# Brain mechanisms of insomnia: new perspectives on causes and consequences

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## Abstract

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

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## Introduction, aims and outline

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

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

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

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

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

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

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

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

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

## 1. Definition and prevalence

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

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

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

developed chronic insomnia that met diagnostic criteria (311). Prevalence estimates vary depending on age, assessment tools and criteria applied. With the stringent DSM-IV diagnostic criteria, point prevalence estimates in a large sample remain approximately 6% (290), while a recent cross-cultural and comparative epidemiological study reported that 10.8% fulfilled DSM5 criteria for insomnia disorder (86), and in a recent meta-analysis the pooled prevalence of insomnia in China was 15.0% (69). All in all, insomnia seems the second-most common mental disorder, with a 12-month prevalence in-between the most prevalent combined anxiety disorders and, closely following insomnia, major depressive disorder (440).

For several reasons, it may surprise many that ID is the second-most common neuropsychiatric disorder. First, the prevalence of insomnia disorder had been increasing over the last decades. Calem et al. reported that the prevalence of insomnia disorder nearly doubled across 15 years (67), and the increasing prevalence is supported by other longitudinal studies (131, 138, 217, 300). Second, many integrative studies on mental disorders just ignore that insomnia is part and parcel of the DSM diagnostic nosology and do not include it (137). Based on the only large integrative study that used identical methods to evaluate the 12-month prevalence across different mental disorders, the different anxiety disorders aggregated rank #1 (14%), insomnia ranks #2 (7%), and unipolar depression ranks #3 (6.9%) . The estimate of a 12-month prevalence of insomnia of 7% is even likely to be underestimated because in many patients, the diagnosis is not noticed in consultation by a general practitioner (170, 272, 289, 292). Indeed, the prevalence rates about double if population-based studies include active diagnosis according to the DSM rather than relying on filed medical dossiers of diagnoses (300, 449).

Insomnia constitutes a dramatic and wide-ranging socioeconomic burden - tens of billions in the U.S. alone (81, 201), not only due to health-care expenses, but also due to decreased

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

## Sex differences in prevalence

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

Across sex and age, difficulty maintaining sleep is never as prevalent as in girls during puberty (28%) (209). The phase of the diurnal rhythm in estradiol varies across the menstrual cycle (24) and sleep complaints are worst during the mid-luteal phase of the menstrual cycle, when ovarian steroid levels have commenced to decline. Women sleep later relative to the internal phase of their diurnal hormone rhythms than men do, which could contribute to their increased risk of insomnia symptoms (268). It is notable that women with major depression have a very late relative sleep timing, because of their much advanced diurnal estradiol rhythm (23): this might contribute to their insomnia symptoms. The increased sensitivity of structures involved in sleep and circadian regulation to sex steroid fluctuations in females could also contribute to their increased risk of insomnia 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 ($CRF_1$) 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

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

More recent work however also indicates that insomnia symptoms already strongly emerge during puberty. As is the case for adults, more so in girls than in boys. A study that followed pubertal development between Tanner stage 1 to 5, reported that the prevalence of insomnia symptoms increased 3.6-fold in girls and 2.1-fold in boys (450). A recent individual participant meta-analysis of insomnia symptoms across life-span in 200,358 people from the general population reported that difficulty maintaining sleep peaked at 23% of the participants in the age category of 14 to 17 years, difficulty initiating peaked at 23% at 18 to 25 years, while early morning awakening peaked only late in life, at 24% in participants older than 65 years of age (209).

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

## II. Nighttime Characteristics of insomnia

This section addresses subjective sleep complaints and objective sleep assessment.

### Subjectively experienced sleep

The diagnosis of ID is strictly based on subjective sleep complaints and doesn't include objective sleep criteria. By definition, people suffering from ID experience difficulties initiating or maintaining sleep and returning to sleep after waking up. It is not that surprising therefore that they remember their nights as filled with thoughts and rumination (248). Interestingly, also during actual sleep in good sleepers, mental content may be more common than once thought, and not specific to REM sleep. Foulkes (133) recognized that awakenings from all sleep stages elicit reports of mental activity if more liberal criteria are applied, instead of specifically asking about 'dreams'. Recent enforced awakening studies showed that even normal sleepers report to have experienced mental activity in two out of three awakenings from NREM sleep (350). This contrasts strongly from the blank slate feeling good sleepers have when waking up in the morning, except possibly for recall of some dreams. Apparently, much from what goes on in the mind during NREM sleep is not consolidated in memory in a way that can be accessed in the morning. It would be interesting to evaluate the hypothesis that people with insomnia might consolidate ongoing mental content during NREM sleep better, and thus wake up in the morning with a head full of memories of thoughts and ruminations. Enhanced memory of thought-like nocturnal mentation during sleep (220) can be hypothesized to be involved in the underestimation of time asleep that is characteristic for many people with insomnia (248).

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

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

## Objectively recorded sleep

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

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

425 other work of this group. These arousals especially fragment REM sleep (123, 330) although
426 they are certainly present throughout NREM sleep as well (330). Markovian sleep stage
427 transition dynamics show that the instability of sleep also shows in an increased propensity
428 to switch to less deep sleep states, which makes it difficult to reach N3 (430). As shown in
429 **Figure 3. "Increased probability to transition to a less deep sleep stage"**, once N3
430 is reached, the sleep of people with insomnia is considerable more like that of normal
431 sleepers, without a significantly increased probability to switch to a less deep sleep state or
432 other classical indicators of instability (304, 430). However, recent novel data-driven analysis
433 techniques could reveal that the sleep EEG of people with ID shows signatures of
434 simultaneous superficial sleep even during the deepest sleep state (85).
435
436 Instability and wake-like signatures in the sleep-EEG of ID is also evident in an objective
437 semi-quantitative visual scoring approach to polysomnography other than the AASM
438 standard (387). Repetitive alterations of specific EEG patterns coined ' cyclic alternating
439 pattern' (CAP) can be observed during NREM sleep. A "phase A" indicates instability with
440 arousals and a "phase B" indicates stability. The NREM sleep EEG of people with ID shows
441 more of such alternating patterns with brief (10-15 seconds) periods of brain activation. The
442 higher CAP rate in insomnia indicates restless NREM sleep (388). The visual scoring of CAPs
443 is less suitable to quantify restlessness of REM sleep for which other EEG features are more
444 appropriate including the power spectrum, arousal density, eye movement density, and shifts
445 to wake or other sleep stages.
446
447 In addition to the semi-quantitative objective methods requiring visual scoring that have
448 been discussed above, the EEG of people with ID has been evaluated with quantitative
449 methods. Findings provide further support for the emerging conclusion that some
450 wakefulness lingers on during sleep, ready to make sleep lighter or even terminate it.
451 Quantitative methods can be more sensitive to differences between people with ID and

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

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

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

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

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

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

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

however, other variables were found to distinguish insomnia best (275). The discrepancy indicated the need of device-independent algorithms that utilize the raw accelerometry data (382).

