d) Skin conductance						
Broman and Hetta (1994)	Case-control	40 INS (primary or secondary to psychiatric disorders), 20 HC	Electrodermal activity (**EDA**) during a habituation paradigm; PSG	(a) SCL was higher in INS *vs.* HC in all three conditions (pre-, during and post-stimulation) ($p < 0.005$ *vs.* HC) (b) Non-habituation of EDA with repeated stimuli 16/40 INS *vs.* 2/17 HC ($\chi^2 = 10.5$, $df = 2$, $p < 0.01$) Sens 40% Spec 88.9%; non-habituation was associated with higher EDA ($p < 0.001$) and shorter sleep duration (subjectively and objectively assessed; $p < 0.005$ for both).	Excessive daytime arousal, as reflected by EDA, is associated with persistent insomnia. Diagnostic Grading for non-habituation of EDA: **A4**	Proof of daytime arousal in insomnia.

(*continued*)

Table 3. Continued.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
(e) Thermoregulation						
Gradisar et al. (2006)	Case-control	11 INS, 8 NS	Core body (**Tc**) and finger (**Tf**) temperature in 26-h constant routine	Greater increases in Tf 5 min after lights out in INS *vs.* NS ($1.5 \pm 1.2\,^{\circ}C$ *vs.* $1.2 \pm 1.2\,^{\circ}C$, $p < 0.001$, $g = 0.24$). Higher mesor of Tc in INS *vs.* NS ($37.0 \pm 0.2\,^{\circ}C$ *vs.* $36.8 \pm 0.2\,^{\circ}C$, $p = 0.03$, $g = 0.96$).	INS have grater finger temperature increases when attempting to sleep, and higher core body temperature. Diagnostic Grading for Tc: **B3**	Insomnia may be a disorder of thermoregulation with impaired heat loss.
(f) Oxygen consumption rate						
Bonnet and Arand (1996)	Case-control	10 INS, 10 HC	2 days PSG; **VO_2 consumption**; MSLT; MMPI; sleep history	Mean VO_2 consumption rate during the whole 24 h period was 296 *vs.* 266 ml/min (INS *vs.* HC, $p < 0.01$, $g = 0.95$). Mean VO_2 consumption during the sleep period was 280 *vs.* 256 ml/min (INS *vs.* HC, $p < 0.0001$, $g = 0.76$).	Metabolic rate (as reflected in VO_2 consumption rate) was elevated in INS *vs.* HC across the day and throughout the night. Diagnostic Grading: **B3**	Insomnia is a state of hyperarousal during the whole 24 h period.
Bonnet and Arand (1998)	Case-control	9 INS with subjective complaint only (relatively normal sleep on their PSG), 9 HC.	2 days PSG; **VO_2 consumption**; MSLT; MMPI; sleep history	Mean VO_2 consumption rate during the whole 24 h period was 304 ± 26 *vs.* 286 ± 34 ml/min (INS *vs.* HC, $p < 0.001$, $g = 0.57$). Mean VO_2 consumption rate during the sleep period did not differ between the two groups.	Increases in VO_2 in patients with Sleep State Misperception Insomnia (SSMI) were found only during daytime. Diagnostic Grading: **B4**	Daytime metabolic rate is increased in insomnia, even in sleep state misperception insomnia.
(g) Neuroimaging						
Smith et al. (2002)	Case-control	5 PI, 4 GSC	**SPECT**; PSG	Cerebral blood flow is reduced in PI *vs.* GSC during NREM for: FMC (212.7 ± 42.6 *vs.* 271.4 ± 26.3, $p < 0.05$, $g = -1.43$), OC (190.9 ± 20.5 *vs.* 239.6 ± 20.5, $p < 0.03$, $g = -2.11$), BG (157.4 ± 21.8 *vs.* 233.1 ± 36.8, $p < 0.006$, $g = -2.31$), PC (182.1 ± 27.1 *vs.* 232.6 ± 27.6, $p < 0.03$, $g = -1.64$).	Cerebral blood flow appeared to be reduced during NREM in primary insomnia. Diagnostic Grading: **B1**	Small sample size; finding seems to be contrary to the findings of other neuroimaging studies, making its high diagnostic validity questionable.
Altena et al. (2008)	Case-control	21 INS, 12 GSC	**fMRI**; verbal fluency tests	INS *vs.* GSC showed less activation in the LMPC ($z = 3.73$–4.18; $d = 1.61$–1.82) and LIFG ($z = 3.30$–4.17; $d = 1.44$–1.82) during fluency tests; these findings were partially restored after non-pharmacological intervention for treating insomnia.	Reduced task-related frontal activity in insomniacs, reversed after treatment. Diagnostic Grading: **B1**	The reduced frontal activity in cognitive tasks may be associated with persistent worry and preoccupation in insomniacs.
Kay et al. (2016)	Case-control	44 PI, 40 GSC	**PET**; PSG	Decline in regional cerebral metabolic rate for glucose from wakefulness to sleep was lower in PI *vs.* GSC in the following cortical areas: praecuneus/posterior cingulate, anterior cingulate/medial frontal, insula, anterior temporal (all $p < 0.05$).	Decrease of brain metabolism from wake to NREM is less pronounced in PI compared to GSC. Diagnostic Grading: **D**	Insomnia may be related to a failure of arousal mechanisms to decline in activity from wake to sleep.

(*continued*)

