Brain mechanisms of insomnia: new perspectives on causes and consequences

Eus J.W. Van Someren

Department of Sleep and Cognition, Netherlands Institute for Neuroscience (NIN), an institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands.

Department of Integrative Neurophysiology, Center for Neurogenomics and Cognitive Research (CNCR), Amsterdam Neuroscience, VU University Amsterdam, Amsterdam, The Netherlands.

Amsterdam UMC, Vrije Universiteit, Psychiatry, Amsterdam Neuroscience, Amsterdam, The Netherlands.

Address for correspondence: Netherlands Institute for Neuroscience (NIN), Dept. Sleep & Cognition, Meibergdreef 47, Amsterdam 1105 BA, The Netherlands. Tel: +31 20566-5500; Fax: +31 30566-6121, E-mail: e.van.someren@nin.knaw.nl

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49 **Abstract**

50

51 While insomnia is the second most common mental disorder, progress in our understanding
52 of underlying neurobiological mechanisms has been limited. The present review addresses
53 the definition and prevalence of insomnia and explores its subjective and objective
54 characteristics across the 24-hour day. Subsequently, the review extensively addresses how
55 the vulnerability to develop insomnia is affected by gene variants, early life stress and major
56 life events and brain structure and function. Further supported by the clear mental health
57 risks conveyed by insomnia, the integrated findings suggest that the vulnerability to develop
58 insomnia could rather be found in brain circuits regulating emotion and arousal than in
59 circuits involved in circadian and homeostatic sleep regulation. Finally, a testable model is
60 presented. The model proposes that in people with a vulnerability to develop insomnia, the
61 locus coeruleus is more sensitive to - or receives more input from - the salience network
62 and related circuits, even during REM sleep, when it should normally be sound asleep. This
63 vulnerability may ignite a downwards spiral of insufficient overnight adaptation to distress,
64 resulting in accumulating hyperarousal which in turn impedes restful sleep and moreover
65 increases the risk of other mental health adversity. Sensitized brain circuits are likely to be
66 subjectively experienced as “sleeping with one eye open”. The proposed model opens up
67 the possibility for novel intervention studies and animal studies, thus accelerating the ignition
68 of a neuroscience of insomnia, which is direly needed for better treatment.

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127 **Introduction, aims and outline**

128

129 This review addresses insomnia disorder (ID), by far the most common sleep disorder as
130 well as the second-most common neuropsychiatric disorder, only outnumbered by the
131 Diagnostic and Statistical Manual of Mental Disorders comprehensive category of all anxiety
132 disorders (8, 440). ID is defined by symptoms that we may all have experienced: difficulties
133 initiating sleep, or waking up from sleep during the night or earlier in the morning than one
134 would like while not being able to resume sleep easily. What discriminates people with ID
135 from those with an incidental bad night of sleep, is that they experience these sleep
136 problems at least three nights a week, for three months or more, even if the circumstances
137 and opportunities for sleep are ideal. Moreover, the diagnosis requires the sleep problems
138 to subjectively cause difficulties with daytime functioning or well-being (8, 105).

139

140 ID is not only a burdening and costly disorder in itself, it also conveys considerable risks of
141 other disorders. Symptomatic treatment of ID with hypnotics is currently discouraged
142 because of the risk of dependency and possible daytime consequences. There are however
143 valid arguments against the conviction that long-term hypnotic treatment is to be strictly
144 avoided (346). Also the current first-line treatment, cognitive behavior therapy for insomnia
145 (CBTI), does not bring sufficient relief for many (161). While meta-analyses of randomized
146 controlled trials report large effect sizes, a considerable proportion of people with ID do
147 not experience sufficient relief. In fact, post-treatment sleep efficiency - an integrated
148 measure of sleep quality - does on average not surpass 80%, the cutoff for normal sleep
149 (345). Moreover, meta-analysis reported that CBTI on average lowered the insomnia
150 severity index by only 4.3 points (345) while a twice as large decrease would be required to
151 even conclude a moderate clinical improvement (270). These numbers indicate that at least
152 half of the first-line treated people still cannot be considered to have normal sleep. It can

153 thus be concluded that there is an urgent unmet need to better understand insomnia and to
154 reveal actionable mechanisms for the development of better treatment.

155

156 This review first aims to provide a systematic overview of insomnia research findings from
157 the perspectives of epidemiology, phenomenology, physiology, genetics and risks for
158 insomnia and of insomnia (§ I-VI). The second aim is to discuss how the findings fit into
159 previously proposed models on underlying mechanisms. To this aim, the review discusses
160 brain imaging findings (§ VII) and evaluates whether the search for mechanisms underlying
161 insomnia should be limited to the circadian and homeostatic sleep regulating circuits of the
162 brain (§ VIII). From there, support for an alternative view will be discussed: that mechanisms
163 underlying insomnia might better be pursued within emotion and arousal regulating circuits
164 of the brain (§ IX). Third, the review aims to provide new vistas on actionable mechanism
165 and suggestions of how human and animal research might explore them. The review
166 therefore outlines a model stating that insomnia results from insufficient overnight
167 adaptation to emotional distress (§ X) and concludes with suggestions for research (§ XI).
168 Importantly, the model can be evaluated not only in humans, but also by utilizing the amazing
169 manipulation and assessment tools that have become available in animal research. It is hoped
170 that the testable hypothesis will accelerate the ignition of a neuroscience of insomnia, which
171 is direly needed to improve treatment of a severely understudied burdensome mental
172 disorder. To provide a framework that will facilitate digesting of the large amount of
173 information provided in the review, this introduction briefly summarizes where it is heading.

174

175 In brief, since insomnia is seen as a sleep disorder, it seems logical to search for underlying
176 mechanisms in sleep-regulating systems of the brain. As will be shown, studies have provided
177 surprisingly little support for involvement of either circadian or homeostatic factors, the two
178 major components of sleep regulation. The reviewed findings are then integrated to provide
179 new vistas on actionable mechanisms. A new perspective is proposed in § X and suggestions

180 for research in § XI. The new view builds on fundamental sleep research findings of the last
181 two decades revealing that one prominent function among multiple important functions of
182 sleep is to provide a dedicated time window for neuronal plasticity. Rather than presuming
183 that sleep serves a single function, it has been proposed that sleep and wakefulness mainly
184 reflect an organizational principle, evolved to separate processes, ranging from the molecular
185 to the behavioral, that would, if taking place simultaneously or close in time, be sub-optimal
186 or even detrimental to the organism (401). While of course neuronal plasticity takes place
187 during wakefulness as well, sleep provides neuromodulatory and oscillatory circumstances
188 that allow for kinds of plasticity that are less feasible during wakefulness, both at the synaptic
189 and the systems level. It will be argued that ongoing noradrenergic activity during REM sleep
190 - when it should be absent - is an example of insufficient separation of processes which
191 indeed is sub-optimal or even detrimental to overnight distress adaptation in people with
192 restless sleep.

193

194 While people with insomnia experience their sleep as nonrestorative, only few studies
195 explored possible deviations in their overnight adaptive plasticity processes. Equivocal
196 findings have been reported by the few studies on overnight changes in explicit and implicit
197 memory that all used tasks without emotional relevance, as will be discussed in detail in
198 section III (15, 151, 283, 284). A few recent studies specifically addressed overnight
199 emotional *distress adaptation* processes in insomnia, with more consistent and remarkable
200 findings (423-426). As will be discussed in detail in section IX. The fragmented sleep that
201 characterizes people with insomnia (§ II) turned out to impede restorative processing
202 underlying overnight adaptation to emotional distress. In cases with severe fragmentation,
203 sleep could even become *maladaptive* and result in overnight *increases* of emotional distress
204 and amygdala activation. It is tempting to suggest that these cases might be better off
205 without any sleep at all, rather than to have their distress worsen overnight due to restless

206 REM sleep. This idea reminisces of early work showing that REM sleep deprivation improved
207 mood in depression (410).
208
209 Specifically *restless REM sleep* was pinpointed to interfere with emotional adaptation. Restful
210 sleep supports overnight adaptations in the limbic circuit of the brain (397), resolving the
211 burden of emotional memories by making them milder and better tractable (205). *Restless*
212 REM sleep interferes with these adaptive processes. Adverse consequences are felt for long
213 (424) and leave traces in brain activation for decades (426).
214
215 Translational studies identified *why* restless REM sleep disrupts overnight adaptive processes
216 (371, 403, 404). Sound REM sleep is the only state during which the brain has a 'time-out' of
217 noradrenaline (NA): the Locus Coeruleus (LC) is silenced. Intricacies of synaptic plasticity
218 like receptor subunit replacement are strongly modulated by the level of NA (326). The NA
219 time-out that only occurs during sound REM sleep therefore allows for a uniquely balanced
220 potentiation and depotentiation of synapses, not found in any other state. Restless REM
221 sleep however indicates insufficient LC silencing. The resulting lack of a NA-free REM sleep
222 period disrupts synaptic plasticity (371, 403, 404).
223
224 These recent insights on the importance of NA-free REM sleep for overnight emotion
225 regulation provide the testable hypothesis that insomnia could be a disorder of overnight
226 emotional memory regulation, originating in a pre-symptomatic vulnerability to have restless
227 sleep. The same vulnerability could moreover contribute to the development of anxiety
228 disorders, depression and post traumatic stress disorder. Indeed, the disorders have a
229 markedly overlapping polygenetic risk, share early life risk factors, and occur commonly
230 comorbid or in sequence. Possibly, diagnostic differences may mostly involve the type of
231 emotional distress that doesn't resolve overnight: fear, anxiety, arousal, stress, tension,
232 sadness etc. The new hypothesis provides a theoretical framework to study the disorders,

233 or symptom constellations, concertedly, where insomnia is not strictly regarded a sleep
234 disorder just like we do not regard anxiety and mood disorders to belong to the category of
235 sleep disorders.

236

237 This review will systematically show how findings from very diverse methodologies concur
238 to support the hypothesis that an initial vulnerability to have insufficient noradrenergic
239 silencing during restless REM may develop into chronic hyperarousal and related complaints.

240

241 **I. Definition and prevalence**

242

243 About a third of the general population experiences *symptoms* of insomnia at least once in a
244 while. Symptoms of insomnia are difficulties with sleep onset or difficulties returning to sleep
245 after waking up during the night or earlier in the morning than desired or necessary. These
246 difficulties are commonly referred to as difficulty initiating sleep (DIS), difficulty maintaining
247 sleep (DMS) and early morning awakening (EMA) respectively. A diagnosis of Insomnia
248 *Disorder* (ID) may apply if these sleep complaints occur despite adequate opportunity and
249 circumstances for sleep, if they subjectively result in some form of daytime suffering or
250 impairment, and if they are present three times a week or more for at least three months.

251

252 In the latest diagnostic nosologies, insomnia is not *a priori* secondary to other disorders, but
253 *comorbid with* other disorders - just as is the case for many other disorders of which the risk
254 increases with age (27). The 'other disorder' may be another sleep disorder as well: Kerkhof
255 (200) even estimated that 12% in a population sample can be diagnosed with two or more
256 comorbid sleep disorders, which is even more than the estimated 10% meeting the criterion
257 for one specific sleep disorder. Insomnia is highly comorbid with obstructive sleep apnea
258 syndrome (OSAS) (36, 155, 214, 262, 434) and with restless legs syndrome (RLS, see III) (34,
259 156). Insomnia *can be* secondary though: in that case, insomnia complaints will disappear
260 when the other disorder is successfully treated.

261

262 Both point prevalence estimates (usually assessed over the previous 1, 3 or 6 months), 12-
263 month prevalence estimates and lifetime prevalence estimates indicate that on average about
264 10% of the population meet the diagnostic criteria of Insomnia *Disorder* (ID, see II.) (67, 189,
265 271). While 1-year *incidence* estimates of insomnia were first reported to vary around that
266 number as well (range 7%-15%) (271), a more recent study following up good sleepers for
267 one year reported a 27.0% incidence of acute insomnia but only a 1.8% incidence of newly

268 developed chronic insomnia that met diagnostic criteria (311). Prevalence estimates vary
 269 depending on age, assessment tools and criteria applied. With the stringent DSM-IV
 270 diagnostic criteria, point prevalence estimates in a large sample remain approximately 6%
 271 (290), while a recent cross-cultural and comparative epidemiological study reported that
 272 10.8% fulfilled DSM5 criteria for insomnia disorder (86), and in a recent meta-analysis the
 273 pooled prevalence of insomnia in China was 15.0% (69). All in all, insomnia seems the
 274 second-most common mental disorder, with a 12-month prevalence in-between the most
 275 prevalent combined anxiety disorders and, closely following insomnia, major depressive
 276 disorder (440).
 277
 278 For several reasons, it may surprise many that ID is the second-most common
 279 neuropsychiatric disorder. First, the prevalence of insomnia disorder had been increasing
 280 over the last decades. Calem et al. reported that the prevalence of insomnia disorder nearly
 281 doubled across 15 years (67), and the increasing prevalence is supported by other
 282 longitudinal studies (131, 138, 217, 300). Second, many integrative studies on mental
 283 disorders just ignore that insomnia is part and parcel of the DSM diagnostic nosology and do
 284 not include it (137). Based on the only large integrative study that used identical methods to
 285 evaluate the 12-month prevalence across different mental disorders, the different anxiety
 286 disorders aggregated rank #1 (14%), insomnia ranks #2 (7%), and unipolar depression ranks
 287 #3 (6.9%) . The estimate of a 12-month prevalence of insomnia of 7% is even likely to be
 288 underestimated because in many patients, the diagnosis is not noticed in consultation by a
 289 general practitioner (170, 272, 289, 292). Indeed, the prevalence rates about double if
 290 population-based studies include active diagnosis according to the DSM rather than relying
 291 on filed medical dossiers of diagnoses (300, 449).
 292
 293 Insomnia constitutes a dramatic and wide-ranging socioeconomic burden - tens of billions in
 294 the U.S. alone (81, 201), not only due to health-care expenses, but also due to decreased

295 work productivity and proneness to injuries. Public health concerns should address
296 specifically the quality of sleep: while the duration of sleep has increased of the last 15 years
297 (29), the prevalence of Insomnia Disorder increased strongly (67, 217).

298

299

300 **Sex differences in prevalence**

301

302 Female sex and higher age have been identified as major determinants of insomnia
303 prevalence (277). Meta-analysis showed a risk ratio of 1.4 for women as compared to men
304 to have insomnia (449). Whereas the mechanisms underlying the difference are not fully
305 understood, sex steroids have been implicated, because complaints increase during periods
306 of ovarian steroid fluctuation: puberty, menstrual cycle, pregnancy and menopause (21, 268).
307 Postmortem studies in humans showed sex differences in brain structures involved in
308 circadian and sleep regulation (370). Animal studies moreover indicate that the response of
309 these structures to fluctuations in sex steroids is much stronger in females than in males
310 (268).

311 Across sex and age, difficulty maintaining sleep is never as prevalent as in girls during
312 puberty (28%) (209). The phase of the diurnal rhythm in estradiol varies across the
313 menstrual cycle (24) and sleep complaints are worst during the mid-luteal phase of the
314 menstrual cycle, when ovarian steroid levels have commenced to decline. Women sleep
315 later relative to the internal phase of their diurnal hormone rhythms than men do, which
316 could contribute to their increased risk of insomnia symptoms (268). It is notable that
317 women with major depression have a very late relative sleep timing, because of their much
318 advanced diurnal estradiol rhythm (23): this might contribute to their insomnia symptoms.
319 The increased sensitivity of structures involved in sleep and circadian regulation to sex
320 steroid fluctuations in females could also contribute to their increased risk of insomnia
321 during pregnancy and the transition to menopause (96, 268).

Sex differences in brain structure and function are not limited to circuits involved in circadian and sleep regulation, but are also seen in the locus coeruleus (LC)-noradrenalin (NA) arousal circuit and how it responds to stress (22). The increased sensitivity in this circuit in females has been implicated in their increased risk of disorders characterised by concurrent insomnia, notably post-traumatic stress disorder (PTSD) and major depression. Animal studies suggest that structural sex differences in the LC bias females towards a stronger arousal response to emotional events (22). Sex differences in the corticotropin releasing factor 1 receptor (CRF₁) make noradrenergic neurons in the LC more sensitive in females. In addition, estrogen increases NE in LC target regions by enhancing its synthesis and reducing its breakdown. The resulting increased sensitivity of the noradrenergic system could underly the general hyperaroused state that is characteristic of insomnia.

A paradox is that the higher prevalence of subjective sleep complaints in women is not mirrored in objective classic polysomnographic measures of sleep. In contrast: objective measures have consistently suggested a better sleep quality in females than in men, at least in humans. In fruit flies, for example, females do have more fragmented sleep-wake patterns (157). This cross-sex discrepancy of subjective and objective indices of sleep quality in humans is just one striking example of our limited understanding of the neural correlates of the subjective experience of insomnia. The limitations of classic polysomnography does not allow it to adequately capture more fine graded neuronal processes and has likely resulted in inappropriate conclusions about discrepancy between objective and subjective assessments in insomnia patients. Big data, artificial intelligence tools and high-density EEG are now beginning to find multivariate and spatio-spectral signatures of objective sleep and wake disturbance that have remained hidden in classic polysomnographic measures of sleep (10, 53, 88, 89, 229, 329, 432, 433).

Insomnia prevalence across life span

349 As previously reviewed (400), epidemiological studies suggest a strong increase of
350 chronically disturbed sleep, including insomnia, with age. Estimates go up to 40-70% of the
351 elderly population, and only about 20% report to sleep fine. Frequent nocturnal awakening is
352 the most common age-related sleep complaint, closely followed by difficulties falling asleep
353 and early awakening.

354 More recent work however also indicates that insomnia symptoms already strongly
355 emerge during puberty. As is the case for adults, more so in girls than in boys. A study that
356 followed pubertal development between Tanner stage I to 5, reported that the prevalence
357 of insomnia symptoms increased 3.6-fold in girls and 2.1-fold in boys (450). A recent
358 individual participant meta-analysis of insomnia symptoms across life-span in 200,358 people
359 from the general population reported that difficulty maintaining sleep peaked at 23% of the
360 participants in the age category of 14 to 17 years, difficulty initiating peaked at 23% at 18 to
361 25 years, while early morning awakening peaked only late in life, at 24% in participants older
362 than 65 years of age (209).

363

364 In summary, one might conclude that the prevalence of insomnia increases with any factor
365 that interferes with the continuity of sleep, due brief arousals or awakenings (comorbidity,
366 aging) or sensitivity of the noradrenergic locus coeruleus (e.g. females).

367

368

369

370

371 **II. Nighttime Characteristics of insomnia**

372

373 This section addresses subjective sleep complaints and objective sleep assessment.

374

375 **Subjectively experienced sleep**

376

377 The diagnosis of ID is strictly based on subjective sleep complaints and doesn't include
378 objective sleep criteria. By definition, people suffering from ID experience difficulties
379 initiating or maintaining sleep and returning to sleep after waking up. It is not that surprising
380 therefore that they remember their nights as filled with thoughts and rumination (248).

381 Interestingly, also during actual sleep in good sleepers, mental content may be more
382 common than once thought, and not specific to REM sleep. Foulkes (133) recognized that
383 awakenings from all sleep stages elicit reports of mental activity if more liberal criteria are
384 applied, instead of specifically asking about 'dreams'. Recent enforced awakening studies
385 showed that even normal sleepers report to have experienced mental activity in two out of
386 three awakenings from NREM sleep (350). This contrasts strongly from the blank slate
387 feeling good sleepers have when waking up in the morning, except possibly for recall of
388 some dreams. Apparently, much from what goes on in the mind during NREM sleep is not
389 consolidated in memory in a way that can be accessed in the morning. It would be
390 interesting to evaluate the hypothesis that people with insomnia might consolidate ongoing
391 mental content during NREM sleep better, and thus wake up in the morning with a head full
392 of memories of thoughts and ruminations. Enhanced memory of thought-like nocturnal
393 mentation during sleep (220) can be hypothesized to be involved in the underestimation of
394 time asleep that is characteristic for many people with insomnia (248).

395

396 In addition, while good sleepers tend to experience vivid dreams in REM sleep, people with
397 ID may continue their tendency of thinking and rumination also during REM sleep. The more

398 someone shows the restless REM-sleep that is so characteristic of insomnia (123, 330), the
399 more likely it is to recall thought-like rather than dream-like nocturnal mentation (424). This
400 finding underlines the importance of side-by-side inquiring about both dreams and thoughts
401 in studies on nocturnal mental content in insomnia (424).

402

403

404 **Objectively recorded sleep**

405

406 Several excellent previous reviews cover most of the findings on ID-deviations in objective
407 sleep recordings (19, 124). The present paragraph therefore merely aims to provide a
408 concise summary, add some recent findings, and place past findings in the new perspective
409 that insomnia could involve disturbed activity in the dedicated time window for neuronal
410 plasticity that sleep normally provides.

411 The gold standard for the semi-objective quantification of sleep is polysomnography
412 (PSG), visually scored according to the AASM guidelines (179). Although PSG is not strictly
413 required for the diagnosis of ID, it may be assessed to rule out other possible causes of
414 disrupted sleep, like sleep apnea or periodic limb movements during sleep. Contrary to what
415 the name 'insomnia' suggests, the EEG of people suffering from insomnia does show
416 signatures of sleep, be it in a fragmented way, indicated by interrupting arousals and stage
417 shifts (**Figure 1. "Polysomnography"**). Meta-analysis showed that PSG variables reflecting
418 disruption of sleep continuity are the most robust PSG signatures of insomnia (19). As
419 shown in **Figure 2. "Meta-analysis polysomnography"** the two largest effect sizes for
420 group differences of people with ID as compared to good sleepers were a higher number of
421 nocturnal awakenings and consequently a lower sleep efficiency, i.e. the time spent asleep
422 while in bed. Total sleep time was consequently also less, due to reductions in both stage
423 N3 sleep and REM sleep. Brief arousals (50) from sleep that may or may not count as wake
424 epochs were not reviewed in the meta-analysis, but have been addressed in great detail in

other work of this group. These arousals especially fragment REM sleep (123, 330) although they are certainly present throughout NREM sleep as well (330). Markovian sleep stage transition dynamics show that the instability of sleep also shows in an increased propensity to switch to less deep sleep states, which makes it difficult to reach N3 (430). As shown in **Figure 3. "Increased probability to transition to a less deep sleep stage"**, once N3 is reached, the sleep of people with insomnia is considerably more like that of normal sleepers, without a significantly increased probability to switch to a less deep sleep state or other classical indicators of instability (304, 430). However, recent novel data-driven analysis techniques could reveal that the sleep EEG of people with ID shows signatures of simultaneous superficial sleep even during the deepest sleep state (85).

Instability and wake-like signatures in the sleep-EEG of ID is also evident in an objective semi-quantitative visual scoring approach to polysomnography other than the AASM standard (387). Repetitive alterations of specific EEG patterns coined 'cyclic alternating pattern' (CAP) can be observed during NREM sleep. A "phase A" indicates instability with arousals and a "phase B" indicates stability. The NREM sleep EEG of people with ID shows more of such alternating patterns with brief (10-15 seconds) periods of brain activation. The higher CAP rate in insomnia indicates restless NREM sleep (388). The visual scoring of CAPs is less suitable to quantify restlessness of REM sleep for which other EEG features are more appropriate including the power spectrum, arousal density, eye movement density, and shifts to wake or other sleep stages.

In addition to the semi-quantitative objective methods requiring visual scoring that have been discussed above, the EEG of people with ID has been evaluated with quantitative methods. Findings provide further support for the emerging conclusion that some wakefulness lingers on during sleep, ready to make sleep lighter or even terminate it. Quantitative methods can be more sensitive to differences between people with ID and

452 controls without sleep complaints, as comprehensively reviewed by Feige et al. (124). A
453 common method is power spectral analysis. The most consistent finding across sleep EEG
454 studies in ID is increased power in the beta range (near 20 Hz and higher) (124),
455 representing cortical oscillations that have been associated with wakefulness, alertness and
456 information processing.

457

458 Fewer studies have applied high-density EEG (HD-EEG) during sleep. Spatial information can
459 be evaluated at the scalp level using each EEG lead as a separate source of information.
460 Preferably, however, this information is used to estimate the underlying cortical sources.
461 Both scalp level topography and source estimates suggested widespread global rather than
462 cortically localized increased beta in people with insomnia while asleep, as well as more local
463 increased alpha band activity (8-12 Hz) in the sensory-motor areas (134, 329).

464

465 In addition to the semi-objective and quantitative features observed in the *unperturbed*
466 resting state EEG during sleep or wakefulness, a few studies used the event-related potential
467 (ERP) technique to investigate the *response* of the brain to incoming stimuli. As reviewed by
468 Feige et al. (124), the scarce studies suggest that people with ID have an increased sensitivity
469 to auditory stimuli, an increased expectation, a lowered response threshold, increased
470 cortical excitability and a compromised ability to inhibit sensory input. Two studies that
471 appeared after the review by Feige et al. (124) moreover suggest that at least part of the
472 people with insomnia have higher amplitude late potentials, indicating enhanced attention to
473 irrelevant stimuli, a failure to familiarize to them, and instead a tendency to keep on labeling
474 them as novel and even emotionally relevant (See **Figure 4. "Late component in the**
475 **heartbeat-evoked potential in insomnia"** and **Figure 5. "Enhanced late**
476 **components in the auditory oddball event-related potential in the reactive**
477 **insomnia subtype"** from references (42) and (432). Given the MRI findings suggesting
478 involvement of the salience network in the vulnerability to insomnia (§ VII), it is noteworthy

479 that the insular cortex interacts with the amygdala to transform novel stimuli into familiar
480 stimuli (38).

481

482 While at the one hand sleep can be assessed with the increasingly advanced methodologies
483 of HD-EEG recording and analysis, sleep can at the other hand also be estimated in a simpler
484 way by use of actigraphy. Actigraphy continuously records wrist activity and uses the signal
485 for several purposes including the estimation of physical activity, pathological movements,
486 rest-activity rhythms and sleep (e.g. 402). Sleep estimation from activity signal is based on
487 the low probability that extended periods of time without movement can occur during
488 wakefulness. While objective sleep estimates (PSG nor actigraphy) are not required for the
489 diagnosis of ID, it has been suggested that actigraphy aids to recognize sleep state
490 misperception or paradoxical insomnia (354). As discussed above, these namings may not be
491 optimal in case insomnia involves enhanced memories of ongoing mental activity during sleep,
492 which are difficult to recognize in EEG, let alone with actigraphy.

493 Actigraphy applied in insomnia has the same drawback as actigraphy applied in people
494 without a sleep disorder. When recorded concurrent with polysomnography, actigraphy has
495 adequate sensitivity to detect sleep, but poor specificity to detect wakefulness (250),
496 because prolonged immobility does not guarantee sleep. On the other hand, a clear
497 advantage of actigraphy over polysomnography is that it is easy to record sleep across many
498 nights to evaluate night-by-night variability. Both actigraphy and sleep diaries show increased
499 night-by-night variability in people suffering from insomnia (64). Interestingly, night-by-night
500 variability as assessed using sleep diaries (393) or the combination of sleep diaries and
501 actigraphy (379) have suggested subtypes of insomnia and of sleep state misperception.

502 Natale and colleagues evaluated the use of actigraphy to distinguish people with insomnia
503 from well-sleeping controls (276). For their specific type of actigraph, the best Linear
504 Discriminant Function made use of three variables: total sleep time, sleep onset latency and
505 the number of awakenings lasting longer than five minutes. Using a different type of actigraph

506 however, other variables were found to distinguish insomnia best (275). The discrepancy
507 indicated the need of device-independent algorithms that utilize the raw accelerometry data
508 (382).
509 Meta-analysis indicated that there is ample evidence of its validity and utility in assessing
510 sleep continuity and that actigraphy provides unique information complementary to sleep
511 diaries (355). The meta-analysis concluded as well that actigraphy didn't always provide
512 sufficiently reliable sleep estimates and could fail to detect intervention effects on sleep that
513 were established by polysomnography. Thus, Smith et al (355) echoed a 15 years earlier
514 conclusion that the function of actigraphy in the assessment and diagnosis of insomnia "is
515 likely to be restricted to the role of an adjunct to clinical history, sleep diary data, and PSG
516 findings" (9). To improve this situation, progress has been made in optimizing actigraphy
517 specifically for use in insomnia (381).

518

519

520 **The discrepancy between subjective and objective sleep: misperception?**

521

522 Across people with and without sleep complaints, there is a notable low correspondence
523 between the subjectively and objectively experienced quality of sleep. What determines the
524 subjective experience of a bad night's sleep? Ramlee et al. (319) extensively investigated the
525 determinants of subjective sleep quality. It was notable that the top three of factors
526 determining subjective sleep quality contained only one sleep feature: total sleep time. The
527 other variables determining sleep quality rather described *how one felt after sleep*, i.e.
528 whether one felt refreshed upon waking, and subsequently experienced good mood during
529 the day. Thus, subjective poor sleep quality primarily reflects a failure of overnight brain
530 processes that promote waking up feeling good.

531

532 As compared to people without sleep complaints, people with ID are prone to experience
533 wakefulness during a considerable part of the time when PSG shows EEG signatures of sleep.
534 (162, 258, 310) or actigraphy (377, 396). This discrepancy was referred to as sleep state
535 misperception (SSM) in earlier versions of the International Classification of Sleep Disorders
536 (ICSD) and renamed to paradoxical insomnia in the third edition of the ICSD (105, 162). As
537 stated above (§ II, Subjectively experienced sleep), we consider it possible that people with
538 insomnia consolidate ongoing mental content during NREM sleep better, and thus wake up
539 in the morning full of memories of thoughts and ruminations. have enhanced consolidation
540 and memories of the mentation that indeed continues during sleep (350). As for
541 determinants of the subjective experience of a bad night's sleep by Ramlee et al. (319),
542 Hebert et al. (167) investigated determinants of the degree of discrepancy between
543 subjective and objective sleep. They found the discrepancy increased in particular with
544 cognitive activity during sleep and worse mood on awakening. Thus, also sleep state
545 misperception seems to reflect a failure of overnight brain processes that promote waking
546 up feeling good.

547

548 In addition to the questionnaire approaches mentioned above, a few studies tried to pinpoint
549 PSG determinants of the cognitive activity during sleep that results in sleep state
550 misperception. Parrino et al. (303) suggested that difficulty to maintain consolidated NREM
551 sleep in-between awakenings makes these NREM periods subjectively feel as continuation of
552 wakefulness. During REM sleep, a high density of arousals and eye movements, concertedly
553 coined 'Restless REM sleep' have been associated with thought-like rather than dream-like
554 nocturnal mental content (120, 424). Arousals and eye movements are related and have
555 concertedly been coined 'Restless REM sleep' (424). Riemann et al. (330) proposed that an
556 increased density of eye movements during REM could follow from REM sleep fragmentation.
557 Restless REM sleep may contribute most strongly to the subjective experience of restless,

558 non-restorative sleep (123, 330, 424). Restless REM sleep is also a biomarker of the
559 vulnerability to MDD in symptom-free probands (267, 314).

560

561

562 **Vulnerability to subjective and objective sleep features characteristic of ID**

563

564 The final part of this section on objective sleep features that are altered in ID, addresses the
565 question of underlying mechanisms. Countless previous papers concluded that both the
566 subjective and the objective deviating features of sleep and wake of people ID indicate an
567 underlying *hyperarousal*. It may be questioned where this conclusion can actually lead. Do
568 people really have insomnia *because* they have hyperarousal? We would rather regard
569 hyperarousal part and parcel of insomnia. It might be more fruitful to search for causes
570 *beneath* an insomnia phenotype that includes hyperarousal. We propose that *genetic variants*
571 and *early life stress* can contribute to *pre-existing restless sleep* in people vulnerable to develop
572 insomnia.

573

574 What we can learn of gene variants that increase the risk of insomnia will be addressed in
575 detail in § IV It suffices here to mention that insomnia risk genes could contribute to the
576 characteristic sleep features of ID described above in the current section. Notably, gene
577 variants may result in pre-existing altered EEG during wake and sleep, pre-sleep arousal and
578 fragmented sleep already prior to any clinical diagnosis of ID.

579 A predisposition to pre-sleep arousal and altered EEG during wake and sleep could
580 involve variants in several genes that have been implicated in the risk of insomnia. Altered
581 sleep and wake EEG spectra along the same dimensions that have been implicated in
582 insomnia disorder (88) are seen in *SNCA* mouse mutants (254). Altered expression in mice
583 changes *DNM1*, which encodes the synaptic protein dynamin I, which is increased in *BTBD9*
584 mutant mice (99) and mediates the sleep-disruptive effect of pre-sleep arousal (369).

585 Fragmented sleep is also seen in *BTBD9* mouse mutants (97). Of note, *BTBD9* is the top gene
586 associated with insomnia (183).

587

588 How early life stress increases the risk of insomnia will be addressed in detail in § V. It
589 suffices here to mention that childhood adversity could contribute to the characteristic sleep
590 features of ID described above in the current section. Notably, childhood adversity may
591 result in pre-existing altered EEG during wake and sleep, pre-sleep arousal and fragmented
592 sleep already prior to any clinical diagnosis of ID. As concisely reviewed by Insana et al.
593 (180), abused children have difficulty initiating sleep and have twice as many nocturnal
594 arousals than nonabused control children (146, 147). People that retrospectively report
595 parental emotional abuse during childhood have worse sleep quality at advanced age (317).
596 Also once people have been diagnosed with ID, childhood adversity leaves its lifetime trace
597 in sleep, indicated by a higher number of arousals (16, 17). With respect to the general
598 hypothesis that will be developed in this review, it is important to note that the strongest
599 late effects were seen in REM sleep. Both in humans and in animal models, REM sleep was
600 more fragmented and restless in proportion to the early life stress experienced (180, 188,
601 246, 305, 306). The lifetime impact of early-life stress on sleep may thus be best noticeable
602 during REM sleep.