Meta-analysis indicated that there is ample evidence of its validity and utility in assessing sleep continuity and that actigraphy provides unique information complementary to sleep diaries (355). The meta-analysis concluded as well that actigraphy didn't always provide sufficiently reliable sleep estimates and could fail to detect intervention effects on sleep that were established by polysomnography. Thus, Smith et al (355) echoed a 15 years earlier conclusion that the function of actigraphy in the assessment and diagnosis of insomnia "is likely to be restricted to the role of an adjunct to clinical history, sleep diary data, and PSG findings" (9). To improve this situation, progress has been made in optimizing actigraphy specifically for use in insomnia (381).

## The discrepancy between subjective and objective sleep: misperception?

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

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

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

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

## Vulnerability to subjective and objective sleep features characteristic of ID

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

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

A predisposition to pre-sleep arousal and altered EEG during wake and sleep could involve variants in several genes that have been implicated in the risk of insomnia. Altered sleep and wake EEG spectra along the same dimensions that have been implicated in insomnia disorder (88) are seen in *SNCA* mouse mutants (254). Altered expression in mice changes *DNM1*, which encodes the synaptic protein dynamin 1, which is increased in *BTBD9* 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

## III. Daytime characteristics of insomnia

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

### Subjectively experienced daytime cognitive and emotional functioning

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

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

633 *Hyperarousal* is commonly mentioned as the key subjective complaint experienced by people
634 with ID, contrasting to the *hypo*arousal 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.

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

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

**Objectively assessed daytime cognitive and emotional functioning**

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

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

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

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

Only few studies compared people with insomnia and well-sleeping controls with respect to *overnight* effects on procedural and declarative memory. While animal studies mimicking aspects of insomnia consistently suggest disrupted sleep-dependent memory effects (136, 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

(88), as is the case during sleep (329). In addition, wake alpha band activity (8-12 Hz) was lower in people insomnia than in controls across the cortex (88), in contrast to their increased alpha band activity specifically in sensory-motor areas during sleep (329). The contrasting lower alpha prior to sleep and higher alpha during sleep had been reported before using regular EEG (134). Both lower alpha and increased beta prior to sleep indicate pre-sleep arousal (134). Wake hyperarousal is also supported by fMRI findings of predominantly salience network activation, as will extensively be discussed in § VII.

The hyperarousal that people with insomnia experience so strongly subjectively is moreover also reflected in some autonomic features, which has extensively been reviewed. In brief, while especially autonomic cardiovascular alterations are widely accepted in insomnia (274), deviations in heart rate and its variability not unequivocally supported by actual findings (108). Likewise, metabolic rate may be increased in only a subsample of people with insomnia, i.e. those that also show a short sleep duration during first exposure to a polysomnographic recording (308). 24-hour HPA axis activation may also be most pronounced in short sleeping insomniacs and support the conception of insomnia as a disorder of hyperarousal rather than one of sleep loss, since sleep deprivation is more often found to decrease cortisol or have no effect (308). It should be noted that too few studies investigated autonomic responses to acute distress, or overnight changes in the autonomic responses to repeated distress. That such a perturbation approach may be more sensitive to detect deviations has been demonstrated for post traumatic stress disorder (102). A perturbation approach seems even more powerful if repeated overnight (425).

## IV. The genetic risk of insomnia

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

### Heritability

Can people be 'born' with a risk to develop insomnia? Family and twin studies indeed suggest that this is the case. As scholarly reviewed by Lind and Gehrman (240) at least five studies evaluated whether insomnia 'runs in the family', and suggested that this was indeed the case. Family studies cannot however unravel whether this has a genetic basis, or rather 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

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

*Candidate gene studies*

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

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

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

*Genome-wide association studies*

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

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

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

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

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

Some of the identified genes have been studied in mouse models. Mice with mutations in *BTBD9*, the top gene associated with insomnia in the study of Jansen et al. (183) or in *DNM1*, another identified insomnia risk gene, both show changes in the synaptic protein dynamin 1 which mediates the sleep-disruptive effect (increased sleep onset latency) of pre-sleep arousal (99, 369). *BTBD9* mouse mutants also show altered plasticity resulting in a stronger fear memory (99) and other phenotypes that match findings in insomnia (98), like increased restless, more fragmented sleep, and altered thermal sensitivity (324, 325).

*Variance explained by GWAS*

So far, GWAS studies have explained only a very small percentage of the phenotypic variation of insomnia: 2,6% in the largest GWAS to data (183). Theoretically, if all genetic variants affecting insomnia were known and if all their effects would be estimated correctly, the maximal variance explained could equal the heritability, which meta-analysis estimated to be 44% (208). The large difference between the variance explained by GWAS versus heritability estimates is common for complex traits and known a the 'missing heritability' (398, 442). Several factors contribute to this missing heritability, including linkage

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

While limitations of genetic methodology received most attention in explaining the missing heritability, phenotypic measurement issues contribute significantly as well (for a review, see 398). While diagnostic nosologies present insomnia is as a clear-cut disorder (8, 105), the actual presence of the disorder may fluctuate during lifetime, and GWAS cohorts may be heterogeneous with respect to established robust subtypes of insomnia (42). Moreover, sleep complaints related to other disorders or environmental conditions can resemble Insomnia Disorder, especially if presence of Insomnia Disorder is estimated with information as limited as a single question. Phenotype validation is therefore important in GWAS studies. One GWAS that extensively validated the UK Biobank insomnia phenotype utilizing an independent deep-phenotyped cohort (37, 42) demonstrated its excellent properties to discriminate cases with probable Insomnia Disorder (see **Figure 7. "UK Biobank insomnia phenotype validation"**, and figures S1 to S4 in Hammerschlag et al. (156)). One may question the value of GWAS if missing heritability remains large in spite of increasingly large discovery sample sizes and the occasional availability of a sensitive and specific phenotype. One important value of GWAS is that it has revealed clues to involvement of specific biological functional pathways, tissues and cell types. Of note, any suboptimal function in these substrates do not necessarily only result from genetic variants, but could of course also emerge during lifetime due to other causes than genetic make-up and thus diluting the variance explained by GWAS. These substrates will be discussed in the paragraph below.