Table 3. Continued.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
Regen et al. (2016)	Case-control	20 PI, 20 GSC	**fMRI**; PSG	Waking DMN connectivity was correlated negatively with SE (hip-ACC $r^2 = 0.24$; hip-PCC $r^2 = 0.28$; hip-vmPFC $r^2 = 0.26$, RSC-vmPFC $r^2 = 0.24$) and positively with SOL (RSC-ACC $r^2 = 0.26$; RSC-PCC $r^2 = 0.17$; RSC-vmPFC $r^2 = 0.31$). No statistically significant group differences between PI and GSC.	No group differences in functional connectivity between primary insomniacs and good sleepers. Diagnostic Grading: **C3**	DMN connectivity was found to be correlated to some PSG indices; no differences were found between insomnia and controls.
Leerssen et al. (2019)	Case-control	65 INS, 65 GSC	**fMRI**; ISI; sleep diary	Stronger functional connectivity in INS *vs.* GSC between bilateral hippocampus and a cluster of voxels in the left middle frontal gyrus ($Z_{max} = 4.22$; $p = 0.035$ in cluster based correction for multiple comparisons, $d = 1.05$); the strength of this connectivity was associated with insomnia severity and sleep quality ($r = 0.37$ and $r = -0.31$, respectively; $p < 0.01$ for both).	In insomnia there is increased hippocampus-prefrontal connectivity; this increase is correlated to subjective measures of insomnia severity and poor sleep quality. Diagnostic Grading: **B1**	A part of the circuit activating with maladaptive rumination and deactivating with sleep shows higher functional connectivity in insomnia.
(h) HPA axis						
Vgontzas et al. (2001)	Case-control	11 INS, 13 HC	**Serial 24h-plasma samplings** of **ACTH** and **cortisol**	INS *vs.* HC: 24h-ACTH 4.2 ± 0.3 *vs.* 3.3 ± 0.3 pM, $p = 0.04$, $d = 3.0$; 24 h-cortisol 218.0 ± 11.0 *vs.* 190.4 ± 8.3 nM, $p = 0.07$, $d = 2.87$. Higher values in INS, most prominent in the evening and first half of the night. Circadian rhythm retained. Degree of cortisol elevation correlates with degree of objective shortening of sleep duration.	HPA-axis activity elevated in INS *vs.* HC, especially in the evenings and first half of the night, related to objectively increased sleep fragmentation. Diagnostic Grading: **B1**	HPA-axis findings are more prominent in insomnia with objectively verified short sleep duration.
Riemann et al. (2002)	Case-control	10 PI, 10 HC	PSG; evening and nocturnal **serum cortisol** and melatonin sampling (from 19:00 to 09:00 h in 30 min intervals)	Differences of PSG sleep continuity and sleep architecture variables between PI and HC were negligible. Cortisol levels were not different between PI and HC: AUC values of cortisol levels (in μg/dl × 30 min) were for PI 214.4 ± 62.5 and for HC 253.7 ± 75.9, $p = 0.245$, $g = -0.54$.	In PI with minor alterations of objective sleep, serum cortisol is not affected. Diagnostic Grading: **B4**	Involvement of HPA axis seems to depend on degree of objective sleep disturbance.
Seelig et al. (2013)	Case-control	13 PI, 12 HC (all women)	PSG; midnight and early morning **salivary cortisol**	Increased mid-night salivary cortisol higher in PI *vs.* HC (1.4 ± 1.4 mmol/lt *vs.* 0.7 ± 0.4 mmol/lt, $d = 0.67$, $p = 0.02$); no significant difference for morning salivary cortisol (10.3 ± 6.3 mmol/lt *vs.* 7.3 ± 3.5 mmol/lt, $p = 0.18$, $d = 0.58$).	Mid-night salivary cortisol levels are increased in primary insomnia. Diagnostic Grading: **B4**	HPA-activity at the first half of the night seems to be more reliable in insomnia than morning cortisol.

(*continued*)

Table 3. Continued.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
Mikoteit et al. (2019)	Case-control	60 INS, 30 HC	ISI; morning **salivary cortisol**.	Insomnia is associated with decreased cortisol awakening reaction (CAR, but the association is rather weak; $g = 0.53–0.59$); ISI correlates inversely with CAR.	Insomnia is not related to increased morning salivary cortisol but rather to decreased CAR. Diagnostic Grading: **B4**	The deficit of cortisol awakening reaction in insomniacs seems to be a characteristic of insomnia, rather than an increase of morning cortisol levels.
(i) Melatonin						
Hajak et al. (1995)	Case-control	10 PI, 5 HC	PSG; hourly sampling of nocturnal plasma **melatonin** concentrations	Melatonin peak at the middle of the night was lower in PI (82.5 ± 26.5 pg/ml) *vs.* HC (116.8 ± 13.5 pg/ml; $g = -1.39$, $p < 0.01$), especially in chronic patients (72.1 ± 25.0 *vs.* 98.2 ± 24.9 pg/ml in patients with PI duration more than 5 *vs.* <5 years, $g = -0.94$); g-values for chronic PI *vs.* HC and for non-chronic PI *vs.* HC were −1.97 and −0.86, respectively. Plasma melatonin levels begin increasing earlier in the evening in PI *vs.* HC.	Earlier onset and lower peak of melatonin typical for chronic primary insomnia. Diagnostic Grading: **B2**	Circadian rhythm of melatonin secretion is disturbed in patients with chronic primary insomnia; proof-of-concept study.
Riemann et al. (2002)	Case-control	10 PI, 10 HC	PSG; evening and nocturnal **serum** cortisol and **melatonin** sampling (from 19:00 to 09:00 h in 30 min intervals)	AUC values of melatonin levels (in pg/ml × 60 min) were lower for PI (515.5 ± 174.6) than for HC (682.8 ± 124.2), $p = 0.029$, $g = -1.06$; the main difference occurred during the first half of the night. The effect of objective measures (PSG) of insomnia was negligible.	Insomnia, even with no objective sleep changes, is related to a deficit in nocturnal melatonin, especially during the first half of the night. Diagnostic Grading: **B2**	Circadian sleep regulation is affected in insomnia.
(j) **Marker of inflammation: CRP**						
Parthasarathy et al. (2015)	Longitudinal, community-based	1409 adults (including 249 intermittent and 128 persistent insomniacs)	**CRP**; assessment for presence of insomnia at two time points with an interval of 6 years; 20 year follow up, for assessment of mortality rate.	Participants with insomnia at both time-points (6 years apart) were more likely to die during the 20-year follow-up period than non-insomniacs (Hazard Ratio: 1.58, 95%CI: 1.02–2.45); no significant difference for those complaining of insomnia at either time-point (Hazard Ratio:1.22, 95%CI: 0.86–1.74). Adjusted mortality Hazard Ratio did not change when CRP was included in the model (1.93 *vs.* 1.97). Geometric means of CRP measurements at the second time-point (but not at baseline) for subjects with insomnia at both time-points *vs.* insomnia at either time point *vs.* non-insomniacs were 2.86 *vs.* 1.61 *vs.* 1.52 mg/lt, respectively (ANOVA $p = 0.02$).	Increase of CRP is associated with persistent insomnia but does not seem to be an important mediator between insomnia and mortality. Diagnostic Grading: **D**	Persistent insomnia relates to increased mortality risk, independent of systematic inflammation.

(*continued*)

Table 3. Continued.