603

604

605

606

607 **III. Daytime characteristics of insomnia**

608

609 This section addresses subjective and objective assessments of daytime cognitive and
610 emotional functioning, their discrepancies, and factors underlying these vulnerabilities.

611

612 **Subjectively experienced daytime cognitive and emotional functioning**

613

614 The diagnosis of ID is strictly based on subjective sleep complaints and doesn't include
615 objective sleep criteria. By definition, the diagnosis of ID requires that someone subjectively
616 experiences at least one form of daytime impairment like fatigue, mood disturbance,
617 interpersonal problems, reduced cognitive function, reduced performance, behavioral
618 problems (e.g. hyperactivity, impulsivity, aggression), reduced motivation or initiative,
619 proneness to errors or accidents. The impairment(s) cause marked personal distress or
620 interfere with functioning in work or personal life (93, 435).

621

622 Daytime fatigue, i.e. a lack of energy, is common, but should not be confused with sleepiness
623 - the propensity to fall asleep. Subtypes of insomnia differ with respect to the fatigue they
624 experience (42). As compared to controls without sleep complaints, a highly distressed
625 insomnia subtype suffers on average almost two standard deviations more, moderately
626 distressed subtypes about one standard deviation more, and low distressed subtypes about
627 half a standard deviation more (42). Sleepiness on the other hand does not differ much
628 between subtypes of insomnia, nor do people with insomnia differ markedly from controls.
629 The largest difference with controls is seen in the low distressed insomnia subtype with low
630 reactivity, who is on average 0.3 standard deviations *less* sleepy than controls without sleep
631 complaints.

632

633 *Hyperarousal* is commonly mentioned as the key subjective complaint experienced by people
634 with ID, contrasting to the *hypoarousal* that can be induced by sleep depriving people
635 without intrinsic insomnia complaints. Hyperarousal resembles the state of acute anxiety or
636 other emotional distress. Hyperarousal is however only one of many persistent, trait-like
637 characteristics that can be experienced subjectively. An extensive survey of personality and
638 affect traits by means of validated questionnaires shows that people with insomnia can
639 experience: a lack of action control, lack of agreeableness, lack of extraversion, neuroticism,
640 lack of behavioral activation, fatigue, response to stress and life events, more negative affect
641 and a lack of positive affect, perfectionism, lack of positive rumination, dampening of positive
642 moods, hyperarousal, rumination, lack of subjective happiness and lack of experiencing
643 pleasure (37, 42). These characteristics are not equally present in all people with insomnia.
644 Different subtypes of insomnia can be defined based on the profile of the presence and
645 severity of each of the characteristics. Interestingly, these non-sleep-related subtypes are
646 very robust and stable over time. This stability contrasts markedly with some previously
647 proposed instable subtype classifications that were based on *sleep characteristics* like ‘sleep
648 onset insomnia’ (223) or on specific predisposing, precipitating, and perpetuating processes
649 (e.g., psychophysiological insomnia (104)). These earlier subtypes were abandoned from the
650 major nosologies due to a lack of reliability and validity (118).

651

652 With respect to subjective emotion, Baglioni et al (18) assessed ratings while exposing
653 people with insomnia and controls to low-to-medium arousing pictures from the
654 International Affective Pictures System, as well as to complementary sleep-related pictures.
655 People with insomnia had enhanced emotional reactivity, especially to sleep-related pictures.
656 In contrast, another study indicated that people with insomnia subjectively rate emotional
657 faces as less emotionally intense (221). The latter finding however seemed driven by anxiety
658 and depression rather than by insomnia severity, because individual differences in intensity
659 ratings correlated four times stronger with anxiety and depression than with sleep efficiency.

660 Wassing et al. found that people with insomnia show a deficit in subjective overnight
661 adaptation to a novel distressing experience (423). As a result, distress more likely to last
662 not only overnight but even up to weeks (424). Jansson-Fröjmark and colleagues (184)
663 surveyed subjective emotional reactivity and insomnia complaints longitudinally. People in
664 whom difficulties in emotion regulation increased over the years were at a higher risk of
665 incident or persistent insomnia. The latter studies suggest that investigating changes over
666 time is more sensitive to deviations in insomnia than single assessments are.

667

668 A recent study employed the experience sampling (ES) method to evaluate current
669 subjective mood across many time points on multiple days in naturalistic conditions (380).
670 Overall, people with insomnia did not differ from people without sleep complaints on their
671 ratings of commonly used positive and negative mood adjectives (65). Groups did differ
672 however on questions that more directly tapped into wanting and liking, the two major
673 discriminable dimensions of reward and hedonic processing (39, 216). In agreement with a
674 previous lab study showing insufficient comfort sensing (325), and a home study indicating
675 that people with insomnia do not judge their bed as comfortable as normal sleepers do (41),
676 the findings indicate deficient hedonic and reward processing in insomnia.

677

678

679 **Objectively assessed daytime cognitive and emotional functioning**

680

681 Objective deficits in daytime *cognitive* functioning in people with insomnia have been
682 systematically reviewed and meta-analyzed (132, 348). Widespread large deficits might have
683 been expected, based on both the subjective complaints of people with insomnia as well as
684 on the marked effects reported in sleep deprived people without insomnia (204, 239, 243).
685 However, systematic review and meta-analysis showed that the overall, cognitive functioning
686 is amazingly intact in people with insomnia. No significant performance deficits were found

687 on tasks that assessed general cognitive function, perceptual and psychomotor processes,
688 procedural learning, verbal functions, attention, verbal fluency and cognitive flexibility. Only
689 small to moderate deficits were found for episodic memory, problem solving and working
690 memory. Systematic reviews on insomnia in older adults likewise conclude that the
691 relationship of cognition and cognitive decline with complaints is inconsistent, in contrast to
692 their relatively consistent relationship with sleep duration, sleep fragmentation, and sleep-
693 disordered breathing (446). Moreover, in the studies that did find worse cognitive
694 performance in insomnia, results might have been secondary to short sleep depressive
695 symptoms, undiagnosed sleep apnea and other medical conditions (57).

696 In fact, a few studies have reported even slightly *better performance* in people with
697 insomnia than in matched controls without sleep complaints, on some tasks assessing
698 reaction time (6, 117), word fluency (5), mental flexibility (90) and across tasks (222).
699 Successful intervention for insomnia may even result in a decrease in performance speed (6,
700 160). Interestingly, fast reaction times are associated with increased EEG power in the beta
701 and gamma band (181). As discussed above in § II-III, high beta power is the most consistent
702 EEG finding in insomnia.

703 Overall, the findings suggest that objective cognitive performance correlates of insomnia
704 differ markedly from those found after sleep deprivation. Rather, the findings suggest that
705 people with insomnia resemble individuals that are stressed. At least in women, stress was
706 also found to be associated with a faster working memory response time (11). Performing
707 better instead of worse in stressful and dangerous situation makes perfect sense from an
708 evolutionary perspective.

709

710 Only few studies compared people with insomnia and well-sleeping controls with respect to
711 *overnight* effects on procedural and declarative memory. While animal studies mimicking
712 aspects of insomnia consistently suggest disrupted sleep-dependent memory effects (136,
713 256, 332, 371), results are not that equivocal in actual patient studies. A first study reported

714 that people with insomnia lacked the overnight explicit memory enhancement of learned
715 associated word pairs that was seen in well-sleeping controls. No group differences were
716 seen in overnight changes on a procedural mirror-tracing task. A subsequent study, first
717 reported as a pilot study (284), in contrast reported results (283) that were dissociating
718 double from those of Backhaus et al. (15). People with insomnia did not have a significantly
719 deviating overnight change in verbal memory, but lacked the overnight improvement on a
720 procedural motor task (mirror tracing) that was seen in well-sleeping controls. The
721 difference however seemed driven mostly by a slow pre-sleep performance in controls:
722 post-sleep performance was identical in people with insomnia and well-sleeping controls.
723 Interpretation of the findings was moreover somewhat complicated by the use of a
724 percentage-change score which results in bias given the baseline imbalance (408). The finding
725 also contrasted with an earlier report of a significant overnight improvement on the same
726 mirror tracing task in a sample among whom 74% had insomnia (148). A study that used
727 another procedural task (finger tapping) also found no deviations in insomnia with respect to
728 overnight performance improvements, nor on unperturbed performance of a declarative
729 word pair memory task (151). Interestingly however, after subsequent interference, people
730 with insomnia showed a stronger drop in declarative performance than good sleepers did in
731 proportion to their individual sleep fragmentation. The study suggests that sleep
732 fragmentation might weaken next day's memory stability and may be revealed only with the
733 use of interference (151). In contrast to Griessenberger et al. (151), Cellini et al. [2014
734 #20411], while using the very same procedural finger tapping task, did report an attenuated
735 overnight performance improvement in people with insomnia. Finally, Wislowska et al.
736 (439) reported unperturbed overnight consolidation of word pairs in insomnia, and noted
737 that overnight forgetting was mostly bound to occur to people with poor baseline
738 performance. In summary, it remains quite equivocal whether people with insomnia show
739 deviations in overnight changes on explicit and implicit tasks. Of note, all of the studies
740 mentioned above used tasks without emotional relevance. A few more recent studies

741 specifically addressed another type of *overnight* learning in insomnia: *emotional distress*
742 *adaptation*, with consistent and remarkable findings, as will be discussed in detail in section
743 IX (423-426).
744
745 Relatively few studies objectified deficits in daytime *emotional* functioning in people with
746 insomnia. Baglioni et al (18, 20) report a stronger emotional reactivity, especially to sleep-
747 related pictures, in facial electromyography, in electrocardiography, and in the fMRI
748 (functional magnetic resonance imaging) BOLD (blood oxygen level dependent) response of
749 the amygdala. Wassing et al. (425) investigated the overnight adaptation in the fMRI BOLD
750 response of the amygdala to a novel self-conscious emotional experience and found worse
751 adaptation in subjects that had more fragmented REM sleep - a key characteristic of
752 insomnia. They also compared responses to novel self-conscious emotional experiences and
753 relived memories of such experiences from the distant past (426). While autonomic and
754 BOLD responses to novel experiences were not altered in people with insomnia, they
755 showed stronger autonomic responses to relived experiences, as well as stronger BOLD
756 responses in the salience network circuit including limbic parts, notably in the dorsal
757 anterior cingulate cortex (ACC).
758
759 Few studies have investigated deviations in insomnia in resting state EEG recorded during
760 wakefulness. EEG differences between people with insomnia and controls are more
761 consistently found during sleep than during wake (445). Wake-like activity during sleep may
762 be easier to detect than 'added' wake-like activity amidst the normal wake EEG activity,
763 where ceiling effects are more likely. As reviewed by Colombo et al. (88) wake-EEG studies
764 overall once more indicate most consistently increased power in the beta range, just as is
765 the case during sleep. High-density EEG (HD-EEG) recordings have added spatial
766 information to spectral findings. Both scalp level topography and source estimates suggested
767 widespread global rather than cortically localized increased beta in people with insomnia

768 (88), as is the case during sleep (329). In addition, wake alpha band activity (8-12 Hz) was
769 lower in people insomnia than in controls across the cortex (88), in contrast to their
770 increased alpha band activity specifically in sensory-motor areas during sleep (329). The
771 contrasting lower alpha prior to sleep and higher alpha during sleep had been reported
772 before using regular EEG (134). Both lower alpha and increased beta prior to sleep indicate
773 pre-sleep arousal (134). Wake hyperarousal is also supported by fMRI findings of
774 predominantly salience network activation, as will extensively be discussed in § VII.
775
776 The hyperarousal that people with insomnia experience so strongly subjectively is moreover
777 also reflected in some autonomic features, which has extensively been reviewed. In brief,
778 while especially autonomic cardiovascular alterations are widely accepted in insomnia (274),
779 deviations in heart rate and its variability not unequivocally supported by actual findings
780 (108). Likewise, metabolic rate may be increased in only a subsample of people with
781 insomnia, i.e. those that also show a short sleep duration during first exposure to a
782 polysomnographic recording (308). 24-hour HPA axis activation may also be most
783 pronounced in short sleeping insomniacs and support the conception of insomnia as a
784 disorder of hyperarousal rather than one of sleep loss, since sleep deprivation is more often
785 found to decrease cortisol or have no effect (308). It should be noted that too few studies
786 investigated autonomic responses to acute distress, or overnight changes in the autonomic
787 responses to repeated distress. That such a perturbation approach may be more sensitive to
788 detect deviations has been demonstrated for post traumatic stress disorder (102). A
789 perturbation approach seems even more powerful if repeated overnight (425).
790
791
792
793

794 **IV. The genetic risk of insomnia**

795

796 The key to a better understanding of any disorder is to examine how it develops. The
797 identification of risk factors can be of great value to formulate hypotheses about underlying
798 mechanism of the disorder. The next sections (§ IV-V) will therefore extensively address risk
799 factors. An early psychological model of insomnia highlighted the need to address three so-
800 called 'P' factors; *predisposing* personality traits like the tendency to worry; *precipitating*
801 events like stress, and *perpetuating* attitudes and practices like misconceptions about
802 required sleep (309, 361). The same heuristic model can used to address the developmental
803 biology of insomnia. A key question is at what moment during life insomnia predisposing
804 factors really commence, whether or not overt measurable signs appear immediately or only
805 later. As for any disorder, it would be most valuable to find risk markers as early in life as
806 possible. Risks for experiencing bad nights of sleep and for the development of ID should
807 therefore be addressed across life, and cover a wide range of individual to societal factors.
808 The next sections (§ IV-V) will therefore systematically review risk factors along the
809 developmental axis, starting with heritability and gene variants (§ IV), followed by prenatal
810 stressors, adverse childhood experiences (ACE's), major life events and trauma (§ V), and
811 current stressors from disease and the socioeconomical and physical environment § V).

812

813

814 **Heritability**

815

816 Can people be 'born' with a risk to develop insomnia? Family and twin studies indeed suggest
817 that this is the case. As scholarly reviewed by Lind and Gehrman (240) at least five studies
818 evaluated whether insomnia 'runs in the family', and suggested that this was indeed the case.
819 Family studies cannot however unravel whether this has a genetic basis, or rather
820 represents similarity of environments and behaviors passed on across generations. To distill

821 the part accounted for by genetics requires twin studies. The heritability estimates reported
822 for specific insomnia phenotypes ranged from .28 to .59 (240) and the most recent meta-
823 analyzed average estimate is 0.44 (208). Two particular estimates, .59 for men and .38 for
824 men seem most representative for trait-like, persistent insomnia vulnerability, because they
825 were found in a longitudinal repeated measures study (241). A higher heritability of
826 insomnia for females than for males was found before (respectively .55 versus .43, 110), and
827 resembles their higher heritability for depression (respectively .40 versus .29, 198, 199). Not
828 only insomnia itself has shown to be partly heritable. Heritability has also been documented
829 for the traits that have been associated with insomnia, as shown in table S1 of Blanken et al.
830 (42).

831 The heritability of insomnia seems at least as pronounced as the heritability for anxiety,
832 depression and neuroticism, arguably the three traits that are most closely related to
833 insomnia (see **Figure 6. "Genetic and phenotypic overlap of insomnia with other**
834 **traits and disorders"**, adapted from reference (156)). Meta-analytic and large-scale studies
835 provide heritability estimates of .32 for anxiety disorder (169), .38 for major depression
836 (199, 368) and .39 for neuroticism (412). Accordingly, one could expect at least as much
837 statistical power to find loci for insomnia in molecular genetics studies as there has been in
838 studies on risk genes for anxiety, depression and neuroticism.

839

840

841 **Gene Variants**

842

843 The heritability of insomnia indicates that variants of specific genes could increase its risk.
844 Involved genes can be found by comparing cases and controls with respect to the presence
845 of DNA base pair differences at specific locations, known as single nucleotide
846 polymorphisms (SNPs). DNA differences can also occur in the number of repeats of short
847 nucleotide sequences, known as variable number tandem repeats (VNTRs). Such SNP and

848 VNTR variations can signal individual differences in the formation or function of proteins
849 that affect biology. Two approaches have been followed. First, candidate gene studies (CGS)
850 evaluate a priori chosen genes of interest. The choice of genes is based on knowledge of the
851 underlying biology, for example the role of a gene in a neurotransmitter system known to be
852 affected in the disorder. In practice, this is a relatively arbitrary and difficult choice given the
853 little we really know about the underlying biology of insomnia - or for that matter any other
854 complex trait. More recent work therefore followed a second approach: genome-wide
855 association studies (GWAS). So far, no studies on insomnia have addressed the intriguing
856 possibility that risk variants predisposing for the *onset* of insomnia could differ from risk
857 variants that contribute its perpetuation, or *chronicity*, as has been suggested for PTSD (389).

858

859 Candidate gene studies

860 CGS on insomnia have been reviewed in Lind and Gehrman (240). Insomnia has been
861 associated with polymorphisms in genes implicated in other psychiatric disorders. Examples
862 are genes involved in the transport (*5-HTTLPR*) (54, 61) or metabolism (*MAO-A*) (62) of
863 serotonin. One study found an increased probability of insomnia in carriers of the Apoε4
864 allele (419). Overall sleep disturbance measured with the Pittsburgh Sleep Quality Index
865 (PSQI) showed no significant association the dopamine-regulating catecholamine-O-
866 methyltransferase (*COMT*) (186). It has also been suggested that insomnia is associated with
867 polymorphisms in genes implicated in circadian rhythm regulation like *PER2* (234), *PER3* (60),
868 *CLOCK* and *BMAL1* (452), and *PGC-1α*, a gene both involved in clock mechanisms and
869 metabolism (419).

870 In addition to the methodological concern on the arbitrary preselection of genes for CGS,
871 there is some concern on the definition of the phenotype selected to represent insomnia
872 disorder. For example, people that are genetic predisposed to be late chronotypes will
873 experience difficulties with sleep onset if they try to adhere to a societally desirable clock
874 times. This is however not the same as insomnia. Likewise, although it is valuable to find

875 genetic variants related to daytime sleepiness (394) or stress reactivity (163, 173), these
876 genes may not necessarily be specific to the risk of insomnia disorder. Gene variants
877 associated with insomnia-related traits have been reviewed in table S2 of Blanken et al. (42).

878

879 Genome-wide association studies

880 The GWAS approach is considered better suited than the candidate gene approach, because
881 complex traits like insomnia are highly polygenic, i.e. determined by any combination of
882 variants in many genes that each individually have a very small effect. GWAS can have two
883 methodological issues. First, finding case-control differences across the genome requires
884 many statistical tests and consequently high statistical thresholds and very large samples.
885 Second, large cohorts may have assessed phenotypes that are not that specific to insomnia
886 disorder. While samples of more than a million have become available and help overcome the
887 first issue, there is no sizable cohort with a detailed clinical diagnosis of insomnia disorder.

888 Hammerschlag et al (156) therefore extensively evaluated the validity of using indirect
889 phenotypes to estimate whether someone suffered from insomnia. They took the seven
890 simple questions about sleep that were available in the UK Biobank - one of the largest
891 genotyped cohorts - and evaluated the discriminative power of these questions in the
892 Netherlands Sleep Registry (37), a cohort that includes extensive diagnosis of sleep
893 disorders. This phenotype validation in an independent sample showed that one particular
894 answer on one particular UK Biobank question on sleep, had an excellent accuracy to
895 discriminate cases with insomnia: not only from controls, but also from people with another
896 sleep disorder, i.e. restless legs syndrome (RLS) (see **Figure 7. "UK Biobank insomnia
897 phenotype validation"** from reference (156).

898 This validation allowed for a valuable GWAS in 113,006 individuals of whom 29% had
899 probable insomnia disorder. The GWAS, complemented with a genome-wide gene-
900 association study (GWAS) and a meta-analysis with an independent cohort, identified
901 involvement of the *MEIS1* and *MED27* genes across sexes, and sex-specific additional genes

902 for males (*HHEX* and *RHCG*), and females (*IPO7* and *TSNARE1*). In part of the same sample
903 (32,155 cases and 26,973 controls), analyzed without replication or meta-analysis, Lane et al.
904 (225) found significant associations of insomnia with *MEIS1*, *TMEM132E* and *CYCL1* across
905 sexes and one additional gene both in females (*TGFB1*) and males (*WDR27*)

906 Following up on these initial studies insomnia genetics, a very large GWAS of
907 N=1,331,010 people replicated *MEIS1*, *MED27*, *IPO7* and *ACBD4*, and moreover provided
908 strong support for the polygenic nature of the risk of insomnia (183). The study identified
909 956 genes that were implicated by at least one of four different strategies (positional
910 mapping, eQTL, chromatin mapping and genome-wide gene-based association analysis -
911 GWAS). Of these genes, 62 were consistently implicated by each of the four different
912 strategies.

913 Some of the identified genes have been studied in mouse models. Mice with mutations in
914 *BTBD9*, the top gene associated with insomnia in the study of Jansen et al. (183) or in *DNM1*,
915 another identified insomnia risk gene, both show changes in the synaptic protein dynamin I
916 which mediates the sleep-disruptive effect (increased sleep onset latency) of pre-sleep
917 arousal (99, 369). *BTBD9* mouse mutants also show altered plasticity resulting in a stronger
918 fear memory (99) and other phenotypes that match findings in insomnia (98), like increased
919 restless, more fragmented sleep, and altered thermal sensitivity (324, 325).

920

921 Variance explained by GWAS

922 So far, GWAS studies have explained only a very small percentage of the phenotypic
923 variation of insomnia: 2.6% in the largest GWAS to date (183). Theoretically, if all genetic
924 variants affecting insomnia were known and if all their effects would be estimated correctly,
925 the maximal variance explained could equal the heritability, which meta-analysis estimated to
926 be 44% (208). The large difference between the variance explained by GWAS versus
927 heritability estimates is common for complex traits and known as the 'missing heritability'
928 (398, 442). Several factors contribute to this missing heritability, including linkage

929 disequilibrium, variants that are both rare and have small relative risks, limited sample sizes
930 of discovery cohorts, and limitations in the statistical estimation (for reviews, see 331, 398,
931 442).

932 While limitations of genetic methodology received most attention in explaining the missing
933 heritability, phenotypic measurement issues contribute significantly as well (for a review, see
934 398). While diagnostic nosologies present insomnia as a clear-cut disorder (8, 105), the
935 actual presence of the disorder may fluctuate during lifetime, and GWAS cohorts may be
936 heterogeneous with respect to established robust subtypes of insomnia (42). Moreover,
937 sleep complaints related to other disorders or environmental conditions can resemble
938 Insomnia Disorder, especially if presence of Insomnia Disorder is estimated with information
939 as limited as a single question. Phenotype validation is therefore important in GWAS studies.

940 One GWAS that extensively validated the UK Biobank insomnia phenotype utilizing an
941 independent deep-phenotyped cohort (37, 42) demonstrated its excellent properties to
942 discriminate cases with probable Insomnia Disorder (see **Figure 7. "UK Biobank**
943 **insomnia phenotype validation"**, and figures S1 to S4 in Hammerschlag et al. (156)).

944 One may question the value of GWAS if missing heritability remains large in spite of
945 increasingly large discovery sample sizes and the occasional availability of a sensitive and
946 specific phenotype. One important value of GWAS is that it has revealed clues to
947 involvement of specific biological functional pathways, tissues and cell types. Of note, any
948 suboptimal function in these substrates do not necessarily only result from genetic variants,
949 but could of course also emerge during lifetime due to other causes than genetic make-up
950 and thus diluting the variance explained by GWAS. These substrates will be discussed in the
951 paragraph below.

952

953 GWAS provides clues on cell types and tissues involved in insomnia

954 Risk genes for insomnia are likely to sort their effect by altering brain function. Jansen et al
955 (183) therefore followed up on the GWAS findings with gene-set analyses to evaluate

956 whether the identified genes converge in functional pathways, tissues and brain cell types.
 957 Three gene ontology (GO) gene-sets were found: locomotor behavior, behavior, and axon
 958 part. Tissue specific gene-set analyses showed strong enrichment of genetic signal in genes
 959 expressed in the brain, especially in a few specific areas. Of the cerebral cortex, enrichment
 960 was found for Brodmann area (BA) 9, which is a part of the dorsolateral and medial
 961 prefrontal cortex, and for BA24, which is a part of the of the anterior cingulate cortex. The
 962 cerebellar hemisphere was enriched as well. Three striatal basal ganglia structures (nucleus
 963 accumbens, caudate nucleus, putamen) showed a gene-expression that was highly similar to
 964 that of the cortical areas ($r > .96$) but fell just below the significant threshold for enrichment.
 965 Concertedly, the tissue gene-set findings suggests involvement of general cellular signatures
 966 more than specific brain tissue structures. Subsequent gene-set analyses on broad cell types
 967 revealed significantly enriched expression of insomnia risk genes expressed in medium spiny
 968 neurons (MSN). Since MSN's represent 95% of human striatal neurons, the cell-type findings
 969 converge with the tissue gene-set results of near-threshold enrichment of gene-expression
 970 in the nucleus accumbens, caudate nucleus and putamen. Because gene-set analyses on broad
 971 cell types are insensitive to associations with distinctive yet rare cell types, specific brain cell-
 972 type categories were evaluated as well. Enrichment was found in medio-lateral neuroblasts,
 973 D2 type medium spiny neurons, claustrum pyramidal neurons, and hypothalamic
 974 glutamatergic neurons. The identified cell types and tissues of the brain are summarized in
 975 **Figure 8. "Brain tissues and cell types associated with genetic vulnerability of**
 976 **insomnia"** (from (183)) and will be discussed where appropriate later on in this review.
 977 The identified cell types and tissues may be involved in shaping the brain circuitry in such a
 978 way that predisposes people to become vulnerable to insomnia.

979

980 Comorbidity: a role for the MEIS1 gene in Insomnia, RLS and PLMS?

981 Across the few large studies on risk genes for insomnia, a consistent significant association
 982 was with MEIS1. A closer study of it's functional roles therefore could be relevant for

983 understanding the physiological mechanisms of insomnia. However, before considering a
984 possible role of *MEIS1* in insomnia, it should be addressed whether *MEIS1* is really involved
985 in the risk of insomnia, or could be the result of confounding. The gene has previously been
986 implicated in two other disorders: restless legs syndrome (RLS) and Periodic Leg
987 Movements during Sleep (PLMS) (269, 437, 438). It is thus conceivable that the suggested
988 involvement of *MEIS1* in insomnia could be a confound of troubled sleep reported not
989 because of insomnia but because of RLS or PLMS. Whereas some confounding is realistic, it
990 is not likely to fully account for the involvement of *MEIS1* in insomnia. The insomnia
991 phenotype studied in the GWAS's concerns people that state to *usually* have trouble falling
992 asleep at night or do you wake up in the middle of the night. 'Usually' is more often than can
993 be expected in most cases with RLS and PLMS. The first report on RLS-genes defined as
994 cases those people who reported at least *two to four times per month*, while at rest, an
995 uncomfortable desire to move the legs that was relieved by movement and that
996 predominated in the evening or at bedtime (363). Such complaints would not be sufficient to
997 state that one *usually* has trouble falling asleep at night or waking up in the middle of the
998 night. Although RLS and PLM are worse during the night, problems falling and staying asleep
999 are not part of the diagnosis of RLS according to the International RLS Study Group
1000 (IRLSSG) (3). In fact only a minor part of RLS patients (13%) experience restless legs
1001 symptoms more than three times a week (59). In contrast, experiencing sleep problems at
1002 least three times a week is a defining characteristic of insomnia disorder. Indeed,
1003 Hammerschlag et al. (156) showed in a large sample that included people with either
1004 insomnia, or RLS, or both, or none, that 'usually having trouble falling or staying' provides
1005 excellent discrimination of the diagnosis of insomnia disorder (sensitivity 0.98, specificity
1006 0.96), yet poor discrimination of the diagnosis of RLS (sensitivity 0.43, specificity 0.74)
1007 (**Figure 7. "UK Biobank insomnia phenotype validation"**, see also figures S1 to S4 in
1008 Hammerschlag et al. (156)). Of course it should be kept in mind that comorbidity of RLS,
1009 PLM and insomnia is common, and that comorbid insomnia is not unlikely in the more

I010 complex and severe cases that report to sleep centers specialized in RLS. Hammerschlag et
I011 al also provided detailed additional analyses to demonstrate that *MEIS1* shows pleiotropy for
I012 insomnia and RLS: the same genetic variant can manifest itself in different phenotypes. In
I013 addition, different loci within the gene may differentially increase the risk of one or the
I014 other phenotype, as has been suggested for involvement of *MEIS1* in RLS and PLMS as well
I015 (269).

I016

I017 If we consider the conceptual hallmarks of RLS, PLMS and ID, there is a striking link of
I018 hyperarousal, restlessness or agitation: *sensory* restlessness in RLS, *motor* restlessness in
I019 PLMS and *higher order* restlessness (cognition, consciousness) in ID. This tripartitioning may
I020 be too strict: the disorders show high comorbidity, and biomarkers and underlying
I021 mechanisms may overlap in several ways. For example, trouble falling asleep in RLS relates
I022 to similar EEG power abnormalities as found in insomnia (126, 127). In *MEIS1* mouse
I023 mutants, hyperactivity, which is most characteristic of insomnia, has even been used as a
I024 readout for RLS rather than for *insomnia* (360). In conclusion, it appears worthwhile to
I025 investigate how known functions *MEIS1* could be relevant to close in on the enigmatic
I026 mechanisms underlying individual differences in vulnerability to insomnia.

I027

I028 Several animal studies addressed the involvement of *MEIS1* in developmental biology. The
I029 gene encodes a protein that activates and regulates transcription that is essential for normal
I030 development of the central nervous system (66, 153, 360). The early recognition of *MEIS1*
I031 involvement in RLS may have promoted a focus on *MEIS1* mutation consequences
I032 specifically for the motor system (360). However, *MEIS1* has longer been known to be
I033 involved on other functions. A relevant example is the regulatory role of *MEIS1* in the
I034 expression of substance P, both in the subset of medium spiny neurons that project to the
I035 substantia nigra (178) and in the human amygdala (94). This is a most interesting lead,
I036 because amygdalar substance P acting on its Neurokinin 1 (NK1) receptor modulates fear

I037 and anxiety. Polymorphism in genes regulating substance P, notably *MEIS1*, could raise
I038 susceptibility to an anxious or depressed phenotype. Of note, anxiety and depression are
I039 both phenotypically and genotypically the traits that are most closely related to insomnia
I040 (see **Figure 6. "Genetic and phenotypic overlap of insomnia with other traits and**
I041 **disorders"** from (156)). In support of suboptimal amygdala functioning in insomnia, fMRI
I042 studies revealed that people with insomnia show an enhanced amygdala responses to
I043 insomnia-related stimuli (20) and a lack of overnight attenuation of its response to emotional
I044 stimuli (425). A more detailed discussion of the link between insomnia, mood and anxiety
I045 will follow in § VI and § IX.
I046

I047 **V. The risk of insomnia conveyed by stressors**

I048

I049 After conception has set the stage for the risk of insomnia as conveyed by specific genetic
I050 variants, early developmental conditions can impact their expression and later life
I051 consequences through epigenetic changes (265). Studies have proposed that early life
I052 epigenetic changes as induced by early traumatization determine whether or not risk
I053 variants evoke late life disease vulnerability. This section will discuss findings on the effects of
I054 early life stress on insomnia later in life.

I055

I056

I057 **Prenatal Stress**

I058

I059 Research on the effects of prenatal stress on insomnia in offspring has remained in its infancy.
I060 In contrast to the vast literature on other health effects of stressors like maternal smoking
I061 during pregnancy, very few studies addressed effects on sleep-related variables. One study
I062 found that prenatal smoking by mothers correlated with an increased frequency and
I063 duration of obstructive apneas in infants (191). Another study suggested that mothers that
I064 smoked during pregnancy were more likely to have a child with an early life trajectory of
I065 increasing sleep problems, but the report does not allow for a conclusion on whether
I066 smoking was an independent or secondary risk factor (210). A systematic review suggests
I067 effects of prenatal stress on infant sleep duration and architecture (299). However, none of
I068 the studies followed up offspring long enough to evaluate consequences for the risk of
I069 insomnia in adulthood.

I070 A few animal studies, discussed in the same review (299), suggest that prenatal stress
I071 alters sleep in adulthood, as indicated by less slow wave sleep and increased REM-sleep
I072 pressure (113, 321). Somewhat more animal studies demonstrated effects of prenatal stress
I073 on adult hypothalamus-pituitary-adrenal (HPA) axis functioning and sympathetic reactivity

1074 (299). Indeed, stress reactivity lasting into the night and disrupting sleep increases the risk of
1075 developing insomnia (4, 111, 185).

1076 One virtually unexplored possible prenatal stressor concerns the maternal sleep
1077 problems that are experienced by about ten percent of pregnant women (296). Studies on
1078 the effects of maternal sleep on fetal outcomes are limited and often conflicting (422). An
1079 intriguing hypothesis is that maternal fatigue, depression and hormonal changes induced by
1080 sleep problems during pregnancy impair the mother-infant relationship (315), which could in
1081 turn could increase the odds of insomnia in adulthood, as described in the next paragraph.

1082

1083

1084 **Adverse Experiences**

1085

1086 Not only prenatal stress, but also stress during early development can lead to persistent
1087 consequences for adult stress sensitivity and regulation (299). These persistent changes in
1088 the stress system can increase the risk of a physical and mental disorders. Among early
1089 developmental stressors, one in five children experience childhood abuse or neglect or
1090 household dysfunction. Are these adverse childhood experiences (ACEs) involved in the risk
1091 and severity of insomnia as well?