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

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

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

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

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

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

1010 complex and severe cases that report to sleep centers specialized in RLS. Hammerschlag et
1011 al also provided detailed additional analyses to demonstrate that *MEIS1* shows pleiotropy for
1012 insomnia and RLS: the same genetic variant can manifest itself in different phenotypes. In
1013 addition, different loci within the gene may differentially increase the risk of one or the
1014 other phenotype, as has been suggested for involvement of *MEIS1* in RLS and PLMS as well
1015 (269).
1016
1017 If we consider the conceptual hallmarks of RLS, PLMS and ID, there is a striking link of
1018 hyperarousal, restlessness or agitation: *sensory* restlessness in RLS, *motor* restlessness in
1019 PLMS and *higher order* restlessness (cognition, consciousness) in ID. This tripartitioning may
1020 be too strict: the disorders show high comorbidity, and biomarkers and underlying
1021 mechanisms may overlap in several ways. For example, trouble falling asleep in RLS relates
1022 to similar EEG power abnormalities as found in insomnia (126, 127). In *MEIS1* mouse
1023 mutants, hyperactivity, which is most characteristic of insomnia, has even been used as a
1024 readout for *RLS* rather than for *insomnia* (360). In conclusion, it appears worthwhile to
1025 investigate how known functions *MEIS1* could be relevant to close in on the enigmatic
1026 mechanisms underlying individual differences in vulnerability to insomnia.
1027
1028 Several animal studies addressed the involvement of *MEIS1* in developmental biology. The
1029 gene encodes a protein that activates and regulates transcription that is essential for normal
1030 development of the central nervous system (66, 153, 360). The early recognition of *MEIS1*
1031 involvement in RLS may have promoted a focus on *MEIS1* mutation consequences
1032 specifically for the motor system (360). However, *MEIS1* has longer been known to be
1033 involved on other functions. A relevant example is the regulatory role of *MEIS1* in the
1034 expression of substance P, both in the subset of medium spiny neurons that project to the
1035 substantia nigra (178) and in the human amygdala (94). This is a most interesting lead,
1036 because amygdalar substance P acting on its Neurokinin 1 (NK1) receptor modulates fear

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

## V. The risk of insomnia conveyed by stressors

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

### Prenatal Stress

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

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

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

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

## **Adverse Experiences**

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

### *ACEs increase the risk of insomnia*

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

1101 experiences including parental divorce, prolonged financial difficulties, serious conflicts,
1102 frequent fear of a family member, poverty and illness or alcoholism of a family member. Of
1103 the different adverse events, frequent fear of a family member and serious conflicts
1104 increased the odds most strongly. Worst off were those that experienced more than two
1105 adversities and additionally had a poor relationship with their mother (OR 10.4) or father
1106 (OR 5.4).

1107 A critical question is whether ACE increases insomnia only secondarily, as a complaint
1108 strictly due to other conditions, like depression. In the study of Koskenvuo et al. (212),
1109 adjustment for current depressive symptoms changed the results only modestly, indicating
1110 that the effect of childhood adversity on sleep complaints is not simply merely secondary to
1111 its know effect on the risk of developing depression in adulthood. Notably, the odds for
1112 poor sleep are much higher than the odds of for depression (OR 4.4) and the majority of
1113 other adverse health sequelae, as recently meta-analyzed (175). Interestingly, adjustment for
1114 recent life events did not considerably change the odds for poor sleep after childhood
1115 adversity either (212).

1116 In summary, the findings suggest that the learning experience of '*not being safe*' *during a critical*
1117 *early life period of brain plasticity* might lead to an unbalanced enhancement of neuronal
1118 activity in circuits supporting *watchfulness*.

1119

1120 *Does the kind of ACE matter?*

1121 Different kinds of ACE's have been subdivided along two dimensions. One dimension
1122 represents physical, sexual and emotional categories. The other dimension distinguishes
1123 abuse from neglect. Intriguing questions are whether the risk of insomnia depends on the
1124 kind and number of ACEs and on whether they involve a single or multiple categories.

1125 This question has been posed previously for the risk of other disorders. For example,
1126 neglect has been suggested to be the strongest predicting ACE subtype for depression (159).
1127 However, as reviewed by Negele et al (279), studies that tried to map specific types of ACEs

1128 to specific mental disorders yielded quite equivocal results. In their own study that aimed to
1129 map specific types of ACEs to features of depression, multiplicity rather than specificity of
1130 adversities predicted symptom severity, and the more chronic the ACEs, the higher the
1131 lifetime prevalence of depression (279).

1132 In insomnia, it has been reported that childhood adversity among people suffering from
1133 insomnia disorder most markedly concerns emotional neglect (17). Insomnia complaints in
1134 elderly have rather been linked primarily to childhood emotional abuse (317). As is the case
1135 for depression, it may rather be the number and categorical multiplicity that primarily drives
1136 increasing severity of insomnia. A large ($N \sim 17{,}000$) epidemiological study (76) showed that
1137 trouble falling or staying asleep increased with the *number* of adversities people had
1138 experienced during childhood. A proportional increase of the risk of current insomnia has
1139 also been seen with an increasing *diversity* of childhood adversities, both in adolescents (421)
1140 and in elderly people (317).

1141 In summary, the findings provide further indirect support for the involvement of early
1142 learning 'not to be safe'. Early life learning of being unsafe and of the need to stay *watchful*
1143 will engrave a stronger memory trace if such learning occurs repeatedly and *across multiple*
1144 *contexts*. Indeed, the increased risk of insomnia after childhood adversity is mediated by
1145 neuroticism (320), which has been defined as a general sensitivity to negative information. It
1146 is tempting to suggest that early life learning of being unsafe and of the need to stay watchful
1147 could result in lasting alterations in brain circuits effectuating a lifelong inclination for
1148 hypervigilance (317, 443), that could even continue into sleep.

1149

1150 *Objective indices of disturbed sleep after trauma*

1151 Childhood adversity predisposes to fragmented REM sleep (180), a key feature of chronic
1152 insomnia (123, 330, 424). Among people suffering from insomnia disorder, those that
1153 reported childhood adversity specifically show more awakenings and movement arousals
1154 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 $CRF_1$ 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

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

*Recent Trauma and Major Life Events*

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

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

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

## VI. Mental health risks conveyed by insomnia

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

Pre-existing insomnia is also key to whether or not a traumatic experience elicits PTSD (140, 143), as well as to the persistence of PTSD (143). Indeed, good-quality sleep may be protective against poor emotion regulation and anxiety in veterans with PTSD (249). Interestingly, the most characteristic polysomnographic findings of disturbed sleep in PTSD are virtually indiscriminable from those found in insomnia disorder: sleep is more fragmented due to an increased number of awakenings and arousals. As in insomnia, especially REM sleep is restless, which may not only show in the number of arousals, but also in the density of eye movements (55, 207). Both arousal and eye movement density have also been linked to experience continuing thoughts during sleep in insomnia, and to insufficient overnight adaptation to emotional distress which may accumulate to chronic hyperarousal (424).