Citation	Type of study	Type and number of subjects	Instruments and methods	Results	Main conclusions	Comments
(k) Marker of neuroplasticity: BDNF						
Mikoteit et al. (2019)	Case-control	60 INS, 30 HC	ISI; PSG; **serum BDNF**	Decreased BDNF separates INS from HC (Hedge's $g = 1.75$), ROC-AUC 0.88, Sens 0.78, Spec 0.79, PPV 0.88, NPV 0.66. Low BDNF correlated with decreased REM sleep, but not with any objective sleep continuity parameters in the PSG.	Decreased BDNF is associated with subjective sleep difficulty, but not for objectively assessed poor sleep continuity. Diagnostic Grading: **A1**	BDNF appears to be a biomarker for the clinical diagnosis of insomnia. A possible link between BDNF and insomnia seems to be *via* regulation of REM sleep
Fan et al. (2019)	Case-control	57 INS: 30 with TST $<$ 6 h (short sleep duration insomniacs, INS-SSD) and 27 with TST $\geq$ 6 h (normal sleep duration insomniacs, INS-NSD), 29 HC	Clinical diagnosis for insomnia; PSG; neuropsychological tests; **serum BDNF**	BDNF levels in INS-SSD *vs.* INS-NSD *vs.* HC were 11.4 ± 0.3 *vs.* 17.4 ± 0.3 *vs.* 20.5 ± 1.2; d-values for INS-SSD *vs.* HC, INS-NSD *vs.* HC and INS-SSD *vs.* INS-NSD were −10.49, −3.49, and −20.00, respectively. In INS-SSD, BDNF levels correlated with test scores of spatial span ($r = 0.42$), visuospatial memory ($r = 0.50$) and continuous performance ($r = 0.42$).	INS-SSD had lower BDNF than INS-NSD and HC. INS-NSD had lower BDNF than HC. Cognitive performance correlated with BDNF levels in INS-SSD. Diagnostic Grading: **B1**	Low BDNF differentiates INS from HC and it may be a mediator between insomnia and cognitive impairment in insomniacs with short sleep duration.

95%CI: 95% confidence interval; ACC: anterior cingulate cortex; ACT: actigraphy; ACTH: adrenocorticotrophin hormone; AIS: Athens Insomnia Scale; AUC: area under the curve; BDNF: brain-derived neurotrophic factor; BG: basal ganglia; CAR: cortisol awakening reaction; CAP: cyclic alternating pattern; CI: chronic insomniacs; CRP: C-reactive protein; DMN: default mode network; EDA: electrodermal activity; EEG: electroencephalography; FMC: frontal medial cortex; fMRI: functional magnetic resonance imaging; *g*: Hedge's *g*; GSC: good sleeper controls; HC: healthy controls; HF: high frequency; hip: hippocampus; HPA: hypothalamus-pituitary-adrenal; HR: heart rate; HRV: heart rate variability; Hz: hertz; ID: Insomnia Disorder; IL-6: interleukin-6; INS: insomniacs; ISI: Insomnia Severity Index; LF: low frequency; LIFG: left inferior frontal gyrus; LMPC: left medial pre-frontal cortex; MMPI: Minnesota Multiphasic Personality Inventory; MSLT: multiple sleep latency test; NA: number of awakenings; NA $>$ 5: number of awakenings longer than 5 min; NPV: negative predictive value; NREM: non-rapid eye movement; NREMP: non-REM period; NS: normal sleepers; NSD: normal sleep duration; OC: occipital cortex; PC: parietal cortex; PCC: posterior singulate cortex; PEP: pre-ejection period; PET: positron emission tomography; PI: primary insomniacs; PPV: positive predictive value; PSG: polysomography; PSQI: Pittsburgh Sleep Quality Index; RCT: randomised controlled trial; REM: rapid eye movement; ROC-AUC: receiver operating characteristic-area under the curve; RSC: retrosplenial cortex; SCL: skin conductance level; SD: standard deviation; SE: sleep efficiency; SEM: standard error of the mean; Sens: sensitivity; SL: sleep latency; sLORETA: standardised low-resolution brain electromagnetic tomography analysis; SOI: sleep onset insomnia; SOL: sleep onset latency; Spec: specificity; SPECT: single photon emission computerised tomography; SSD: short sleep duration; SWS: slow wave sleep; Tc: core body temperature; Tf: finger temperature; TIB: time in bed; TNF-α: tumour necrosis factor-a; TST: total sleep time; TWT: total wake time; vmPFC: ventromedical pre-frontal cortex; VO_2: volume of oxygen; WASO: wake after sleep onset.

Primary measure(s) assessed in each study are highlighted by the use of bold characters in the Instruments and Methods column.

*Range of *d*-values based on a range of *SD* values in different populations, as reported in the study by O'Neil et al. (2016).

for establishing diagnosis, as applied to the studies of Table 3(a), CAP rate emerges as the most reliable biomarker for diagnosing insomnia (diagnostic grading A1), while there is rather weak evidence that reduced sleep efficiency and SWS duration (as measures of sleep macro-architecture) as well as the increased power of fast frequency EEG bands sigma and beta (as measures of sleep micro-architecture) may also be considered as potential biomarkers (diagnostic grading B3 for measures of both macro- and micro-architecture of sleep). It should be noted, however, that the high diagnostic grading found for CAP is based on just one study as yet.

Actigraphy

Actigraphy is a non-invasive method for monitoring physical activity and the rest-activity cycle. In sleep medicine it is used to assess circadian sleep-wake rhythm and the duration of rest periods (Wichniak et al. 2017; Smith et al. 2018); yet, the usefulness of this method in the assessment of insomnia is still being discussed. Actually, many studies on actigraphy in insomnia report only group differences and their level of significance, without providing diagnostic cut-off scores of derived sleep parameters and their sensitivity, specificity, and predictive values.

Actigraphy as a diagnostic method suffers also from an absence of common standards of technical solutions and software algorithms for detecting sleep; thus, published results of studies using a certain device cannot be generalised to apply to devices of other manufacturers. Another obstacle for the use of actigraphy as a diagnostic or research biomarker for insomnia is related to its lower accuracy to detect wakefulness in case of low sleep efficiency, since insomniacs may frequently lie immobile in bed while not asleep. Nonetheless, two large studies that reported on the diagnostic accuracy of actigraphy for insomnia (Table 3(b)) show that actigraphy has very satisfactory diagnostic validity (Natale et al. 2009, 2014), diagnostic grading A1 and A2, respectively. In addition, it seems that actigraphy can also be useful for the prediction of treatment response to Cognitive Behavioural Therapy for insomnia (Bathgate et al. 2017, see Supplementary Table S3).

Heart rate and heart rate variability

Psychophysiological stress and the consequent arousal lead to an increase of heart rate (HR) and to a decrease of heart rate variability (HRV), i.e. of the variability of time between consecutive heart beats, commonly referred to as the RR (R-wave to R-wave) intervals. Electrocardiographic (ECG) recordings during wake time or sleep allow the assessment of RR-intervals, which vary as a function of autonomic nervous system (for more details see Malik et al. 1996; Stein and Pu 2012). Spectral analyses describe the oscillations of RR-intervals in three frequency bands: high frequency power (HF), reflecting parasympathetic input; low frequency power (LF), which depends on both sympathetic and parasympathetic input; very low frequency power (VLF), which is affected by parasympathetic influences. An indicator of the sympathovagal balance appears to be the LF/HF-ratio (but, see for opposite positions Billman 2013).