1092

1093 **ACEs increase the risk of insomnia**

1094 The question whether ACEs increase in the risk and severity of insomnia has been
1095 addressed in several studies, reviewed in Palagini et al. (299). Some earlier samples small to
1096 medium-sized studies indeed suggested that childhood adversity could increase the risk of
1097 insomnia in adulthood (17), but also in in adolescence (421) and early adulthood (150, 212).
1098 Koskenvuo et al. (212) were the first to report a very large epidemiological study. About
1099 26,000 Finns answered questions about current sleep quality, recent stressful life events,
1100 healthy behaviors, the quality of child-parent relationships, and several adverse childhood

experiences including parental divorce, prolonged financial difficulties, serious conflicts, frequent fear of a family member, poverty and illness or alcoholism of a family member. Of the different adverse events, frequent fear of a family member and serious conflicts increased the odds most strongly. Worst off were those that experienced more than two adversities and additionally had a poor relationship with their mother (OR 10.4) or father (OR 5.4).

A critical question is whether ACE increases insomnia only secondarily, as a complaint strictly due to other conditions, like depression. In the study of Koskenvuo et al. (212), adjustment for current depressive symptoms changed the results only modestly, indicating that the effect of childhood adversity on sleep complaints is not simply merely secondary to its known effect on the risk of developing depression in adulthood. Notably, the odds for poor sleep are much higher than the odds of for depression (OR 4.4) and the majority of other adverse health sequelae, as recently meta-analyzed (175). Interestingly, adjustment for recent life events did not considerably change the odds for poor sleep after childhood adversity either (212).

In summary, the findings suggest that the learning experience of *'not being safe' during a critical early life period of brain plasticity* might lead to an unbalanced enhancement of neuronal activity in circuits supporting *watchfulness*.

Does the kind of ACE matter?

Different kinds of ACE's have been subdivided along two dimensions. One dimension represents physical, sexual and emotional categories. The other dimension distinguishes abuse from neglect. Intriguing questions are whether the risk of insomnia depends on the kind and number of ACEs and on whether they involve a single or multiple categories.

This question has been posed previously for the risk of other disorders. For example, neglect has been suggested to be the strongest predicting ACE subtype for depression (159). However, as reviewed by Negele et al (279), studies that tried to map specific types of ACEs

to specific mental disorders yielded quite equivocal results. In their own study that aimed to map specific types of ACEs to features of depression, multiplicity rather than specificity of adversities predicted symptom severity, and the more chronic the ACEs, the higher the lifetime prevalence of depression (279).

In insomnia, it has been reported that childhood adversity among people suffering from insomnia disorder most markedly concerns emotional neglect (17). Insomnia complaints in elderly have rather been linked primarily to childhood emotional abuse (317). As is the case for depression, it may rather be the number and categorical multiplicity that primarily drives increasing severity of insomnia. A large ($N \sim 17,000$) epidemiological study (76) showed that trouble falling or staying asleep increased with the *number* of adversities people had experienced during childhood. A proportional increase of the risk of current insomnia has also been seen with an increasing *diversity* of childhood adversities, both in adolescents (421) and in elderly people (317).

In summary, the findings provide further indirect support for the involvement of early learning 'not to be safe'. Early life learning of being unsafe and of the need to stay *watchful* will engrave a stronger memory trace if such learning occurs repeatedly and *across multiple contexts*. Indeed, the increased risk of insomnia after childhood adversity is mediated by neuroticism (320), which has been defined as a general sensitivity to negative information. It is tempting to suggest that early life learning of being unsafe and of the need to stay watchful could result in lasting alterations in brain circuits effectuating a lifelong inclination for hypervigilance (317, 443), that could even continue into sleep.

Objective indices of disturbed sleep after trauma

Childhood adversity predisposes to fragmented REM sleep (180), a key feature of chronic insomnia (123, 330, 424). Among people suffering from insomnia disorder, those that reported childhood adversity specifically show more awakenings and movement arousals both in polysomnographic and actigraphic recordings of their sleep, while other sleep

variables did not differ (17). The interpretation coined above, that the learning experience of 'not being safe' during a critical early life period of brain plasticity might lead to an unbalanced overexpression of neuronal activity in circuits supporting watchfulness, is also supported by a study showing that the trait of *attachment insecurity* relates to abiding alpha oscillations in the sleep-EEG - a marker of insomnia (352).

Memory traces of ACEs hidden in gene expression

ACEs can have a persistent impact on gene expression and behavior through epigenetic mechanisms (391). For example, ACEs increase DNA methylation in the promoter region of the serotonin transporter gene (SERT) (32, 295). This epigenetic effect alters SERT expression and stress reactivity throughout life. This mechanism could be relevant for at least one subtype of insomnia (see § VII, § IX and **Figure 9. "Multivariate profile plots of insomnia subtypes"**) that is indeed characterized both by ACEs and by more severe and longer lasting effects of recent life events on insomnia symptoms (42).

'Stress diathesis' models propose that ACEs affect brain circuit development in a manner that leads to enhanced responses to stress in adulthood. One example of persistent circuit changes that seems relevant to insomnia concerns the ACE-induced lasting increased corticotrophin-releasing factor (CRF) signaling, which is critical for the activation of behavioral, emotional, autonomic, and endocrine hyperarousal responses to stressors (257). During stress, projections originating from the amygdala result in CRF release, which acts on the CRF₁ receptors of noradrenergic neurons in the locus coeruleus to stimulate NA release in corticolimbic structures.

The study of gene-by-environment interactions with a specific involvement in insomnia is in its infancy. Some early findings are promising. For example, ACEs were shown to increase DNA methylation of the stress-related genes SLC6A4 (32, 286) and FKBP5 (286). Polymorphisms in SLC6A4 increase the risk of insomnia (103). Moreover, in interaction with

1181 ACEs, polymorphisms in both SLC6A4 (338, 417) and FKBP5 (427), specifically promote
1182 hyperarousal symptoms - which are most characteristic of insomnia as well.

1183

1184 Recent Trauma and Major Life Events

1185 The risk of insomnia increases not only with adverse childhood experiences but also after
1186 recent trauma and major life events (212, 351). Stressful life events include for example the
1187 death of a spouse, child, close relative or friend, the severe illness of a family member, and
1188 physical, sexual or emotional violence. Trauma increases the risk of insomnia also if it does
1189 not lead to post traumatic stress disorder (PTSD). However, different from earlier-life
1190 trauma, which leads to a highly significant increased REM fragmentation, later-life trauma
1191 does not increase REM fragmentation (180).

1192 People that show a trait-like tendency to experience poor sleep in response to a stressful
1193 situation - a trait called 'sleep reactivity' - are more likely to develop insomnia (111, 185,
1194 192). Indeed, current poor sleep is among the strongest risk factors for future insomnia
1195 (OR=11.07) (182). Here once more overlap of insomnia with depression and anxiety is seen:
1196 people with high sleep reactivity are also more likely to develop depression and anxiety
1197 disorders (192).

1198 Stressful life events that someone perceives as being responsible for are more likely to
1199 result in insomnia than events that are beyond one's control (26). This finding indicates that
1200 studies on emotion processing in insomnia could be most sensitive if they address
1201 *selfconscious* emotions like guilt, shame and embarrassment, rather than the basic emotions
1202 that are usually studied, e.g. using the International Affective Picture System (227). Indeed,
1203 strong findings recently emerged in a series of studies on overnight dissolving of
1204 selfconscious emotional distress in insomnia (423-426). A more detailed discussion of the
1205 deficiency in overnight dissolving of selfconscious emotional distress in insomnia will follow
1206 below in § VI and § IX.

1207

1208 **VI. Mental health risks conveyed by insomnia**

1209

1210 Insomnia increases the risk of many disorders. Of note, the predictive effect of poor sleep
1211 quality on future health issues is much stronger than the predictive effect of short sleep
1212 duration (376). Somatic conditions of which the risk increases are for example obesity (158),
1213 type 2 diabetes (158), and cardiovascular disease (298). Insomnia however most notably
1214 increases the risk mental disorders including anxiety disorders, major depressive disorder,
1215 bipolar disorder and post traumatic stress disorder (83, 273, 278, 312). A cross-mental
1216 disorder meta-analysis reported that insomnia is most significantly predicts onset of anxiety
1217 disorders (six studies, OR 3.23) and depression (10 studies, OR 2.83) (168). Only studies
1218 on the risk of depression that didn't find insomnia have not included it as a possible
1219 predictor e.g. (31). Males and females do not differ with respect to the risk of depression
1220 conveyed by insomnia disorder (235). The risk of inflammation-induced depressive
1221 symptoms can however be stronger in mildly sleep-disturbed women than men (82).

1222 Pre-existing insomnia is also key to whether or not a traumatic experience elicits PTSD
1223 (140, 143), as well as to the persistence of PTSD (143). Indeed, good-quality sleep may be
1224 protective against poor emotion regulation and anxiety in veterans with PTSD (249).

1225 Interestingly, the most characteristic polysomnographic findings of disturbed sleep in PTSD
1226 are virtually indiscriminable from those found in insomnia disorder: sleep is more
1227 fragmented due to an increased number of awakenings and arousals. As in insomnia,
1228 especially REM sleep is restless, which may not only show in the number of arousals, but
1229 also in the density of eye movements (55, 207). Both arousal and eye movement density
1230 have also been linked to experience continuing thoughts during sleep in insomnia, and to
1231 insufficient overnight adaptation to emotional distress which may accumulate to chronic
1232 hyperarousal (424).

1233 Across psychiatric brain disorders, insomnia is probably the most common and burdening
1234 co-occurring symptom. While this is generally recognized for major depressive disorder (35),

1235 it may hold for other disorders of mood or distress regulation as well. Zhou et al. (451)
1236 found that four out of five of GAD patients have comorbid Insomnia Disorder. Sleep studies
1237 have also shown that these subjective complaints have their objective counterpart in sleep
1238 EEG recordings. Based on similar polysomnographic sleep feature in primary insomnia and
1239 major depression, Hein et al. (165) suggested a common underlying pathophysiology.
1240 Restless sleep was also found in people with high trait anxiety (372), PTSD (180, 259, 260)
1241 and GAD (302). Finally, difficulties coping with stressful events make people vulnerable to
1242 develop a first-onset disorder of mood or distress regulation or relapse to a new episode
1243 after recovery. Again, insomnia is involved: people that show 'sleep reactivity', a trait-like
1244 tendency to experience insomnia in response to a stressful situation are more likely to
1245 develop disorders of mood or distress regulation (192). Insomnia aggravates the disease
1246 state, worsens the prognosis, impedes treatment response, and promotes relapse after
1247 recovery (74, 281, 390).

1248 Importantly, interventions on insomnia also ameliorate depressive symptoms (44, 46, 47,
1249 84, 247, 399) (for meta-analysis, see (139)). While it has been demonstrated that insomnia is
1250 indeed an independent risk factor contributing to *first onset* depression (43), a six month
1251 insomnia intervention follow-up was insufficiently sensitive to find differences between
1252 treatment and placebo with respect to the incidence of new onset major depressive
1253 disorder (84). Given the incidence rate of depression it may take a longer follow-up to
1254 establish whether or not an intervention on insomnia can mitigate the risk of future
1255 depression.

1256

1257 **VII. MRI findings on brain structure and function in insomnia**

1258

1259 Several imaging studies compared brain structure or function in people with insomnia and
1260 controls without sleep complaints. For reviews, see (197, 358, 373). Findings do not
1261 converge robustly at voxel-level (374). We here first briefly discuss the limited
1262 convergence at the level of voxels and subsequently propose that integrated approaches may
1263 be required to detect *variable distributed deviations*. Finally, we will give some examples of
1264 findings supporting involvement of distributed deviations in particular in the salience
1265 network and connected structures. This section limits itself to a sampler of magnetic
1266 resonance imaging studies and does not aim to review all insomnia studies with all imaging
1267 modalities, for which we refer to previous reviews (197, 358). For magnetic resonance
1268 spectroscopy (MRS) studies to assess concentrations of neurotransmitters including
1269 glutamate GABA, we refer to (197), who concluded that increased high-frequency EEG in
1270 insomnia may result from impaired GABAergic inhibition.

1271

1272 Meta-analysis on differences between people with insomnia and controls across imaging
1273 modalities could not identify consistently affected clusters of voxels (374). Several reasons
1274 can be mentioned for the lack of consistent results at the voxel level. First, relatively few
1275 studies were available for inclusion, and both the total sample size and the sample size of
1276 individual studies is much lower than what has been accomplished for other disorders.
1277 Second, methodologies differed widely: there were six task-based functional magnetic
1278 resonance imaging studies, eight resting-state functional magnetic resonance imaging studies,
1279 three voxel-based morphometry studies, and two positron emission tomography studies.
1280 Third, none of the included studies investigated *overnight* changes in resting state or task-
1281 related activation and connectivity, which is surprising given that the primary complaint of
1282 people with insomnia is that their sleep brings no overnight relief. Indeed, recent work
1283 showed highly significant differences in the overnight changes in brain activation between

people with insomnia and controls without sleep complaints. Fourth, differences in recruitment strategies and inclusion criteria make it highly likely that the samples included in the meta-analyzed studies differed considerably in the proportion of each of the different subtypes of insomnia that have been identified (42). These subtypes are distinguished by specific profiles of traits, which were mostly selected on being associated with specific brain structural- and brain functional characteristics. Gene variants associated with insomnia-related traits have been reviewed in table S3 of Blanken et al. (42). Subtypes are likely to differ with respect to their *distributed deviations* of brain characteristics (45). Moreover, even within an individual, dysfunction may not necessarily relate to the same voxels across time. Metaphorical examples can be given to explain this. A brain structural metaphor would be the white-matter intensities in multiple sclerosis that may disappear from one location and later appear at another location. A brain functional metaphor would be a slow car anywhere on a crowded highway that result in a queue that increases the time it takes to reach one's destination.

The concept of a distributed large number of small deviations that each on their own have a negligible effect is well accepted in the field of complex trait genetics. A person's polygenic risk score (PRS) for a particular phenotype, such as insomnia, reflects a count of the number of genes with the variant that slightly increases the risk. People with the same PRS may have different contributing genes. A similar quantifying concept has not yet been established for brain imaging studies. We will therefore here qualitatively discuss a number of studies in a narrative way. Reading through the imaging literature supports the perspective that insomnia may be promoted by insufficiently compensated minor deficiencies anywhere in the brain circuits that signal salience. Such deficiency may, directly or indirectly, either promote alertness and arousal, or interfere with inhibition, resulting in difficulties disengaging from alertness and arousal.

1311

1312 **Volumetric and voxel-based morphology studies**

1313

1314 As mentioned above, meta-analysis did not reveal consistently affected voxel in insomnia
1315 (374). At the extremes, poor sleep quality has been related to both cortical atrophy (343,
1316 344) and hypertrophy (448). However, some consistency exists for more localized
1317 differences between people with insomnia and controls without sleep complaints. Quite a
1318 few volumetric and voxel-based morphology studies suggested that deficiencies anywhere in
1319 the orbitofrontal cortex could increase the risk of insomnia. The orbitofrontal cortex is
1320 strongly implicated in hedonic evaluation (115, 215), which indeed is compromised in people
1321 with insomnia (106, 325, 380). People with a low gray matter density in a part of their
1322 orbitofrontal cortex are vulnerable to early morning awakening (366), insomnia (7, 190, 436),
1323 fragmented sleep (238) and low perceived sleep quality (75). In contrast, people with a high
1324 orbitofrontal gray matter density succeed to habitually sleep longer than they consider
1325 strictly necessary (428). Some of these studies located low orbitofrontal gray matter
1326 especially at its the border of the insula, the part that is strongly implicated in the salience
1327 network (7, 366). Of relevance to insomnia and emotion regulation (see § III and § IX) is that
1328 the OFC is implicated in downregulating and reappraising emotional distress (149, 288)

1329

1330

1331 **Structural connectivity**

1332

1333 Structural connectivity of white matter can be assessed by diffusion tensor imaging and
1334 probabilistic tractography. Several studies reported associations of sleep quality and quantity
1335 in areas that are also suggested by other methods discussed in this section. Jespersen et al
1336 (187) used network-based statistics to compare people with insomnia and controls without
1337 sleep complaints to reveal a particular reduction in the connectivity in a network with the

1338 insula as a key node. Khalsa et al. found that sleep quality and duration were associated with
1339 fractional anisotropy and/or mean diffusivity in white matter in the anterior cingulum, the
1340 orbitofrontal and insula region and the caudate nucleus (202). Findings from a connectome
1341 analysis once more included compromised connectivity of the orbitofrontal-anterior insula
1342 and anterior cingulate cortex in people with insomnia (444).

1343 Probably the most consistent findings on white matter alterations in insomnia concern
1344 the anterior limb of the capsula interna (56, 194, 236, 359). The anterior limb of the capsula
1345 interna accommodates numerous fiber bundles to and from structures discussed in this
1346 section as being involved in insomnia, including connections among the anterior cingulate
1347 cortex, orbitofrontal cortex, claustrum, head of the caudate nucleus and pontine brainstem.
1348 Structures connected through the anterior limb of the capsula interna fibers include
1349 structures regulating sleep and underlying the sleep-disrupting effect of stress (68). Fronto-
1350 subcortical networks subserved by the anterior limb of the capsula interna show functional
1351 and structural network connectivity alterations in insomnia (187, 244, 285).

1352 Network deviations disorders are commonly considered within predefined networks
1353 such as the salience network, the dorsal and ventral attention networks, the central
1354 executive network and many others. A recent whole-brain structural connectivity network
1355 study stresses the importance to consider distributed deviations beyond a prior defined
1356 networks. Wei et al. (429) found that people with insomnia show reactivity-related
1357 hyperconnectivity in a previously unrecognized network that was anchored at the right
1358 angular gyrus of the inferior parietal lobe. The affected network was a part of multiple
1359 predefined networks including the frontoparietal control network, the cingulo-opercular
1360 network, the default-mode network, and the right-lateralized ventral attention network.

1361

1362

1363 **Functional connectivity**

1364

1365 Functional connectivity during resting-state fMRI (rsfMRI) quantifies coactivation areas in the
1366 brain, usually referred to as 'networks', even though the actual connections are not assessed.
1367 Findings of rsfMRI studies in insomnia have been reviewed by Khazaie et al. (203). The
1368 findings did not show robust convergence, yet somewhat consistently suggested alterations
1369 in the *salience network* in both the hyperarousal and affective symptoms of people with
1370 insomnia. The salience network comprises paralimbic structures including the dorsal
1371 anterior cingulate cortex, the orbitofrontal-insular cortices; subcortical limbic structures
1372 involved in emotion, homeostatic regulation, and reward (263, 293); and the dorsomedial
1373 nucleus of the thalamus (341). Of note, the coactivation of the anterior cingulate cortex
1374 within the salience network shows an exceptionally strong correlation with individual
1375 differences in anxiety levels assessed immediately prior to the MRI scan.

1376 Increased salience network activity may be a transdiagnostic marker of insomnia severity,
1377 since it was found as well in association with poor sleep in people suffering from major
1378 depressive disorder (242). Further support of its robust involvement in insomnia was by
1379 using a different methodology to assess resting state dynamics, i.e. quantifying EEG
1380 microstates also pointed to involvement of the salience network (433). Within the salience
1381 network, especially the insula shows enhanced activation in people with insomnia, in
1382 proportion to their EEG gamma band activity and negative mood (77). In addition to the
1383 voxel-based morphometry and volume studies mentioned above, several functional
1384 connectivity study supports the involvement of the orbitofrontal cortex in altered salience
1385 network functioning in insomnia (233). Reduced grey matter density in the orbitofrontal
1386 cortex was found to attenuate its efferent functional connectivity to head of the caudate
1387 nucleus (365). Lee et al. (231) confirmed weaker functional connectivity between the
1388 orbitofrontal cortex and the caudate in insomnia and moreover showed that this did not
1389 recover after successful intervention of insomnia, suggesting a vulnerability biomarker. Of

I390 relevance to insomnia is that the head of the caudate nucleus is implicated both in
 I391 distinguishing pleasantness (226) and suppressing cortical excitability (see, 365).
 I392
 I393 Resting state fMRI may also be studied under different pharmacological conditions.
 I394 Although not specifically targeted at insomnia, one study is particularly worthwhile
 I395 mentioning given the hypothesis developed in the current review. Song et al (356) assessed
 I396 locus coeruleus connectivity while pharmacologically suppressing its activity using an agonist
 I397 of inhibitory autoreceptors on noradrenergic cells. Silencing of locus coeruleus activity
 I398 particularly affected its connectivity with multiple regions that have previously been shown
 I399 to functionally or structurally deviate in insomnia, notably the anterior cingulate cortex (426),
 I400 insula (187) precuneus (7), thalamus (236) and caudate nucleus (365).
 I401 Dynamic functional connectivity (DFC) of resting-state fMRI is a method with a
 I402 somewhat higher sensitivity to detect distributed dysfunctions that are only subtle. Only one
 I403 study so far investigated DFC in insomnia (431). The study included 65 people with insomnia
 I404 and 65 controls without sleep complaints. In support of the sensitivity of the method, the
 I405 study showed that while none of the *average* between-network functional connectivity
 I406 strength deviations in insomnia reached significance, people with insomnia did show
 I407 significantly less *variability* in functional connectivity between the anterior salience network
 I408 and the left executive-control network. The finding suggests less flexible interaction between
 I409 the salience network and the executive-control network during resting state in people with
 I410 insomnia.
 I411 The salience network interacts with other networks. It modulates activation of the
 I412 default-mode network and the executive-control network (79). Reduced dynamic FC of the
 I413 salience network could compromise switching between networks in response to changing
 I414 environments and needs. fMRI during demanding cognitive tasks provide some support for
 I415 this idea. They reported hypoactivation of the left inferior frontal gyrus which is part of the
 I416 executive-control network (5), and a failure to deactivate the default-mode network (112) in

people with insomnia. The salience network also strongly interacts with the amygdala. A study with a small sample size reported altered functional connectivity between the insula and the amygdala in people with insomnia (174), as previously reported for generalized anxiety disorder as well (121). Interestingly, altered insula connectivity seems key in the exaggerated interoceptive and exteroceptive processing in people at risk of anxiety due to a polymorphism in the ADORA2A gene (141), which alters the function of the receptor for adenosine, the key molecule involved in homeostatic regulation of slow wave sleep (318, 328). Transdiagnostic involvement of the areas here discussed in both sleep and mood complaints is also reported by a study utilizing the large human connectome sample (80). Both types of complaints were associated with altered functional connectivity in several of these areas including the orbitofrontal, insula and anterior cingulate cortices and the amygdala.

Brain activation during tasks

Surprisingly few studies evaluated differences between people with insomnia and controls without sleep complaints in task-related brain activation. As mentioned in this section, fMRI during demanding *cognitive* tasks suggest hypoactivation of the left inferior frontal gyrus which is part of the executive-control network (5), and a failure to deactivate the default-mode network (112) in people with insomnia. As mentioned in § III, a few studies assessed fMRI during *emotional* tasks Baglioni et al (18, 20) report a stronger reactivity of the amygdala to sleep-related pictures. Wassing et al. (425) moreover found insufficient overnight adaptation of the amygdala in subjects with fragmented REM sleep - a key characteristic of insomnia. They also reported stronger activation in the salience network circuit including the limbic parts, notably in the dorsal anterior cingulate cortex in people with insomnia while reliving emotional memories from the distant past (426). Seo et al. (342)

1444 reported delayed fear extinction in individuals with insomnia disorder measured across
1445 nights, and differences in brain activation once more including the amygdala and the insula
1446 and anterior cingulate cortices.

1447

1448

1449 **Concluding remarks on MRI findings**

1450

1451 Concertedly, imaging findings imply a particular importance of the wider salience network
1452 and associated structures in insomnia. The orbitofrontal, insular and anterior cingulate
1453 cortices of the wider salience network are all connected (63) and concertedly affect
1454 consciousness, sleep and arousal. All three areas are also involved in sensing pleasantness
1455 (48, 353). The pontine brainstem locus coeruleus receives extensive direct inputs from the
1456 anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC) reflecting contextual
1457 relevance (14). The LC thus monitors activity in the salience network to adapt its activity
1458 accordingly (14). Lesions of the anterior insula affect sleep through strong reciprocal
1459 connectivity with wake and sleep-regulating hypothalamic and brainstem regions (78).
1460 Electrical stimulation of orbitofrontal cortical areas can induce EEG and behavioral
1461 manifestations of sleep (409). The anterior insula and the subcortical claustrum that it lines is
1462 an important part of a network that subserves consciousness (213). Of note, several of
1463 these structures, including the claustrum and the anterior cingulate cortex that it activates
1464 during REM sleep (245, 327), as well as the caudate nucleus, are significantly implicated in the
1465 genetic vulnerability of insomnia, as shown in **Figure 8. "Brain tissues and cell types**
1466 **associated with genetic vulnerability of insomnia"** (183). Convergence of genetic and
1467 MRI approaches lends credibility to the involvement of these structures in insomnia.
1468 Vulnerability to insomnia might originate anywhere in the orbitofrontal-insula and anterior
1469 cingulate cortices, the subcortical claustrum and head of the caudate nucleus, and the white
1470 matter bundles in the anterior limb of the internal capsule that line and connect them.

1471 Alterations in grey and white matter associated with poor sleep may emerge already early in
1472 development, as indicated by their establishment at the age of 7 years (211). While minor
1473 and/or distributed alterations anywhere in this circuit could result in a suboptimal
1474 functioning and predispose individuals to develop insomnia, the stringent correction for
1475 multiple testing that is required for whole-brain voxel-based analysis impedes their detection
1476 unless massive sample sizes are available. Moreover, as discussed, alterations are likely to be
1477 different depending on the subtype of insomnia (42). Future studies may reduce unexplained
1478 variance by subtyping their participants, and increase statistical power even more by
1479 evaluating a predefined network rather than the whole brain.

1480 **VIII. Towards mechanisms underlying insomnia vulnerability: sleep regulation?**

1481

1482 In search of mechanisms, the name 'insomnia', translating as 'no sleep', would suggest a
1483 primary involvement of brain circuits involved in the circadian and a homeostatic
1484 components of sleep regulation (52, 92). The so-called 'two process' model has been
1485 extended to allow for a better description of ultradian processes (49, 128, 253), of sleep
1486 inertia (2), and of sleep-permissive external conditions (333, 383). While deviations in
1487 circadian and a homeostatic regulation are certainly likely to compromise sleep quality, a
1488 reversal of this statement does not hold. In fact, there is surprisingly little support for
1489 insomnia being primarily due to circadian or homeostatic dysfunction.

1490

1491 With respect to the circadian component of sleep regulation, in only few people with
1492 insomnia, complaints are primarily due to trying to initiate sleep at an inappropriate circadian
1493 phase (129). In a constant routine lab study to assess circadian rhythms in cardiovascular
1494 parameters, cortisol and body temperature, no deviations could be found (405). Likewise, in
1495 a field study, no deviations could be found in activity rhythms (275). Recent GWAS studies
1496 did not reveal a predominance of variants in the well-known clock genes: pathway analysis
1497 did not reveal significance of the gene ontology pathways involved in PER, BMAL1, CLOCK
1498 and NPAS2 (156, 183). As far as we know, other support for the possibility that insomnia
1499 would primarily be caused by circadian dysfunction is also lacking.

1500

1501 Likewise, insomnia does not seem to be caused primarily by insufficient functioning of the
1502 homeostatic component of sleep regulation. Studies on homeostasis assess how sleep
1503 deprivation alters EEG slow wave activity during subsequent recovery sleep (336).
1504 Surprisingly few studies aimed to investigate the homeostatic process in insomnia disorder.
1505 In an early study Bonnet (51) concluded that the restorative function of sleep operates
1506 efficiently in people suffering from insomnia. Besset et al. (40) sleep deprived seven patients

1507 with insomnia and seven controls for 21 hours. During subsequent recovery sleep, slow
1508 wave activity (SWA) was assessed as a measure of build-up sleep pressure. Relative to the
1509 baseline night, SWA increased both in people with insomnia and in controls, be it somewhat
1510 less. The authors concluded that the homeostatic process was operating, but weaker in
1511 people with insomnia. While some other studies have also suggested homeostatic
1512 deficiencies in insomnia (280, 313), others could not confirm this (100), and all conclusions
1513 were based on studies that did not apply the strict deprivation protocols and analyses
1514 required to allow for any conclusion on homeostatic sleep regulation (336). Altered slow
1515 wave sleep may or may not exist in insomnia, but is not sufficient to derive any conclusion
1516 about a homeostatic deficiency.

1517 The molecule thought to play a key role in sleep homeostasis is adenosine (318). Indeed
1518 functional genetic variations in its regulation alter the duration and intensity of slow wave
1519 sleep in humans (328). Interestingly, the same variations predispose people to anxiety (171,
1520 172). Recent GWAS studies did however not reveal a predominance of variants in genes
1521 involved in the regulation of adenosine. Analyses did not reveal even a hint of significance of
1522 the gene sets involved in adenosine deaminase activity ($P=0.64$) or the adenosine A1
1523 ($P=0.47$), A2a ($P=0.84$), A2b ($P=0.65$) or A3 ($P=0.30$) receptor (156, 183).

1524

1525 It has recently been suggested that the two-process model may have to be extended even
1526 more, to include sleep-permissive factors (333, 383). People fall asleep more easily after
1527 closing their eyes (418), in a dark environment (291), in a lying posture (87), and with a
1528 sleep-permissive comfortable skin temperature profile. A recent study systematically
1529 manipulated posture, light, and temperature in people with insomnia and matched healthy
1530 controls without sleep complaints while assessing elicited effects on cognitive and autonomic
1531 nervous system variables of relevance to sleep. Overall, people with insomnia showed
1532 comparable sleep-compatible cognitive and autonomic responses to *physical* sleep-permissive
1533 conditions (384). Surprisingly, and contrary to individual experiences, insomnia does not

I534 seem to be systematically characterized by a lower wake-threshold to external acoustic
 I535 perturbation: it only takes them longer to return to sleep once awakened (164, 261). The
 I536 unaltered threshold to *external* stimulation is in strong contrast to the increased density of
 I537 *spontaneous* arousals and awakenings (123, 330), and the *intrinsic* tendency to go from
 I538 deeper sleep stages back to more superficial sleep stages (430). N3 is the only sleep stage
 I539 that seems 'safe': once people with insomnia reach this state, they don't differ from normal
 I540 sleeping controls in the probability to switch to a more superficial sleep stage. If we would
 I541 consider arousal threshold and N3 related to sleep homeostasis, these findings also do not
 I542 support the idea that insomnia would be a disorder of homeostatic sleep regulation.
 I543
 I544 An interesting new perspective on the subjective sleep complaints of people with insomnia is
 I545 the possibility that sleep and wakefulness occurring in a non-integrated way simultaneously
 I546 in different neuronal ensembles in the brain. Traditionally, the states of sleep and
 I547 wakefulness have been regarded as strictly separated in time: the brain is either asleep, or
 I548 awake. During the last decade, the presumption of a strictly sequential occurrence and of all-
 I549 or-none global brain states of sleep and wakefulness has been challenged. Krueger and
 I550 colleagues (218, 219) proposed that sleep could be a fundamental property of even small
 I551 local neuronal networks. Accordingly, individual cerebral cortical columns could show sleep-
 I552 like states that are to some extent independent of the occurrence of sleep-like states in
 I553 other cortical columns. Intracerebral recordings in rodents and humans have indeed
 I554 demonstrated concurrent sleep- and wake-type neuronal activity (135, 282, 413). Several
 I555 authors proposed, or demonstrated, that the ongoing nocturnal rumination that people with
 I556 insomnia experience subjectively may have its neural correlate in an inappropriately large
 I557 proportion of neuronal ensembles showing wake-like activity during sleep (85, 229, 232, 264,
 I558 362). It should be noted however that the concept of 'local islands of wakefulness' (362) to
 I559 explain a subjective wake experience while asleep would seem too large a simplification.
 I560 Conscious awareness is considered to require integration of global recurrent spreading of

I 561 information in widely distributed connected networks. Given the limited spatial resolution of
I 562 scalp EEG, it would be difficult to disentangle whether concurrent sleep- and wake-like
I 563 cortical activity in insomnia would be topologically separated versus overlapping. Irrespective
I 564 of these considerations, the concept of wakefulness and sleep occurring simultaneously is
I 565 most interesting. A data-driven approach indicated that people with ID have more EEG
I 566 signatures typical of light sleep than controls do even during deep sleep (85). This study
I 567 suggest that the sleep of people with ID shows insufficient shut-down of neuronal activity
I 568 representing arousal, just as has been seen during sleep of strongly distressed rats (68). Of
I 569 note, and compatible with a distress model, increased arousal is however not limited to the
I 570 sleep period, but also the most consistent finding in wake EEG (for a review, see 88).

I 571

I 572 In summary, there is little support for the logical idea that insomnia would primarily involve
I 573 deviations in circadian, homeostatic and extrinsic physical sleep-permissive factors. The next
I 574 section builds on the intriguing idea of ongoing arousal during both sleep and wakefulness.
I 575 The section will address the possibility that insomnia involves deviations in *intrinsic* sleep-
I 576 permissive conditions, originating in circuits regulating arousal and emotional distress.

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1581 **IX. Towards mechanisms underlying insomnia vulnerability: emotion regulation?**

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1583 In addition to circadian, homeostatic and external sleep-permissive factors, sleep regulation
1584 has been recognized to interact with emotional and motivational factors (33, 116, 301, 337)
1585 that may intrinsically interfere with sleep.

