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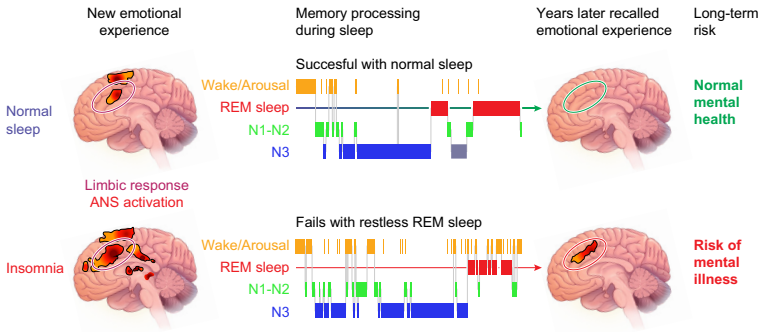

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KEY WORDS

insomnia; plasticity; locus coeruleus; anxiety; depression

CLINICAL HIGHLIGHTS

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VAN SOMEREN, 2021, *Physiol Rev* 101: 995–1046
August 13, 2020; Copyright © 2021 the American Physiological Society
https://doi.org/10.1152/physrev.00046.2019

american physiological society
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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 genetic variants, early life stress, 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 rapid eye movement sleep, when it should normally be sound asleep. This vulnerability may ignite a downward 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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1. INTRODUCTION, AIMS, AND OUTLINE

1.1. The Definition of Insomnia

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 (1, 2). 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, after which 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 (1, 3).

1.2. The Need of Better Treatment

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 (4). Also, the current first-line treatment, cognitive behavior therapy for insomnia (CBTI), does not bring sufficient relief for many (5). 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, posttreatment sleep efficiency—an integrated measure of sleep quality—does, on average, not surpass 80%, the cutoff for normal sleep (6). Moreover, meta-analysis reported that CBTI on average lowered the insomnia severity index by only 4.3 points (6), whereas a twice as large decrease would be required to even conclude a moderate clinical improvement (7). These numbers indicate that at least half of the first-line treated people still cannot be considered to have normal sleep. Thus, it can be concluded that there is an urgent, unmet need to better understand insomnia and to reveal actionable mechanisms for the development of better treatment.

1.3. Review Outline

First, this review 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 (sects. 2–7). 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 (sect. 8) and evaluates whether the search for mechanisms underlying insomnia should be limited to the circadian and homeostatic sleep-regulating circuits of the brain (sect. 9). 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 (sect. 10). Third, the review aims to provide new vistas on actionable mechanisms and suggestions of how human and animal research might explore them. Therefore, the review outlines a model stating that insomnia results from insufficient overnight adaptation to emotional distress (sect. 11) and concludes with suggestions for research (sect. 12). Importantly, the model can be evaluated not only in humans, but also by using 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.

1.4. A Role for Sleep-Dependent Plasticity?

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 sect. 11, and suggestions for research are provided in sect. 12. 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 suboptimal or even detrimental to the organism (8). While it is understood, of course, that 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 rapid eye movement (REM) sleep—when it should be absent—is an example of insufficient separation of processes, which, indeed, is suboptimal or even detrimental to overnight distress adaptation in people with restless sleep.

1.5. Insufficient Overnight Distress Adaptation?

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 sect. 4 (9–12). A few recent studies specifically addressed overnight emotional *distress adaptation* processes in insomnia, with more consistent and remarkable findings (13–16), as will be discussed in detail in sect. 10. The fragmented sleep that characterizes people with insomnia (sect. 3) 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 REM sleep at all, rather than to have their distress worsen overnight because of restless REM sleep. This idea is reminiscent of early work showing that REM sleep deprivation improved mood in depression (17).

1.6. Restless REM Sleep Impedes Adaptation

Specifically, *restless REM sleep* was pinpointed to interfere with emotional adaptation. *Restful* sleep supports overnight adaptation in the limbic circuit of the brain (18), resolving the burden of emotional memories by making them milder and more tractable (19). *Restless* REM sleep interferes with these adaptive processes. Adverse consequences are felt for long (14) and leave traces in brain activation for decades (16).