In insomnia, HR was shown to be increased (or heart period shortened) especially in the wake period before sleep and in early stage 2 sleep, although the level of diagnostic accuracy of this marker was found to be variable across studies (Bonnet and Arand 1998; de Zambotti et al. 2013; Farina et al. 2014, diagnostic grading ranging from B1 to B3, see Table 3(c)).

Specific alterations of HRV patterns have been reported in insomniacs (Tobaldini et al. 2013). Bonnet and Arand (1998, see Table 3(c)) in a small sample of individuals with objectively defined insomnia found increased LF and decreased HF during all sleep stages; this pattern of results mirrored the expected alteration in sympathovagal balance. Others examined HRV of insomniacs *vs.* healthy controls in resting state, before and after sleep onset, or during specific sleep stages (Fang et al. 2008; de Zambotti et al. 2013; Farina et al. 2014, see Table 3(c)); two patterns emerged for insomnia: either, there was no difference between LF or HF, or there was a tendency for decreased HF as indicator for decreased parasympathetic tone (Fang et al. 2008) or an increase in LF as indicator for increased sympathetic activity (de Zambotti et al. 2013; Farina et al. 2014). Findings were most prominent in wake before sleep onset and Stage 2 sleep (Farina et al. 2014). To explain these inconsistent results, sleep duration should be considered as a possible confounder. Findings on HF seem to refer prevalently to insomnia with short sleep duration, while HF and LF was normal in insomnia with normal sleep duration (Spiegelhalder et al. 2011, see Table 3(c); Miller et al. 2016, see Supplementary Table S3). Nevertheless, the level of diagnostic accuracy of HRV, wherever it was possible to be assessed, was virtually absent (diagnostic grading B4). On the same line, Dodds et al. (2017) having thoroughly reviewed 22 studies on HRV and insomnia concluded that the heterogeneity in regards to sample

selection, methods of HRV assessment, and reporting bias precluded empirical evidence to support the hypothesis of HRV impairment in insomnia.

To summarise, an increased HR before and after sleep onset can be considered as a promising psychophysiological biomarker for diagnosing insomnia (diagnostic grading ranging from B1 to B3). Based on the reviewed studies, however, HRV does not seem to be useful as a diagnostic biomarker for insomnia (diagnostic grading B4).

Skin conductance

Skin conductance level (SCL) is another psychophysiological index of ANS, representing the sympathetic activity in reaction to emotional stimuli. In an experimental habituation study in wake time, Broman and Hetta (1994, see Table 3(d)) found in individuals with insomnia compared to healthy controls increased SCL (without, however, providing indices useful for estimation of diagnostic accuracy) and poor habituation to repeated stimuli, although the diagnostic sensitivity of the latter for insomnia was very low (40%), indicating that the habituation paradigm cannot be used as a diagnostic marker (grading A4). In contrast to the finding of an increased SCL in insomnia during daytime, which is compatible with the hyperarousal model, other findings of SCL during sleep were shown to be inconsistent in a review paper by Riemann et al. (2010).

Thermoregulation

Thermoregulation refers to the circadian rhythm of core body temperature and skin temperature (Lack et al. 2008; Te Lindert and Van Someren 2018). Healthy sleep goes along with a decline in core body temperature at night. In contrast, the desynchronisation between wake-sleep and temperature rhythms may underlie certain specific types of insomnia (Morris et al. 1990, see Table S3; Lack et al. 2008). Accordingly, objective sleep maintenance insomnia in the elderly was related to elevated nocturnal core body temperature (Lushington et al. 2000, see Supplementary Table S3), which might be associated with hyperarousal and hypermetabolism. Increased core body temperature in insomniacs *vs.* normal sleepers, as shown by Gradisar et al. (2006, see Table 3(e)), could be considered as a potential biomarker of insomnia based on a finding of low diagnostic accuracy (diagnostic grading B3). Moreover, while warming of the body is associated with increased sleep propensity in healthy sleepers, this does not seem to be the case for individuals with insomnia (Raymann et al. 2007, see Supplementary Table S3).

Oxygen consumption rate

Overall oxygen use (VO_2) as a proxy of whole body metabolic rate enables to assess the physiological activity. Chapman et al. (2018) concluded in a systematic review that metabolic rate in insomnia is modestly elevated during the day and throughout the night. This finding is in line with the hyperarousal model, which refers both to wake and to sleep time. Remarkably, the metabolic rate was not only found to be increased in objectively verified insomnia (Bonnet and Arand 1996), but was also shown to be increased in 'sleep state misperception' insomnia, albeit to a lesser degree (Bonnet and Arand 1998), as shown in Table 3(f), with diagnostic grading being B3 and B4, respectively. Consequently, there is some evidence that VO_2 consumption rate may be considered as a potential biomarker for objectively verified insomnia.

Neuroimaging

In the last two decades, neuroradiological and nuclear medicine techniques have been used to investigate biological markers of insomnia. The first study in this field acquired single photon emission computerised tomography (SPECT) data from five patients with insomnia and four healthy controls (Smith et al. 2002, see Table 3(g)), and surprisingly, reported a reduced cerebral blood flow in medial frontal, parietal and occipital brain areas as well as in the basal ganglia of insomnia patients during NREM sleep. This finding, which shows high diagnostic validity (grading B1), is in disagreement with the hyperarousal model of insomnia (Riemann et al. 2010), and has not been replicated.

Some further studies used ^{18}F-FDG-PET ([^{18}F]fluorodeoxyglucose positron emission tomography) to quantify brain metabolic patterns. Nofzinger et al. (2004) investigated seven patients with insomnia in comparison to 20 healthy controls during NREM sleep and wakefulness. One of the key findings was that patients with insomnia had a smaller decrease in brain metabolism from wakefulness to NREM sleep than healthy controls, in particular in the ascending reticular activating system (ARAS) as well as in areas related to emotion regulation (amygdala, hippocampus, and anterior cingulate cortex) and cognition (prefrontal cortex). This finding has been partially replicated in a

later study from the same group of 44 patients with insomnia and 40 healthy controls (Kay et al. 2016, diagnostic grading D, see Table 3(g)). A further study of this group suggests that brain areas involved in conscious awareness might also be involved in the perception of wake-sleep transitions (Kay et al. 2017), which is characteristically altered in insomnia (Harvey and Tang 2012).