1586

1587

1588 **Why study emotion regulation to understand insomnia?**

1589

1590 There is good reason to study emotion regulation to understand insomnia. Insomnia differs
1591 in all aspects from enforced sleep deprivation (§ III). In contrast, polysomnography (§ II),
1592 epidemiology (§ I) and recent GWAS studies on genetic vulnerability (§ IV) all suggest that
1593 insomnia may somehow be due to malfunctioning emotion regulation: insomnia resembles
1594 distress. Although this may seem a bold statement at first sight, the following question may
1595 be revealing. If the clock and homeostat tell us that it would be a good time to shut down
1596 conscious awareness of the environment and fall asleep, could there be any reason *not* to?
1597 Surely! As discussed in the previous section, extrinsic and intrinsic 'sleep-permissive' and
1598 'wake-promoting' conditions co-determine whether the transition to sleep is made. Physical
1599 components include environmental light, temperature and posture, but equally important are
1600 intrinsically experienced factors including pain, discomfort, danger and stress (333). There
1601 can be emotional and motivational reasons to promote wakefulness and resist giving in to
1602 sound sleep (116, 337).

1603 Thus, if other processes than the circadian and homeostatic processes are involved in
1604 sleep regulation, it is only logical to include circuits involved in their regulation in our search
1605 for underlying mechanisms of insomnia. There may be good emotional-motivational reasons
1606 to override sleep pressure dictated by clock and homeostat, and the capacity to stay awake
1607 has to be deeply rooted in the evolution of the brain: if falling asleep is not safe given the

1608 current circumstances, sleep should be prevented to safeguard survival. For example,
1609 mammals sleep less in sites where they are more exposed to predators (70). The main
1610 intention of the current section is to explore whether such 'watchfulness' could be involved
1611 in insomnia. The key questions addressed here is whether and how individual differences in
1612 the brain circuits involved in emotion and motivation could contribute to the vulnerability
1613 and expression of insomnia.

1614

1615

1616 **Sleep reactivity and emotional reactivity**

1617

1618 As mentioned in § III, difficulties in emotion regulation have been found in people suffering
1619 from insomnia. Importantly, such difficulties *predict* incident insomnia and its persistence,
1620 suggesting that altered emotion regulation rather seems a risk of insomnia, than to merely
1621 result from insomnia (184). Most of us are aware of how stressful and emotional
1622 experiences affect sleep (for reviews see e.g. 101). There are strong individual differences in
1623 the disrupting effect of major life events and stressful or emotional experiences on sleep,
1624 both with respect to the *severity* and the *duration* of disrupted sleep (37, 42, 109). Drake and
1625 colleagues (109) hypothesized a trait-like vulnerability to experience disturbed sleep in
1626 response to a stressor. They coined the phrases 'sleep reactivity' and 'insomnia response to
1627 stress' and developed and extensively validated a scale to quantify these individual
1628 differences: the Ford Insomnia Response to Stress Test (FIRST). The instrument addresses
1629 difficulties sleeping because of events that happened today, or in anticipation of events that
1630 will happen tomorrow. A complementary approach has been to systematically query the
1631 occurrence of major life events with the validated Life Experiences Survey (LES), and then
1632 conditionally to an occurrence further ask about the severity and duration of experiencing
1633 insomnia due to the experience (37, 42). The scales are only modestly correlated (42) and
1634 differ in two aspects: whereas the FIRST assesses acute responses to daily stressor types,

the extended LES assesses possibly more sustained responses to less common, not-everyday major life events. Using the FIRST, Drake and colleagues demonstrated extensively that sleep reactivity is a trait, and that insomnia is more likely to develop in people that respond to stress with very poor sleep (111, 185, 192). Using the extended LES, Blanken et al. (42) showed that the *severity* and the *duration* of disrupted sleep in response to a major life event co-define specific insomnia subtypes. Concertedly, the studies on emotional reactivity suggest that altered emotion regulation rather seems a risk of insomnia, than to result from insomnia.

Sleep aids to remembering: Emotional experiences

Emotionally arousing experiences are better remembered than neutral experiences. Better long-term retainment of emotional than neutral experiences is ignited during the initial exposure, when emotional experiences lead to stronger activation of noradrenergic, adrenergic and glucocorticoid signaling, integrated in the basolateral complex of the amygdala (255). Indeed, emotional memories can last for a lifetime. Their biological substrate, called 'engram', can be extensively reorganized over time. This process of memory transformation is called system consolidation. Across time, from encoding and immediate retrieval towards late retrieval, the engram or network activation shift from hippocampal to neocortical dominance (375). The progressive disengagement of the hippocampus and engagement of especially prefrontal cortical regions is strongly facilitated by post-training sleep. Sleep thus aids to the bias for a stronger consolidation of emotional experiences than neutral memories (reviewed in e.g. 307). Even if memorizing whether a stimulus or context is emotionally relevant or neutral concerns the "factual" cognitive part, it will be highly relevant for future distress. For example, if the stimuli or contexts are not properly distinguished, the neutral ones may elicit distress without good reason.

1662 The sleep-supported bias for better remembering of emotional events has long-term
1663 relevance: it has even been shown to last at least for four years after just exposing people to
1664 emotional text in a laboratory environment (415). Recently, long-term effects of sleep were
1665 for the first time examined in a mouse model (335). The findings suggested that sleep, and
1666 notably REM sleep, following an emotional experience was even more important for proper
1667 recall in the far future than for next day's recall, to which most animal research paradigms
1668 had been restricted so far (335).

1669 Few studies addressed whether the overnight downregulation of emotional distress is
1670 affected in people suffering from insomnia. Within a larger study including sleep deprivation,
1671 Tempesta et al. (385) assessed overnight changes in subjective valence and arousal when re-
1672 exposed to emotionally negative, positive and neutral pictures from the IAPS (227). Both
1673 good sleepers and people with probable insomnia were included in the study. Across the
1674 night, valence ratings had become more negative across emotionally negative, positive and
1675 neutral pictures in people with probable insomnia, as compared to the overnight changes
1676 seen in good sleepers.

1677

1678

1679 **Sleep aids to forgetting: Resolution of emotional distress**

1680

1681 It has long been observed that subjects with normal sleep generally experience an overnight
1682 improvement in mood (73). That good sleep contributes to emotion regulation, i.e. aids to
1683 getting rid of the distressing part of emotional memories, may at first seem counterintuitive.
1684 As discussed above, emotionally arousing experiences are *better* remembered than neutral
1685 ones, and that sleep contributes to the bias in their consolidation. The role of sleep in
1686 processing emotional experiences is however not limited to biasing a better storage of
1687 emotional events, event types, or contexts into episodic or semantic memory. So-called
1688 "Sleep to Remember and Sleep to Forget" hypotheses suggested a dual role for sleep in

memory and forgetting (316, 416): while sleep indeed adds to the consolidation of the declarative, contextual or semantic aspects of an emotional experience, at the same time it aids to separating these engrams from the emotional tone and somatic arousal the emotional experiences originally elicited. In other words, post-learning sleep also has an impact on the functional connections of limbic areas with the network representing the declarative, contextual or semantic engram.

Subjective distress

Although several studies indicate that sleep supports the downregulation of emotional distress, findings are not unequivocal (reviewed in 386). A sleep-dependent decrease in subjective arousal ratings of the same stimuli presented both before and after periods of sleep or wakefulness has not always been found (25). Also, an advantage of late sleep rich in REM-sleep over early sleep rich in non-REM-sleep has not systematically been found (152, 414). Both sleep-related enhancement and attenuation of subjectively experienced emotional intensity has been reported when comparing periods of sleep and sleep deprivation (154, 228, 334). In an early-sleep versus late-sleep protocol, REM-rich late sleep supported the 'factual' recognition part of emotional stimuli better than NREM-rich early sleep did, while subjective valence and arousal ratings of emotional pictures were not differentially affected by REM or NREM-rich sleep (152). However, subjective valence and arousal ratings involve higher-order emotional appraisal, and may be dissociated from brain and somatic reactivity (230). Indeed, a recent sleep study demonstrated brain activation in the salience circuit as well as and correlated GSR amplitudes, in the absence of corresponding subjective emotional intensity ratings (426). Within subjective rating surveys, subscales that immediately address somatic reactivity seem most sensitive (423).

1714 Objective measures

1715 Objective measures tend to give more consistent results: re-exposure of an emotional
1716 stimulus after a period of sleep elicits less autonomic arousal and less activation of the
1717 amygdala, than when a stimulus is repeated across a comparable period without sleep (91,
1718 297, 364, 397). In a series of studies, Wassing et al. (423-426) addressed the variability in
1719 findings on sleep-dependent downregulation of emotional distress. They pinpointed the
1720 relevance of *restful* versus *restless* REM sleep, which could make the difference between
1721 'forgetting' of the emotional tone and somatic arousal, no effect, or even a maladaptive
1722 overnight increase in distress (see **Figure 10. "Restless REM sleep impedes overnight**
1723 **emotion regulation"** and **Figure 11. "Long-term effects of insufficient overnight**
1724 **adaptation?"**).

1725 .

1726 There is support beyond people with insomnia only, of the finding that restful REM sleep
1727 aids to 'forgetting' the emotional tone and somatic arousal that emotional experiences
1728 initially elicited. Sopp et al (357) recently reported on how sleep modulates whether
1729 traumatic experiences will or will not result in symptoms of PTSD. They exposed
1730 participants to a traumatic film and found that later analogues of overall PTSD symptoms
1731 were lower in participants that had REM sleep of longer duration. Moreover, the specific
1732 PTSD symptom of *intrusive re-experiencing* was less in participants with high REM theta
1733 activity. Animal studies suggest that this EEG spectral signature is associated with low LC
1734 activity (371).

1735

1736 Concertedly, the findings suggest that restful REM sleep aids to the overnight resolution of
1737 emotional distress. In contrast, restless REM sleep does not, or can even be maladaptive to
1738 the dissolving of distress. Restless REM sleep is not only characteristic of insomnia, but also
1739 of other mood, anxiety and stress-related disorders. The next paragraph proposes a key
1740 role of noradrenergic locus coeruleus activity.

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Restless REM sleep, locus coeruleus and neuronal plasticity

During sleep, an active reprocessing of memory traces of wake experiences takes place. If memory engrams of relevant wake experiences are reactivated, synapses involved can either be weakened or strengthened, depending on several factors including the type of neuronal activity and the milieu of neuromodulators like noradrenalin, acetylcholine and serotonin (316, 404). The net result of this process is thought to favor the generation of semanticized memories, represented in distributed cortical connectivity biases (142). REM sleep may be most important for amygdala-related memory processing. REM sleep is associated with activation of the amygdala–hippocampus–medial prefrontal cortex circuit that is key to emotional processing, fear memory and valence consolidation (142). During non-REM sleep, the hippocampus–medial prefrontal cortex part of the circuit is activated as well, but without involvement of the amygdala.

Animal studies indicate that REM sleep is a state that favors selective pruning and consolidation of new synapses formed during learning (237). The decreased levels of norepinephrine during sleep, reaching complete absence during REM sleep, favor depotentiation and sleep-dependent synaptic downscaling (107, 195, 287), which are essential for memory processing. Erroneous memory processing indeed occurs when levels of norepinephrine are slightly elevated during sleep using optogenetic stimulation of the LC (371). Sleep-related selective pruning and consolidation of new synapses formed during learning can thus shape the brain circuits that host the episodic, semantic and self-identity components of autobiographical memory (251). It can be hypothesized that malfunction results in *distributed deviations*, because there are only few brain areas that are not innervated by the LC (14, 340).

1769 **X. Insomnia by insufficient overnight adaptation to emotional distress?**
 1770
 1771 Integrating all reviewed above, a testable model on the vulnerability to develop insomnia
 1772 emerges. A first key feature of the proposed model is that differently *distributed deviations* in
 1773 the nodes and connections of the circuits involved can all converge to a final common path
 1774 of insomnia. A second feature of the proposed model is that the involvement of sleep
 1775 regulating circuits may be limited to an initial vulnerability to have insufficient locus
 1776 coeruleus silencing during REM sleep. Circuits involved in the regulation of salience, emotion
 1777 and arousal could play major roles. A consequential third characteristic of the model is that
 1778 it proposes more overlap than differences in mechanisms underlying insomnia, anxiety
 1779 disorders, major depressive disorder and post traumatic stress disorder. A fourth
 1780 characteristic of the model is that deviating overnight synaptic and systems level plasticity
 1781 contributes to all these disorders. This common mechanism may be summarized as
 1782 'insufficient overnight adaptation to emotional distress'. **Figure 12. "Insufficient silencing**
 1783 **of the locus coeruleus during sleep" and Figure 13. "Developmental model**
 1784 **linking the vulnerability to restless sleep, insomnia and other mental disorders"**
 1785 sketch the main components of the model.
 1786
 1787 As is commonly considered for other mental disorders, the vulnerability of insomnia
 1788 commences at conception. Large genome wide association studies have identified that the
 1789 risk of insomnia increases in proportion to the number of variants in a large number of risk
 1790 genes. Each of the individual variants contributes only very little to the risk. Concertedly
 1791 however, they provide clues to brain tissues and cell types involved in insomnia. Of note,
 1792 vulnerabilities in these tissues and cells do not necessarily have to result only from their
 1793 significant expression of risk genes. Other reasons include early developmental influences on
 1794 these tissues and cells. As extensively discussed in § IV, GWAS suggests vulnerability in
 1795 several parts of the salience network and related structures that were also identified as

1796 relevant in MRI studies. These areas include the anterior cingulate cortex, caudate nucleus
1797 and claustrum. Of note, the anterior cingulate cortex is one of the few areas activated
1798 during REM sleep, triggered by input from the claustrum (245, 327). In addition to tissues
1799 and cell types, genes also point to vulnerabilities detected in mouse mutant studies. Notably,
1800 the top-risk gene for insomnia, *BTBD9* and another identified gene, *DNMI* are involved the
1801 sleep-disruptive effect (increased sleep onset latency) of pre-sleep arousal (99, 369). *BTBD9*
1802 mouse mutants also show altered plasticity resulting in a stronger fear memory (99) and
1803 other phenotypes that match findings in insomnia (98), like increased restless, more
1804 fragmented sleep, and altered thermal sensitivity (324, 325). We posit that genetic
1805 vulnerability to insomnia, but also to the genetically strongly related anxiety and depression
1806 (156), is mediated by functional alterations that increase reactivity and sustained activity of
1807 the salience network, resulting in difficulties to reach a low level of arousal prior to sleep, as
1808 a consequence less deep sleep (145) with lingering arousal. Moreover, genetic vulnerability
1809 may be mediated by subtle changes in claustrum-initiated activation of the anterior cingulate
1810 cortex during REM sleep. The genetic predisposition to arousal during sleep can additionally
1811 be boosted by childhood adversity (17, 180, 352). After gene variants have set the stage for
1812 an increased risk of insomnia, early developmental conditions can impact their expression
1813 and later life consequences through epigenetic changes (265). Studies have proposed that
1814 early life epigenetic changes as induced by early traumatization determine whether or not
1815 risk variants evoke late life disease vulnerability.

1816

1817 We next posit that entering sleep with lingering arousal means that locus coeruleus activity
1818 will not reach the low levels that can be expected during sound sleep (**Figure 12.**
1819 **"Insufficient silencing of the locus coeruleus during sleep"**). This may become
1820 problematic especially during REM sleep. Ground-breaking animal studies of others identified
1821 why restless REM sleep disrupts overnight adaptive processes (371, 403, 404). Sound REM
1822 sleep is the only state during which the brain has a 'time-out' of noradrenaline (NA): the

1823 Locus Coeruleus (LC) is silenced. The NA time-out allows for a uniquely balanced
 1824 potentiation and depotentiation of synapses, not found in any other state. Restless REM
 1825 sleep however indicates insufficient LC silencing. The resulting lack of a NA-free REM sleep
 1826 period disrupts synaptic plasticity (371, 403, 404).
 1827
 1828 Indeed we and others pinpointed specifically *restless REM sleep* to interfere with emotional
 1829 adaptation. Restful REM sleep helps the limbic circuit of the brain to adapt overnight (397),
 1830 resolving the burden by making emotions milder and better tractable (205). Restless REM
 1831 sleep, in contrast, does not work well. REM sleep that is fragmented by arousals indicates
 1832 persistence of LC activity during a time window that should normally provide a NA-free
 1833 period. Restless REM sleep impedes processes involved in overnight emotion regulation. The
 1834 resulting distress 'accumulation' is experienced as hyperarousal and resembles anxiety.
 1835 Restless REM sleep interferes with restructuring of brain circuits involved in emotional
 1836 memories and salience. People with insomnia in particular fail to disengage the anterior
 1837 cingulate cortex. The anterior cingulate cortex is one of the few areas activated during REM
 1838 sleep, triggered by input from the claustrum (245, 327). As mentioned, our recent genome-
 1839 wide analysis identified particular enrichment of these two regions for insomnia risk genes.
 1840 These genes include *BTBD9*, involved in fragmented sleep, fear memory, and difficulties falling
 1841 asleep following arousal (98, 99, 369).
 1842
 1843 Restless REM sleep can even inverse beneficial effects of sleep on overnight adaptation to
 1844 emotional distress, and become *maladaptive* (423, 425). It can not only impede overnight
 1845 resolving of distress but even aggravate it (423). Adverse consequences leave traces in brain
 1846 activation for decades especially in the anterior cingulate cortex. Due to failing overnight
 1847 plasticity, distress may not resolve sufficiently, linger on for long, and contribute to the
 1848 development of a generalized hyperaroused state which in turn perpetuates insomnia (424)

1849 (see **Figure 10. "Restless REM sleep impedes overnight emotion regulation"** and
 1850 **Figure 11. "Long-term effects of insufficient overnight adaptation?"**).
 1851
 1852 This model on the importance of NA-free REM sleep for overnight emotion regulation
 1853 provides a new avenue for *transdiagnostic* treatment innovation. A duality-of-effect
 1854 hypothesis considers that common neural substrates could underlie insomnia and mood or
 1855 anxiety disorders (1, 347, 392). Animal studies support the hypothesis that common neural
 1856 substrates may underlie disturbed sleep and mental health. Already in early animal models
 1857 for depression, co-expression of an insomnia phenotype was noted to be common (114, 349,
 1858 392). There is a two-way reinforcement of adverse effects of insomnia and stress. On the
 1859 one hand, insomnia is more likely to develop in people that respond to stress with very
 1860 poor sleep (111, 185, 192). On the other hand, pre-existing insomnia puts individuals at
 1861 elevated risk of developing posttraumatic stress disorder when exposed to a traumatic event
 1862 (140, 420). Likewise, post-deployment sleep continuity disturbance co-determines whether
 1863 combat exposure results in post-traumatic stress symptoms (294).
 1864
 1865 Trouble distancing oneself from negative memories is not only found in insomnia, but also
 1866 holds for people with depression or other mood disorders (196). Already before disease
 1867 onset, sleep in people at risk of these disorders may be altered, as demonstrated for
 1868 insomnia and posttraumatic stress disorder (145, 180). Our model proposes that restless
 1869 sleep is not merely a coincidental transdiagnostic nuisance, but in fact has key involvement in
 1870 both the vulnerability and the persistence of the disorders. While in good sleepers 'sleeping
 1871 on it' helps to resolve distress overnight, people with restless sleep take their burdens
 1872 unresolved to the next day. For them, a night's sleep doesn't resolve anxiety, tension and
 1873 sadness at all. They may even wake up worse than they were the night before (423, 425). A
 1874 common distinguishing feature from the 'occasional bad day' of a healthy subject, is thus that
 1875 people with anxiety, insomnia, depression or post traumatic stress disorder take their

1876 emotional distress to the next day. Night after night. Sleep brings no relief. While sound
1877 consolidated REM sleep might be beneficial for overnight adaptation to emotional distress,
1878 people with highly fragmented REM sleep may even be better off without, as previously
1879 proposed for depression (411) (see **Figure 10. "Restless REM sleep impedes**
1880 **overnight emotion regulation"** and **Figure 11. "Long-term effects of insufficient**
1881 **overnight adaptation?"**).

1882

1883 Many main features characterizing people with ID according to the present review are
1884 compatible with increased LC activity, for example higher levels of arousal (72, 406); a
1885 strong expression of >20 Hz EEG (122); an increased probability to transition from sleep to
1886 wake that is especially prominent in response to stress (13, 176, 177, 192, 193, 430); active
1887 cognitive task engagement (12, 130); sensitized salience detection (407); increased cortical
1888 excitability [Colombo, 2016 #13020; Colombo, 2016 #15821; Van Der Werf, 2010 #9925]
1889 and enhanced late potentials evoked by intrinsic and extrinsic stimuli (45, 95, 432).

1890

1891

1892 **XI. Recovering restful REM sleep: a research agenda**

1893

1894 Restless REM sleep is one of the most distinguishing sleep characteristics of insomnia (53,
1895 123, 330). Given the review and reasoning provided above, the question arises whether
1896 people with insomnia could reduce restless REM sleep or even recover restful REM sleep.
1897 First, since both the probability of REM sleep and the probability of fragmented sleep
1898 increases with time asleep (124), one may evaluate whether curtailment of the time in bed
1899 reduces the amount of restless REM sleep and its adverse consequences for distress and
1900 hyperarousal. Interestingly, sleep curtailment has been noted to be the most effective
1901 component of the multicomponent cognitive behavioral therapy for insomnia. Another
1902 approach to reduce adverse consequences of restless REM sleep and restore the NA time-

1903 out that should accompany REM sleep might be off-label use of existing medication that
1904 either blocks NA receptors (e.g. beta-blockers) or suppresses LC activity (e.g. guanfacin).
1905 Below, it is briefly discussed whether such pharmacological approaches would be feasible
1906 without by themselves disturbing mood or sleep.

1907

1908 Since the 1950s the 'monoamine hypothesis' proposed a role of the noradrenaline in
1909 depressive disorders. Findings and hypotheses include noradrenergic deficiency as well as the
1910 opposite, a prolonged increased activity of the noradrenergic, and alterations of downstream
1911 receptor sensitivity in response (224, 441). While 70 years later the exact role of
1912 noradrenergic transmission has remained enigmatic, it is relevant to consider whether the
1913 proposed nocturnal pharmacological suppression of noradrenergic activity during REM sleep
1914 using e.g. beta-blockers could induce depression or disrupt sleep.

1915 A meta-analysis including 15 controlled trials with a total of more than 35,000 patients
1916 concluded that beta-blockers did not increase depressive symptoms (206). A systematic
1917 review on beta-blockers side effects including 13 controlled trials even found less depression
1918 across the groups randomized to beta-blockers than across the groups randomized to
1919 placebo (28). These overviews indicate that the risk of depression is no a priori reason to
1920 refrain from the proposed use of noradrenergic agents to with the aim to mitigate
1921 restlessness of REM sleep.

1922

1923 Disrupted sleep by using beta-blockers is more common. A concise review of the literature
1924 reveals that several beta-blockers have undesirable effects like suppression of REM sleep
1925 rather than enhancing its consolidation, or worsening of sleep quality, possibly by
1926 suppressing melatonin release, which might be mitigated by exogenous melatonin (166, 339,
1927 367). However, at least one beta-blocker, Nebivolol, has been suggested to improve sleep
1928 quality (119, 447) and moreover had the desired safety and strong lipophilic profile, i.e.

1929 acting on the brain, so this would be a good candidate to start evaluating for the mitigation
1930 of restless REM sleep. No studies on insomnia disorder have been reported yet.

1931 Downstream effects of noradrenalin may also be blocked using α 1-receptor antagonists.
1932 As reviewed Broese et al. (58), the α 1-receptor antagonist prazosin has a promising profile
1933 of actions that they proposed it for evaluation in the treatment of insomnia. The disturbed
1934 sleep in PTSD has been proposed to specifically involve enhanced responsiveness of α 1-
1935 receptors (378). Indeed, in PTSD patients, prazosin improved subjective sleep in three
1936 studies (144, 322, 323) and polysomnographically recorded sleep in one out of two studies
1937 (144, 378). Importantly, since mitigating restlessness of REM sleep would be preferable over
1938 complete suppression of REM sleep, one study found that prazosin increased both the
1939 continuity and total duration of REM sleep (378). The promise of these studies is somewhat
1940 moderated by a letter questioning the conclusion of one of the studies (395) and a more
1941 recent study reported in fact significant adverse effects of prazosin on sleep, as compared to
1942 placebo, in PTSD patients (252). No studies on insomnia have been reported yet.

1943 While beta-blockers and α 1-receptor antagonists could be used to prevent adverse
1944 postsynaptic downstream effects of a LC that is insufficiently silenced during REM sleep, a
1945 more direct approach would be to target inhibitory receptors on noradrenergic LC neurons.
1946 GABA-A receptors on LC neurons can be targeted directly and indirectly with the common
1947 sleeping pills, i.e. benzodiazepines and "z-drugs" like zolpidem and zopiclone. However, these
1948 GABA-A targeting drugs have been reported to reduce REM sleep (for review, see 266),
1949 which may be a second-best solution, since mitigating restlessness of REM sleep would be
1950 preferable over suppression of REM sleep. Moreover, benzodiazepines have been reported
1951 to increase beta power in the sleep EEG (30, 125), which does not suggest an optimal
1952 natural arousal reduction. Broese et al. (58) proposed that the noradrenergic α 2-
1953 autoreceptor agonists could be evaluated to treat insomnia and discussed several drugs with
1954 different affinities for the α 2-receptor subtypes α 2A, α 2B and α 2C: clonidine,
1955 dexmedetomidine, guanfacine and tizanidine. The drugs have been used in attention deficit

1956 and hyperactivity disorder, borderline personality disorder, Tourette and tic disorders and
1957 restless legs syndrome. Their effects on sleep have been evaluated in a limited number of
1958 studies. Guanfacine and even more so clonidine have been reported to suppress REM sleep,
1959 while ideally the amount of REM sleep would be left intact and only the restlessness of REM
1960 sleep would be improved. Clonidine has also been shown to perturb sleep by increasing
1961 arousal and instability, arguing against its use in insomnia (71). No studies on use of $\alpha 2$ -
1962 autoreceptor agonists in insomnia disorder have been reported yet.

1963

1964 In conclusion, a research agenda for the understanding of insomnia could include clinical
1965 evaluations of possible suppression of restless REM sleep and recovery of restful REM sleep
1966 by means of sleep restriction, cognitive-behavioral therapy for insomnia and off-label use of
1967 drugs targeting noradrenergic transmission - ideally especially during the later part of sleep
1968 when sleep is most restless and most REM sleep occurs. In addition to such novel
1969 approaches the proposed model opens up the possibility for animal studies, thus accelerating
1970 the ignition of a neuroscience of insomnia, which is direly needed for better treatment of
1971 one of the most burdensome disorders.

1972

1974 **Figure 1. "Polysomnography".** Schematic representation of how epochs of sleep EEG
1975 can be scored as Wake or REM, N1, N2 or N3 sleep and brief arousals to for a
1976 polysomnogram (PSG) representation of a whole night of sleep. Contrary to what the name
1977 'insomnia' suggests, the EEG of people suffering from insomnia does show signatures of sleep,
1978 be it in a fragmented way, indicated by interrupting arousals and stage shifts. Colored PSG
1979 graphs kindly provided by Prof. D. Riemann, Freiburg. From reference (330).
1980
1981

1982 **Figure 2. "Meta-analysis polysomnography".** Forest plot of the meta-analyzed effect
1983 sizes of differences between people with insomnia versus people without sleep complaints
1984 for the major polysomnographic features. Std diff, standardized difference; CI, confidence
1985 interval. From reference (19).
1986
1987
1988

Figure 3. "Increased probability to transition to a less deep sleep stage".

Markovian state diagram comparing sleep stage transition probabilities in PSG data of 100 people with ID and 100 healthy controls, generously provided by the Freiburg University Medical Center, Freiburg, Germany (123, 330). Red arrows indicate transitions with higher probabilities in people with Insomnia Disorder than in controls: from stage W to stage W ($W = 6646$, $Z = 4.02$, $P = 0.001$), from stage R to stage W ($W = 6492$, $Z = 3.64$, $P = 0.002$), from stage N2 to stage W ($W = 6176.5$, $Z = 2.87$, $P = 0.02$), from stage N2 to stage N1 ($W = 6122.5$, $Z = 2.74$, $P = 0.02$) and from stage N1 to stage W ($W = 5979.5$, $Z = 2.39$, $P = 0.05$). Blue arrows indicate transitions with lower probabilities in people with Insomnia Disorder than in controls: from stage W to stage N1 ($W = 3437.5$, $Z = -3.81$, $P = 0.001$) and from stage W to stage N2 ($W = 4057.5$, $Z = -2.31$, $P = 0.05$). Gray arrows indicate transitions with no significant differences in transition probabilities between the groups ($0.16 < P < 0.92$). The following transitions did not occur in at least half of the participants in each group and are not visualized: from stage W to stage R, from stage W to stage N3, from stage N1 to stage N3, from stage R to stage N3, from stage N3 to stage W, from stage N3 to stage N1, from stage N3 to stage R. (All P-values are false discovery rate corrected).

From reference (430).

2008 **Figure 4. "Late component in the heartbeat-evoked potential in insomnia"**

2009 **Upper panel:** Waveforms show the frontal dynamics of the heartbeat-evoked (HEP) during

2010 the eyes-closed (EC) resting state in people with Insomnia Disorder (ID) and controls

2011 (CTRL). People with insomnia show a significant late amplitude within the 376–500 ms time

2012 window (gray bar) that is not present in controls without sleep complaints. Shaded areas

2013 indicate one standard error of the mean (SEM).

2014 **Lower panel:** Source localization of between-group differences in activity over the 376–500

2015 ms time window after the electrocardiogram R-wave displayed on the Montreal

2016 Neurological Institute (MNI) standard brain image. Increased late activity in people with ID is

2017 especially pronounced at bilateral anterior cingulate and medial frontal cortices.

2018 From reference (432).

2019

2020

2021

2022 **Figure 5. "Enhanced late components in the auditory oddball event-related**
2023 **potential in the reactive insomnia subtype"**

2024 Auditory event-related potentials (ERPs) for frequent standard tones (dashed lines) and
2025 infrequent deviant target tones (solid lines), recorded during an auditory oddball task in 13
2026 people with the reactive subtype of insomnia (ID-S4, purple lines) as compared to 31
2027 controls without sleep complaints (CTRL, black lines). Artifact free ERPs at the midline
2028 parietal (Pz) electrode referenced to both mastoids were averaged over 170 standard tones
2029 and 30 deviating tones. Shaded areas indicate one standard error of the mean (SEM). People
2030 with the reactive subtype showed a stronger positive deflection during a wide late period of
2031 information processing as of 273 ms up to at least 1000 ms after standard tones were played.
2032 This indicates hyper-reactive late processing specifically in the insomnia subtype that was
2033 labeled as highly reactive based on trait questionnaires. They experience even standard
2034 tones as salient (as indicated by the enhanced P300 potential amplitude) and emotionally
2035 relevant (as indicated by the late positive potential amplitude). From reference (42).

2036
2037
2038

2039 **Figure 6. "Genetic and phenotypic overlap of insomnia with other traits and**
2040 **disorders".**

2041 Bars in the left panel show genetic correlations (r_g) between the frequency of experiencing
2042 trouble falling asleep or waking up in the middle of the night and various other traits and
2043 diseases. Error bars represent standard errors of the estimates. Red bars represent traits
2044 that showed a significant genetic correlation after correction for multiple testing ($P < 1.72 \times$
2045 10^{-3}), pink bars represent traits that showed nominal association ($P < 0.05$) and blue bars
2046 represent traits that did not show a significant genetic association. Of these 29 disorders,
2047 traits and characteristics, 18 had been assessed in the Netherlands Sleep Registry (37, 42).
2048 Bars in the right panel show phenotypic overlap of insomnia with the same subject
2049 characteristics assessed in this independent sample. The profiles of genetic and phenotypic
2050 correlations are strikingly similar. Adapted from reference (156).

2051

2052

2053

2054 **Figure 7. "UK Biobank insomnia phenotype validation"**

2055 Receiver Operating Characteristic (ROC) curve shows excellent accuracy of the UK
2056 Biobank question on insomnia to discriminate insomnia (defined with two different methods
2057 in an independent sample) against controls and restless legs syndrome (RLS) in an
2058 independent sample. Two questions on trouble falling or staying asleep were assessed in the
2059 Netherlands Sleep Registry (37, 42), along with the Pittsburgh Sleep Quality Index (PSQI),
2060 the Insomnia Severity Index (ISI) and DSM-5+ICSD3 and IRLSS diagnoses obtained in a
2061 structured interview. The five markers from left to right on each curve indicate answering at
2062 of two questions on trouble falling or staying asleep with very severe, with severe, with
2063 moderate, with mild or with none of either. Solid line, filled circles: people with probable
2064 Insomnia Disorder (ID) according to ISI+PSQI criteria versus controls. Dashed line, open
2065 diamonds: people with probable ID (ISI+PSQI) versus RLS (IRLSS). Dash-dotted line, filled
2066 triangles: ID (DSM-5+ICSD3 criteria) versus controls. Dotted line, open squares: RLS
2067 (IRLSS) versus controls. The cut-off with the highest accuracy (i.e., closest proximity to
2068 coordinate 0,1) is consistently located at the third marker which corresponds to having at
2069 least one moderate complaint. The UK Biobank question on insomnia thus provides an
2070 excellent possibility to discriminate cases with probable Insomnia Disorder, validating its
2071 usefulness for GWAS.