1.7. Plasticity and the REM Sleep Noradrenaline Timeout

Translational studies identified *why* restless REM sleep disrupts overnight adaptive processes (20–22). Sound REM sleep is the only state during which the brain has a "time-out" of noradrenaline (NA): the locus coeruleus (LC) is silenced. Intricacies of synaptic plasticity like receptor subunit replacement are strongly modulated by the level of NA (23). The NA timeout that only occurs during sound REM sleep, therefore, allows for a uniquely balanced potentiation and depotentiation of synapses, not found in any other state. Restless REM sleep, however, indicates insufficient LC silencing. The resulting lack of a NA-free REM sleep period disrupts synaptic plasticity (20–22).

1.8. Insomnia: A Disorder of Overnight Emotional Memory Regulation?

These recent insights on the importance of NA-free REM sleep for overnight emotion regulation provide the testable hypothesis that insomnia could be a disorder of overnight emotional memory regulation, originating in a presymptomatic vulnerability to have restless sleep. The same vulnerability could, moreover, contribute to the development of anxiety disorders, depression, and posttraumatic stress disorder. Indeed, the disorders have a markedly overlapping polygenetic risk, share early life risk factors, and occur commonly comorbid or in sequence. Possibly, diagnostic differences may mostly involve the type of emotional distress that does not resolve overnight, like fear, anxiety, arousal, stress, tension, or sadness. The new hypothesis provides a theoretical framework to study the disorders, or symptom constellations, concertedly, where insomnia is not strictly regarded as a sleep disorder just as we do not regard anxiety and mood disorders to belong to the category of sleep disorders.

1.9. Outlook

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 sleep may develop into chronic hyperarousal and related complaints.

2. DEFINITION AND PREVALENCE

2.1. Symptoms and Diagnosis

About one-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 per week or more for at least three months.

2.2. Comorbidity

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 (24). The "other disorder" may be another sleep disorder as well:

Kerkhof (25) 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) (26–30) and with restless legs syndrome (RLS; see sect. 5) (31, 32). Insomnia *can* be secondary though; in this case, insomnia complaints will disappear when the other disorder is successfully treated.

2.3. Prevalence

Both point prevalence estimates (usually assessed over the previous 1, 3, or 6 months), 12-mo prevalence estimates, and lifetime prevalence estimates indicate that on average ~10% of the population meet the diagnostic criteria of ID (see sect. 3) (33–35). While 1-yr *incidence* estimates of insomnia were first reported to vary around that number as well (range 7–15%) (35), 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 (36). 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 remained ~6% (37), whereas a recent cross-cultural and comparative epidemiological study reported that 10.8% fulfilled the newer DSM5 criteria for insomnia disorder (38). In a recent meta-analysis, the pooled prevalence of insomnia in China was 15.0% (39). All in all, insomnia seems the second most common mental disorder, with a 12-mo prevalence in between the most prevalent combined anxiety disorders and, closely following insomnia, major depressive disorder (2).

2.4. Increasingly Common Yet Too Often Ignored

For several reasons, it may surprise many that ID is the second most common neuropsychiatric disorder. First, the prevalence of insomnia disorder has been increasing over the last few decades. Calem et al. (33) reported that the prevalence of insomnia disorder nearly doubled across 15 years, and the increasing prevalence is supported by other longitudinal studies (40–43). 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 (44). On the basis of the only large integrative study that used identical methods to evaluate the 12-mo prevalence across different mental disorders, the combined anxiety disorders aggregated rank #1 (14%), insomnia ranks #2 (7%), and unipolar depression ranks #3 (6.9%) . The estimate of a 12-mo 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 (45–48). 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 (43, 49).