Studies using functional magnetic resonance imaging (fMRI) in insomnia can be divided into those that used specific tasks in the scanner and those that investigated functional connectivity during resting state conditions. One task-related study investigated 22 patients with insomnia and 38 healthy controls and suggested an increased reactivity of the amygdala in patients with insomnia in response to the presentation of sleep-related stimuli (Baglioni, Spiegelhalder, et al. 2014). Furthermore, during the performance of cognitive tasks, a reduced recruitment of frontal brain areas has been reported in several studies using Tower of London, working memory, and category and letter fluency tasks (Altena et al. 2008 with diagnostic grading B1, see Table 3(g); Drummond et al. 2013; Stoffers et al. 2014). More recently, Seo et al. (2018) reported a delayed deactivation of the fear extinction network in 23 patients with insomnia compared to an equal number of healthy controls.

Resting-state functional connectivity (RSFC) in insomnia was investigated in many recent studies; however, the results are clearly very inconsistent, partly due to a liberal use of statistical significance thresholds. Most notably, Leerssen et al. (2019, see Table 3(g)) reported an increased connectivity between the hippocampus and the prefrontal cortex in 65 patients with insomnia compared to 65 healthy controls (diagnostic grading B1) while Regen et al. (2016, see Table 3(g)) did not find significant group differences in 20 patients with insomnia and 20 healthy controls; however, RSFC components were found to be weakly correlated to sleep efficiency and sleep latency (diagnostic grading C3).

Reviewing the literature summarised above, previous narrative reviews came to the conclusion that corticolimbic overactivity is a key feature of patients with insomnia (e.g. Riemann et al. 2015). However, an activation likelihood estimation meta-analysis reported a lack of consistent brain alterations in insomnia across studies (Tahmasian et al. 2018). While this kind of meta-analysis has specific strengths and limitations, it still appears to be too early to draw definitive conclusions based on reported data from neuroradiological and nuclear medicine studies on insomnia. In particular, small sample sizes in combination with purely exploratory data analysis strategies limit the validity of this literature and confer a high risk for false negative and false positive findings (Button et al. 2013). Moreover, based on our data it seems that some studies provide evidence that various indices could have diagnostic validity for insomnia (see Table 3(g) where diagnostic grading values are B1 for three studies and C3 for another one); yet, the inconsistencies and large diversity of these indices make it difficult to establish common standards across neuroimaging approaches for diagnostic purposes.

HPA axis

Findings of alterations in cortisol levels in individuals with insomnia have been inconsistent. Some studies described statistically significantly elevated ACTH and cortisol levels in the evening and in the first half of the night in insomniacs compared to healthy controls (Vgontzas et al. 2001 and Seelig et al. 2013, see Table 3(h); Steiger 2007; Zhang et al. 2014, see Supplementary Table S3), and other studies did not (Riemann et al. 2002; van Neijenhof et al. 2018). Different degrees of insomnia severity across studies may explain these discrepant findings: individuals with insomnia and a shortened total sleep time (TST) demonstrate elevated ACTH and cortisol concentrations in the first half of the night and also in the morning; in contrast, individuals with insomnia and a normal or only slightly decreased TST show unaltered cortisol levels (Vgontzas et al. 2001 see Table 3(h); Fernandez-Mendoza et al. 2014; D'Aurea et al. 2015, see Supplementary Table S3).

A similarly inconsistent pattern of results is observed for the morning HPA axis activity: salivary morning cortisol after awakening was either decreased (Backhaus et al. 2004, see Supplementary Table S3; Mikoteit et al. 2019, see Table 3(h)) or comparable to cortisol levels of normal sleepers (Seelig et al. 2013; Zhang et al. 2014; van Neijenhof et al. 2018). Lower morning cortisol concentrations correlated with lower sleep quality and with non-restorative sleep (Backhaus et al. 2004; Mikoteit et al. 2019). On the other hand short objective TST was related to increased morning cortisol levels (D'Aurea et al. 2015; Fernandez-Mendoza et al. 2017). Finally, the dexamethasone/corticotropin releasing hormone (Dex/CRH) test, the gold standard of a pharmacological HPA axis challenge, does not show a hyperactivity of HPA axis in insomnia (Lattova et al. 2011, see Supplementary Table S3). One explanation for this finding may be that chronic

insomnia is often associated only with a mild to moderate shortened sleep time, which appears to allow for adaptation of the HPA axis activity.

Regarding the diagnostic usefulness of HPA axis measures as a biomarker for insomnia, one study showed that higher 24-h serum ACTH and cortisol levels can distinguish insomniacs from healthy controls (Vgontzas et al. 2001, see Table 3(h); diagnostic grading B1), while for three other studies using either evening and nocturnal serum cortisol levels (Riemann et al. 2002, see Table 3(h)) or midnight and morning salivary cortisol levels (Seelig et al. 2013 and Mikoteit et al. 2019, see Table 3(h)) diagnostic grading was B4.

Melatonin

The hormone melatonin is an important moderator of the circadian sleep-wake rhythm. The nocturnal darkness-dependent rise of melatonin levels induces proneness to sleep and seems to be also involved in the physiological sleep structure characterised by the preponderance of SWS in the first half of the night (Zhang et al. 2014; Xie et al. 2017). Moreover, melatonin is considered to regulate the circadian rhythm of the HPA axis activity (Lattova et al. 2011). Melatonin has been found to start its rise earlier in the evening and to have a lower peak at night in insomniacs compared to healthy controls; this finding has a satisfactory diagnostic validity for insomnia (Hajak et al. 1995 and Riemann et al. 2002; for both B2 diagnostic grading, see Table 3(i)).

Markers of inflammation

Insomnia was related to moderately increased CRP levels and unrelated to IL-6 and TNF-α levels (Okun et al. 2009; Laugsand et al. 2012, see Supplementary Table S3; Slavish et al. 2018). Higher CRP levels were also observed in patients with insomnia persisting over a six-year period compared to non-insomniacs as well as to patients with non-persistent insomnia, although the data in that study (being expressed as geometric means only) were not pertinent for the assessment of the usefulness of CRP level as a biomarker of insomnia (Parthasarathy et al. 2015, see Table 3(j), diagnostic grading D).

Markers of neuroplasticity

After controlling for comorbid depression, individuals with insomnia had lower serum BDNF levels than healthy controls (Giese et al. 2014, see Supplementary Table S3). A subsequent study provided support for this finding, also showing that serum BDNF seems to be a valuable biomarker for insomnia irrespectively of objectively assessed sleep continuity (Mikoteit et al. 2019, diagnostic grading A1, see Table 3(k)). In another study, as well, low BDNF levels were found to be a biomarker for the diagnosis of insomnia with short sleep duration in PSG, as well as of insomnia with normal sleep duration (Fan et al. 2019, diagnostic grading B1, see Table 3(k)).