2072

2073

2074 **Figure 8. "Brain tissues and cell types associated with genetic vulnerability of**
2075 **insomnia"**. Genes with a genome wide significant association with insomnia were found in a
2076 GWAS in 1,331,010 individuals. Gene-set analyses subsequently identified genes that
2077 significantly converged in tissue- or cell-specific gene expression. From reference (183).
2078
2079

2080 **Figure 9. "Multivariate profile plots of insomnia subtypes"**
2081
2082 Data are scaled subtype group means (95% CIs), in which Z scores have been standardized to
2083 the mean and standard deviation of controls for each characteristic, with the subtype-
2084 explained variance, ranked clockwise from the top. (A) Highly distressed subtype (subtype 1).
2085 (B) Moderately distressed subtypes (subtype 2, which was reward sensitive, and subtype 3,
2086 which was reward insensitive). (C) Low distress subtypes (subtype 4, which was high reactive,
2087 and subtype 5, which was low reactive). Positive characteristics (eg, positive rumination)
2088 were reverse-coded and renamed (eg, reduced positive rumination), such that higher values
2089 uniformly indicate higher general distress for all characteristics throughout the plot. Colored
2090 boxes indicate the three characteristics that differentiate each subtype most from people
2091 without sleep complaints. From reference (42)
2092 .
2093
2094
2095

2096 **Figure 10. "Restless REM sleep impedes overnight emotion regulation"**
2097 Schematic representation of how the amygdala response during an emotional experience
2098 changes overnight. Participants were presented with an upsetting stimulus during fMRI scans
2099 in the evening and again in the morning. The induced distress was associated with amygdala
2100 activation which decreased overnight in people with consolidated REM sleep. People with
2101 restless REM sleep showed insufficient overnight adaptation. Those with the most
2102 fragmented REM sleep even showed sensitization of the amygdala response: they might have
2103 been better off without REM sleep. Graphical representation of references (423) and (425)
2104 kindly provided by R. Wassing, PhD, Sydney.
2105
2106
2107
2108

2109 **Figure 11. "Long-term effects of insufficient overnight adaptation?"**
2110 Schematic representation of an fMRI study comparing brain activation during a novel
2111 shameful experience with brain activation while participants relived their most shameful
2112 experiences of decades ago, which could be prior to the onset of clinical insomnia. The
2113 novel experience (left) elicited a limbic response including the anterior cingulate cortex both
2114 in normal sleepers (upper part) and people with insomnia (lower part). Marked group
2115 differences were however seen for reliving shameful experiences from the distant past
2116 (right). These memories no longer elicited a limbic response in normal sleepers while people
2117 with insomnia responded as if they just now happened. While good sleepers literally settled
2118 those experiences in their head as neutralized memories, people with insomnia were
2119 apparently not able to do so. This finding suggests that failing neutralization of emotional
2120 distress could contribute to the development of insomnia. It's tempting to suggest that the
2121 deficiency also facilitates the development of anxiety disorders, major depressive disorder
2122 and posttraumatic stress disorder. Graphical representation of references (424) and (426)
2123 kindly provided by R. Wassing, PhD, Sydney.
2124
2125

2126 **Figure 12. "Insufficient silencing of the locus coeruleus during sleep"**

2127 Model of lingering arousal during sleep in people with insomnia or a vulnerability to develop
2128 it. Distributed deviations in networks including the salience network and the locus coeruleus
2129 may put lead to a vulnerability to insufficiently silence the locus coeruleus during sleep. Pre-
2130 sleep arousal may aggravate the lingering of locus coeruleus activity. This may become
2131 problematic especially during REM sleep, the only state during which the brain has a 'time-
2132 out' of noradrenaline. The NA time-out allows for a uniquely balanced potentiation and
2133 depotentiation of synapses, not found in any other state. Restless REM sleep marked by
2134 frequent arousals indicate insufficient LC silencing. The resulting lack of a NA-free REM sleep
2135 period disrupts synaptic plasticity (371, 403, 404) during a time with extensive activation
2136 and reorganization of limbic circuits of the brain, including claustrum-induced activation of
2137 the anterior cingulate cortex (245, 327). Moreover, significant enrichment for insomnia risk
2138 genes has been found in these circuits (183) and their possible subtle functional
2139 consequences could further contribute to suboptimal overnight circuit adaptation. Colored
2140 PSG graph kindly provided by Prof. D. Riemann, Freiburg.

2141

2142

2143

2144 **Figure 13. "Developmental model linking the vulnerability to restless sleep,**
2145 **insomnia and other mental disorders".**

2146 It is proposed that gene variants and early life adversity can make the locus coeruleus is
2147 more sensitive to input from the salience network and related circuits, even during REM
2148 sleep, when the nucleus should normally be sound asleep. This may initially not necessarily
2149 be observable in clinical symptoms. The resulting long-term insufficiency in dissolving
2150 emotional distress can generate a downward spiral, showing as distressed days and nights in
2151 people with insomnia. Depending on the type emotions that are most stuck, insufficient
2152 overnight amelioration of distress can subsequently show as anxiety disorders, depression
2153 and post traumatic stress disorder.

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2162 **References**

- 2163 1. **Adrien JI.** Neurobiological bases for the relation between sleep and depression. *Sleep*
2164 *Med Rev* 6: 341-351, 2002.
- 2165 2. **Akerstedt T, and Folkard S.** The three-process model of alertness and its extension
2166 to performance, sleep latency, and sleep length. *Chronobiol Int* 14: 115-123, 1997.
- 2167 3. **Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisir**
2168 **J, and the participants in the Restless Legs Syndrome Diagnosis**
2169 **Epidemiology workshop at the National Institutes of Health International**
2170 **Restless Legs Syndrome Study Group.** Restless legs syndrome: diagnostic criteria,
2171 special considerations, and epidemiology. A report from the restless legs syndrome
2172 diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 4:
2173 101-119, 2003.
- 2174 4. **Altena E, Micoulaud-Franchi JA, Geoffroy PA, Sanz-Arigita E, Bioulac S, and**
2175 **Philip P.** The bidirectional relation between emotional reactivity and sleep: From
2176 disruption to recovery. *Behav Neurosci* 130: 336-350, 2016.
- 2177 5. **Altena E, Van Der Werf YD, Sanz-Arigita EJ, Voorn TA, Rombouts SA,**
2178 **Kuijter JP, and Van Someren EJW.** Prefrontal hypoactivation and recovery in
2179 insomnia. *Sleep* 31: 1271-1276, 2008.
- 2180 6. **Altena E, Van Der Werf YD, Strijers RLM, and Van Someren EJW.** Sleep loss
2181 affects vigilance. Effects of chronic insomnia and sleep therapy. *J Sleep Res* 17: 335-343,
2182 2008.
- 2183 7. **Altena E, Vrenken H, Van Der Werf YD, Van Den Heuvel OAV, and Van**
2184 **Someren EJW.** Reduced orbitofrontal and parietal grey matter in chronic insomnia: a
2185 voxel-based morphometric study. *Biol Psychiatry* 67: 182-185, 2010.
- 2186 8. **American Psychiatric Association.** *DSM-5: Diagnostic and Statistical Manual of*
2187 *Mental Disorders*. Washington, DC: American Psychiatric Press, 2013.
- 2188 9. **Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, and Pollak CP.**
2189 The role of actigraphy in the study of sleep and circadian rhythms. *Sleep* 26: 342-392,
2190 2003.
- 2191 10. **Andrillon T, Solelhac G, Bouchequet P, Romano F, Le Brun M-P, Brigham M,**
2192 **Chennaoui M, and Léger D.** Revisiting the value of polysomnographic data in
2193 insomnia: more than meets the eye. *Sleep Med* 66: 184-200, 2020.
- 2194 11. **Archer JA, Lee A, Qiu A, and Annabel Chen S-H.** Functional connectivity of
2195 resting-state, working memory and inhibition networks in perceived stress. *Neurobiol*
2196 *Stress* 8: 186-201, 2018.

- 2197 12. **Aston-Jones G.** Behavioral functions of locus coeruleus derived from cellular
2198 attributes. *Physiol Psychol* 13: 118-126, 1985.
- 2199 13. **Aston-Jones G, and Bloom F.** Activity of norepinephrine-containing locus coeruleus
2200 neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *J Neurosci* 1:
2201 876-886, 1981.
- 2202 14. **Aston-Jones G, and Cohen JD.** An integrative theory of locus coeruleus-
2203 norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci* 28:
2204 403-450, 2005.
- 2205 15. **Backhaus J, Junghanns K, Born J, Hohaus K, Faasch F, and Hohagen F.**
2206 Impaired declarative memory consolidation during sleep in patients with primary
2207 insomnia: Influence of sleep architecture and nocturnal cortisol release. *Biol Psychiatry*
2208 60: 1324-1330, 2006.
- 2209 16. **Bader K, and Schäfer V.** Sleep disturbances following traumatic experiences in
2210 childhood and adolescence: a review. *Somnologie - Schlafforschung und Schlafmedizin* 11:
2211 101-110, 2007.
- 2212 17. **Bader K, Schäfer V, Schenkel M, Nissen L, and Schwander J.** Adverse childhood
2213 experiences associated with sleep in primary insomnia. *J Sleep Res* 16: 285-296, 2007.
- 2214 18. **Baglioni C, Lombardo C, Bux E, Hansen S, Salveta C, Biello S, Violani C, and**
2215 **Espie CA.** Psychophysiological reactivity to sleep-related emotional stimuli in primary
2216 insomnia. *Behav Res Ther* 48: 467-475, 2010.
- 2217 19. **Baglioni C, Regen W, Teghen A, Spiegelhalder K, Feige B, Nissen C, and**
2218 **Riemann D.** Sleep changes in the disorder of insomnia: a meta-analysis of
2219 polysomnographic studies. *Sleep Med Rev* 18: 195-213, 2014.
- 2220 20. **Baglioni C, Spiegelhalder K, Regen W, Feige B, Nissen C, Lombardo C,**
2221 **Violani C, Hennig J, and Riemann D.** Insomnia disorder is associated with
2222 increased amygdala reactivity to insomnia-related stimuli. *Sleep* 37: 1907-1917, 2014.
- 2223 21. **Baker FC, and Driver HS.** Circadian rhythms, sleep, and the menstrual cycle. *Sleep*
2224 *Med* 8: 613-622, 2007.
- 2225 22. **Bangasser DA, Wiersielis KR, and Khantsis S.** Sex differences in the locus
2226 coeruleus-norepinephrine system and its regulation by stress. *Brain Res* 1641: 177-188,
2227 2016.
- 2228 23. **Bao A-M, Ji Y-F, Van Someren EJW, Hofman MA, Chu X-H, Liu R-Y, and**
2229 **Zhou J-N.** Diurnal rhythms of free estradiol and cortisol during the normal menstrual
2230 cycle in women with major depression. *Horm Behav* 45: 93-102, 2004.

- 2231 24. **Bao A-M, Liu R-Y, Van Someren EJW, Hofman MA, Cao Y-X, and Zhou J-N.**
2232 Diurnal rhythm of free estradiol during the menstrual cycle. *Eur J Endocrinol* 148: 227-
2233 232, 2003.
- 2234 25. **Baran B, Pace-Schott EF, Ericson C, and Spencer RM.** Processing of emotional
2235 reactivity and emotional memory over sleep. *J Neurosci* 32: 1035-1042, 2012.
- 2236 26. **Barclay NL, Eley TC, Rijdsdijk FV, and Gregory AM.** Dependent negative life
2237 events and sleep quality: An examination of gene–environment interplay. *Sleep Med* 12:
2238 403-409, 2011.
- 2239 27. **Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, and Guthrie B.**
2240 Epidemiology of multimorbidity and implications for health care, research, and medical
2241 education: a cross-sectional study. *Lancet* 380: 37-43, 2012.
- 2242 28. **Barron AJ, Zaman N, Cole GD, Wensel R, Okonko DO, and Francis DP.**
2243 Systematic review of genuine versus spurious side-effects of beta-blockers in heart
2244 failure using placebo control: Recommendations for patient information. *Int J Cardiol*
2245 168: 3572-3579, 2013.
- 2246 29. **Basner M, and Dinges DF.** Sleep duration in the United States 2003–2016: first signs
2247 of success in the fight against sleep deficiency? *Sleep* zsy012-zsy012, 2018.
- 2248 30. **Bastien CH, LeBlanc M, Carrier J, and Morin CM.** Sleep EEG power spectra,
2249 insomnia, and chronic use of benzodiazepines. *Sleep* 26: 313-317, 2003.
- 2250 31. **Batterham PJ, Christensen H, and Mackinnon AJ.** Modifiable risk factors
2251 predicting major depressive disorder at four year follow-up: a decision tree approach.
2252 *BMC Psychiatry* 9: 75, 2009.
- 2253 32. **Beach SRH, Brody GH, Todorov AA, Gunter TD, and Philibert RA.**
2254 Methylation at SLC6A4 is linked to family history of child abuse: An examination of the
2255 Iowa Adoptee sample. *Am J Med Genet Part B* 153B: 710-713, 2010.
- 2256 33. **Beattie L, Kyle SD, Espie CA, and Biello SM.** Social interactions, emotion and
2257 sleep: A systematic review and research agenda. *Sleep Med Rev* 24: 83-100, 2015.
- 2258 34. **Becker PM, and Novak M.** Diagnosis, comorbidities, and management of restless
2259 legs syndrome. *Curr Med Res Opin* 30: 1441-1460, 2014.
- 2260 35. **Benca RM, Obermeyer WH, Thisted RA, and Gillin JC.** Sleep and psychiatric
2261 disorders. A meta-analysis. *Arch Gen Psychiatry* 49: 651-668; discussion 669-670, 1992.
- 2262 36. **Benetó A, Gomez-Siurana E, and Rubio-Sanchez P.** Comorbidity between sleep
2263 apnea and insomnia. *Sleep Med Rev* 13: 287-293, 2009.
- 2264 37. **Benjamins JS, Migliorati F, Dekker K, Wassing R, Moens S, Blanken TF, te**
2265 **Lindert BHW, Sjaauw Mook J, and Van Someren EJW.** Insomnia heterogeneity:

- 2266 Characteristics to consider for data-driven multivariate subtyping. *Sleep Med Rev* 36: 71-
2267 81, 2017.
- 2268 38. **Bermudez-Rattoni F.** The forgotten insular cortex: Its role on recognition memory
2269 formation. *Neurobiol Learn Mem* 109: 207-216, 2014.
- 2270 39. **Berridge KC, and Robinson TE.** Parsing reward. *TINS* 26: 507-513, 2003.
- 2271 40. **Beset A, Villemain E, Tafti M, and Billiard M.** Homeostatic process and sleep
2272 spindles in patients with sleep-maintenance insomnia: effect of partial (21 h) sleep
2273 deprivation. *Electroencephalogr Clin Neurophysiol* 107: 122-132, 1998.
- 2274 41. **Bjorvatn B, Waage S, and Pallesen S.** The association between insomnia and
2275 bedroom habits and bedroom characteristics: an exploratory cross-sectional study of a
2276 representative sample of adults. *Sleep Health* 4: 188-193, 2018.
- 2277 42. **Blanken TF, Benjamins JS, Borsboom D, Vermunt JK, Paquola C, Ramautar
2278 J, Dekker K, Stoffers D, Wassing R, Wei Y, and Van Someren EJW.** Insomnia
2279 disorder subtypes derived from life history and traits of affect and personality. *Lancet
2280 Psychiatry* 6: 151-163, 2019.
- 2281 43. **Blanken TF, Borsboom D, Penninx BW, and Someren EJW.** Network Outcome
2282 Analysis identifies difficulty initiating sleep as primary target for prevention of
2283 depression: A six-year prospective study. *Sleep* 43: zsz288, 2019.
- 2284 44. **Blanken TF, Van Der Zweerde T, Van Straten A, Van Someren EJW,
2285 Borsboom D, and Lancee J.** Introducing Network Intervention Analysis to
2286 investigate sequential, symptom-specific treatment effects: A demonstration in co-
2287 occurring insomnia and depression. *Psychother Psychosom* 88: 52-54, 2019.
- 2288 45. **Blanken TF, and van Someren EJW.** Subtyping insomnia disorder. *Lancet Psychiatry*
2289 6: 285-286, 2019.
- 2290 46. **Blom K, Jernelov S, Kraepelien M, Bergdahl MO, Jungmarker K, Ankartjarn
2291 L, Lindefors N, and Kaldo V.** Internet treatment addressing either insomnia or
2292 depression, for patients with both diagnoses: A randomized trial. *Sleep* 38: 267-277,
2293 2015.
- 2294 47. **Blom K, Jernelöv S, Rück C, Lindefors N, and Kaldo V.** Three-year follow-up
2295 comparing cognitive behavioral therapy for depression to cognitive behavioral therapy
2296 for insomnia, for patients with both diagnoses. *Sleep* 40: zsx108, 2017.
- 2297 48. **Blood AJ, and Zatorre RJ.** Intensely pleasurable responses to music correlate with
2298 activity in brain regions implicated in reward and emotion. *PNAS* 98: 11818-11823, 2001.
- 2299 49. **Blum ID, Zhu L, Moquin L, Kokoeva MV, Gratton A, Giros B, and Storch KF.**
2300 A highly tunable dopaminergic oscillator generates ultradian rhythms of behavioral
2301 arousal. *eLife* 3: e05105, 2014.

- 2302 50. **Bonnet M, Carley D, Carskadon M, Easton P, Guilleminault C, Harper R,**
2303 **Hayes B, Hirschkowitz M, Ktonas P, Keenan S, Pressman M, Roehrs T,**
2304 **Smith J, Walsh J, Weber S, and Westbrook P.** EEG arousals: scoring rules and
2305 examples. A preliminary report from the Sleep Disorders Atlas Task force of the
2306 American Sleep Disorders Association. *Sleep* 15: 173-184, 1992.
- 2307 51. **Bonnet MH.** Recovery of performance during sleep following sleep deprivation in
2308 older normal and insomniac adult males. *Percept Mot Skills* 60: 323-334, 1985.
- 2309 52. **Borbely AA.** A two process model of sleep regulation. *Hum Neurobiol* 1: 195-204,
2310 1982.
- 2311 53. **Bouchequet P, Solelhac G, Andrillon T, Romano F, Brigham M, Chennaoui**
2312 **M, and Léger D.** Quantifying importance of electroencephalography spectral domain
2313 features in automatic diagnosis of chronic insomnia. *Sleep* 42: A130, 2019.
- 2314 54. **Bouvette-Turcot A-A, Pluess M, Bernier A, Pennestri M-H, Levitan R,**
2315 **Sokolowski MB, Kennedy JL, Minde K, Steiner M, Pokhvisneva I, Meaney MJ,**
2316 **and Gaudreau H.** Effects of genotype and sleep on temperament. *Pediatrics* 136: e914-
2317 e921, 2015.
- 2318 55. **Breslau N, Roth T, Burduvali E, Kapke A, Schultz L, and Roehrs T.** Sleep in
2319 lifetime posttraumatic stress disorder: A community-based polysomnographic study.
2320 *Arch Gen Psychiatry* 61: 508-516, 2004.
- 2321 56. **Bresser T, Foster-Dingley JC, Wassing R, Leerssen J, Ramautar JR, Stoffers**
2322 **D, Lakbila-Kamal O, van den Heuvel M, and van Someren EJW.** Consistent
2323 altered internal capsule white matter microstructure in insomnia disorder. *Sleep*
2324 zsa031, 2020.
- 2325 57. **Brewster G, Varrasse M, and Rowe M.** Sleep and cognition in community-dwelling
2326 older adults: A review of literature. *Healthcare* 3: 1243-1270, 2015.
- 2327 58. **Broese M, Riemann D, Hein L, and Nissen C.** Alpha-adrenergic receptor function,
2328 arousal and sleep: Mechanisms and therapeutic implications. *Pharmacopsychiatry* 45: 209-
2329 216, 2012.
- 2330 59. **Broman JE, Mallon L, and Hetta J.** Restless legs syndrome and its relationship with
2331 insomnia symptoms and daytime distress: epidemiological survey in Sweden. *Psychiatry*
2332 *Clin Neurosci* 62: 472-475, 2008.
- 2333 60. **Brower KJ, Wojnar M, Sliwerska E, Armitage R, and Burmeister M.** Per3
2334 polymorphism and insomnia severity in alcohol dependence. *Sleep* 35: 571-577, 2012.
- 2335 61. **Brummett BH, Krystal AD, Ashley-Koch A, Kuhn CM, Zuchner S, Siegler IC,**
2336 **Barefoot JC, Ballard EL, Gwyther LP, and Williams RB.** Sleep quality varies as a
2337 function of 5-HTTLPR genotype and stress. *Psychosom Med* 69: 621-624, 2007.

- 2338 62. **Brummett BH, Krystal AD, Siegler IC, Kuhn C, Surwit RS, Zuchner S,**
2339 **Ashley-Koch A, Barefoot JC, and Williams RB.** Associations of a regulatory
2340 polymorphism of monoamine oxidase-A gene promoter (MAOA-uVNTR) with
2341 symptoms of depression and sleep quality. *Psychosom Med* 69: 396-401, 2007.
- 2342 63. **Burks JD, Conner AK, Bonney PA, Glenn CA, Baker CM, Boettcher LB,**
2343 **Briggs RG, O'Donoghue DL, Wu DH, and Sughrue ME.** Anatomy and white
2344 matter connections of the orbitofrontal gyrus. *J Neurosurg* 128: 1865-1872, 2018.
- 2345 64. **Buysse DJ, Cheng Y, Germain A, Moul DE, Franzen PL, Fletcher M, and**
2346 **Monk TH.** Night-to-night sleep variability in older adults with and without chronic
2347 insomnia. *Sleep Med* 11: 56-64, 2010.
- 2348 65. **Buysse DJ, Thompson W, Scott J, Franzen PL, Germain A, Hall M, Moul DE,**
2349 **Nofzinger EA, and Kupfer DJ.** Daytime symptoms in primary insomnia: a
2350 prospective analysis using ecological momentary assessment. *Sleep Med* 8: 198-208,
2351 2007.
- 2352 66. **Cai M, Langer EM, Gill JG, Satpathy AT, Albring JC, Kc W, Murphy TL, and**
2353 **Murphy KM.** Dual actions of Meis1 inhibit erythroid progenitor development and
2354 sustain general hematopoietic cell proliferation. *Blood* 120: 335-346, 2012.
- 2355 67. **Calem M, Bisla J, Begum A, Dewey M, Bebbington PE, Brugha T, Cooper C,**
2356 **Jenkins R, Lindesay J, McManus S, Meltzer H, Spiers N, Weich S, and**
2357 **Stewart R.** Increased prevalence of insomnia and changes in hypnotics use in England
2358 over 15 years: analysis of the 1993, 2000, and 2007 National Psychiatric Morbidity
2359 Surveys. *Sleep* 35: 377-384, 2012.
- 2360 68. **Cano G, Mochizuki T, and Saper CB.** Neural circuitry of stress-induced insomnia
2361 in rats. *J Neurosci* 28: 10167-10184, 2008.
- 2362 69. **Cao X-L, Wang S-B, Zhong B-L, Zhang L, Ungvari GS, Ng CH, Li L, Chiu**
2363 **HFK, Lok GKI, Lu J-P, Jia F-J, and Xiang Y-T.** The prevalence of insomnia in the
2364 general population in China: A meta-analysis. *PLoS ONE* 12: e0170772, 2017.
- 2365 70. **Capellini I, Barton RA, McNamara P, Preston BT, and Nunn CL.** Phylogenetic
2366 analysis of the ecology and evolution of mammalian sleep. *Evolution* 62: 1764-1776, 2008.
- 2367 71. **Carra MC, Macaluso GM, Rompré PH, Huynh N, Parrino L, Terzano MG,**
2368 **and Lavigne GJ.** Clonidine has a paradoxical effect on cyclic arousal and sleep bruxism
2369 during NREM sleep. *Sleep* 33: 1711-1716, 2010.
- 2370 72. **Carter ME, Yizhar O, Chikahisa S, Nguyen H, Adamantidis A, Nishino S,**
2371 **Deisseroth K, and de Lecea L.** Tuning arousal with optogenetic modulation of locus
2372 coeruleus neurons. *Nat Neurosci* 13: 1526-1533, 2010.

- 2373 73. **Cartwright R, Luten A, Young M, Mercer P, and Bears M.** Role of REM sleep
2374 and dream affect in overnight mood regulation: a study of normal volunteers. *Psychiatry*
2375 *Res* 81: 1-8, 1998.
- 2376 74. **Chan JW, Lam SP, Li SX, Yu MW, Chan NY, Zhang J, and Wing YK.**
2377 Eveningness and insomnia: independent risk factors of nonremission in major depressive
2378 disorder. *Sleep* 37: 911-917, 2014.
- 2379 75. **Chao LL, Mohlenhoff BS, Weiner MW, and Neylan TC.** Associations between
2380 subjective sleep quality and brain volume in Gulf War veterans. *Sleep* 37: 445-452, 2014.
- 2381 76. **Chapman DP, Wheaton AG, Anda RF, Croft JB, Edwards VJ, Liu Y, Sturgis**
2382 **SL, and Perry GS.** Adverse childhood experiences and sleep disturbances in adults.
2383 *Sleep Med* 12: 773-779, 2011.
- 2384 77. **Chen MC, Chang C, Glover GH, and Gotlib IH.** Increased insula coactivation with
2385 salience networks in insomnia. *Biol Psychol* 97: 1-8, 2014.
- 2386 78. **Chen MC, Chiang W-Y, Yugay T, Patxot M, Özçivit İB, Hu K, and Lu J.**
2387 Anterior insula regulates multiscale temporal organization of sleep and wake activity. *J*
2388 *Biol Rhythms* 2016.
- 2389 79. **Chen T, Cai W, Ryali S, Supekar K, and Menon V.** Distinct global brain dynamics
2390 and spatiotemporal organization of the salience network. *PLOS Biology* 14: e1002469,
2391 2016.
- 2392 80. **Cheng W, Rolls ET, Ruan H, and Feng J.** Functional connectivities in the brain that
2393 mediate the association between depressive problems and sleep quality. *JAMA Psychiatry*
2394 75: 1052-1061, 2018.
- 2395 81. **Chilcott LA, and Shapiro CM.** The socioeconomic impact of insomnia.
2396 *Pharmacoeconomics* 10 S1: 1-14, 1996.
- 2397 82. **Cho HJ, Eisenberger NI, Olmstead R, Breen EC, and Irwin MR.** Preexisting
2398 mild sleep disturbance as a vulnerability factor for inflammation-induced depressed
2399 mood: a human experimental study. *Transl Psychiatry* 6: e750, 2016.
- 2400 83. **Choueiry N, Salamoun T, Jabbour H, El Osta N, Hajj A, and Rabbaa**
2401 **Khabbaz L.** Insomnia and relationship with anxiety in university students: A cross-
2402 sectional designed study. *PLOS One* 11: e0149643, 2016.
- 2403 84. **Christensen H, Batterham PJ, Gosling JA, Ritterband LM, Griffiths KM,**
2404 **Thorndike FP, Glozier N, O'Dea B, Hickie IB, and Mackinnon AJ.** Effectiveness
2405 of an online insomnia program (SHUTi) for prevention of depressive episodes (the
2406 GoodNight Study): a randomised controlled trial. *Lancet Psychiatry* 3: 333-341, 2016.

- 2407 85. **Christensen JAE, Wassing R, Wei Y, Ramautar JR, Lakbila-Kamal O, Jennum**
2408 **PJ, and Van Someren EJW.** Data-driven analysis of EEG reveals concomitant
2409 superficial sleep during deep sleep in insomnia disorder. *Front Neurosci* 13: 598, 2019.
- 2410 86. **Chung K-F, Yeung W-F, Ho FY-Y, Yung K-P, Yu Y-M, and Kwok C-W.** Cross-
2411 cultural and comparative epidemiology of insomnia: the Diagnostic and Statistical
2412 Manual (DSM), International Classification of Diseases (ICD) and International
2413 Classification of Sleep Disorders (ICSD). *Sleep Med* 16: 477-482, 2015.
- 2414 87. **Cole RJ.** Postural baroreflex stimuli may affect EEG arousal and sleep in humans. *J Appl*
2415 *Physiol* 67: 2369-2375., 1989.
- 2416 88. **Colombo M, Ramautar JR, Wei Y, Gomez-Herrero G, Stoffers D, Wassing R,**
2417 **Benjamins J, Tagliazucchi E, Van Der Werf YD, Cajochen C, and Van**
2418 **Someren EJW.** Wake high-density electroencephalographic spatio-spectral signatures
2419 of insomnia. *Sleep* 39: 1015-1027, 2016.
- 2420 89. **Colombo MA, Wei Y, Ramautar JR, Linkenkaer-Hansen K, Tagliazucchi E,**
2421 **and Van Someren EJ.** More severe insomnia complaints in people with stronger
2422 long-range temporal correlations in wake resting-state EEG. *Front Physiol* 7: 576, 2016.
- 2423 90. **Cross NE, Carrier J, Postuma RB, Gosselin N, Kakinami L, Thompson C,**
2424 **Chouchou F, and Dang-Vu TT.** Association between insomnia disorder and
2425 cognitive function in middle-aged and older adults: a cross-sectional analysis of the
2426 Canadian Longitudinal Study on Aging. *Sleep* 42: 14, 2019.
- 2427 91. **Cunningham TJ, Crowell CR, Alger SE, Kensinger EA, Villano MA, Mattingly**
2428 **SM, and Payne JD.** Psychophysiological arousal at encoding leads to reduced
2429 reactivity but enhanced emotional memory following sleep. *Neurobiol Learn Mem* 114:
2430 155-164, 2014.
- 2431 92. **Daan S, Beersma DG, and Borbely AA.** Timing of human sleep: recovery process
2432 gated by a circadian pacemaker. *Am J Physiol* 246: R161-183, 1984.
- 2433 93. **Daley M, Morin CM, LeBlanc M, Gregoire JP, and Savard J.** The economic
2434 burden of insomnia: direct and indirect costs for individuals with insomnia syndrome,
2435 insomnia symptoms, and good sleepers. *Sleep* 32: 55-64, 2009.
- 2436 94. **Davidson S, Miller KA, Dowell A, Gildea A, and MacKenzie A.** A remote and
2437 highly conserved enhancer supports amygdala specific expression of the gene encoding
2438 the anxiogenic neuropeptide substance-P. *Mol Psychiatry* 11: 410-421, 2006.
- 2439 95. **de Rover M, Brown SBRE, Boot N, Hajcak G, van Noorden MS, van der Wee**
2440 **NJA, and Nieuwenhuis S.** Beta receptor-mediated modulation of the late positive
2441 potential in humans. *Psychopharmacology (Berl)* 219: 971-979, 2012.