2.5. A Public Health Concern

Insomnia constitutes a dramatic and wide-ranging socioeconomic burden, representing tens of billions of dollars in the United States alone (50, 51), not only because of health-care expenses, but also because of decreased work productivity and proneness to injuries. Public health concerns should address specifically the quality of sleep; while insufficient sleep duration has become less prevalent the last 15 years (52), the prevalence of insomnia disorder has increased dramatically (33, 42).

2.6. Sex Differences in Prevalence

Female sex and age have been identified as major determinants of insomnia prevalence (53). Meta-analysis showed a risk ratio of 1.4 for women compared to men to have insomnia (49). Whereas the mechanisms underlying this 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 (54, 55). Postmortem studies in humans showed sex differences in brain structures involved in circadian and sleep regulation (56). Animal studies, moreover, indicate that the response of these structures to fluctuations in sex steroids is much stronger in females than in males (55).

Across sex and age, difficulty maintaining sleep is never as prevalent as in girls during puberty (28%) (57). The phase of the diurnal rhythm in estradiol varies across the menstrual cycle (58), and sleep complaints are worst during the midluteal 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 (55). It is notable that women with major depression have a very late relative sleep timing, because of their much advanced diurnal estradiol rhythm (59): 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 (55, 60).

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)-noradrenaline (NA) arousal circuit and how it responds to stress (61). The increased sensitivity in this circuit in females has been implicated in their increased risk of disorders characterized by concurrent insomnia: notably posttraumatic stress disorder (PTSD) and major depression. Animal studies suggest that structural sex differences in the LC bias females toward a stronger arousal response to emotional events (61). 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 have more fragmented sleep-wake patterns (62). The 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 finely 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 spatiospectral signatures of objective sleep and wake disturbance that have remained hidden in classic polysomnographic measures of sleep (63–70).

2.7. Insomnia Prevalence Across Life Span

As previously reviewed (71), 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 ~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 (72). A recent individual participant meta-analysis of insomnia symptoms across life-span in 1.1 million 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 sleep 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 (57).

2.8. Summarizing Risk Factors

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

3. NIGHTTIME CHARACTERISTICS OF INSOMNIA

3.1. Subjective Sleep

This section addresses subjective sleep complaints and objective sleep assessment.

3.1.1. Subjectively experienced sleep.

The diagnosis of ID is strictly based on subjective sleep complaints and does not include objective sleep criteria. By definition, people suffering from ID experience difficulties initiating or maintaining sleep and returning to sleep after waking up. Therefore, it is not that surprising that they remember their nights as filled with thoughts and rumination (73). Interestingly, also during actual sleep in good sleepers, mental content may be more common than once thought, and not specific to REM sleep. Foulkes (74) 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 non-rapid eye movement (NREM) sleep (75). This contrasts strongly from the blank-slate feeling that good sleepers have when waking up in the morning, except possibly for recall of some dreams. Apparently, much of 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