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

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

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

## VII. MRI findings on brain structure and function in insomnia

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

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

1284 people with insomnia and controls without sleep complaints. Fourth, differences in
1285 recruitment strategies and inclusion criteria make it highly likely that the samples included in
1286 the meta-analyzed studies differed considerably in the proportion of each of the different
1287 subtypes of insomnia that have been identified (42). These subtypes are distinguished by
1288 specific profiles of traits, which were mostly selected on being associated with specific brain
1289 structural- and brain functional characteristics. Gene variants associated with insomnia-
1290 related traits have been reviewed in table S3 of Blanken et al. (42). Subtypes are likely to
1291 differ with respect to their *distributed deviations* of brain characteristics (45). Moreover, even
1292 within an individual, dysfunction may not necessarily relate to the same voxels across time.
1293 Metaphorical examples can be given to explain this. A brain structural metaphor would be
1294 the white-matter intensities in multiple sclerosis that may disappear from one location and
1295 later appear at another location. A brain functional metaphor would be a slow car
1296 anywhere on a crowded highway that result in a queue that increases the time it takes to
1297 reach one's destination.
1298
1299 The concept of a distributed large number of small deviations that each on their own have a
1300 negligible effect is well accepted in the field of complex trait genetics. A person's polygenic
1301 risk score (PRS) for a particular phenotype, such as insomnia, reflects a count of the number
1302 of genes with the variant that slightly increases the risk. People with the same PRS may have
1303 different contributing genes. A similar quantifying concept has not yet been established for
1304 brain imaging studies. We will therefore here qualitatively discuss a number of studies in a
1305 narrative way. Reading through the imaging literature supports the perspective that insomnia
1306 may be promoted by insufficiently compensated minor deficiencies anywhere in the brain
1307 circuits that signal salience. Such deficiency may, directly or indirectly, either promote
1308 alertness and arousal, or interfere with inhibition, resulting in difficulties disengaging from
1309 alertness and arousal.
1310

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

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

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

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

## Functional connectivity

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

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

1390 relevance to insomnia is that the head of the caudate nucleus is implicated both in
1391 distinguishing pleasantness (226) and suppressing cortical excitability (see, 365).
1392
1393 Resting state fMRI may also be studied under different pharmacological conditions.
1394 Although not specifically targeted at insomnia, one study is particularly worthwhile
1395 mentioning given the hypothesis developed in the current review. Song et al (356) assessed
1396 locus coeruleus connectivity while pharmacologically suppressing its activity using an agonist
1397 of inhibitory autoreceptors on noradrenergic cells. Silencing of locus coeruleus activity
1398 particularly affected its connectivity with multiple regions that have previously been shown
1399 to functionally or structurally deviate in insomnia, notably the anterior cingulate cortex (426),
1400 insula (187) precuneus (7), thalamus (236) and caudate nucleus (365).
1401 Dynamic functional connectivity (DFC) of resting-state fMRI is a method with a
1402 somewhat higher sensitivity to detect distributed dysfunctions that are only subtle. Only one
1403 study so far investigated DFC in insomnia (431). The study included 65 people with insomnia
1404 and 65 controls without sleep complaints. In support of the sensitivity of the method, the
1405 study showed that while none of the *average* between-network functional connectivity
1406 strength deviations in insomnia reached significance, people with insomnia did show
1407 significantly less *variability* in functional connectivity between the anterior salience network
1408 and the left executive-control network. The finding suggests less flexible interaction between
1409 the salience network and the executive-control network during resting state in people with
1410 insomnia.
1411 The salience network interacts with other networks. It modulates activation of the
1412 default-mode network and the executive-control network (79). Reduced dynamic FC of the
1413 salience network could compromise switching between networks in response to changing
1414 environments and needs. fMRI during demanding cognitive tasks provide some support for
1415 this idea. They reported hypoactivation of the left inferior frontal gyrus which is part of the
1416 executive-control network (5), and a failure to deactivate the default-mode network (112) in

1417 people with insomnia. The salience network also strongly interacts with the amygdala. A
1418 study with a small sample size reported altered functional connectivity between the insula
1419 and the amygdala in people with insomnia (174), as previously reported for generalized
1420 anxiety disorder as well (121). Interestingly, altered insula connectivity seems key in the
1421 exaggerated interoceptive and exteroceptive processing in people at risk of anxiety due to a
1422 polymorphism in the ADORA2A gene (141), which alters the function of the receptor for
1423 adenosine, the key molecule involved in homeostatic regulation of slow wave sleep (318,
1424 328). Transdiagnostic involvement of the areas here discussed in both sleep and mood
1425 complaints is also reported by a study utilizing the large human connectome sample (80).
1426 Both types of complaints were associated with altered functional connectivity in several of
1427 these areas including the orbitofrontal, insula and anterior cingulate cortices and the
1428 amygdala.
1429
1430
1431 **Brain activation during tasks**
1432
1433 Surprisingly few studies evaluated differences between people with insomnia and controls
1434 without sleep complaints in task-related brain activation. As mentioned in this section, fMRI
1435 during demanding *cognitive* tasks suggest hypoactivation of the left inferior frontal gyrus
1436 which is part of the executive-control network (5), and a failure to deactivate the default-
1437 mode network (112) in people with insomnia. As mentioned in § III, a few studies assessed
1438 fMRI during *emotional* tasks Baglioni et al (18, 20) report a stronger reactivity of the
1439 amygdala to sleep-related pictures. Wassing et al. (425) moreover found insufficient
1440 overnight adaptation of the amygdala in subjects with fragmented REM sleep - a key
1441 characteristic of insomnia. They also reported stronger activation in the salience network
1442 circuit including the limbic parts, notably in the dorsal anterior cingulate cortex in people
1443 with insomnia while reliving emotional memories from the distant past (426). Seo et al. (342)

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

## Concluding remarks on MRI findings

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

## VIII. Towards mechanisms underlying insomnia vulnerability: sleep regulation?

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

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

Likewise, insomnia does not seem to be caused primarily by insufficient functioning of the homeostatic component of sleep regulation. Studies on homeostasis assess how sleep deprivation alters EEG slow wave activity during subsequent recovery sleep (336). Surprisingly few studies aimed to investigate the homeostatic process in insomnia disorder. In an early study Bonnet (51) concluded that the restorative function of sleep operates 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

seem to be systematically characterized by a lower wake-threshold to external acoustic perturbation: it only takes them longer to return to sleep once awakened (164, 261). The unaltered threshold to *external* stimulation is in strong contrast to the increased density of *spontaneous* arousals and awakenings (123, 330), and the *intrinsic* tendency to go from deeper sleep stages back to more superficial sleep stages (430). N3 is the only sleep stage that seems 'safe': once people with insomnia reach this state, they don't differ from normal sleeping controls in the probability to switch to a more superficial sleep stage. If we would consider arousal threshold and N3 related to sleep homeostasis, these findings also do not support the idea that insomnia would be a disorder of homeostatic sleep regulation.