- 2442 96. **de Zambotti M, Willoughby AR, Baker FC, Sugarbaker DS, and Colrain IM.**
2443 Cardiac autonomic function during sleep: Effects of alcohol dependence and evidence of
2444 partial recovery with abstinence. *Alcohol* 49: 409-415, 2015.
- 2445 97. **DeAndrade MP, Johnson Jr RL, Unger EL, Zhang L, van Groen T, Gamble**
2446 **KL, and Li Y.** Motor restlessness, sleep disturbances, thermal sensory alterations and
2447 elevated serum iron levels in Btbd9 mutant mice. *Human Molecular Genetics* 21: 3984-
2448 3992, 2012.
- 2449 98. **DeAndrade MP, Johnson JRL, Unger EL, Zhang L, van Groen T, Gamble KL,**
2450 **and Li Y.** Motor restlessness, sleep disturbances, thermal sensory alterations and
2451 elevated serum iron levels in Btbd9 mutant mice. *Hum Mol Genet* 21: 3984-3992, 2012.
- 2452 99. **DeAndrade MP, Zhang L, Doroodchi A, Yokoi F, Cheetham CC, Chen H-X,**
2453 **Roper SN, Sweatt JD, and Li Y.** Enhanced hippocampal long-term potentiation and
2454 fear memory in btbd9 mutant mice. *PLOS ONE* 7: e35518, 2012.
- 2455 100. **Delgado Rosado GM, Wilckens K, He F, Hall M, and Buysse DJ.** Is chronic
2456 insomnia associated with reduced EEG delta power? *Sleep* 38: A219, 2015.
- 2457 101. **Deliens Gt, Gilson Md, and Peigneux P.** Sleep and the processing of emotions. *Exp*
2458 *Brain Res* 232: 1403-1414, 2014.
- 2459 102. **Dennis PA, Dedert EA, Van Voorhees EE, Watkins LL, Hayano J, Calhoun**
2460 **PS, Sherwood A, Dennis MF, and Beckham JC.** Examining the crux of autonomic
2461 dysfunction in Posttraumatic Stress Disorder: whether chronic or situational distress
2462 underlies elevated heart rate and attenuated heart rate variability. *Psychosom Med* 78:
2463 805-809, 2016.
- 2464 103. **Deuschle M, Schredl M, Schilling C, Wust S, Frank J, Witt SH, Rietschel M,**
2465 **Buckert M, Meyer-Lindenberg A, and Schulze TG.** Association between a
2466 serotonin transporter length polymorphism and primary insomnia. *Sleep* 33: 343-347,
2467 2010.
- 2468 104. **Diagnostic Classification Steering Committee.** *ICSD2 - International classification of*
2469 *sleep disorders: Diagnostic and coding manual.* Rochester, Minnesota: American Sleep
2470 Disorders Association, 2005.
- 2471 105. **Diagnostic Classification Steering Committee.** *ICSD3 - International classification of*
2472 *sleep disorders: Diagnostic and coding manual.* Rochester, Minnesota: American Sleep
2473 Disorders Association, 2014.
- 2474 106. **Diaz BA, Van Der Sluis S, Moens S, Benjamins JS, Migliorati F, Stoffers D,**
2475 **Den Braber A, Poil SS, Hardstone R, Van't Ent D, Boomsma DI, De Geus E,**
2476 **Mansvelder HD, Van Someren EJ, and Linkenkaer-Hansen K.** The Amsterdam

- 2477 Resting-State Questionnaire reveals multiple phenotypes of resting-state cognition. *Front*
 2478 *Hum Neurosci* 7: 446, 2013.
- 2479 107. **Diering GH, Nirujogi RS, Roth RH, Worley PF, Pandey A, and Huganir RL.**
 2480 Homer1a drives homeostatic scaling-down of excitatory synapses during sleep. *Science*
 2481 355: 511-515, 2017.
- 2482 108. **Dodds KL, Miller CB, Kyle SD, Marshall NS, and Gordon CJ.** Heart rate
 2483 variability in insomnia patients: A critical review of the literature. *Sleep Med Rev* 33: 88-
 2484 100, 2017.
- 2485 109. **Drake C, Richardson G, Roehrs T, Scofield H, and Roth T.** Vulnerability to
 2486 stress-related sleep disturbance and hyperarousal. *Sleep* 27: 285-291, 2004.
- 2487 110. **Drake CL, Friedman NP, Wright KP, Jr., and Roth T.** Sleep reactivity and
 2488 insomnia: genetic and environmental influences. *Sleep* 34: 1179-1188, 2011.
- 2489 111. **Drake CL, Pillai V, and Roth T.** Stress and sleep reactivity: a prospective
 2490 investigation of the stress-diathesis model of insomnia. *Sleep* 37: 1295-1304, 2014.
- 2491 112. **Drummond SP, Walker M, Almklov E, Campos M, Anderson DE, and Straus**
 2492 **LD.** Neural correlates of working memory performance in primary insomnia. *Sleep* 36:
 2493 1307-1316, 2013.
- 2494 113. **Dugovic C, Maccari S, Weibel L, Turek FW, and Van Reeth a O.** High
 2495 corticosterone levels in prenatally stressed rats predict persistent paradoxical sleep
 2496 alterations. *J Neurosci* 19: 8656-8664, 1999.
- 2497 114. **Dugovic C, Solberg LC, Redei E, Reeth OV, and Turek FW.** Sleep in the
 2498 Wistar-Kyoto rat, a putative genetic animal model for depression. *Neuroreport* 11: 627-
 2499 631, 2000.
- 2500 115. **Dunn BJ, Conover K, Plourde G, Munro D, Kilgour R, and Shizgal P.** Hedonic
 2501 valuation during thermal alliesthesia. In: *Abstracts of the 16th Annual Meeting of the*
 2502 *Organization for Human Brain Mapping*. Barcelona: 2010.
- 2503 116. **Eban-Rothschild A, Giardino WJ, and de Lecea L.** To sleep or not to sleep:
 2504 neuronal and ecological insights. *Curr Opin Neurobiol* 44: 132-138, 2017.
- 2505 117. **Edinger JD, Fins AI, Sullivan RJ, Marsh GR, Dailey DS, Hope TV, Young M,**
 2506 **Shaw E, Carlson D, and Vasilas D.** Do our methods lead to insomniacs madness -
 2507 daytime testing after laboratory and home-based polysomnographic studies. *Sleep* 20:
 2508 1127-1134, 1997.
- 2509 118. **Edinger JD, Wyatt JK, Stepanski EJ, Olsen MK, Stechuchak KM, Carney CE,**
 2510 **Chiang A, Crisostomo MI, Lineberger MD, Means MK, Radtke RA,**
 2511 **Wohlgemuth WK, and Krystal AD.** Testing the reliability and validity of DSM-IV-

- 2512 TR and ICSD-2 insomnia diagnoses. Results of a multitrait-multimethod analysis. *Arch*
2513 *Gen Psychiatry* 68: 992-1002, 2011.
- 2514 119. **Erdem A, Yilmaz MB, Turgut OO, Yilmaz A, Yalta K, and Tandogan I.**
2515 Nebivolol is different from Atenolol in terms of impact onto sleep. *Anatol J Clin Invest* 1:
2516 25-29, 2006.
- 2517 120. **Ermann M, Peichl J, Pohl H, Schneider MM, and Winkelmann Y.** Spontaneous
2518 awakening and dreams of patients with psychophysiologic sleep disorders. *Psychotherapie,*
2519 *Psychosomatik, Medizinische Psychologie* 43: 333-340, 1993.
- 2520 121. **Etkin A, Prater KE, Schatzberg AF, Menon V, and Greicius MD.** Disrupted
2521 amygdalar subregion functional connectivity and evidence of a compensatory network in
2522 generalized anxiety disorder. *Arch Gen Psychiatry* 66: 1361-1372, 2009.
- 2523 122. **Fazlali Z, Ranjbar-Slamloo Y, Adibi M, and Arabzadeh E.** Correlation between
2524 cortical state and locus coeruleus activity: Implications for sensory coding in rat barrel
2525 cortex. *Frontiers in Neural Circuits* 10: 2016.
- 2526 123. **Feige B, Al-Shajlawi A, Nissen C, Voderholzer U, Hornyak M, Spiegelhalder**
2527 **K, Kloepfer C, Perlis M, and Riemann D.** Does REM sleep contribute to subjective
2528 wake time in primary insomnia? A comparison of polysomnographic and subjective
2529 sleep in 100 patients. *J Sleep Res* 17: 180-190, 2008.
- 2530 124. **Feige B, Baglioni C, Spiegelhalder K, Hirschner V, Nissen C, and Riemann D.**
2531 The microstructure of sleep in primary insomnia: An overview and extension. *Int J*
2532 *Psychophysiol* 89: 171-180, 2013.
- 2533 125. **Feige B, Voderholzer U, Riemann D, Hohagen F, and Berger M.** Independent
2534 sleep EEG slow-wave and spindle band dynamics associated with 4 weeks of continuous
2535 application of short-half-life hypnotics in healthy subjects. *Clin Neurophysiol* 110: 1965-
2536 1974, 1999.
- 2537 126. **Ferri R, Cosentino FII, Manconi M, Rundo F, Bruni O, and Zucconi M.**
2538 Increased electroencephalographic high frequencies during the sleep onset period in
2539 patients with restless legs syndrome. *Sleep* 37: 1375-1381, 2014.
- 2540 127. **Ferri R, Rundo F, Zucconi M, Manconi M, Bruni O, Ferini-Strambi L, and**
2541 **Fulda S.** An evidence-based analysis of the association between Periodic Leg
2542 Movements during sleep and arousals in Restless Legs Syndrome. *Sleep* 38: 919-924,
2543 2015.
- 2544 128. **Ferrillo F, Donadio S, De Carli Phy F, Garbarino S, and Nobili L.** A model-
2545 based approach to homeostatic and ultradian aspects of nocturnal sleep structure in
2546 narcolepsy. *Sleep* 30: 157-165, 2007.

- 2547 129. **Flynn-Evans EE, Shekleton JA, Miller B, Epstein LJ, Kirsch D, Brogna LA,**
 2548 **Burke LM, Bremer E, Murray JM, Gehrman P, Rajaratnam SMW, and**
 2549 **Lockley SW.** Circadian phase and phase angle disorders in primary insomnia. *Sleep* 40:
 2550 zsx163, 2017.
- 2551 130. **Foote SL, Aston-Jones G, and Bloom FE.** Impulse activity of locus coeruleus
 2552 neurons in awake rats and monkeys is a function of sensory stimulation and arousal.
 2553 *PNAS* 77: 3033-3037, 1980.
- 2554 131. **Ford ES, Cunningham TJ, Giles WH, and Croft JB.** Trends in insomnia and
 2555 excessive daytime sleepiness among U.S. adults from 2002 to 2012. *Sleep Med* 16: 372-
 2556 378, 2015.
- 2557 132. **Fortier-Brochu E, Beaulieu-Bonneau S, Ivers H, and Morin CM.** Insomnia and
 2558 daytime cognitive performance: A meta-analysis. *Sleep Med Rev* 16: 83-94, 2011.
- 2559 133. **Foulkes WD.** Dream reports from different stages of sleep. *J Abnorm Soc Psychol* 65:
 2560 14-25, 1962.
- 2561 134. **Freedman RR.** EEG power spectra in sleep-onset insomnia. *Electroencephalogr Clin*
 2562 *Neurophysiol* 63: 408-413, 1986.
- 2563 135. **Funk Chadd M, Honjoh S, Rodriguez Alexander V, Cirelli C, and Tononi G.**
 2564 Local slow waves in superficial layers of primary cortical areas during REM sleep. *Curr*
 2565 *Biol* 26: 396-403, 2016.
- 2566 136. **Gamble MC, Katsuki F, McCoy JG, Strecker RE, and McKenna JT.** The dual
 2567 orexinergic receptor antagonist DORA-22 improves the sleep disruption and memory
 2568 impairment produced by a rodent insomnia model. *Sleep* 43: 2019.
- 2569 137. **Gandal MJ, Haney JR, Parikshak NN, Leppa V, Ramaswami G, Hartl C,**
 2570 **Schork AJ, Appadurai V, Buil A, Werge TM, Liu C, White KP, Horvath S,**
 2571 **and Geschwind DH.** Shared molecular neuropathology across major psychiatric
 2572 disorders parallels polygenic overlap. *Science* 359: 693-697, 2018.
- 2573 138. **Garland SN, Rowe H, Repa LM, Fowler K, Zhou ES, and Grandner MA.** A
 2574 decade's difference: 10-year change in insomnia symptom prevalence in Canada depends
 2575 on sociodemographics and health status. *Sleep Health* 4: 160-165, 2018.
- 2576 139. **Gebara MA, Siripong N, DiNapoli Elizabeth A, Maree Rachel D, Germain A,**
 2577 **Reynolds Charles F, Kasckow John W, Weiss Patricia M, and Karp Jordan F.**
 2578 Effect of insomnia treatments on depression: A systematic review and meta - analysis.
 2579 *Depress Anxiety* 0: 2018.
- 2580 140. **Gehrman P, Seelig AD, Jacobson IG, Boyko EJ, Hooper TI, Gackstetter GD,**
 2581 **Ulmer CS, Smith TC, and the Millennium Cohort Study Team.** Predeployment

- 2582 sleep duration and insomnia symptoms as risk factors for new-onset mental health
2583 disorders following military deployment. *Sleep* 36: 1009-1018, 2013.
- 2584 141. **Geiger MJ, Domschke K, Homola GA, Schulz SM, Nowak J, Akhrif A, Pauli P,**
2585 **Deckert J, and Neufang S.** ADORA2A genotype modulates interoceptive and
2586 exteroceptive processing in a fronto-insular network. *Eur Neuropsychopharmacol* 26:
2587 1274-1285, 2016.
- 2588 142. **Genzel L, Spoormaker VI, Konrad BN, and Dresler M.** The role of rapid eye
2589 movement sleep for amygdala-related memory processing. *Neurobiol Learn Mem* 122:
2590 110-121, 2015.
- 2591 143. **Germain A, Buysse DJ, and Nofzinger E.** Sleep-specific mechanisms underlying
2592 posttraumatic stress disorder: Integrative review and neurobiological hypotheses. *Sleep*
2593 *Med Rev* 12: 185-195, 2008.
- 2594 144. **Germain A, Richardson R, Moul DE, Mammen O, Haas G, Forman SD, Rode**
2595 **N, Begley A, and Nofzinger EA.** Placebo-controlled comparison of prazosin and
2596 cognitive-behavioral treatments for sleep disturbances in US Military Veterans. *J*
2597 *Psychosom Res* 72: 89-96, 2012.
- 2598 145. **Ghaemmaghami P, Muto V, Jaspar M, meyer c, Elansary M, VanEgroot M,**
2599 **Berthomier C, Lambot E, Brandewinder M, Luxen A, Degueldre C, Salmon**
2600 **E, Archer SN, Phillips C, Dijk D-J, posthuma d, Van Someren E, Collette F,**
2601 **Georges M, Maquet P, and Vandewalle G.** The genetic liability for insomnia is
2602 associated with lower amount of slow wave sleep in young and healthy individuals. *Front*
2603 *Neurosci* 10.3389/conf.fnins.2018.3395.00069, 2018.
- 2604 146. **Glod CA, Teicher MH, Hartman CR, and Harakal T.** Increased nocturnal activity
2605 and impaired sleep maintenance in abused children. *J Am Acad Child Adolesc Psychiatry* 36:
2606 1236-1243, 1997.
- 2607 147. **Glod CA, Teicher MH, Hartman CR, Harakal T, and McGreenery CE.**
2608 Enduring effects of early abuse on locomotor activity, sleep, and circadian rhythms. *Ann*
2609 *NY Ac Sci* 821: 465-467, 1997.
- 2610 148. **Göder R, Scharffetter F, Aldenhoff JB, and Fritzer G.** Visual declarative memory
2611 is associated with non-rapid eye movement sleep and sleep cycles in patients with
2612 chronic non-restorative sleep. *Sleep Med* 8: 503-508, 2007.
- 2613 149. **Goldin PR, McRae K, Ramel W, and Gross JJ.** The neural bases of emotion
2614 regulation: reappraisal and suppression of negative emotion. *Biol Psychiatry* 63: 577-586,
2615 2008.
- 2616 150. **Gregory AM, Caspi A, Moffitt TE, and Poulton R.** Family conflict in childhood: a
2617 predictor of later insomnia. *Sleep* 29: 1063-1067, 2006.

- 2618 151. **Griessenberger H, Heib DPJ, Lechinger J, Luketina N, Petzka M, Moeckel T,**
 2619 **Hoedlmoser K, and Schabus M.** Susceptibility to declarative memory interference is
 2620 pronounced in primary insomnia. *PLoS One* 8: e57394, 2013.
- 2621 152. **Groch S, Wilhelm I, Diekelmann S, and Born J.** The role of REM sleep in the
 2622 processing of emotional memories: evidence from behavior and event-related potentials.
 2623 *Neurobiol Learn Mem* 99: 1-9, 2013.
- 2624 153. **GTEx Consortium.** The Genotype-Tissue Expression (GTEx) pilot analysis:
 2625 Multitissue gene regulation in humans. *Science* 348: 648-660, 2015.
- 2626 154. **Gujar N, McDonald SA, Nishida M, and Walker MP.** A role for REM sleep in
 2627 recalibrating the sensitivity of the human brain to specific emotions. *Cerebr Cortex* 21:
 2628 115-123, 2011.
- 2629 155. **Hagen C, Patel A, and McCall WV.** Prevalence of insomnia symptoms in sleep
 2630 laboratory patients with and without sleep apnea. *Psychiatry Res* 170: 276-277, 2009.
- 2631 156. **Hammerslag AR, Stringer S, de Leeuw CA, Sniekers S, Taskesen E,**
 2632 **Watanabe K, Blanken TF, Dekker K, te Lindert BHW, Wassing R, Jonsdottir**
 2633 **I, Thorleifsson G, Stefansson H, Gislason T, Berger K, Schormair B,**
 2634 **Wellmann J, Winkelmann J, Stefansson K, Oexle K, Van Someren* EJW,**
 2635 **Posthuma* D, and (* authors contributed equally).** Genome-wide association
 2636 analysis of insomnia complaints identifies risk genes and genetic overlap with psychiatric
 2637 and metabolic traits. *Nat Genet* 49: 1584-1592, 2017.
- 2638 157. **Harbison ST, Carbone MA, Ayroles JF, Stone EA, Lyman RF, and Mackay**
 2639 **TFC.** Co-regulated transcriptional networks contribute to natural genetic variation in
 2640 *Drosophila* sleep. *Nat Genet* 41: 371-375, 2009.
- 2641 158. **Hargens TA, Kaleth AS, Edwards ES, and Butner KL.** Association between sleep
 2642 disorders, obesity, and exercise: a review. *Nat Sci Sleep* 5: 27-35, 2013.
- 2643 159. **Harkness KL, and Monroe SM.** Childhood adversity and the endogenous versus
 2644 nonendogenous distinction in women with major depression. *Am J Psychiatry* 159: 387-
 2645 393, 2002.
- 2646 160. **Hartescu I, Morgan K, and Stevinson C.** Psychomotor performance decrements
 2647 following a successful physical activity intervention for insomnia. *Behav Sleep Med* 1-11,
 2648 2019.
- 2649 161. **Harvey AG, and Tang NK.** Cognitive behaviour therapy for primary insomnia: can
 2650 we rest yet? *Sleep Med Rev* 7: 237-262, 2003.
- 2651 162. **Harvey AG, and Tang NK.** (Mis)perception of sleep in insomnia: a puzzle and a
 2652 resolution. *Psychol Bull* 138: 77-101, 2012.

- 2653 163. **Harvey CJ, Gehrman P, and Espie CA.** Who is predisposed to insomnia: a review
2654 of familial aggregation, stress-reactivity, personality and coping style. *Sleep Med Rev* 18:
2655 237-247, 2014.
- 2656 164. **Haynes SN, Fitzgerald SG, Shute G, and O'Meara M.** Responses of
2657 psychophysiologic and subjective insomniacs to auditory stimuli during sleep: a
2658 replication and extension. *J Abnorm Psychol* 94: 338-345, 1985.
- 2659 165. **Hein M, Lanquart J-P, Loas G, Hubain P, and Linkowski P.** Similar
2660 polysomnographic pattern in primary insomnia and major depression with objective
2661 insomnia: a sign of common pathophysiology? *BMC Psychiatry* 17: 273, 2017.
- 2662 166. **Heitmann J, Greulich T, Reinke C, Koehler U, Vogelmeier C, Becker HF,**
2663 **Schmidt AC, and Canisius S.** Comparison of the effects of nebivolol and valsartan
2664 on BP reduction and sleep apnoea activity in patients with essential hypertension and
2665 OSA. *Curr Med Res Opin* 26: 1925-1932, 2010.
- 2666 167. **Herbert V, Pratt D, Emsley R, and Kyle S.** Predictors of nightly subjective-
2667 objective sleep discrepancy in poor sleepers over a seven-day period. *Brain Sci* 7: 29,
2668 2017.
- 2669 168. **Hertenstein E, Feige B, Gmeiner T, Kienzler C, Spiegelhalder K, Johann A,**
2670 **Jansson-Fröjmark M, Palagini L, Rücker G, Riemann D, and Baglioni C.**
2671 Insomnia as a predictor of mental disorders: A systematic review and meta-analysis.
2672 *Sleep Med Rev* 43: 96-105, 2019.
- 2673 169. **Hettema JM, Neale MC, and Kendler KS.** A review and meta-analysis of the
2674 genetic epidemiology of anxiety disorders. *Am J Psychiatry* 158: 1568-1578, 2001.
- 2675 170. **Hohagen F, Kappler C, Schramm E, Rink K, Weyerer S, Riemann D, and**
2676 **Berger M.** Prevalence of insomnia in elderly general practice attenders and the current
2677 treatment modalities. *Acta Psychiatr Scand* 90: 102-108, 1994.
- 2678 171. **Hohoff C, Garibotto V, Elmenhorst D, Baffa A, Kroll T, Hoffmann A,**
2679 **Schwarte K, Zhang W, Arolt V, Deckert J, and Bauer A.** Association of
2680 adenosine receptor gene polymorphisms and in vivo adenosine A1 receptor binding in
2681 the human brain. *Neuropsychopharmacol* 39: 2989, 2014.
- 2682 172. **Hohoff C, Mullings EL, Heatherley SV, Freitag CM, Neumann LC, Domschke**
2683 **K, Krakowitzky P, Rothermundt M, Keck ME, Erhardt A, Unschuld PG,**
2684 **Jacob C, Fritze J, Bandelow B, Maier W, Holsboer F, Rogers PJ, and Deckert**
2685 **J.** Adenosine A2A receptor gene: Evidence for association of risk variants with panic
2686 disorder and anxious personality. *J Psychiatr Res* 44: 930-937, 2010.
- 2687 173. **Huang C, Li J, Lu L, Ren X, Li Y, Huang Q, Lan Y, and Wang Y.** Interaction
2688 between serotonin transporter gene-linked polymorphic region (5-HTTLPR) and job-

- 2689 related stress in insomnia: a cross-sectional study in Sichuan, China. *Sleep Med* 15: 1269-
2690 1275, 2014.
- 2691 174. **Huang Z, Liang P, Jia X, Zhan S, Li N, Ding Y, Lu J, Wang Y, and Li K.**
2692 Abnormal amygdala connectivity in patients with primary insomnia: evidence from
2693 resting state fMRI. *Eur J Radiol* 81: 1288-1295, 2012.
- 2694 175. **Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, Jones L,**
2695 **and Dunne MP.** The effect of multiple adverse childhood experiences on health: a
2696 systematic review and meta-analysis. *Lancet Public Health* 2: e356-e366, 2017.
- 2697 176. **Hunsley MS, and Palmiter RD.** Altered sleep latency and arousal regulation in mice
2698 lacking norepinephrine. *Pharmacol Biochem Behav* 78: 765-773, 2004.
- 2699 177. **Hunsley MS, and Palmiter RD.** Norepinephrine-deficient mice exhibit normal sleep-
2700 wake states but have shorter sleep latency after mild stress and low doses of
2701 amphetamine. *Sleep* 26: 521-526, 2003.
- 2702 178. **Hutcherson L, and Roberts RC.** The immunocytochemical localization of substance
2703 P in the human striatum: A postmortem ultrastructural study. *Synapse* 57: 191-201,
2704 2005.
- 2705 179. **Iber C, Ancoli-Israel S, Chesson AL, and Quan SF.** *The AASM manual for the*
2706 *scoring of sleep and associated events: rules, terminology, and technical specifications.*
2707 Westchester, IL: American Academy of Sleep Medicine, 2007.
- 2708 180. **Insana SP, Kolko DJ, and Germain A.** Early-life trauma is associated with rapid eye
2709 movement sleep fragmentation among military veterans. *Biol Psychol* 89: 570-579, 2012.
- 2710 181. **Irrmischer M, Poil S-S, Mansvelder HD, Intra FS, and Linkenkaer-Hansen K.**
2711 Strong long-range temporal correlations of beta/gamma oscillations are associated with
2712 poor sustained visual attention performance. *Eur J Neurosci* 48: 2674-2683, 2017.
- 2713 182. **Jackson ML, Sztendur EM, Diamond NT, Byles JE, and Bruck D.** Chronic sleep
2714 difficulties in non-depressed young women: a longitudinal population-based investigation.
2715 *Sleep Med* 16: 1116-1122, 2015.
- 2716 183. **Jansen PR, Watanabe K, Stringer S, Skene N, Bryois J, Hammerschlag AR,**
2717 **de Leeuw CA, Benjamins JS, Muñoz-Manchado AB, Nagel M, Savage JE,**
2718 **Tiemeier H, White T, Agee M, Alipanahi B, Auton A, Bell RK, Bryc K, Elson**
2719 **SL, Fontanillas P, Furlotte NA, Hinds DA, Huber KE, Kleinman A, Litterman**
2720 **NK, McCreight JC, McIntyre MH, Mountain JL, Noblin ES, Northover CAM,**
2721 **Pitts SJ, Sathirapongsasuti JF, Sazonova OV, Shelton JF, Shringarpure S,**
2722 **Tian C, Wilson CH, Tung JY, Hinds DA, Vacic V, Wang X, Sullivan PF, van**
2723 **der Sluis S, Polderman TJC, Smit AB, Hjerling-Leffler J, Van Someren* EJW,**
2724 **Posthuma* D, and The 23andMe Research Team.** Genome-wide analysis of

- 2725 insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nat*
2726 *Genet* 51: 394-403, 2019.
- 2727 184. **Jansson-Fröjmark M, Norell-Clarke A, and Linton SJ.** The role of emotion
2728 dysregulation in insomnia: Longitudinal findings from a large community sample. *Br J*
2729 *Health Psychol* 21: 93-113, 2016.
- 2730 185. **Jarrin DC, Chen IY, Ivers H, and Morin CM.** The role of vulnerability in stress-
2731 related insomnia, social support and coping styles on incidence and persistence of
2732 insomnia. *J Sleep Res* 23: 681-688, 2014.
- 2733 186. **Jawinski P, Tegelkamp S, Sander C, Häntzsch M, Huang J, Mauche N, Scholz**
2734 **M, Spada J, Ulke C, Burkhardt R, Reif A, Hegerl U, and Hensch T.** Time to
2735 wake up: No impact of COMT Val158Met gene variation on circadian preferences,
2736 arousal regulation and sleep. *Chronobiol Int* 33: 893-905, 2016.
- 2737 187. **Jespersen KV, Stevner A, Fernandes H, Sørensen SD, Van Someren E,**
2738 **Kringelbach M, and Vuust P.** Reduced structural connectivity in Insomnia Disorder.
2739 *J Sleep Res* 29: e12901, 2020.
- 2740 188. **Jha SK, Brennan FX, Pawlyk AC, Ross RJ, and Morrison AR.** REM sleep: a
2741 sensitive index of fear conditioning in rats. *Eur J Neurosci* 21: 1077-1080, 2005.
- 2742 189. **Johnson EO, Roth T, Schultz L, and Breslau N.** Epidemiology of DSM-IV insomnia
2743 in adolescence: lifetime prevalence, chronicity, and an emergent gender difference.
2744 *Pediatrics* 117: e247-256, 2006.
- 2745 190. **Joo EY, Noh HJ, Kim J-S, Koo DL, Kim D, Hwang KJ, Kim JY, Kim ST, Kim**
2746 **MR, and Hong SB.** Brain gray matter deficits in patients with chronic primary
2747 insomnia. *Sleep* 36: 999-1007, 2013.
- 2748 191. **Kahn A, Groswasser J, Sottiaux M, Kelmanson I, Franco P, Rebuffat E,**
2749 **Dramaix M, and Wayenberg JL.** Prenatal exposure to cigarettes in infants with
2750 obstructive sleep apneas. *Pediatrics* 93: 778-783, 1994.
- 2751 192. **Kalmbach DA, Anderson JR, and Drake CL.** The impact of stress on sleep:
2752 Pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. *J Sleep*
2753 *Res* 27: e12710, 2018.
- 2754 193. **Kalmbach DA, Cuamatzi-Castelan AS, Tonnu CV, Tran KM, Anderson JR,**
2755 **Roth T, and Drake CL.** Hyperarousal and sleep reactivity in insomnia: current
2756 insights. *Nat Sci Sleep* 10: 193-201, 2018.
- 2757 194. **Kang JM, Joo SW, Son Y-D, Kim H, Ko K-P, Lee JS, and Kang S-G.** Low white-
2758 matter integrity between the left thalamus and inferior frontal gyrus in patients with
2759 insomnia disorder. *J Psychiatry Neurosci* 43: 366-374, 2018.

- 2760 195. **Katsuki H, Izumi Y, and Zorumski CF.** Noradrenergic regulation of synaptic
2761 plasticity in the hippocampal CA1 region. *J Neurophysiol* 77: 3013-3020, 1997.
- 2762 196. **Katsumi Y, and Dolcos S.** Suppress to feel and remember less: Neural correlates of
2763 explicit and implicit emotional suppression on perception and memory. *Neuropsychologia*
2764 2018.
- 2765 197. **Kay D, and Buysse D.** Hyperarousal and beyond: New insights to the
2766 pathophysiology of insomnia disorder through functional neuroimaging studies. *Brain Sci*
2767 7: 23, 2017.
- 2768 198. **Kendler KS, Gardner CO, Neale MC, and Prescott CA.** Genetic risk factors for
2769 major depression in men and women: Similar or different heritabilities and same or
2770 partly distinct genes? *Psychol Med* 31: 605-616, 2001.
- 2771 199. **Kendler KS, Gatz M, Gardner CO, and Pedersen NL.** A Swedish national twin
2772 study of lifetime major depression. *Am J Psychiatry* 163: 109-114, 2006.
- 2773 200. **Kerkhof GA.** Epidemiology of sleep and sleep disorders in The Netherlands. *Sleep Med*
2774 30: 229-239, 2017.
- 2775 201. **Kessler RC, Berglund PA, Coulouvrat C, Hajak G, Roth T, Shahly V,**
2776 **Shillington AC, Stephenson JJ, and Walsh JK.** Insomnia and the performance of
2777 US workers: Results from the America Insomnia Survey. *Sleep* 34: 1161-1171, 2011.
- 2778 202. **Khalsa S, Hale JR, Goldstone A, Wilson RS, Mayhew SD, Bagary M, and**
2779 **Bagshaw AP.** Habitual sleep durations and subjective sleep quality predict white
2780 matter differences in the human brain. *Neurobiol Sleep Circadian Rhythm* 3: 17-25, 2017.
- 2781 203. **Khazaie H, Veronese M, Noori K, Emamian F, Zarei M, Ashkan K,**
2782 **Leschziner GD, Eickhoff CR, Eickhoff SB, Morrell MJ, Osorio RS,**
2783 **Spiegelhalder K, Tahmasian M, and Rosenzweig I.** Functional reorganization in
2784 obstructive sleep apnoea and insomnia: A systematic review of the resting-state fMRI.
2785 *Neurosci Biobehav Rev* 77: 219-231, 2017.
- 2786 204. **Killgore WD.** Effects of sleep deprivation on cognition. *Prog Brain Res* 185: 105-129,
2787 2010.
- 2788 205. **Kindt M, and Soeter M.** Pharmacologically induced amnesia for learned fear is time
2789 and sleep dependent. *Nat Commun* 9: 1316, 2018.
- 2790 206. **Ko DT, Hebert PR, Coffey CS, Sedrakyan A, Curtis JP, and Krumholz HM.**
2791 β -Blocker therapy and symptoms of depression, fatigue, and sexual dysfunction. *JAMA*
2792 288: 351-357, 2002.
- 2793 207. **Kobayashi I, Boarts JM, and Delahanty DL.** Polysomnographically measured sleep
2794 abnormalities in PTSD: A meta-analytic review. *Psychophysiol* 44: 660-669, 2007.

- 2795 208. **Kocevska D, Barclay NL, Bramer WM, Gehrman P, and Van Someren EJW.**
 2796 Heritability of sleep duration and quality: A systematic review and meta-analysis. *Sleep*
 2797 *Med Rev* under review: 2020.
- 2798 209. **Kocevska D, Lysen TS, Lifelines, Luijk MPCM, Antypa N, Biermasz N,**
 2799 **Blokstra A, Brug J, Comijs HC, Corpeleijn E, de Bruin EJ, Graaf Rd, Derks I,**
 2800 **Dewald-Kaufmann J, Elders PM, Gemke RBJ, Grievink L, Hartman CA,**
 2801 **Heijnen CJ, Huisman MA, Huss A, Ikram MA, Jaddoe VWV, Klein**
 2802 **Velderman M, Koning M, Noordam R, Oldehinkel TAJ, Groeniger JO,**
 2803 **Penninx BWJH, Picavet SJ, Reijneveld SA, Reitz E, Renders CM, Rodenburg**
 2804 **G, Rutters F, Singh A, Snijder MB, Stronks K, ten Have M, Twisk JWR, Van**
 2805 **de Mheen D, van der Ende J, van der Heijden KB, van der Velden PG, van**
 2806 **Lenthe F, van Litsenburg RRL, van Oostrom SH, van Schalkwijk FJ, Verheij**
 2807 **R, Verhoeff ME, Verhulst FC, Vermeulen MCM, Vermeulen R, Verschuren**
 2808 **MWM, Vrijkotte TGM, Wijga AH, Willemen AM, Wissink IB, ter Wolbeek**
 2809 **M, Xerxa Y, Franco OH, Bramer WM, Luik AI, Van Someren* E, and**
 2810 **Tiemeier* H.** Sleep characteristics across the lifespan in 1.1 million persons from the
 2811 general population of the Netherlands, UK and USA. A systematic-review and individual
 2812 participant meta-analysis. *Nat Commun* under review: 2020.
- 2813 210. **Kocevska D, Meinderts S, Verhoeff ME, Luijk MP, Verhulst FC, and Tiemeier**
 2814 **H.** Prenatal and early infant brain development is related to childhood sleep patterns.
 2815 The generation R study. *Sleep* 40: A349-A349, 2017.
- 2816 211. **Kocevska D, Muetzel RL, Luik AI, Luijk MPCM, Jaddoe VW, Verhulst FC,**
 2817 **White T, and Tiemeier H.** The developmental course of sleep disturbances across
 2818 childhood relates to brain morphology at age 7: The generation F study. *Sleep* 40:
 2819 zsw022, 2017.
- 2820 212. **Koskenvuo K, Hublin C, Partinen M, Paunio T, and Koskenvuo M.** Childhood
 2821 adversities and quality of sleep in adulthood: A population-based study of 26,000 Finns.
 2822 *Sleep Med* 11: 17-22, 2010.
- 2823 213. **Koubeissi MZ, Bartolomei F, Beltagy A, and Picard F.** Electrical stimulation of a
 2824 small brain area reversibly disrupts consciousness. *Epilepsy & Behavior* 37: 32-35, 2014.
- 2825 214. **Krakov B, Ulibarri VA, Romero EA, and McIver ND.** A two-year prospective
 2826 study on the frequency and co-occurrence of insomnia and sleep-disordered breathing
 2827 symptoms in a primary care population. *Sleep Med* 14: 814-823, 2013.
- 2828 215. **Kringelbach ML.** The human orbitofrontal cortex: linking reward to hedonic
 2829 experience. *Nat Rev Neurosci* 6: 691-702, 2005.