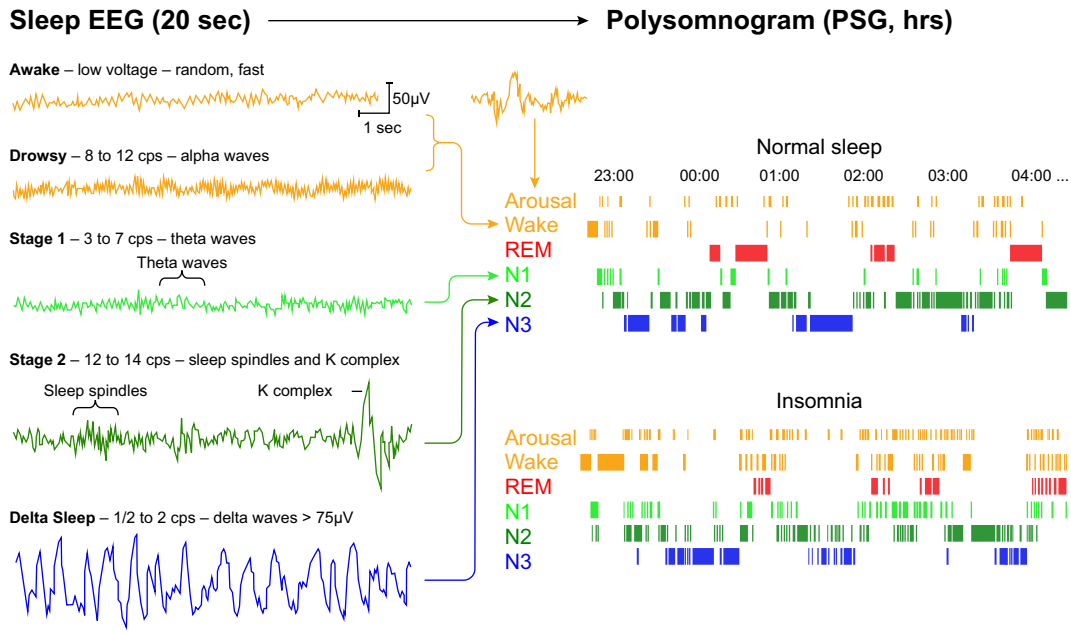

FIGURE 1. Polysomnography. Schematic representation of how epochs of sleep EEG can be scored as Wake or rapid eye movement (REM), N1, N2, or N3 sleep and brief arousals to for a polysomnogram (PSG) representation of a whole night of sleep. Contrary to what the name "insomnia" suggests, the EEG of people 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, University of Freiburg; from Ref. 78.]

ongoing mental content during NREM sleep better, and thus wake up at night or in the morning with a head full of memories of thoughts and ruminations. Enhanced memory of thought-like nocturnal mentation during sleep (76) can be hypothesized to be involved in the underestimation of time asleep that is characteristic for many people with insomnia (73).

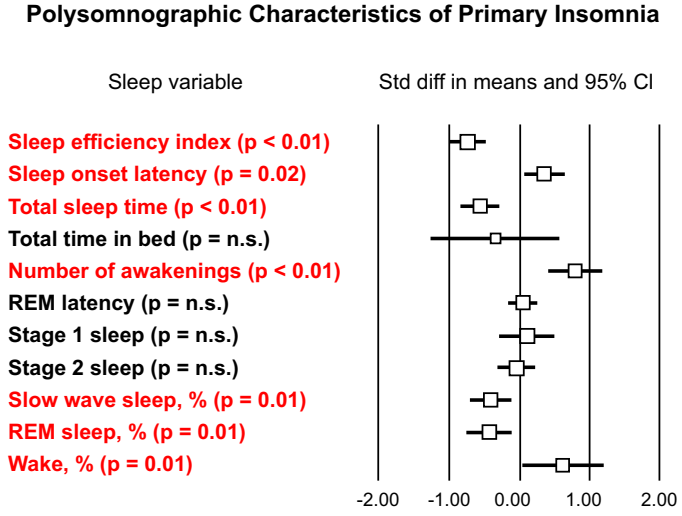

FIGURE 2. Meta-analysis polysomnography. Forest plot of the meta-analyzed effect sizes of differences between people with insomnia versus people without sleep complaints for the major polysomnographic features. CI, confidence interval; Std diff, standardized difference. [From Ref. 79.]

3.1.2. Subjectively experienced REM sleep.

In addition, although 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 (77, 78), the more likely is one with insomnia likely to recall thought-like rather than dream-like nocturnal mentation (14). This finding underlines the importance of side-by-side inquiring about both dreams and thoughts in studies on nocturnal mental content in insomnia (14).

3.2. Objectively Recorded Sleep

Several excellent previous reviews cover most of the findings on ID deviations in objective sleep recordings (79, 80). 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.