An interesting new perspective on the subjective sleep complaints of people with insomnia is the possibility that sleep and wakefulness occurring in a non-integrated way simultaneously in different neuronal ensembles in the brain. Traditionally, the states of sleep and wakefulness have been regarded as strictly separated in time: the brain is either asleep, or awake. During the last decade, the presumption of a strictly sequential occurrence and of all-or-none global brain states of sleep and wakefulness has been challenged. Krueger and colleagues (218, 219) proposed that sleep could be a fundamental property of even small local neuronal networks. Accordingly, individual cerebral cortical columns could show sleep-like states that are to some extent independent of the occurrence of sleep-like states in other cortical columns. Intracerebral recordings in rodents and humans have indeed demonstrated concurrent sleep- and wake-type neuronal activity (135, 282, 413). Several authors proposed, or demonstrated, that the ongoing nocturnal rumination that people with insomnia experience subjectively may have its neural correlate in an inappropriately large proportion of neuronal ensembles showing wake-like activity during sleep (85, 229, 232, 264, 362). It should be noted however that the concept of 'local islands of wakefulness' (362) to explain a subjective wake experience while asleep would seem too large a simplification. Conscious awareness is considered to require integration of global recurrent spreading of

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

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

## IX. Towards mechanisms underlying insomnia vulnerability: emotion regulation?

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

### Why study emotion regulation to understand insomnia?

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

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

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

**Sleep reactivity and emotional reactivity**

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

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

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

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

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

1689 memory and forgetting (316, 416): while sleep indeed adds to the consolidation of the
1690 declarative, contextual or semantic aspects of an emotional experience, at the same time it
1691 aids to separating these engrams from the emotional tone and somatic arousal the emotional
1692 experiences originally elicited. In other words, post-learning sleep also has an impact on the
1693 functional connections of limbic areas with the network representing the declarative,
1694 contextual or semantic engram.
1695
1696 *Subjective distress*
1697 Although several studies indicate that sleep supports the downregulation of emotional
1698 distress, findings are not unequivocal (reviewed in 386). A sleep-dependent decrease in
1699 *subjective* arousal ratings of the same stimuli presented both before and after periods of sleep
1700 or wakefulness has not always ben found (25). Also, an advantage of late sleep rich in REM-
1701 sleep over early sleep rich in non-REM-sleep has not systematically been found (152, 414).
1702 Both sleep-related enhancement and attenuation of subjectively experienced emotional
1703 intensity has been reported when comparing periods of sleep and sleep deprivation (154,
1704 228, 334). In an early-sleep versus late-sleep protocol, REM-rich late sleep supported the
1705 'factual' recognition part of emotional stimuli better than NREM-rich early sleep did, while
1706 subjective valence and arousal ratings of emotional pictures were not differentially affected
1707 by REM or NREM-rich sleep (152). However, subjective valence and arousal ratings involve
1708 higher-order emotional appraisal, and may be dissociated from brain and somatic reactivity
1709 (230). Indeed, a recent sleep study demonstrated brain activation in the salience circuit as
1710 well as and correlated GSR amplitudes, in the absence of corresponding subjective
1711 emotional intensity ratings (426). Within subjective rating surveys, subscales that
1712 immediately address somatic reactivity seem most sensitive (423).
1713

*Objective measures*

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

.

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

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

## 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).

## X. Insomnia by insufficient overnight adaptation to emotional distress?

Integrating all reviewed above, a testable model on the vulnerability to develop insomnia emerges. A first key feature of the proposed model is that differently *distributed deviations* in the nodes and connections of the circuits involved can all converge to a final common path of insomnia. A second feature of the proposed model is that the involvement of sleep regulating circuits may be limited to an initial vulnerability to have insufficient locus coeruleus silencing during REM sleep. Circuits involved in the regulation of salience, emotion and arousal could play major roles. A consequential third characteristic of the model is that it proposes more overlap than differences in mechanisms underlying insomnia, anxiety disorders, major depressive disorder and post traumatic stress disorder. A fourth characteristic of the model is that deviating overnight synaptic and systems level plasticity contributes to all these disorders. This common mechanism may be summarized as 'insufficient overnight adaptation to emotional distress'. **Figure 12. "Insufficient silencing of the locus coeruleus during sleep" and Figure 13. "Developmental model linking the vulnerability to restless sleep, insomnia and other mental disorders"** sketch the main components of the model.

As is commonly considered for other mental disorders, the vulnerability of insomnia commences at conception. Large genome wide association studies have identified that the risk of insomnia increases in proportion to the number of variants in a large number of risk genes. Each of the individual variants contributes only very little to the risk. Concertedly however, they provide clues to brain tissues and cell types involved in insomnia. Of note, vulnerabilities in these tissues and cells do not necessarily have to result only from their significant expression of risk genes. Other reasons include early developmental influences on these tissues and cells. As extensively discussed in § IV, GWAS suggests vulnerability in 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)

(see **Figure 10. "Restless REM sleep impedes overnight emotion regulation"** and **Figure 11. "Long-term effects of insufficient overnight adaptation?"**).

This model on the importance of NA-free REM sleep for overnight emotion regulation provides a new avenue for *transdiagnostic* treatment innovation. A duality-of-effect hypothesis considers that common neural substrates could underlie insomnia and mood or anxiety disorders (1, 347, 392). Animal studies support the hypothesis that common neural substrates may underlie disturbed sleep and mental health. Already in early animal models for depression, co-expression of an insomnia phenotype was noted to be common (114, 349, 392). There is a two-way reinforcement of adverse effects of insomnia and stress. On the one hand, insomnia is more likely to develop in people that respond to stress with very poor sleep (111, 185, 192). On the other hand, pre-existing insomnia puts individuals at elevated risk of developing posttraumatic stress disorder when exposed to a traumatic event (140, 420). Likewise, post-deployment sleep continuity disturbance co-determines whether combat exposure results in post-traumatic stress symptoms (294).

Trouble distancing oneself from negative memories is not only found in insomnia, but also holds for people with depression or other mood disorders (196). Already before disease onset, sleep in people at risk of these disorders may be altered, as demonstrated for insomnia and posttraumatic stress disorder (145, 180). Our model proposes that restless sleep is not merely a coincidental transdiagnostic nuisance, but in fact has key involvement in both the vulnerability and the persistence of the disorders. While in good sleepers 'sleeping on it' helps to resolve distress overnight, people with restless sleep take their burdens unresolved to the next day. For them, a night's sleep doesn't resolve anxiety, tension and sadness at all. They may even wake up worse than they were the night before (423, 425). A common distinguishing feature from the ‘occasional bad day’ of a healthy subject, is thus that people with anxiety, insomnia, depression or post traumatic stress disorder take their

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

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

## XI. Recovering restful REM sleep: a research agenda

Restless REM sleep is one of the most distinguishing sleep characteristics of insomnia (53, 123, 330). Given the review and reasoning provided above, the question arises whether people with insomnia could reduce restless REM sleep or even recover restful REM sleep. First, since both the probability of REM sleep and the probability of fragmented sleep increases with time asleep (124), one may evaluate whether curtailment of the time in bed reduces the amount of restless REM sleep and its adverse consequences for distress and hyperarousal. Interestingly, sleep curtailment has been noted to be the most effective component of the multicomponent cognitive behavioral therapy for insomnia. Another 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 α1-receptor antagonists.
1932 As reviewed Broese et al. (58), the α1-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 α1-
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 α1-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 α2-
1953 autoreceptor agonists could be evaluated to treat insomnia and discussed several drugs with
1954 different affinities for the α2-receptor subtypes α2A, α2B and α2C: clonidine,
1955 dexmedetomidine, guanfacine and tizanidine. The drugs have been used in attention deficit

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

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

## Figure legends

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

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

**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).

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

***Upper panel:*** Waveforms show the frontal dynamics of the heartbeat-evoked (HEP) during the eyes-closed (EC) resting state in people with Insomnia Disorder (ID) and controls (CTRL). People with insomnia show a significant late amplitude within the 376–500 ms time window (gray bar) that is not present in controls without sleep complaints. Shaded areas indicate one standard error of the mean (SEM).