- 2830 216. **Kringelbach ML, and Berridge KC.** Towards a functional neuroanatomy of pleasure
2831 and happiness. *Trends Cogn Sci* 13: 479-487, 2009.
- 2832 217. **Kronholm E, Partonen T, Härmä M, Hublin C, Lallukka T, Peltonen M, and**
2833 **Laatikainen T.** Prevalence of insomnia-related symptoms continues to increase in the
2834 Finnish working-age population. *J Sleep Res* 25: 454-457, 2016.
- 2835 218. **Krueger JM, and Obal F.** A neuronal group theory of sleep function. *J Sleep Res* 2:
2836 63-69, 1993.
- 2837 219. **Krueger JM, Rector DM, Roy S, Van Dongen HP, Belenky G, and Panksepp J.**
2838 Sleep as a fundamental property of neuronal assemblies. *Nat Rev Neurosci* 9: 910-919,
2839 2008.
- 2840 220. **Krystal AD, Edinger JD, Wohlgemuth WK, and Marsh GR.** NREM sleep EEG
2841 frequency spectral correlates of sleep complaints in primary insomnia subtypes. *Sleep*
2842 25: 626-636, 2002.
- 2843 221. **Kyle SD, Beattie L, Spiegelhalder K, Rogers Z, and Espie CA.** Altered emotion
2844 perception in insomnia disorder. *Sleep* 37: 775-783, 2014.
- 2845 222. **Kyle SD, Sexton CE, Feige B, Luik AI, Lane J, Saxena R, Anderson SG,**
2846 **Bechtold DA, Dixon W, Little MA, Ray D, Riemann D, Espie CA, Rutter MK,**
2847 **and Spiegelhalder K.** Sleep and cognitive performance: cross-sectional associations
2848 in the UK Biobank. *Sleep Med* 38: 85-91, 2017.
- 2849 223. **Lack LC, Gradisar M, Van Someren EJW, Wright HR, and Lushington K.** The
2850 relationship between insomnia and body temperatures. *Sleep Med Rev* 12: 307-317,
2851 2008.
- 2852 224. **Lambert G, Johansson M, Ågren H, and Friberg P.** Reduced brain
2853 norepinephrine and dopamine release in treatment-refractory depressive illness:
2854 Evidence in support of the catecholamine hypothesis of mood disorders. *Arch Gen*
2855 *Psychiatry* 57: 787-793, 2000.
- 2856 225. **Lane JM, Liang J, Vlasac I, Anderson SG, Bechtold DA, Bowden J, Emsley R,**
2857 **Gill S, Little MA, Luik AI, Loudon A, Scheer FAJL, Purcell SM, Kyle SD,**
2858 **Lawlor DA, Zhu X, Redline S, Ray DW, Rutter MK, and Saxena R.** Genome-
2859 wide association analyses of sleep disturbance traits identify new loci and highlight
2860 shared genetics with neuropsychiatric and metabolic traits. *Nat Genet* 49: 274-281, 2017.
- 2861 226. **Lane RD, Reiman EM, Bradley MM, Lang PJ, Ahern GL, Davidson RJ, and**
2862 **Schwartz GE.** Neuroanatomical correlates of pleasant and unpleasant emotion.
2863 *Neuropsychologia* 35: 1437-1444, 1997.

- 2864 227. **Lang PJ, Bradley MM, and Cuthbert BN.** *International affective picture system (IAPS):*
 2865 *Affective ratings of pictures and instruction manual. Technical Report A-8.* Gainesville, FL:
 2866 University of Florida, 2008.
- 2867 228. **Lara-Carrasco J, Nielsen TA, Solomonova E, Levrier K, and Popova A.**
 2868 Overnight emotional adaptation to negative stimuli is altered by REM sleep deprivation
 2869 and is correlated with intervening dream emotions. *J Sleep Res* 18: 178-187, 2009.
- 2870 229. **Lecci S, Cataldi J, Betta M, Bernardi G, Heinzer R, and Siclari F.** EEG changes
 2871 associated with subjective under- and overestimation of sleep duration. *Sleep* zsa094,
 2872 2020.
- 2873 230. **LeDoux JE, and Hofmann SG.** The subjective experience of emotion: a fearful view.
 2874 *Curr Opin Behav Sci* 19: 67-72, 2018.
- 2875 231. **Lee Y-JG, Kim S, Kim N, Choi J-W, Park J, Kim SJ, Gwak AR, and Lee YJ.**
 2876 Changes in subcortical resting-state functional connectivity in patients with
 2877 psychophysiological insomnia after cognitive-behavioral therapy. *NeuroImage: Clinical* 17:
 2878 115-123, 2018.
- 2879 232. **Levenson JC, Kay DB, and Buysse DJ.** The Pathophysiology of Insomnia. *Chest* 147:
 2880 1179-1192, 2015.
- 2881 233. **Li C, Ma X, Dong M, Yin Y, Hua K, Li M, Li C, Zhan W, Li C, and Jiang G.**
 2882 Abnormal spontaneous regional brain activity in primary insomnia: a resting-state
 2883 functional magnetic resonance imaging study. *Neuropsychiatr Dis Treat* 12: 1371-1378,
 2884 2016.
- 2885 234. **Li J, Huang C, Lan Y, and Wang Y.** A cross-sectional study on the relationships
 2886 among the polymorphism of period2 gene, work stress, and insomnia. *Sleep Breath* 19:
 2887 1399-1406, 2015.
- 2888 235. **Li L, Wu C, Gan Y, Qu X, and Lu Z.** Insomnia and the risk of depression: a meta-
 2889 analysis of prospective cohort studies. *BMC Psychiatry* 16: 375, 2016.
- 2890 236. **Li S, Tian J, Bauer A, Huang R, Wen H, Li M, Wang T, Xia L, and Jiang G.**
 2891 Reduced integrity of right lateralized white matter in patients with primary insomnia: A
 2892 diffusion-tensor imaging study. *Radiology* 280: 520-528, 2016.
- 2893 237. **Li W, Ma L, Yang G, and Gan WB.** REM sleep selectively prunes and maintains new
 2894 synapses in development and learning. *Nat Neurosci* 20: 427-437, 2017.
- 2895 238. **Lim ASP, Fleischman DA, Dawe RJ, Yu L, Arfanakis K, Buchman AS, and**
 2896 **Bennett DA.** Regional neocortical gray matter structure and sleep fragmentation in
 2897 older adults. *Sleep* 39: 227-235, 2016.
- 2898 239. **Lim J, and Dinges DF.** A meta-analysis of the impact of short-term sleep deprivation
 2899 on cognitive variables. *Psychol Bull* 136: 375-389, 2010.

- 2900 240. **Lind M, and Gehrman P.** Genetic pathways to insomnia. *Brain Sci* 6: 64, 2016.
- 2901 241. **Lind MJ, Aggen SH, Kirkpatrick RM, Kendler KS, and Amstadter AB.** A
- 2902 longitudinal twin study of insomnia symptoms in adults. *Sleep* 38: 1423-1430, 2015.
- 2903 242. **Liu C-H, Guo J, Lu S-L, Tang L-R, Fan J, Wang C-Y, Wang L, Liu Q-Q, and**
- 2904 **Liu C-Z.** Increased salience network activity in patients with insomnia complaints in
- 2905 major depressive disorder. *Front Psychiatry* 9: 2018.
- 2906 243. **Lo JC, Groeger JA, Santhi N, Arbon EL, Lazar AS, Hasan S, von Schantz M,**
- 2907 **Archer SN, and Dijk DJ.** Effects of partial and acute total sleep deprivation on
- 2908 performance across cognitive domains, individuals and circadian phase. *PLoS One* 7:
- 2909 e45987, 2012.
- 2910 244. **Lu F-M, Dai J, Couto TA, Liu C-H, Chen H, Lu S-L, Tang L-R, Tie C-L, Chen**
- 2911 **H-F, He M-X, Xiang Y-T, and Yuan Z.** Diffusion Tensor Imaging tractography
- 2912 reveals disrupted white matter structural connectivity network in healthy adults with
- 2913 insomnia symptoms. *Front Hum Neurosci* 11: 583, 2017.
- 2914 245. **Luppi P-H, Billwiller F, and Fort P.** Selective activation of a few limbic structures
- 2915 during paradoxical (REM) sleep by the claustrum and the supramammillary nucleus:
- 2916 evidence and function. *Curr Opin Neurobiol* 44: 59-64, 2017.
- 2917 246. **Madan V, Brennan F, Mann G, Horbal A, Dunn G, Ross R, and Morrison A.**
- 2918 Long-term effect of cued fear conditioning on REM sleep microarchitecture in rats.
- 2919 *Sleep* 31: 497-503, 2008.
- 2920 247. **Manber R, Edinger JD, Gress JL, San Pedro-Salcedo MG, Kuo TF, and Kalista**
- 2921 **T.** Cognitive behavioral therapy for insomnia enhances depression outcome in patients
- 2922 with comorbid major depressive disorder and insomnia. *Sleep* 31: 489-495, 2008.
- 2923 248. **Manconi M, Ferri R, Sagrada C, Punjabi NM, Tettamanzi E, Zucconi M,**
- 2924 **Oldani A, Castronovo V, and Ferini-Strambi L.** Measuring the error in sleep
- 2925 estimation in normal subjects and in patients with insomnia. *J Sleep Res* 19: 478-486,
- 2926 2010.
- 2927 249. **Mantua J, Helms SM, Weymann KB, Capaldi VF, and Lim MM.** Sleep quality
- 2928 and emotion regulation interact to predict anxiety in veterans with PTSD. *Behav Neurol*
- 2929 2018: 7940832, 2018.
- 2930 250. **Marino M, Li Y, Rueschman MN, Winkelman JW, Ellenbogen JM, Solet JM,**
- 2931 **Dulin H, Berkman LF, and Buxton OM.** Measuring sleep: accuracy, sensitivity, and
- 2932 specificity of wrist actigraphy compared to polysomnography. *Sleep* 36: 1747-1755, 2013.
- 2933 251. **Martinelli P, Sperduti M, and Piolino P.** Neural substrates of the self - memory
- 2934 system: New insights from a meta - analysis. *Hum Brain Mapp* 34: 1515-1529, 2012.

- 2935 252. **McCall WV, Pillai A, Case D, McCloud L, Nolla T, Branch F, Youssef NA,**
 2936 **Moraczewski J, Tauhidul L, Pandya CD, and Rosenquist PB.** A pilot,
 2937 randomized clinical trial of bedtime doses of prazosin versus placebo in suicidal
 2938 posttraumatic stress disorder patients with nightmares. *J Clin Psychopharmacol* 38: 618-
 2939 621, 2018.
- 2940 253. **McCarley RW, and Hobson JA.** Neuronal excitability modulation over the sleep
 2941 cycle: A structural and mathematical model. *Science* 189: 58-60, 1975.
- 2942 254. **McDowell KA, Shin D, Roos KP, and Chesselet M-F.** Sleep dysfunction and EEG
 2943 alterations in mice overexpressing alpha-synuclein. *J Parkinson's Dis* 4: 531-539, 2014.
- 2944 255. **McGaugh JL.** Emotional arousal regulation of memory consolidation. *Curr Opin Behav*
 2945 *Sci* 19: 55-60, 2018.
- 2946 256. **McKenna JT, Gamble MC, Anderson-Chernishof MB, Shah SR, McCoy JG,**
 2947 **and Strecker RE.** A rodent cage change insomnia model disrupts memory
 2948 consolidation. *J Sleep Res* 28: e12792, 2019.
- 2949 257. **Meaney MJ.** Epigenetics and the biological definition of gene $\times$ environment
 2950 interactions. *Child Dev* 81: 41-79, 2010.
- 2951 258. **Means MK, Edinger JD, Glenn DM, and Fins AI.** Accuracy of sleep perceptions
 2952 among insomnia sufferers and normal sleepers. *Sleep Med* 4: 285-296, 2003.
- 2953 259. **Mellman TA, Bustamante V, Fins AI, Pigeon WR, and Nolan B.** REM sleep and
 2954 the early development of posttraumatic stress disorder. *Am J Psychiatry* 159: 1696-1701,
 2955 2002.
- 2956 260. **Mellman TA, Pigeon WR, Nowell PD, and Nolan B.** Relationships between REM
 2957 sleep findings and PTSD symptoms during the early aftermath of trauma. *J Trauma Stress*
 2958 20: 893-901, 2007.
- 2959 261. **Mendelson WB, James SP, Garnett D, Sack DA, and Rosenthal NE.** A
 2960 psychophysiological study of insomnia. *Psychiatry Res* 19: 267-284, 1986.
- 2961 262. **Mendes MS, and dos Santos JM.** Insomnia as an expression of obstructive sleep
 2962 apnea syndrome – the effect of treatment with nocturnal ventilatory support. *Revista*
 2963 *Portuguesa de Pneumologia (English Edition)* 21: 203-208, 2015.
- 2964 263. **Menon V, and Levitin DJ.** The rewards of music listening: Response and physiological
 2965 connectivity of the mesolimbic system. *NeuroImage* 28: 175-184, 2005.
- 2966 264. **Merica H, Blois R, and Gaillard JM.** Spectral characteristics of sleep EEG in chronic
 2967 insomnia. *Eur J Neurosci* 10: 1826-1834, 1998.
- 2968 265. **Mitchell C, Schnepfer LM, and Notterman DA.** DNA methylation, early life
 2969 environment, and health outcomes. *Pediatr Res* 79: 212-219, 2016.

- 2970 266. **Mitchell HA, and Weinshenker D.** Good night and good luck: Norepinephrine in
2971 sleep pharmacology. *Biochem Pharmacol* 79: 801-809, 2010.
- 2972 267. **Modell S, Ising M, Holsboer F, and Lauer CJ.** The Munich vulnerability study on
2973 affective disorders: Premorbid polysomnographic profile of affected high-risk probands.
2974 *Biol Psychiatry* 58: 694-699, 2005.
- 2975 268. **Mong JA, and Cusmano DM.** Sex differences in sleep: impact of biological sex and
2976 sex steroids. *Philos T R Soc B* 371: 20150110, 2016.
- 2977 269. **Moore IVH, Winkelmann J, Lin L, Finn L, Peppard P, and Mignot E.** Periodic
2978 Leg Movements during Sleep are associated with polymorphisms in BTBD9,
2979 TOX3/BC034767, MEIS1, MAP2K5/SKOR1, and PTPRD. *Sleep* 37: 1535-1542, 2014.
- 2980 270. **Morin CM, Belleville G, Belanger L, and Ivers H.** The insomnia severity index:
2981 psychometric indicators to detect insomnia cases and evaluate treatment response.
2982 *Sleep* 34: 601-608, 2011.
- 2983 271. **Morin CM, Drake CL, Harvey AG, Krystal AD, Manber R, Riemann D, and**
2984 **Spiegelhalder K.** Insomnia disorder. *Nat Rev Dis Primers* 15026, 2015.
- 2985 272. **Morin CM, LeBlanc M, Daley M, Gregoire JP, and Merette C.** Epidemiology of
2986 insomnia: prevalence, self-help treatments, consultations, and determinants of help-
2987 seeking behaviors. *Sleep Med* 7: 123-130, 2006.
- 2988 273. **Morphy H, Dunn KM, Lewis M, Boardman HF, and Croft PR.** Epidemiology of
2989 insomnia: a longitudinal study in a UK population. *Sleep* 30: 274-280, 2007.
- 2990 274. **Nano M-M, Fonseca P, Vullings R, and Aarts RM.** Measures of cardiovascular
2991 autonomic activity in insomnia disorder: A systematic review. *PLOS ONE* 12: e0186716,
2992 2017.
- 2993 275. **Natale V, Léger D, Martoni M, Bayon V, and Erbacci A.** The role of actigraphy
2994 in the assessment of primary insomnia: a retrospective study. *Sleep Med* 15: 111-115,
2995 2014.
- 2996 276. **Natale V, Plazzi G, and Martoni M.** Actigraphy in the assessment of insomnia: a
2997 quantitative approach. *Sleep* 32: 767-771, 2009.
- 2998 277. **National Institutes of Health.** State of the Science Conference statement on
2999 Manifestations and Management of Chronic Insomnia in Adults, June 13-15, 2005. *Sleep*
3000 28: 1049-1057, 2005.
- 3001 278. **Neckelmann D, Mykletun A, and Dahl AA.** Chronic insomnia as a risk factor for
3002 developing anxiety and depression. *Sleep* 30: 873-880, 2007.
- 3003 279. **Negele A, Kaufhold J, Kallenbach L, and Leuzinger-Bohleber M.** Childhood
3004 trauma and its relation to chronic depression in adulthood. *Depression Research and*
3005 *Treatment* 2015: 11, 2015.

- 3006 280. **Neu D, Mairesse O, Verbanck P, and Le Bon O.** Slow wave sleep in the
3007 chronically fatigued: Power spectra distribution patterns in chronic fatigue syndrome
3008 and primary insomnia. *Clin Neurophysiol* 126: 1926-1933, 2015.
- 3009 281. **Ng C-L.** The relationships between insomnia & depression. *J Family Med Community*
3010 *Health* 2: 1027, 2015.
- 3011 282. **Nir Y, Staba RJ, Andrillon T, Vyazovskiy VV, Cirelli C, Fried I, and Tononi G.**
3012 Regional slow waves and spindles in human sleep. *Neuron* 70: 153-169, 2011.
- 3013 283. **Nissen C, Kloepper C, Feige B, Piosczyk H, Spiegelhalder K, Voderholzer U,**
3014 **and Riemann D.** Sleep-related memory consolidation in primary insomnia. *J Sleep Res*
3015 20: 129-136, 2010.
- 3016 284. **Nissen C, Kloepper C, Nofzinger EA, Feige B, Voderholzer U, and Riemann**
3017 **D.** Impaired sleep-related memory consolidation in primary insomnia--a pilot study.
3018 *Sleep* 29: 1068-1073, 2006.
- 3019 285. **Nofzinger EA, Buysse DJ, Germain A, Price JC, Miewald JM, and Kupfer DJ.**
3020 Functional neuroimaging evidence for hyperarousal in insomnia. *Am J Psychiatry* 161:
3021 2126-2128, 2004.
- 3022 286. **Non AL, Hollister BM, Humphreys KL, Childebayeva A, Esteves K, Zeanah**
3023 **CH, Fox NA, Nelson CA, and Drury SS.** DNA methylation at stress-related genes
3024 is associated with exposure to early life institutionalization. *American Journal of Physical*
3025 *Anthropology* 161: 84-93, 2016.
- 3026 287. **O'Dell TJ, Connor SA, Guglietta R, and Nguyen PV.** β -Adrenergic receptor
3027 signaling and modulation of long-term potentiation in the mammalian hippocampus.
3028 *Learn Mem* 22: 461-471, 2015.
- 3029 288. **Ochsner KN, Ray RD, Cooper JC, Robertson ER, Chopra S, Gabrieli JDE,**
3030 **and Gross JJ.** For better or for worse: neural systems supporting the cognitive down-
3031 and up-regulation of negative emotion. *NeuroImage* 23: 483-499, 2004.
- 3032 289. **Ohayon MM.** Epidemiology of insomnia: what we know and what we still need to
3033 learn. *Sleep Med Rev* 6: 97-111, 2002.
- 3034 290. **Ohayon MM.** Prevalence of DSM-IV diagnostic criteria of insomnia: distinguishing
3035 insomnia related to mental disorders from sleep disorders. *J Psychiatr Res* 31: 333-346,
3036 1997.
- 3037 291. **Ohayon MM, and Milesi C.** Artificial outdoor nighttime lights associate with altered
3038 sleep behavior in the American general population. *Sleep* 39: 1311-1320, 2016.
- 3039 292. **Ohayon MM, and Roth T.** What are the contributing factors for insomnia in the
3040 general population? *J Psychosom Res* 51: 745-755, 2001.

- 3041 293. **Ongur D, and Price JL.** The organization of networks within the orbital and medial
3042 prefrontal cortex of rats, monkeys and humans. *Cerebr Cortex* 10: 206-219, 2000.
- 3043 294. **Osgood JM, Finan PH, Hinman SJ, So CJ, and Quartana PJ.** Combat exposure,
3044 post-traumatic stress symptoms, and health-related behaviors: The role of sleep
3045 continuity and duration. *Sleep* 42: zsy257, 2019.
- 3046 295. **Ouellet-Morin I, Wong CCY, Danese A, Pariante CM, Papadopoulos AS, Mill
3047 J, and Arseneault L.** Increased serotonin transporter gene (SERT) DNA methylation
3048 is associated with bullying victimization and blunted cortisol response to stress in
3049 childhood: a longitudinal study of discordant monozygotic twins. *Psychol Med* 43: 1813-
3050 1823, 2013.
- 3051 296. **Paavonen EJ, Saarenpää-Heikkilä O, Pölkki P, Kylliäinen A, Porkka-
3052 Heiskanen T, and Paunio T.** Maternal and paternal sleep during pregnancy in the
3053 Child-sleep birth cohort. *Sleep Med* 29: 47-56, 2017.
- 3054 297. **Pace-Schott EF, Shepherd E, Spencer RM, Marcello M, Tucker M, Propper
3055 RE, and Stickgold R.** Napping promotes inter-session habituation to emotional
3056 stimuli. *Neurobiol Learn Mem* 95: 24-36, 2011.
- 3057 298. **Palagini L, Bruno RM, Gemignani A, Baglioni C, Ghiadoni L, and Riemann D.**
3058 Sleep loss and hypertension: a systematic review. *Curr Pharm Des* 19: 2409-2419, 2013.
- 3059 299. **Palagini L, Drake CL, Gehrman P, Meerlo P, and Riemann D.** Early-life origin of
3060 adult insomnia: does prenatal-early-life stress play a role? *Sleep Med* 16: 446-456, 2015.
- 3061 300. **Pallesen S, Sivertsen B, Nordhus IH, and Bjorvatn B.** A 10-year trend of
3062 insomnia prevalence in the adult Norwegian population. *Sleep Med* 15: 173-179, 2014.
- 3063 301. **Palmer CA, and Alfano CA.** Sleep and emotion regulation: An organizing,
3064 integrative review. *Sleep Med Rev* 31: 6-16, 2017.
- 3065 302. **Papadimitriou GN, Kerkhofs M, Kempenaers C, and Mendlewicz J.** EEG sleep
3066 studies in patients with generalized anxiety disorder. *Psychiatry Res* 26: 183-190, 1988.
- 3067 303. **Parrino L, Ferri R, Bruni O, and Terzano MG.** Cyclic alternating pattern (CAP):
3068 the marker of sleep instability. *Sleep Med Rev* 16: 27-45, 2012.
- 3069 304. **Parrino L, Milioli G, De Paolis F, Grassi A, and Terzano MG.** Paradoxical
3070 insomnia: the role of CAP and arousals in sleep misperception. *Sleep Med* 10: 1139-
3071 1145, 2009.
- 3072 305. **Pawlyk AC, Jha SK, Brennan FX, Morrison AR, and Ross RJ.** A rodent model of
3073 sleep disturbances in posttraumatic stress disorder: The role of context after fear
3074 conditioning. *Biol Psychiatry* 57: 268-277, 2005.
- 3075 306. **Pawlyk AC, Morrison AR, Ross RJ, and Brennan FX.** Stress-induced changes in
3076 sleep in rodents: Models and mechanisms. *Neurosci Biobehav Rev* 32: 99-117, 2008.

- 3077 307. **Payne JD, and Kensinger EA.** Stress, sleep, and the selective consolidation of
3078 emotional memories. *Curr Opin Behav Sci* 19: 36-43, 2018.
- 3079 308. **Pejovic S, and Vgontzas AN.** Neurobiological disturbances in insomnia: Clinical
3080 utility of objective measures of sleep. *Medical Psychiatry* 44: 65-76, 2010.
- 3081 309. **Perlis ML, Giles DE, Mendelson WB, Bootzin RR, and Wyatt JK.**
3082 Psychophysiological insomnia: the behavioural model and a neurocognitive perspective. *J*
3083 *Sleep Res* 6: 179-188, 1997.
- 3084 310. **Perlis ML, Smith MT, Andrews PJ, Orff H, and Giles DE.** Beta/Gamma EEG
3085 activity in patients with primary and secondary insomnia and good sleeper controls.
3086 *Sleep* 24: 110-117, 2001.
- 3087 311. **Perlis ML, Vargas I, Ellis JG, Grandner MA, Morales KH, Gencarelli A,**
3088 **Khader W, Kloss JD, Gooneratne NS, and Thase ME.** The Natural History of
3089 Insomnia: the incidence of acute insomnia and subsequent progression to chronic
3090 insomnia or recovery in good sleeper subjects. *Sleep* zsz299, 2019.
- 3091 312. **Pigeon WR, Bishop TM, and Krueger KM.** Insomnia as a precipitating factor in
3092 new onset mental illness: A systematic review of recent findings. *Curr Psychiatry Rep* 19:
3093 44, 2017.
- 3094 313. **Pigeon WR, and Perlis ML.** Sleep homeostasis in primary insomnia. *Sleep Med Rev*
3095 10: 247-254, 2006.
- 3096 314. **Pillai V, Kalmbach DA, and Ciesla JA.** A meta-analysis of electroencephalographic
3097 sleep in depression: Evidence for genetic biomarkers. *Biol Psychiatry* 70: 912-919, 2011.
- 3098 315. **Pires GN, Andersen ML, Giovenardi M, and Tufik S.** Sleep impairment during
3099 pregnancy: Possible implications on mother–infant relationship. *Med Hypotheses* 75: 578-
3100 582, 2010.
- 3101 316. **Poe GR.** Sleep is for forgetting. *J Neurosci* 37: 464-473, 2017.
- 3102 317. **Poon CYM, and Knight BG.** Impact of childhood parental abuse and neglect on sleep
3103 problems in old age. *J Gerontol B Psychol Sci Soc Sci* 66B: 307-310, 2011.
- 3104 318. **Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkum AA, Greene RW,**
3105 **and McCarley RW.** Adenosine: a mediator of the sleep-inducing effects of prolonged
3106 wakefulness. *Science* 276: 1265-1268, 1997.
- 3107 319. **Ramlee F, Sanborn AN, and Tang NKY.** What sways people's judgment of sleep
3108 quality? A quantitative choice-making study with good and poor sleepers. *Sleep* 40:
3109 zsx091, 2017.
- 3110 320. **Ramsawh HJ, Ancoli-Israel S, Sullivan SG, Hitchcock CA, and Stein MB.**
3111 Neuroticism mediates the relationship between childhood adversity and adult sleep
3112 quality. *Behav Sleep Med* 9: 130-143, 2011.

- 3113 321. **Rao U, McGinty DJ, Shinde A, McCracken JT, and Poland RE.** Prenatal stress is
 3114 associated with depression-related electroencephalographic sleep changes in adult male
 3115 rats: A preliminary report. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*
 3116 23: 929-939, 1999.
- 3117 322. **Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, Shofer J,**
 3118 **O'Connell J, Taylor F, Gross C, Rohde K, and McFall ME.** A parallel group
 3119 placebo controlled study of prazosin for trauma nightmares and sleep disturbance in
 3120 combat veterans with post-traumatic stress disorder. *Biol Psychiatry* 61: 928-934, 2007.
- 3121 323. **Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE,**
 3122 **Dobie DJ, Hoff D, Rein RJ, Straits-Tröster K, Thomas RG, and McFall MM.**
 3123 Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: A
 3124 placebo-controlled study. *Am J Psychiatry* 160: 371-373, 2003.
- 3125 324. **Raymann RJEM, Swaab DF, and Van Someren EJW.** Skin temperature and sleep-
 3126 onset latency: Changes with age and insomnia. *Physiol Behav* 90: 257-266, 2007.
- 3127 325. **Raymann RJEM, and Van Someren EJW.** Diminished capability to recognize the
 3128 optimal temperature for sleep initiation may contribute to poor sleep in elderly people.
 3129 *Sleep* 31: 1301-1309, 2008.
- 3130 326. **Renner MC, Albers EHH, Gutierrez-Castellanos N, Reinders NR, van**
 3131 **Huijstee AN, Xiong H, Lodder TR, and Kessels HW.** Synaptic plasticity through
 3132 activation of GluA3-containing AMPA-receptors. *eLife* 6: e25462, 2017.
- 3133 327. **Renouard L, Billwiller F, Ogawa K, Clement O, Camargo N, Abdelkarim M,**
 3134 **Gay N, Scote-Blachon C, Toure R, Libourel PA, Ravassard P, Salvart D,**
 3135 **Peyron C, Claustrat B, Leger L, Salin P, Malleret G, Fort P, and Luppi PH.**
 3136 The supramammillary nucleus and the claustrum activate the cortex during REM sleep.
 3137 *Sci Adv* 1: e1400177, 2015.
- 3138 328. **Reitey JV, Adam M, Honegger E, Khatami R, Luhmann UF, Jung HH, Berger**
 3139 **W, and Landolt HP.** A functional genetic variation of adenosine deaminase affects the
 3140 duration and intensity of deep sleep in humans. *PNAS* 102: 15676-15681, 2005.
- 3141 329. **Riedner BA, Goldstein MR, Plante DT, Rumble ME, Ferrarelli F, Tononi G,**
 3142 **and Benca RM.** Regional patterns of elevated alpha and high-frequency
 3143 electroencephalographic activity during nonrapid eye movement sleep in chronic
 3144 insomnia: A pilot study. *Sleep* 39: 801-812, 2016.
- 3145 330. **Riemann D, Spiegelhalder K, Nissen C, Hirschner V, Baglioni C, and Feige B.**
 3146 REM sleep instability - A new pathway for insomnia? *Pharmacopsychiatry* 45: 167-176,
 3147 2012.

- 3148 331. **Robinson MR, Wray NR, and Visscher PM.** Explaining additional genetic variation
3149 in complex traits. *Trends Genet* 30: 124-132, 2014.
- 3150 332. **Rolls A, Colas D, Adamantidis A, Carter M, Lanre-Amos T, Heller HC, and**
3151 **de Lecea L.** Optogenetic disruption of sleep continuity impairs memory consolidation.
3152 *PNAS* 108: 13305-13310, 2011.
- 3153 333. **Romeijn N, Raymann RJ, Most E, Te Lindert B, Van Der Meijden WP,**
3154 **Fronczek R, Gomez-Herrero G, and Van Someren EJ.** Sleep, vigilance, and
3155 thermosensitivity. *Pflügers Archiv Eur J Physiol* 463: 169-176, 2012.
- 3156 334. **Rosales-Lagarde A, Armony JL, Del Rio-Portilla Y, Trejo-Martinez D, Conde**
3157 **R, and Corsi-Cabrera M.** Enhanced emotional reactivity after selective REM sleep
3158 deprivation in humans: an fMRI study. *Front Behav Neurosci* 6: 25, 2012.
- 3159 335. **Rosier M, Le Barillier L, Meunier D, El Yacoubi M, Malleret G, and Salin P-A.**
3160 Post-learning paradoxical sleep deprivation impairs reorganization of limbic and cortical
3161 networks associated with consolidation of remote contextual fear memory in mice.
3162 *Sleep* 41: zsy188, 2018.
- 3163 336. **Rusterholz T, Durr R, and Achermann P.** Inter-individual differences in the
3164 dynamics of sleep homeostasis. *Sleep* 33: 491-498, 2010.
- 3165 337. **Saper CB, Cano G, and Scammell TE.** Homeostatic, circadian, and emotional
3166 regulation of sleep. *J Comp Neurol* 493: 92-98, 2005.
- 3167 338. **Sayin A, Kucukyildirim S, Akar T, Bakkaloglu Z, Demircan A, Kurtoglu G,**
3168 **Demirel B, Candansayar S, and Mergen H.** A prospective study of serotonin
3169 transporter gene promoter (5-HTT gene linked polymorphic region) and intron 2
3170 (variable number of tandem repeats) polymorphisms as predictors of trauma response
3171 to mild physical injury. *DNA Cell Biol* 29: 71-77, 2009.
- 3172 339. **Scheer FA, Morris CJ, Garcia JL, Smales C, Kelly EE, Marks J, Malhotra A,**
3173 **and Shea SA.** Repeated melatonin supplementation improves sleep in hypertensive
3174 patients treated with beta-blockers: a randomized controlled trial. *Sleep* 35: 1395-1402,
3175 2012.
- 3176 340. **Schwarz LA, and Luo L.** Organization of the Locus Coeruleus-Norepinephrine
3177 system. *Curr Biol* 25: R1051-R1056, 2015.
- 3178 341. **Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss**
3179 **AL, and Greicius MD.** Dissociable intrinsic connectivity networks for salience
3180 processing and executive control. *J Neurosci* 27: 2349-2356, 2007.
- 3181 342. **Seo J, Pace-Schott EF, Moore KN, Bottary RM, Gazecki S, Milad MR, and**
3182 **Song H.** Delayed fear extinction in individuals with insomnia disorder. *Sleep* 41: 2018.