Among individuals with insomnia, lower BDNF levels were associated with a lower percentage of REM sleep, although this was not the case for objective sleep continuity parameters assessed through polysomnography (Deuschle et al. 2018, see Supplementary Table S3; Mikoteit et al. 2019). Finally, an association between low BDNF levels and poor cognitive performance has been found in individuals with insomnia and shortened sleep duration (Fan et al. 2019, see Table 3(k)).

Discussion

This is the first study to establish the usefulness of various methods for the diagnosis of insomnia by comparing diagnostic validity indices of psychometric and biological measurements. To achieve this goal, a diagnostic grading system was developed consisting of the estimation of both diagnostic pertinence and diagnostic accuracy for the evaluation of the measurements used in each study. In most studies reviewed, there was adequate data to extract an index of diagnostic discrimination, provided that the actual diagnosis of each study's sample had been performed by accepted means (i.e. following recommendation of diagnostic manuals); it must be noted, however, that in a few studies, it was stated that the patient group had the diagnosis of insomnia, without specifying the exact diagnostic procedure. Some of the studies examined did not provide data adequate enough for the evaluation of diagnostic accuracy (grade D of diagnostic pertinence); nonetheless, their data on the existing differences between insomniacs and control subjects are still scientifically valuable for understanding the nature and mechanisms of insomnia as well as to potentially guide treatment practices (Dikeos and Soldatos 2005; Pevernagie 2021).

As expected, scales and questionnaires specifically developed for diagnosing insomnia were found to have the highest diagnostic gradings; this is understandable taking into account that the diagnostic criteria for insomnia are based solely on subjective

complaints of poor sleep quantity and/or quality, without including any biological or other objectively measurable parameters (APA 2013; AASM 2014; WHO 2019). This finding shows that the assessment of subjective sleep complaints, which actually constitute the condition of insomnia, reflects the impact of insomnia on the suffering of the individual and the accompanying help-seeking behaviour. Moreover, the existence of cut-off scores of insomnia scales allows them to be useful tools in clinical and research practice for reliably establishing the diagnosis of insomnia (Soldatos et al. 2003).

The fact that high diagnostic gradings were also found for scales and questionnaires assessing beliefs and attitudes about sleep is not surprising since the dysfunctional beliefs about sleep are intrinsically related to the development of insomnia (Doos Ali Vand et al. 2014; Yang et al. 2014), as well as to its persistence (Norell-Clarke et al. 2014). In addition, these dysfunctional beliefs have been associated with treatment adherence (Cvengros et al. 2015) and treatment response (Tremblay et al. 2009); thus, their knowledge by clinicians may guide optimal treatment choice (Montserrat Sánchez-Ortuño and Edinger 2010). Consequently, it seems that scales on dysfunctional beliefs about sleep are useful tools for the prevention, diagnosis, and treatment of insomnia.

The potential of MMPI as a tool for diagnosing insomnia was found to be quite satisfactory, although lower than that of the scales and questionnaires mentioned above. The personality profile of insomniacs according to MMPI is characterised by a pattern of elevation of certain scales denoting the presence of neurotic depression, rumination, anxiety, and internalisation of negative emotions leading to psychophysiological activation and ultimately to the vicious cycle of generation and perpetuation of insomnia (Kales et al. 1983; Dikeos and Soldatos 2005; Van de Laar et al. 2010). It is noteworthy that in a study by Vgontzas et al. (1994) comparing the validity and clinical utility of sleep laboratory measurements for diagnosing insomnia to those of MMPI patterns, the latter were found to have a better positive predictive value than the former (73 *vs.* 48%, $p < 0.01$). Neuroticism and perfectionism were also found to be predictors of insomnia through the Big Five inventory and other personality assessment tools; however, contrary to the MMPI, these tools do not seem to be useful for diagnosing insomnia. Neurotic persons show negative mood, anxiety, dysfunctional thoughts, as well as behaviours and coping strategies leading to emotional distress (Costa and McCrae 1992). This may add to vulnerability for stress-related sleep disturbance and the development of insomnia (Williams and Moroz 2009; Van de Laar et al. 2010; Harvey et al. 2014).

It has been also reported that personality characteristics, degree of psychopathology, comorbid psychiatric disorders, and levels of sleep disturbance can be used to subclassify insomnia into various phenotypes; early onset insomnia was the most severe of these phenotypes (Van de Laar et al. 2017, see Supplementary Table S2). In another study, five robust insomnia disorder subtypes have been identified based on life history, personality traits, and affect (Blanken et al. 2019, see Supplementary Table S2), opening the door widely for further research.

Etiologic models of insomnia emphasise the bidirectional interaction between psychological symptoms, such as extensive worrying about sleep (Harvey 2002), and physiological conditions, such as hyperarousal (Riemann et al. 2010). Insomnia patients trapped in this vicious cycle show more or less homogenous patterns of personality and psychopathology, although whether the persistence of insomnia leads to further changes in personality or vice versa has not been clearly understood (Van de Laar et al. 2010).

The review on the usefulness of biological measures for the diagnosis of insomnia showed that these measures have a lower diagnostic potential than that of scales and questionnaires. It also showed that there is a marked variability of the level of evidence across studies both for the diagnostic pertinence of measures provided as well as for the diagnostic accuracy of the methods examined.

The evidence for diagnostic accuracy of PSG-based macroarchitecture of sleep as diagnostic marker for insomnia is shown to be rather weak. For many years it has been reasonably assumed that PSG would be a very helpful tool for the diagnosis of insomnia. Yet, this has not been proven to be the case and, consequently, US guidelines (Chesson et al. 2000) do not routinely recommend polysomnography (PSG) as a diagnostic tool for insomnia in clinical practice, while the European guidelines (Riemann et al. 2017) suggest a broader indication to perform polysomnography only in certain cases of insomnia. One of the main reasons for the hesitant approach to include PSG in the diagnostic process for insomnia resulted from the fact that polysomnographic data do not strongly correlate with the subjective assessment of sleep by insomniac patients themselves. An early study to document this (Carskadon et al. 1976), clearly showed that patients with insomnia consistently underestimate the time spent asleep and overestimate the time it takes them

to fall asleep, denoting that there is a significant discrepancy between objective and subjective findings (for overview see Harvey and Tang 2012). However, in spite of the overall weak diagnostic potential of PSG, objectively assessed sleep quantity parameters may distinguish insomniacs from those with short or with normal sleep duration, with the former constituting the most biologically severe phenotype, with significant therapeutic and prognostic implications (Vgontzas et al. 2013; Bertisch et al. 2018).