***Lower panel:*** Source localization of between-group differences in activity over the 376–500 ms time window after the electrocardiogram R-wave displayed on the Montreal Neurological Institute (MNI) standard brain image. Increased late activity in people with ID is especially pronounced at bilateral anterior cingulate and medial frontal cortices.

From reference (432).

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

Auditory event-related potentials (ERPs) for frequent standard tones (dashed lines) and infrequent deviant target tones (solid lines), recorded during an auditory oddball task in 13 people with the reactive subtype of insomnia (ID-S4, purple lines) as compared to 31 controls without sleep complaints (CTRL, black lines). Artifact free ERPs at the midline parietal (Pz) electrode referenced to both mastoids were averaged over 170 standard tones and 30 deviating tones. Shaded areas indicate one standard error of the mean (SEM). People with the reactive subtype showed a stronger positive deflection during a wide late period of information processing as of 273 ms up to at least1000 ms after standard tones were played. The indicates hyper-reactive late processing specifically in in the insomnia subtype that was labeled as highly reactive based on trait questionnaires. They experience even standard tones as salient (as indicated by the enhanced P300 potential amplitude) and emotionally relevant (as indicated by the late positive potential amplitude). From reference (42).

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

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

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

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

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

**Figure 9. "Multivariat**

**e profile plots of insomnia subtypes"**

Data are scaled subtype group means (95% CIs), in which Z scores have been standardized to the mean and standard deviation of controls for each characteristic, with the subtype-explained variance, ranked clockwise from the top. (A) Highly distressed subtype (subtype 1). (B) Moderately distressed subtypes (subtype 2, which was reward sensitive, and subtype 3, which was reward insensitive). (C) Low distress subtypes (subtype 4, which was high reactive, and subtype 5, which was low reactive). Positive characteristics (eg, positive rumination) were reverse-coded and renamed (eg, reduced positive rumination), such that higher values uniformly indicate higher general distress for all characteristics throughout the plot. Colored boxes indicate the three characteristics that differentiate each subtype most from people without sleep complaints. From reference (42)

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**Figure 10. "Restless REM sleep impedes overnight emotion regulation"**

Schematic representation of how the amygdala response during an emotional experience changes overnight. Participants were presented with an upsetting stimulus during fMRI scans in the evening and again in the morning. The induced distress was associated with amygdala activation which decreased overnight in people with consolidated REM sleep. People with restless REM sleep showed insufficient overnight adaptation. Those with the most fragmented REM sleep even showed sensitization of the amygdala response: they might have been better of without REM sleep. Graphical representation of references (423) and (425) kindly provided by R. Wassing, PhD, Sydney.