- 3183 343. **Sexton CE, Storsve AB, Walhovd KB, Johansen-Berg H, and Fjell AM.** Poor
 3184 sleep quality is associated with increased cortical atrophy in community-dwelling adults.
 3185 *Neurol* 83: 967-973, 2014.
- 3186 344. **Sexton CE, Zsoldos E, Filippini N, Griffanti L, Winkler A, Mahmood A, Allan**
 3187 **CL, Topiwala A, Kyle SD, Spiegelhalter K, Singh-Manoux A, Kivimaki M,**
 3188 **Mackay CE, Johansen-Berg H, and Ebmeier KP.** Associations between self-
 3189 reported sleep quality and white matter in community-dwelling older adults: A
 3190 prospective cohort study. *Hum Brain Mapp* 38: 5465-5473, 2017.
- 3191 345. **Seyffert M, Lagisetty P, Landgraf J, Chopra V, Pfeiffer PN, Conte ML, and**
 3192 **Rogers MAM.** Internet-delivered cognitive behavioral therapy to treat insomnia: A
 3193 systematic review and meta-analysis. *PLoS One* 11: e0149139, 2016.
- 3194 346. **Shahid A, Chung SA, Phillipson R, and Shapiro CM.** An approach to long-term
 3195 sedative-hypnotic use. *Nat Sci Sleep* 4: 53-61, 2012.
- 3196 347. **Sharpley AL, and Cowen PJ.** Effect of pharmacologic treatments on the sleep of
 3197 depressed patients. *Biol Psychiatry* 37: 85-98, 1995.
- 3198 348. **Shekleton JA, Rogers NL, and Rajaratnam SM.** Searching for the daytime
 3199 impairments of primary insomnia. *Sleep Med Rev* 14: 47-60, 2010.
- 3200 349. **Shiromani PJ, Overstreet D, Levy D, Goodrich CA, Campbell SS, and Gillin**
 3201 **JC.** Increased REM sleep in rats selectively bred for cholinergic hyperactivity.
 3202 *Neuropsychopharmacol* 1: 127-133, 1988.
- 3203 350. **Siclari F, Larocque JJ, Postle BR, and Tononi G.** Assessing sleep consciousness
 3204 within subjects using a serial awakening paradigm. *Front Psychol* 4: 542, 2013.
- 3205 351. **Sinha SS.** Trauma-induced insomnia: A novel model for trauma and sleep research.
 3206 *Sleep Med Rev* 25: 74-83, 2016.
- 3207 352. **Sloan EP, Maunder RG, Hunter JJ, and Moldofsky H.** Insecure attachment is
 3208 associated with the α -EEG anomaly during sleep. *BioPsychoSocial Medicine* 1: 20, 2007.
- 3209 353. **Smith KS, Mahler SV, Peciña S, and Berridge KC.** Hedonic hotspots: Generating
 3210 sensory pleasure in the brain. In: *Pleasures of the Brain*, edited by Kringelbach ML, and
 3211 Berridge KC. New York: Oxford University Press, 2009, p. 27-49.
- 3212 354. **Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, and**
 3213 **Carden KA.** Use of actigraphy for the evaluation of sleep disorders and circadian
 3214 rhythm sleep-wake disorders: An American Academy of Sleep Medicine clinical practice
 3215 guideline. *J Clin Sleep Med* 14: 1231-1237, 2018.
- 3216 355. **Smith MT, McCrae CS, Cheung J, Martin JL, Harrod CG, Heald JL, and**
 3217 **Carden KA.** Use of actigraphy for the evaluation of sleep disorders and circadian

- 3218 rhythm sleep-wake disorders: An American Academy of Sleep Medicine systematic
3219 review, meta-analysis, and GRADE assessment. *J Clin Sleep Med* 14: 1209-1230, 2018.
- 3220 356. **Song AH, Kucyi A, Napadow V, Brown EN, Loggia ML, and Akeju O.**
3221 Pharmacological modulation of noradrenergic arousal circuitry disrupts functional
3222 connectivity of the locus ceruleus in humans. *J Neurosci* 37: 6938-6945, 2017.
- 3223 357. **Sopp MR, Brueckner AH, Schäfer SK, Lass-Hennemann J, and Michael T.**
3224 REM theta activity predicts re-experiencing symptoms after exposure to a traumatic
3225 film. *Sleep Med* 54: 142-152, 2019.
- 3226 358. **Spiegelhalder K, Regen W, Baglioni C, Nissen C, Riemann D, and Kyle SD.**
3227 Neuroimaging insights into insomnia. *Current Neurology and Neuroscience Reports* 15: 9,
3228 2015.
- 3229 359. **Spiegelhalder K, Regen W, Prem M, Baglioni C, Nissen C, Feige B, Schnell S,**
3230 **Kiselev VG, Hennig J, and Riemann D.** Reduced anterior internal capsule white
3231 matter integrity in primary insomnia. *Hum Brain Mapp* 35: 3431-3438, 2014.
- 3232 360. **Spieler D, Kaffe M, Knauf F, Bessa J, Tena JJ, Giesert F, Schormair B, Tilch E,**
3233 **Lee H, Horsch M, Czamara D, Karbalai N, von Toerne C, Waldenberger M,**
3234 **Gieger C, Lichtner P, Claussnitzer M, Naumann R, Müller-Myhsok B, Torres**
3235 **M, Garrett L, Rozman J, Klingenspor M, Gailus-Durner V, Fuchs H, Hrabě de**
3236 **Angelis M, Beckers J, Hölter SM, Meitinger T, Hauck SM, Laumen H, Wurst**
3237 **W, Casares F, Gómez-Skarmeta JL, and Winkelmann J.** Restless Legs
3238 Syndrome-associated intronic common variant in *Meis1* alters enhancer function in the
3239 developing telencephalon. *Genome Res* 24: 592-603, 2014.
- 3240 361. **Spielman AJ.** Assessment of Insomnia. *Clinical Psychology Reviews* 6: 11-25, 1986.
- 3241 362. **Stålesen Ramfjord L, Hertenstein E, Fehér K, Mikutta C, Schneider CL,**
3242 **Nissen C, and Maier JG.** Local sleep and wakefulness—the concept and its potential
3243 for the understanding and treatment of insomnia disorder. *Somnologie* 2020.
- 3244 363. **Stefansson H, Rye DB, Hicks A, Petursson H, Ingason A, Thorgeirsson TE,**
3245 **Palsson S, Sigmundsson T, Sigurdsson AP, Eiriksdottir I, Soebach E, Bliwise**
3246 **D, Beck JM, Rosen A, Waddy S, Trotti LM, Iranzo A, Thambisetty M,**
3247 **Hardarson GA, Kristjansson K, Gudmundsson LJ, Thorsteinsdottir U, Kong**
3248 **A, Gulcher JR, Gudbjartsson D, and Stefansson K.** A genetic risk factor for
3249 periodic limb movements in sleep. *N Engl J Med* 357: 639-647, 2007.
- 3250 364. **Sterpenich V, Albouy G, Boly M, Vandewalle G, Darsaud A, Balteau E, Dang-**
3251 **Vu TT, Desseilles M, D'Argembeau A, Gais S, Rauchs G, Schabus M,**
3252 **Degueudre C, Luxen A, Collette F, and Maquet P.** Sleep-related hippocampo-
3253 cortical interplay during emotional memory recollection. *PLoS Biology* 5: e282, 2007.

- 3254 365. **Stoffers D, Altena E, van der Werf YD, Sanz-Arigita EJ, Voorn TA, Astill RG,**
 3255 **Strijers RL, Waterman D, and Van Someren EJ.** The caudate: a key node in the
 3256 neuronal network imbalance of insomnia? *Brain* 137: 610-620, 2014.
- 3257 366. **Stoffers D, Moens S, Benjamins J, van Tol M-J, Penninx BWJH, Veltman DJ,**
 3258 **van der Wee NJA, and Van Someren EJW.** Orbitofrontal gray matter relates to
 3259 early morning awakening: a neural correlate of insomnia complaints? *Front Neurol* 3: 105,
 3260 2012.
- 3261 367. **Stoschitzky K, Stoschitzky G, Brussee H, Bonell C, and Dobnig H.** Comparing
 3262 beta-blocking effects of bisoprolol, carvedilol and nebivolol. *Cardiology* 106: 199-206,
 3263 2006.
- 3264 368. **Sullivan PF, Neale MC, and Kendler KS.** Genetic epidemiology of major
 3265 depression: Review and meta-analysis. *Am J Psychiatry* 157: 1552-1562, 2000.
- 3266 369. **Suzuki A, Sinton CM, Greene RW, and Yanagisawa M.** Behavioral and
 3267 biochemical dissociation of arousal and homeostatic sleep need influenced by prior
 3268 wakeful experience in mice. *PNAS* 110: 10288-10293, 2013.
- 3269 370. **Swaab DF, Van Someren EJW, Zhou JN, and Hofman MA.** Biological rhythms in
 3270 the human life cycle and their relationship to functional changes in the suprachiasmatic
 3271 nucleus. *Prog Brain Res* 111: 349-368, 1996.
- 3272 371. **Swift KM, Gross BA, Frazer MA, Bauer DS, Clark KJD, Vazey EM, Aston-**
 3273 **Jones G, Li Y, Pickering AE, Sara SJ, and Poe GR.** Abnormal locus coeruleus
 3274 sleep activity alters sleep signatures of memory consolidation and impairs place cell
 3275 stability and spatial memory. *Curr Biol* 28: 3599-3609.e3594, 2018.
- 3276 372. **Sysoeva YY, and Verbitsky EV.** Influence of the level of trait anxiety on sleep EEG
 3277 of men and women. *Hum Physiol* 39: 655-662, 2013.
- 3278 373. **Tagliazucchi E, and van Someren EJW.** The large-scale functional connectivity
 3279 correlates of consciousness and arousal during the healthy and pathological human sleep
 3280 cycle. *NeuroImage* 160: 55-72, 2017.
- 3281 374. **Tahmasian M, Noori K, Samea F, Zarei M, Spiegelhalder K, Eickhoff SB, Van**
 3282 **Someren E, Khazaie H, and Eickhoff CR.** A lack of consistent brain alterations in
 3283 insomnia disorder: An activation likelihood estimation meta-analysis. *Sleep Med Rev* 42:
 3284 111-118, 2018.
- 3285 375. **Takashima A, Nieuwenhuis IL, Jensen O, Talamini LM, Rijpkema M, and**
 3286 **Fernandez G.** Shift from hippocampal to neocortical centered retrieval network with
 3287 consolidation. *J Neurosci* 29: 10087-10093, 2009.

- 3288 376. **Tang NK, Fiecas M, Afolalu EF, and Wolke D.** Changes in sleep duration, quality,
3289 and medication use are prospectively associated with health and well-being: Analysis of
3290 the uk household longitudinal study. *Sleep* 40: zsw079, 2017.
- 3291 377. **Tang NKY, and Harvey AG.** Altering misperception of sleep in insomnia: Behavioral
3292 experiment versus verbal feedback. *J Consult Clin Psychol* 74: 767-776, 2006.
- 3293 378. **Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C,**
3294 **Peskind ER, and Raskind MA.** Prazosin effects on objective sleep measures and
3295 clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled
3296 study. *Biol Psychiatry* 63: 629-632, 2008.
- 3297 379. **te Lindert BHW, Blanken TF, van der Meijden WP, Dekker K, Wassing R,**
3298 **van der Werf YD, Ramautar JR, and Van Someren EJW.** Actigraphic multi-night
3299 home-recorded sleep estimates reveal three types of sleep misperception in Insomnia
3300 Disorder and good sleepers. *J Sleep Res* 29: e12937, 2020.
- 3301 380. **te Lindert BHW, Itzhacki J, van der Meijden WP, Kringelbach ML, Mendoza**
3302 **J, and Van Someren EJW.** Bright environmental light ameliorates deficient subjective
3303 'liking' in insomnia: an experience sampling study. *Sleep* 41: zsy022, 2018.
- 3304 381. **Te Lindert BHW, Van Der Meijden WP, Wassing R, Lakbila-Kamal O, Wei**
3305 **Y, Van Someren* EJW, and Ramautar* JR.** Optimizing actigraphic estimates of
3306 polysomnography sleep features in Insomnia Disorder. *Sleep* 43: zsa090, 2020.
- 3307 382. **Te Lindert BHW, and Van Someren EJW.** Affordable sleep estimates using micro
3308 electro-mechanical systems (MEMS) accelerometry. *Sleep* 36: 781-789, 2013.
- 3309 383. **Te Lindert BHW, and Van Someren EJW.** Skin temperature, sleep, and vigilance.
3310 In: *Handbook of Clinical Neurology*, edited by Romanovsky AA. San Diego: Elsevier, 2018,
3311 p. 353-365.
- 3312 384. **Te Lindert BHW, Wei Y, van der Meijden WP, Ramautar JR, and Van**
3313 **Someren EJW.** Cognitive and autonomic responses to sleep-permissive conditions in
3314 Insomnia Disorder. under review.
- 3315 385. **Tempesta D, De Gennaro L, Natale V, and Ferrara M.** Emotional memory
3316 processing is influenced by sleep quality. *Sleep Med* 16: 862-870, 2015.
- 3317 386. **Tempesta D, Succi V, De Gennaro L, and Ferrara M.** Sleep and emotional
3318 processing. *Sleep Med Rev* 40: 183-195, 2018.
- 3319 387. **Terzano MG, Parrino L, and Smerieri A.** Neurophysiological basis of insomnia:
3320 role of cyclic alternating patterns. *Rev Neurol (Paris)* 157: S62-66, 2001.
- 3321 388. **Terzano MG, Parrino L, Spaggiari MC, Palomba V, Rossi M, and Smerieri A.**
3322 CAP variables and arousals as sleep electroencephalogram markers for primary
3323 insomnia. *Clin Neurophysiol* 114: 1715-1723, 2003.

- 3324 389. **Thakur GA, Joobar R, and Brunet A.** Development and persistence of
 3325 posttraumatic stress disorder and the 5-HTTLPR polymorphism. *J Trauma Stress* 22:
 3326 240-243, 2009.
- 3327 390. **Thase ME, Buysse DJ, Frank E, Cherry CR, Cornes CL, Mallinger AG, and**
 3328 **Kupfer DJ.** Which depressed patients will respond to interpersonal psychotherapy?
 3329 The role of abnormal EEG sleep profiles. *Am J Psychiatry* 154: 502-509, 1997.
- 3330 391. **Turecki G, and Meaney MJ.** Effects of the social environment and stress on
 3331 glucocorticoid receptor gene methylation: A systematic review. *Biol Psychiatry* 79: 87-96,
 3332 2016.
- 3333 392. **Turek FW.** Insomnia and depression: if it looks and walks like a duck. *Sleep* 28: 1362-
 3334 1363, 2005.
- 3335 393. **Vallieres A, Ivers H, Bastien CH, Beaulieu-Bonneau S, and Morin CM.**
 3336 Variability and predictability in sleep patterns of chronic insomniacs. *J Sleep Res* 14: 447-
 3337 453, 2005.
- 3338 394. **Valomon A, Holst SC, Bachmann V, Viola AU, Schmidt C, Zürcher J, Berger**
 3339 **W, Cajochen C, and Landolt H-P.** Genetic polymorphisms of DAT1 and COMT
 3340 differentially associate with actigraphy-derived sleep–wake cycles in young adults.
 3341 *Chronobiol Int* 31: 705-714, 2014.
- 3342 395. **van Berkel VMT, Bevelander SE, and Mommersteeg PMC.** Placebo-controlled
 3343 comparison of prazosin and cognitive–behavioral treatments for sleep disturbances in
 3344 US Military Veterans. *J Psychosom Res* 73: 153, 2012.
- 3345 396. **van Den Berg JF, van Rooij F, Vos H, Tulen JH, Hofman A, Miedema HM,**
 3346 **Neven AK, and Tiemeier H.** Disagreement between subjective and actigraphic
 3347 measures of sleep duration in a population-based study of elderly persons. *J Sleep Res*
 3348 17: 295-302, 2008.
- 3349 397. **van der Helm E, Yao J, Dutt S, Rao V, Saletin JM, and Walker MP.** REM sleep
 3350 depotentiates amygdala activity to previous emotional experiences. *Curr Biol* 21: 2029-
 3351 2032, 2011.
- 3352 398. **van der Sluis S, Verhage M, Posthuma D, and Dolan CV.** Phenotypic complexity,
 3353 measurement bias, and poor phenotypic resolution contribute to the missing heritability
 3354 problem in genetic association studies. *PLoS One* 5: e13929, 2010.
- 3355 399. **van der Zweerde T, van Straten A, Effting M, Kyle SD, and Lancee J.** Does
 3356 online insomnia treatment reduce depressive symptoms? A randomized controlled trial
 3357 in individuals with both insomnia and depressive symptoms. *Psychol Med* 49: 501-509,
 3358 2018.

- 3359 400. **Van Someren EJW**. Circadian rhythms and sleep in human aging. *Chronobiol Int* 17:
3360 233-243, 2000.
- 3361 401. **Van Someren EJW**. Doing with less sleep remains a dream. *PNAS* 107: 16003-16004,
3362 2010.
- 3363 402. **Van Someren EJW, Vonk BFM, Thijssen W, Speelman JD, Schuurman PR,**
3364 **Mirmiran M, and Swaab DF**. A new actigraph for long-term registration of the
3365 duration and intensity of tremor and movement. *IEEE Trans Biomed Eng* 45: 386-395,
3366 1998.
- 3367 403. **Vanderheyden WM, George SA, Urpa L, Kehoe M, Liberzon I, and Poe GR**.
3368 Sleep alterations following exposure to stress predict fear-associated memory
3369 impairments in a rodent model of PTSD. *Exp Brain Res* 233: 2335-2346, 2015.
- 3370 404. **Vanderheyden WM, Poe GR, and Liberzon I**. Trauma exposure and sleep: using a
3371 rodent model to understand sleep function in PTSD. *Exp Brain Res* 232: 1575-1584,
3372 2014.
- 3373 405. **Varkevisser M, and Kerkhof GA**. Chronic insomnia and performance in a 24-h
3374 constant routine study. *J Sleep Res* 14: 49-59, 2005.
- 3375 406. **Vazey EM, and Aston-Jones G**. Designer receptor manipulations reveal a role of the
3376 locus coeruleus noradrenergic system in isoflurane general anesthesia. *PNAS* 111: 3859-
3377 3864, 2014.
- 3378 407. **Vazey EM, Moorman DE, and Aston-Jones G**. Phasic locus coeruleus activity
3379 regulates cortical encoding of salience information. *PNAS* 115: E9439-E9448, 2018.
- 3380 408. **Vickers A**. The use of percentage change from baseline as an outcome in a controlled
3381 trial is statistically inefficient: A simulation study. *BMC Med Res Methodol* 1: 6, 2001.
- 3382 409. **Villablanca JR, Marcus RJ, and Olmstead CE**. Effects of caudate nuclei or frontal
3383 cortex ablations in cats. II. Sleep-wakefulness, EEG, and motor activity. *Exp Neurol* 53:
3384 31-50, 1976.
- 3385 410. **Vogel GW, Thurmond A, Gibbons P, Sloan K, and Walker M**. REM sleep
3386 reduction effects on depression syndromes. *Arch Gen Psychiatry* 32: 765-777, 1975.
- 3387 411. **Vogel GW, Vogel F, McAbee RS, and Thurmond AJ**. Improvement of depression
3388 by REM sleep deprivation. New findings and a theory. *Arch Gen Psychiatry* 37: 247-253,
3389 1980.
- 3390 412. **Vukasović T, and Bratko D**. Heritability of personality: A meta-analysis of behavior
3391 genetic studies. *Psychol Bull* 141: 769-785, 2015.
- 3392 413. **Vyazovskiy VV, Olcese U, Hanlon EC, Nir Y, Cirelli C, and Tononi G**. Local
3393 sleep in awake rats. *Nature* 472: 443-447, 2011.

- 3394 414. **Wagner U, Fischer S, and Born J.** Changes in emotional responses to aversive
3395 pictures across periods rich in slow-wave sleep versus rapid eye movement sleep.
3396 *Psychosom Med* 64: 627-634, 2002.
- 3397 415. **Wagner U, Hallschmid M, Rasch B, and Born J.** Brief sleep after learning keeps
3398 emotional memories alive for years. *Biol Psychiatry* 60: 788-790, 2006.
- 3399 416. **Walker MP, and van der Helm E.** Overnight therapy? The role of sleep in
3400 emotional brain processing. *Psychol Bull* 135: 731-748, 2009.
- 3401 417. **Walsh K, Uddin M, Soliven R, Wildman DE, and Bradley B.** Associations
3402 between the SS variant of 5-HTTLPR and PTSD among adults with histories of
3403 childhood emotional abuse: Results from two African American independent samples. *J*
3404 *Affect Disord* 161: 91-96, 2014.
- 3405 418. **Wang C, Ong JL, Patanaik A, Zhou J, and Chee MWL.** Spontaneous eyelid
3406 closures link vigilance fluctuation with fMRI dynamic connectivity states. *PNAS* 113:
3407 9653-9658, 2016.
- 3408 419. **Wang CC, and Lung FW.** The role of PGC-1 and Apoepsilon4 in insomnia. *Psychiatr*
3409 *Genet* 22: 82-87, 2012.
- 3410 420. **Wang HE, Campbell-Sills L, Kessler RC, Sun X, Heeringa SG, Nock MK,**
3411 **Ursano RJ, Jain S, and Stein MB.** Pre-deployment insomnia is associated with post-
3412 deployment PTSD and suicidal ideation in US army soldiers. *Sleep* zsy229, 2018.
- 3413 421. **Wang Y, Raffeld MR, Slopen N, Hale L, and Dunn EC.** Childhood adversity and
3414 insomnia in adolescence. *Sleep Med* 21: 12-18, 2016.
- 3415 422. **Warland J, Dorrian J, Morrison JL, and O'Brien LM.** Maternal sleep during
3416 pregnancy and poor fetal outcomes: A scoping review of the literature with meta-
3417 analysis. *Sleep Med Rev* 41: 197-219, 2018.
- 3418 423. **Wassing R, Benjamins J, Schalkwijk F, and Van Someren EJW.** Overnight
3419 worsening of emotional distress indicates maladaptive sleep in insomnia. *Sleep* 42:
3420 zsy268, 2019.
- 3421 424. **Wassing R, Benjamins JS, Dekker K, Moens S, Spiegelhalder K, Feige B,**
3422 **Riemann D, van der Sluis S, Van Der Werf YD, Talamini LM, Walker MP,**
3423 **Schalkwijk F, and Van Someren EJW.** Slow dissolving of emotional distress
3424 contributes to hyperarousal. *PNAS* 113: 2538-2543, 2016.
- 3425 425. **Wassing R, Lakbila-Kamal O, Ramautar JR, Stoffers D, Schalkwijk F, and Van**
3426 **Someren EJW.** Restless REM sleep impedes overnight amygdala adaptation. *Curr Biol*
3427 29: 2351-2358.e2354, 2019.

- 3428 426. **Wassing R, Schalkwijk F, Kamal O, Ramautar J, Stoffers D, Mutsaerts H-J,**
3429 **Talamini LM, and Van Someren EJW.** Haunted by the past: old emotions remain
3430 salient in insomnia disorder. *Brain* 142: 1783–1796, 2019.
- 3431 427. **Watkins LE, Han S, Harpaz-Rotem I, Mota NP, Southwick SM, Krystal JH,**
3432 **Gelernter J, and Pietrzak RH.** FKBP5 polymorphisms, childhood abuse, and PTSD
3433 symptoms: Results from the National Health and Resilience in Veterans Study.
3434 *Psychoneuroendocrinology* 69: 98-105, 2016.
- 3435 428. **Weber M, Webb CA, Deldonno SR, Kipman M, Schwab ZJ, Weiner MR, and**
3436 **Killgore WD.** Habitual 'sleep credit' is associated with greater grey matter volume of
3437 the medial prefrontal cortex, higher emotional intelligence and better mental health. *J*
3438 *Sleep Res* 22: 527-534, 2013.
- 3439 429. **Wei Y, Bresser T, Wassing R, Stoffers D, Van Someren* EJW, and Foster-**
3440 **Dingley* JC.** Brain structural connectivity network alterations in insomnia disorder
3441 reveal a central role of the right angular gyrus. *NeuroImage: Clinical* 24: 102019, 2019.
- 3442 430. **Wei Y, Colombo MA, Ramautar JR, Blanken TF, van der Werf YD,**
3443 **Spiegelhalder K, Feige B, Riemann D, and Van Someren EJW.** Sleep stage
3444 transition dynamics reveal specific stage 2 vulnerability in insomnia. *Sleep* 40: zsx117,
3445 2017.
- 3446 431. **Wei Y, Leerssen J, Wassing R, Stoffers D, Perrier J, and Van Someren EJW.**
3447 Reduced dynamic functional connectivity between salience and executive brain
3448 networks in insomnia disorder. *J Sleep Res* 29: e12953, 2020.
- 3449 432. **Wei Y, Ramautar JR, Colombo MA, Stoffers D, Gomez-Herrero G, van der**
3450 **Meijden WP, Te Lindert BH, van der Werf YD, and Van Someren EJ.** I keep a
3451 close watch on this heart of mine: Increased interoception in insomnia. *Sleep* 39: 2113-
3452 2124, 2016.
- 3453 433. **Wei Y, Ramautar JR, Colombo MA, te Lindert BHW, and Van Someren**
3454 **EJW.** EEG microstates indicate heightened somatic awareness in insomnia: Toward
3455 objective assessment of subjective mental content. *Front Psychiatry* 9: 395, 2018.
- 3456 434. **Wickwire EM, and Collop NA.** Insomnia and sleep-related breathing disorders.
3457 *Chest* 137: 1449-1463, 2010.
- 3458 435. **Wilson SJ, Nutt DJ, Alford C, Argyropoulos SV, Baldwin DS, Bateson AN,**
3459 **Britton TC, Crowe C, Dijk DJ, Espie CA, Gringras P, Hajak G, Idzikowski C,**
3460 **Krystal AD, Nash JR, Selsick H, Sharpley AL, and Wade AG.** British
3461 Association for Psychopharmacology consensus statement on evidence-based treatment
3462 of insomnia, parasomnias and circadian rhythm disorders. *J Psychopharmacol* 24: 1577-
3463 1601, 2010.

- 3464 436. **Winkelman JW, Plante DT, Schoerning L, Benson K, Buxton OM, O'Connor**
3465 **SP, Jensen JE, Renshaw PF, and Gonenc A.** Increased rostral anterior cingulate
3466 cortex volume in chronic primary insomnia. *Sleep* 36: 991-998, 2013.
- 3467 437. **Winkelmann J, Czamara D, Schormair B, Knauf F, Schulte EC, Trenkwalder**
3468 **C, Dauvilliers Y, Polo O, Högl B, Berger K, Fuhs A, Gross N, Stiasny-Kolster**
3469 **K, Oertel W, Bachmann CG, Paulus W, Xiong L, Montplaisir J, Rouleau GA,**
3470 **Fietze I, Vávrová J, Kemlink D, Sonka K, Nevsimalova S, Lin S-C, Wszolek Z,**
3471 **Vilariño-Güell C, Farrer MJ, Gschliesser V, Frauscher B, Falkenstetter T,**
3472 **Poewe W, Allen RP, Earley CJ, Ondo WG, Le W-D, Spieler D, Kaffe M,**
3473 **Zimprich A, Kettunen J, Perola M, Silander K, Cournu-Rebeix I, Francavilla**
3474 **M, Fontenille C, Fontaine B, Vodicka P, Prokisch H, Lichtner P, Peppard P,**
3475 **Faraco J, Mignot E, Gieger C, Illig T, Wichmann HE, Müller-Myhsok B, and**
3476 **Meitinger T.** Genome-wide association study identifies novel restless legs syndrome
3477 susceptibility loci on 2p14 and 16q12.1. *PLoS Genet* 7: e1002171, 2011.
- 3478 438. **Winkelmann J, Schormair B, Lichtner P, Ripke S, Xiong L, Jalilzadeh S,**
3479 **Fulda S, Pütz B, Eckstein G, Hauk S, Trenkwalder C, Zimprich A, Stiasny-**
3480 **Kolster K, Oertel W, Bachmann CG, Paulus W, Peglau I, Eisensehr I,**
3481 **Montplaisir J, Turecki G, Rouleau G, Gieger C, Illig T, Wichmann HE,**
3482 **Holsboer F, Müller-Myhsok B, and Meitinger T.** Genome-wide association study
3483 of restless legs syndrome identifies common variants in three genomic regions. *Nat*
3484 *Genet* 39: 1000-1006, 2007.
- 3485 439. **Wisłowska M, Heib DPJ, Griessenberger H, Hoedlmoser K, and Schabus M.**
3486 Individual baseline memory performance and its significance for sleep-dependent
3487 memory consolidation. *Sleep Spindles & Cortical Up States* 1: 2-13, 2017.
- 3488 440. **Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jonsson B,**
3489 **Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jenum P, Lieb R,**
3490 **Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, and**
3491 **Steinhausen HC.** The size and burden of mental disorders and other disorders of the
3492 brain in Europe 2010. *Eur Neuropsychopharmacol* 21: 655-679, 2011.
- 3493 441. **Wong M-L, Kling MA, Munson PJ, Listwak S, Licinio J, Prolo P, Karp B,**
3494 **McCutcheon IE, Geraciotti TD, DeBellis MD, Rice KC, Goldstein DS,**
3495 **Veldhuis JD, Chrousos GP, Oldfield EH, McCann SM, and Gold PW.**
3496 Pronounced and sustained central hypernoradrenergic function in major depression
3497 with melancholic features: Relation to hypercortisolism and corticotropin-releasing
3498 hormone. *PNAS* 97: 325-330, 2000.

- 3499 442. **Wray NR, Yang J, Hayes BJ, Price AL, Goddard ME, and Visscher PM.** Pitfalls
3500 of predicting complex traits from SNPs. *Nat Rev Genetics* 14: 507-515, 2013.
- 3501 443. **Wright MOD, Crawford E, and Del Castillo D.** Childhood emotional
3502 maltreatment and later psychological distress among college students: The mediating
3503 role of maladaptive schemas. *Child Abuse Negl* 33: 59-68, 2009.
- 3504 444. **Wu Y, Liu M, Zeng S, Ma X, Yan J, Lin C, Xu G, Li G, Yin Y, Fu S, Hua K, Li
3505 C, Wang T, Li C, and Jiang G.** Abnormal topology of the structural connectome in
3506 the limbic cortico-basal-ganglia circuit and default-mode network among primary
3507 insomnia patients. *Front Neurosci* 12: 860, 2018.
- 3508 445. **Wu YM, Pietrone R, Cashmere JD, Begley A, Miewald JM, Germain A, and
3509 Buysse DJ.** EEG power during waking and NREM sleep in primary insomnia. *J Clin Sleep
3510 Med* 9: 1031-1037, 2013.
- 3511 446. **Yaffe K, Falvey CM, and Hoang T.** Connections between sleep and cognition in
3512 older adults. *Lancet Neurol* 13: 1017-1028, 2014.
- 3513 447. **Yilmaz MB, Erdem A, Yalta K, Turgut OO, Yilmaz A, and Tandogan I.** Impact
3514 of beta-blockers on sleep in patients with mild hypertension: a randomized trial
3515 between nebivolol and metoprolol. *Adv Ther* 25: 871-883, 2008.
- 3516 448. **Yu S, Feng F, Zhang Q, Shen Z, Wang Z, Hu Y, and Gong L.** Gray matter
3517 hypertrophy in primary insomnia: a surface-based morphometric study. *Brain Imaging
3518 Behav* 2018.
- 3519 449. **Zhang B, and Wing YK.** Sex differences in insomnia: a meta-analysis. *Sleep* 29: 85-93,
3520 2006.
- 3521 450. **Zhang J, Chan NY, Lam SP, Li SX, Liu Y, Chan JWY, Kong APS, Ma RCW,
3522 Chan KCC, Li AM, and Wing Y-K.** Emergence of sex differences in insomnia
3523 symptoms in adolescents: A large-scale school-based study. *Sleep* 39: 1563-1570, 2016.
- 3524 451. **Zhou Y, Cao Z, Yang M, Xi X, Guo Y, Fang M, Cheng L, and Du Y.** Comorbid
3525 generalized anxiety disorder and its association with quality of life in patients with major
3526 depressive disorder. *Sci Rep* 7: 40511, 2017.
- 3527 452. **Ziv-Gal A, Flaws JA, Mahoney MM, Miller SR, Zacur HA, and Gallicchio L.**
3528 Genetic polymorphisms in the aryl hydrocarbon receptor-signaling pathway and sleep
3529 disturbances in middle-aged women. *Sleep Med* 14: 883-887, 2013.
- 3530
- 3531

Sleep EEG (20 sec) → Polysomnogram (PSG, hrs)

Awake – low voltage – random, fast

Drowsy – 8 to 12 cps – alpha waves

Stage 1 – 3 to 7 cps – theta waves

Stage 2 – 12 to 14 cps – sleep spindles and K complex

Delta Sleep – 1/2 to 2 cps – delta waves > 75µV

Arousal

Wake

REM

N1

N2

N3

Normal sleep

Insomnia

Polysomnographic Characteristics of Primary Insomnia

Sleep variable

Std diff in means and 95% CI

Sleep efficiency index ($p < 0.01$)

Sleep onset latency ($p = 0.02$)

Total sleep time ($p < 0.01$)

Total time in bed ($p = \text{n.s.}$)

Number of awakenings ($p < 0.01$)

REM latency ($p = \text{n.s.}$)

Stage 1 sleep ($p = \text{n.s.}$)

Stage 2 sleep ($p = \text{n.s.}$)

Slow wave sleep, % ($p = 0.01$)

REM sleep, % ($p = 0.01$)

Wake, % ($p = 0.01$)

A **B**

Tissue gene-sets

Cell type gene-sets

Brain areas:

- Claustrum
- Thalamus
- Striatum: Putamen/Caudate nucleus
- Striatum: Nucleus accumbens
- Hypothalamus
- Globus Pallidus
- Cortex

Cell types:

- Medium spiny neuron
- Claustrum neuron
- Hypothalamic neuron

- +
 -
 - ↔
- Excitatory
Inhibitory
Synaps

A

B

C

Emotional experience

Overnight regulation of emotions...

Next day re-exposure

Risks

Genes

Early Life Stress

Observed

Restless
sleep

Diagnosis

Early life: no clinical
symptoms yet

Insufficient
dissolving of
emotional
distress

Hyperarousal,
Insomnia

Stuck emotions

PTSD, Anxiety,
Depression

New emotional
experience

Memory processing
during sleep

Years later recalled
emotional experience

Long-term
risk

Normal
sleep

Normal
mental
health

Limbic response
ANS activation

Insomnia

Risk of
mental
illness