Since the publication of the neurocognitive model of insomnia (Perlis et al. 1997), spectral analysis of sleep EEG is assumed to provide a more fine grained approach to evaluate changes in sleep of patients with insomnia; fast frequencies (in the sigma/beta range), which seem to be overexpressed in the sleep of insomniac patients, may reflect increased levels of consciousness during sleep, thus corresponding or even reflecting the increased ruminations patients with insomnia typically suffer from. As shown in Table 3(a), all four studies reviewed indicate the presence of sleep EEG spectral analysis findings denoting a considerable degree of hyperarousal during sleep; however, in three of them, the data reported were inadequate to establish diagnostic validity (Buysse et al. 2008; Riedner et al. 2016; Svetnik et al. 2017), while the diagnostic grading of the remaining one (Spiegelhalder et al. 2012) corresponds to low diagnostic accuracy. To the contrary, a study on CAP rate analysis showed high diagnostic accuracy (Chouvarda et al. 2012). In general, the evidence from studies applying more fine-grained neurophysiological methods, such as sleep EEG spectral analysis or CAP rate analysis, favours the hypothesis of an increased CNS hyperarousal in patients with insomnia in relation to good sleepers (Riemann et al. 2010, 2015; Morin et al. 2015; Zhao et al. 2021), which may be reduced after cognitive behavioural therapy for insomnia (Cervena et al. 2004; Krystal and Edinger 2010, see Supplementary Table S2 for both).

Actigraphy seems to be a valuable method for the diagnosis of insomnia, with the studies reviewed herein showing high diagnostic accuracy (Natale et al. 2009, 2014), although the quantification of the resulting recordings and the establishment of relevant diagnostic cut-offs have not been achieved as yet. Actually, recent guidelines for the treatment of insomnia (Riemann et al. 2017), recommend actigraphy only in the case of clinical suspicion of irregular sleep-wake schedule or circadian rhythm disorders (strong recommendation), but to a much smaller extent for the quantitative assessment of sleep parameters (weak recommendation). On the other hand, the value of actigraphy is also supported by the fact that actigraphs are easy to use across many nights with almost no impact on patient's activities and habits. Finally, with the existing pace of progress regarding personal electronic devices and wearables, we can look forward to new methods of collection and analysis of actigraphic data.

The studies presented in Table 3(c) show that an increase of heart rate before and after sleep onset can be considered as a psychophysiological biomarker for the diagnosis of insomnia. To the contrary, no diagnostic usefulness has been shown for heart rate variability (HRV), although alterations of HRV patterns have been reported, as an indication of autonomic hyperarousal and a sympathovagal disbalance in insomnia. Consequently, it has been suggested that more research needs to be conducted including further HRV measures, such as VLF, non-linear complexity indices, or qEEG-ECG coupling analyses (Jurysta et al. 2009; Yang et al. 2011; Mikoteit et al. 2017, 2019).

Regarding other psychophysiological measures, which have been studied in insomnia and are reviewed in this paper (Tables 3(d–f)), an increased core body temperature in insomniancs shows some promise for diagnostic potential, although the procedure of measuring core body temperature is obviously impractical for clinical purposes. Oxygen consumption rate has also shown to have some diagnostic ability, but not for insomniacs with only subjective complaint; the clinical application of this method, however, is also impractical. As far as skin conductance is concerned, it has not shown diagnostic accuracy. In spite of the lack of usefulness of the above methods for diagnostic purposes, converging evidence from many studies on different psychophysiological markers of the autonomic nervous system (ANS), support the hyperarousal model for insomnia (Riemann et al. 2010). However, there is a need for further research to clarify if indicators of hyperarousal are secondary to sleep disturbance and fragmentation caused by insomnia, or if hyperarousal is a primary background of insomnia itself.

Neuroimaging studies, especially those based on PET scan and fMRI, generally indicate that in insomnia there is a failure of arousal mechanisms to decline in activity from wake to sleep; besides, in certain studies, a lower recruitment of frontal areas during cognitive tasks has been observed. While these findings are in keeping with the understanding that insomnia is characterised by the persistence of hyperarousal, it is difficult to draw definitive conclusions due to small

number of participants and the variability of methods used across various studies. Also, even if the diagnostic validity is satisfactory, as shown in certain studies, the use of the neuroimaging methods for diagnostic purposes in insomnia is practically prohibited by their complexity and high cost. The recently established sleep working group within the ENIGMA neuroimaging genetic consortium constitutes a promising international effort, which is expected to provide further insight regarding neuroimaging of sleep disorders (Tahmasian et al. 2018).

The development and maintenance of insomnia is most often associated with chronic stress (Basta et al. 2007; Lo Martire et al. 2020). It appears plausible that insomnia is associated with alterations of the neuroendocrine stress response system, i.e. with the hypothalamic-pituitary-adrenal (HPA) axis, and with increased cortisol concentrations. Actually, certain studies on the HPA activity indices show that cortisol levels and ACTH are elevated in insomnia either throughout the 24-h period or at certain time-points before, during, or after sleep. The findings of some other studies, however, did not show differences between insomniacs and controls for cortisol or ACTH levels, neither for the Dexamethasone Suppression Test. Differences in hormonal sampling methods (serum *vs.* saliva and/or collection time-points) across studies may partly explain such discrepancies; also, participant characteristics may play a role, since it has been shown that HPA axis irregularities are more pronounced in insomniacs with objectively verified short sleeping time (Vgontzas et al. 2001; Fernandez-Mendoza et al. 2017). Regarding the value of HPA axis activity indices for diagnosing insomnia, in only one of the two studies on 24-h cortisol and ACTH serum levels reviewed herein, the level of diagnostic accuracy was high; moreover, in both studies on salivary cortisol the differences found between insomniacs and controls were significant, but not strong enough to reach even a low level of diagnostic accuracy.

Plasma melatonin levels are lower among insomniacs than among good sleepers, regarding the entire night and especially the first half and the middle of the night. Melatonin levels, also, start rising earlier in the evening, thus showing a more flattened circadian rhythm in insomnia. This finding seems to be independent of objectively assessed sleep parameters through PSG. The association of melatonin levels with insomnia is further strengthened by the fact that melatonin administration has been found to improve sleep onset insomnia (Brzezinski et al. 2005) both in children (Van Der Heijden et al. 2005, 2007; Van Maanen et al. 2017) and in adults (Lemoine et al. 2007; Luthringer et al. 2009). Melatonin level differences between insomniacs and controls in the two studies reviewed herein (Hajak et al. 1995; Riemann et al. 2002) show a satisfactory level of diagnostic accuracy, although the fact that this finding regards night-time blood sampling poses limitations for its clinical application.