**Figure 11. "Long-term effects of insufficient overnight adaptation?"**

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

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

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

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

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

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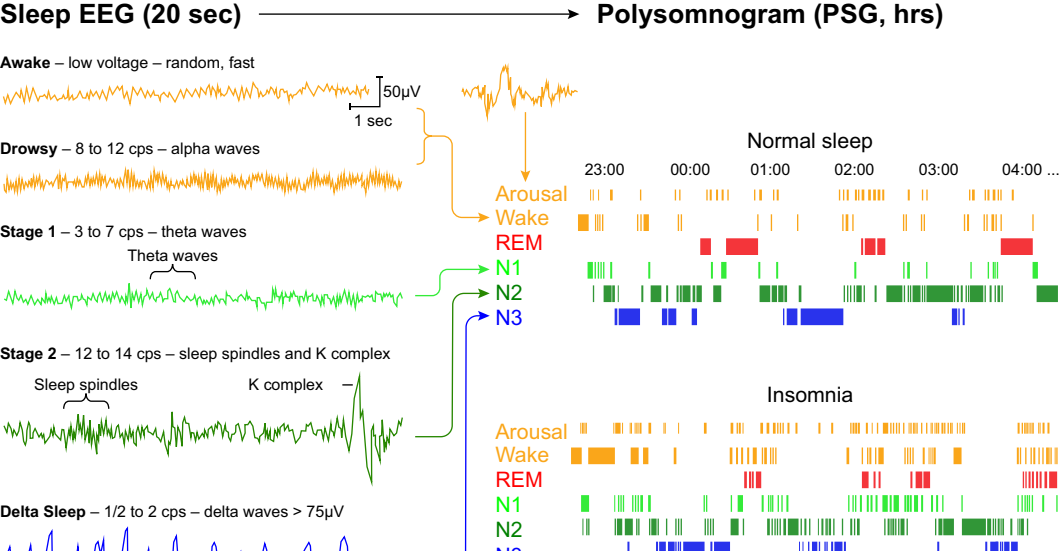
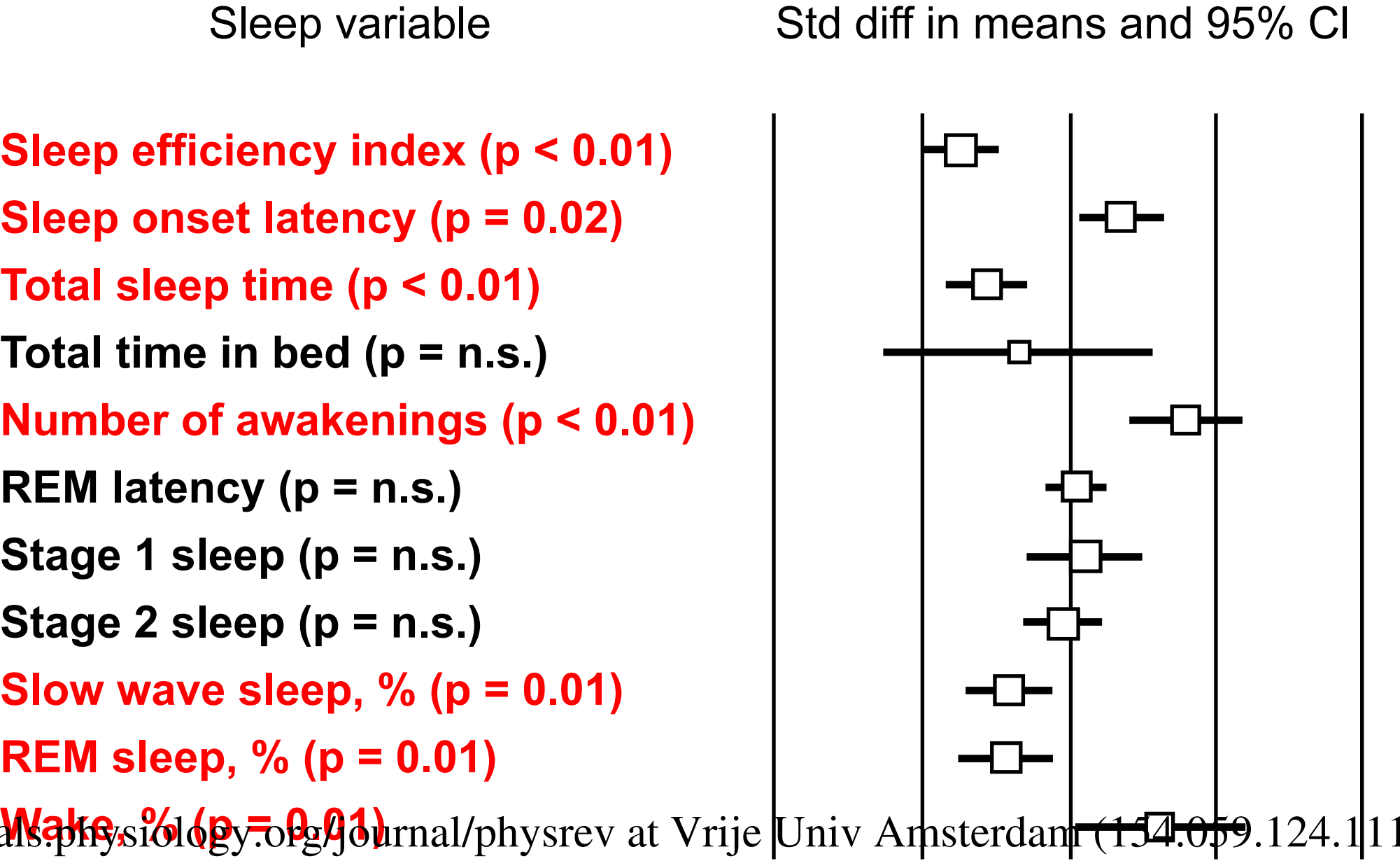
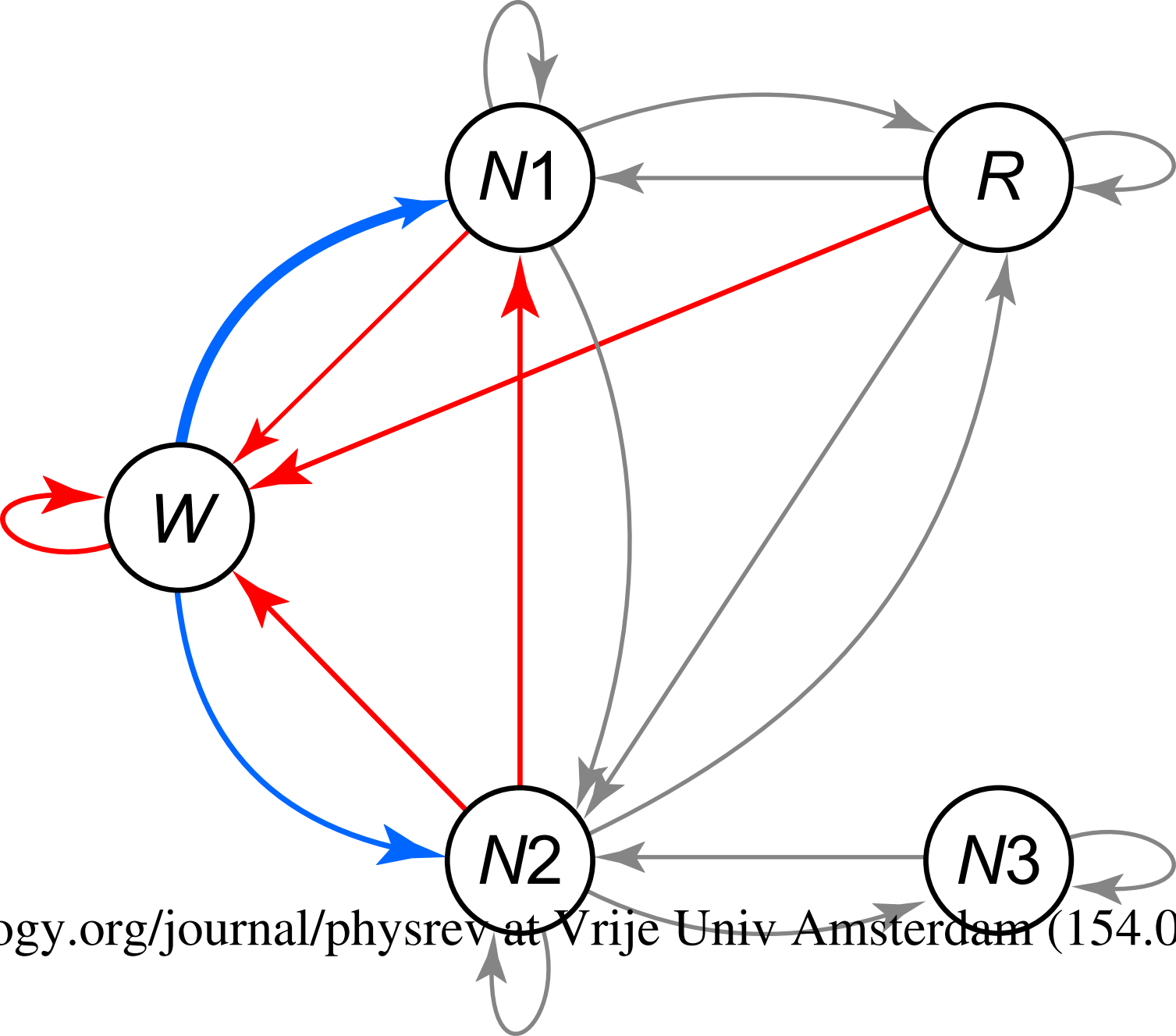
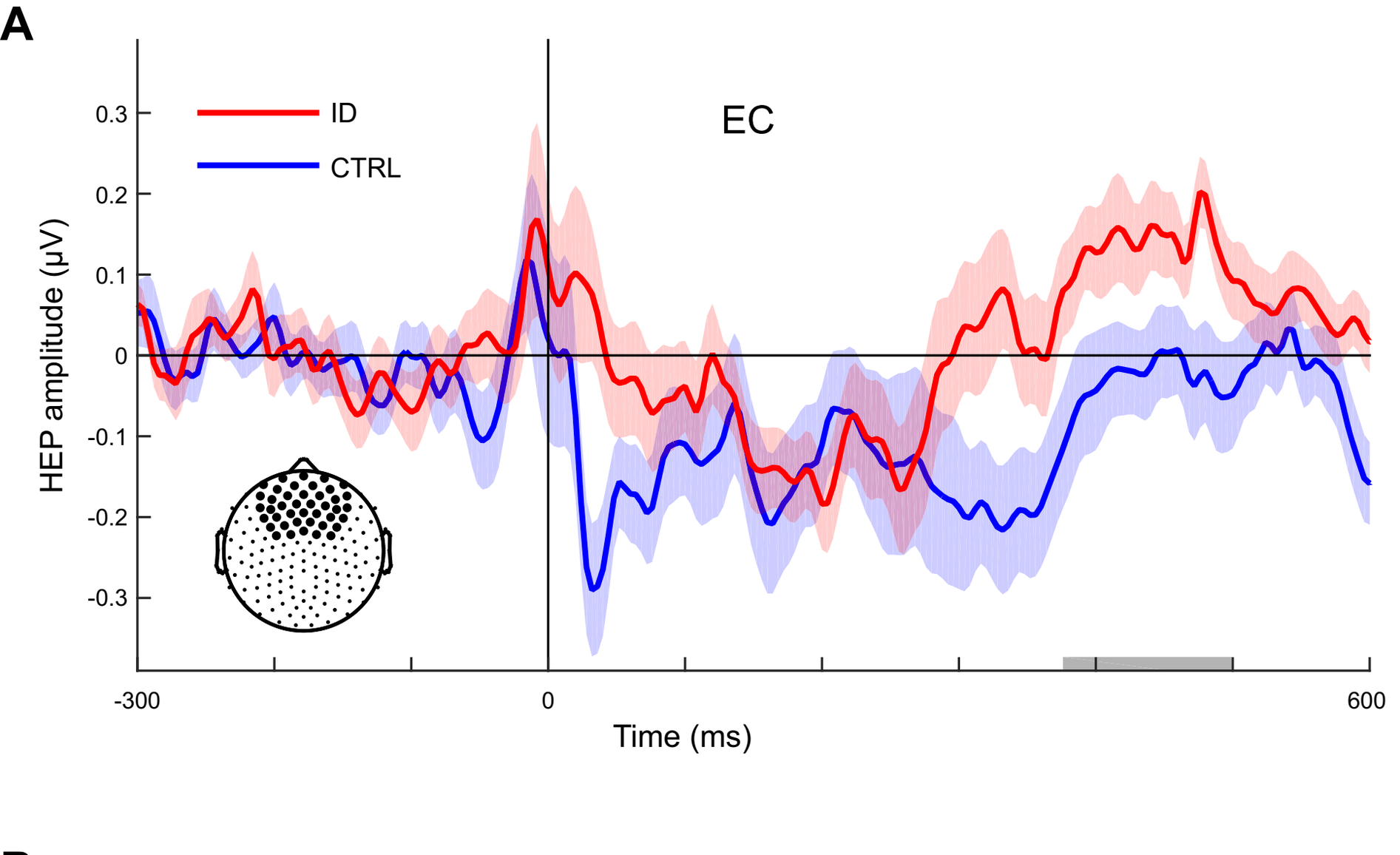


# Polysomnographic Characteristics of Primary Insomnia



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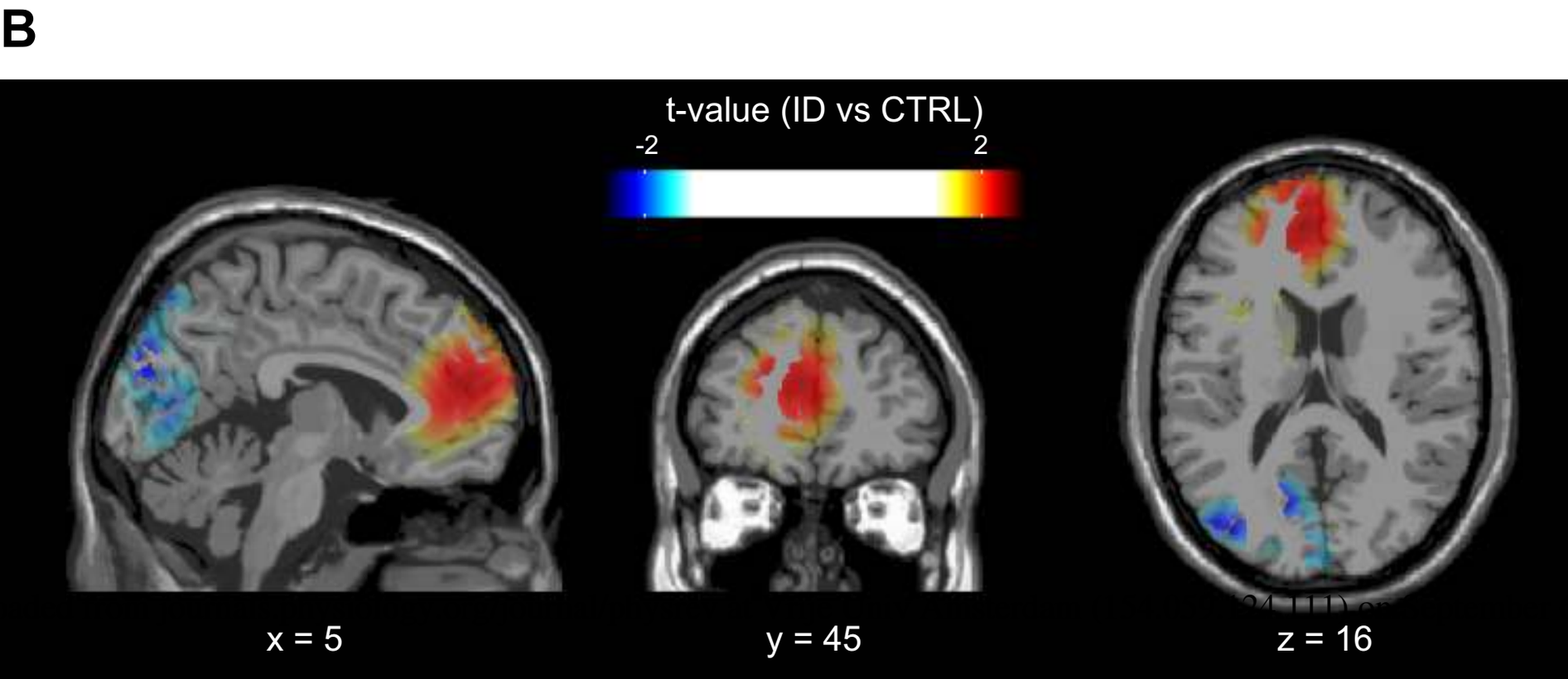
B
t-value (ID vs CTRL)
-2
2
x = 5
y = 45
z = 16