The levels of C-reactive protein (CRP), as a marker of inflammation, were found to be moderately elevated in insomnia (particularly when its course is chronic) in comparison to normal levels, but no diagnostic use of this marker could be established based on the study reviewed herein. Since insomnia, especially in its chronic form, is characterised by stress and anxiety, it is expected to be accompanied by high levels of markers of inflammation. CRP and proinflammatory cytokines, such as Interleukin-6 (IL-6) and tumour necrosis factor (TNF-α), have been reported to be elevated in individuals with chronically disturbed sleep and to mediate the association between chronic sleep deprivation and somatic diseases, e.g. inflammatory diseases or cancer (Irwin et al. 2016). However, of the above markers, insomnia was only found to be associated with elevated CRP, while, in addition, chronically elevated CRP levels were not found to mediate the association between insomnia and mortality (Parthasarathy et al. 2015), thus obscuring the exact relationship of inflammation to either insomnia or chronic sleep deprivation.

Serum levels of BDNF, a marker of neuroplasticity, have been found to be significantly reduced in insomniacs compared with normal controls; the diagnostic accuracy of low BDNF for insomnia was high in both of the two studies reviewed herein. It is known that serum levels of BDNF correlate with central BDNF concentrations (Duman and Monteggia 2006) and that synaptic homeostasis and memory consolidation occur during sleep (Tononi and Cirelli 2014), which suggests that poor sleep may be associated with impaired neuroplasticity. Also, an acute stress challenge, such as acute sleep deprivation, increases BDNF levels; in contrast, chronically poor sleep is associated with decreased BDNF (Schmitt et al. 2016). Finally, a causality relationship between abnormal BDNF values and insomnia is supported by the finding that a genetic association has been observed between insomnia and the BDNF gene (Zaki et al. 2019, see Supplementary Table S3).

Conclusion

In conclusion, as shown in the overview presented in Table 4, besides the psychometric instruments (scales

Table 4. Overview of the diagnostic potential for insomnia of psychometric tools and biological measurements.

Diagnostic potential	Psychometric tools	Biomarkers
Excellent[a]	Scales for assessing insomnia	Actigraphy*
	Scales for assessing beliefs and attitudes about sleep	BDNF
		CAP**
Moderate[b]	MMPI	HR around sleep onset
		Neuroimaging***
Limited[c]		Melatonin
Inconsistent[d]		HPA axis

BDNF: brain-derived neurotrophic factor; CAP: cyclic alternating pattern; HPA: hypothalamus-pituitary-adrenal; HR: heart rate; HR: heart rate variability; MMPI: Minnesota Multiphasic Personality Inventory.
*Absence of common standards of technical solutions and cut-off values.
**Based on only one study.
***Varying methodologies.
[a]Diagnostic grading A1 in at least one study.
[b]Diagnostic grading A2 or B1 in at least one study.
[c]Diagnostic grading B2 in at least one study.
[d]One study providing positive evidence is outweighed by studies providing negative evidence.

and questionnaires for insomnia or beliefs about sleep) which are the gold standard for the diagnosis of insomnia based on established cut-off scores, the biological measurements which emerge with high diagnostic performance for insomnia and can be considered as its diagnostic biomarkers are the polysomnography-derived cyclic alternating pattern (CAP), actigraphy, and low serum BDNF levels; they are followed by increased heart rate (immediately before or right after sleep onset), neuroimaging findings (showing high activation of certain brain circuits during sleep and/or wakefulness) and a deficient circadian melatonin rhythm. It must be noted, however, that for some of the above potential biomarkers for diagnosing insomnia (e.g. for MRI or for measurements requiring serial blood sampling) their applicability as widespread methods for diagnosing insomnia is curtailed, both in terms of their cost-effectiveness as well as in terms of the complexity of the procedures involved. Another issue that needs to be taken into account for the majority of emerging biomarkers is that, after having evaluated their discrimination power, they should be further examined regarding the domain they assess (e.g. HPA axis) as well as regarding possible diagnostic entities that these markers may add information to. Thus, more work is needed in order: (a) to replicate findings that are based on one or a very small number of studies, in view of the need of having a sufficient number of studies to assess diagnostic discrimination, (b) to create commonly accepted methodologies and algorithms for their outcome measures across studies, and (c) to establish appropriate diagnostic cut-off points for insomnia and other diagnostic entities. In any event, for future research, it is most important to report diagnostic accuracy measures for all identified group differences. Further to their use as diagnostic indices, biomarkers are relevant in understanding the nature and mechanisms of insomnia, in distinguishing among subtypes of this disorder, and in potentially guiding targeted treatment. For example, macro-architecture of sleep, as assessed through polysomnography and measurements of HPA axis activity, although they are not proven as yet to be diagnostically useful, may have the potential to distinguish subtypes of insomnia with different clinical characteristics, prognosis, and treatment needs. Another major observation regarding the value of most biomarkers (diagnostically useful or not) in understanding the nature of insomnia is the proof they provide in favour of the hyperarousal concept of insomnia both during sleep and wakefulness.

Acknowledgements

The authors DD and CS appreciate the most valuable contribution to the establishment of the Diagnostic Grading System utilized in this study of the following members of the Department of Hygiene, Epidemiology, and Medical Statistics, Medical School of National and Kapodistrian University of Athens, Athens, Greece: Professor Giota Touloumi, Assistant Professor Nikos Pantazis, and Valia Baralou, MSc.

WFSBP Task Force on Sleep Disorders

Constantin R. Soldatos (Chair), Dimitris Dikeos (Co-Chair), Adam Wichniak (Secretary), Francesco Benedetti, Tatiana Crönlein, Anne Eckert, Martin Hatzinger, Jana Kopřivová, Periklis Ktonas, Birendra N. Malik, Thorsten Mikoteit, Maria Ntafouli, Tatsuro Ohta, Fuat Őzgen, Dieter Riemann, Kai Spiegelhalder, Giedrius Varoneckas.

Statement of interest

None to declare.

ORCID

Dimitris Dikeos http://orcid.org/0000-0003-4217-5282
Adam Wichniak http://orcid.org/0000-0002-5352-601X
Thorsten Mikoteit http://orcid.org/0000-0003-2166-6330
Tatjana Crönlein http://orcid.org/0000-0003-3505-7595
Anne Eckert http://orcid.org/0000-0002-9341-3669
Jana Kopřivová http://orcid.org/0000-0002-3626-5372
Maria Ntafouli http://orcid.org/0000-0002-6074-2124
Kai Spiegelhalder http://orcid.org/0000-0002-4133-3464
Martin Hatzinger http://orcid.org/0000-0002-6146-3602
Dieter Riemann http://orcid.org/0000-0002-1968-6220
Constantin Soldatos http://orcid.org/0000-0002-7791-8712

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