3.2.1. Standard polysomnography.

The gold standard for the semi-objective quantification of sleep is polysomnography (PSG), visually scored according to the American Academy of Sleep Medicine guidelines (AASM) (81). Although PSG is not strictly required for the

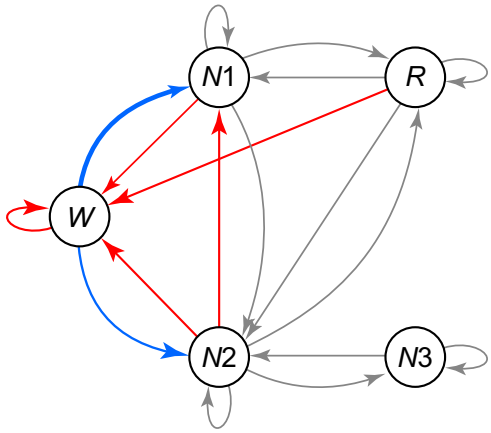

FIGURE 3. Increased probability to transition to a less deep sleep stage. Markovian state diagram comparing sleep stage transition probabilities in polysomnogram (PSG) data of 100 people with insomnia disorder (ID) and 100 healthy controls, generously provided by the Freiburg University Medical Center, Freiburg, Germany (77, 78). Red arrows indicate transitions with higher probabilities in people with insomnia disorder than in controls: from stage *W* to stage *W* ($W = 6{,}646$, $Z = 4.02$; $P = 0.001$), from stage *R* to stage *W* ($W = 6{,}492$, $Z = 3.64$; $P = 0.002$), from stage N2 to stage *W* ($W = 6{,}176.5$, $Z = 2.87$; $P = 0.02$), 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 have been false discovery rate corrected.). [From Ref. 83.]

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**). Meta-analysis showed that PSG variables reflecting disruption of sleep continuity are the most robust PSG signatures of insomnia (79). As shown in **FIGURE 2**, 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 percentage of time spent asleep while in bed. Total sleep time was consequently also less, due to reductions in both stages N3 sleep and REM sleep. Brief arousals (82) from sleep that may or may not count as wake epochs were not reviewed in the meta-analysis, but they have been addressed in great detail in other work from this group. These arousals especially fragment REM sleep (77, 78), although they are certainly present throughout NREM sleep as well (78). Markovian sleep stage transition dynamics show that the instability of sleep also shows in an increased propensity to switch to less deep sleep states, which makes it difficult to reach N3 (430). As shown in **FIGURE 3**, with ID, there is an increased probability to transition to a less-deep sleep stage, but once N3 is reached, the sleep of people with insomnia is considerably more like that of normal sleepers, without a significantly increased probability to switch to a less-deep sleep state or other classical indicators of instability (83, 84). However, recent novel data-driven analysis techniques could reveal that the sleep EEG of people with ID shows signatures of simultaneous superficial sleep even during the deepest sleep state (85).

3.2.2. Instability in cyclic alternating patterns.

Instability and wake-like signatures in the sleep-EEG of ID are also evident in an objective semiquantitative visual scoring approach to polysomnography other than the AASM standard (86). Repetitive alterations of specific EEG patterns coined the "cyclic alternating pattern" (CAP) can be observed during NREM sleep. A "phase A" indicates instability with arousals, and a "phase B" indicates stability. The NREM sleep EEG of people with ID shows more of such alternating patterns with brief (10–15 s) periods of brain activation. The higher CAP rate in insomnia indicates restless NREM sleep (87). The visual scoring of CAPs is less suitable to quantify restlessness of REM sleep for which other EEG features are more appropriate, including the power spectrum, arousal density, eye movement density, and shifts to wake or other sleep stages.

3.2.3. Power spectral density.

In addition to the semiquantitative objective methods requiring visual scoring that have been discussed above, the EEG of people with ID has been evaluated with quantitative methods. Findings provide further support for the emerging conclusion that some wakefulness lingers on during sleep, ready to make sleep lighter or even terminate it. Quantitative methods can be more sensitive to differences between people with ID and controls without sleep complaints, as comprehensively reviewed by Feige et al. (80). 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) (80), representing cortical oscillations that have been associated with wakefulness, alertness and information processing (451).

3.2.4. High-density EEG.

Fewer studies have applied high-density EEG (HD-EEG) during sleep. Spatial information can be evaluated at the

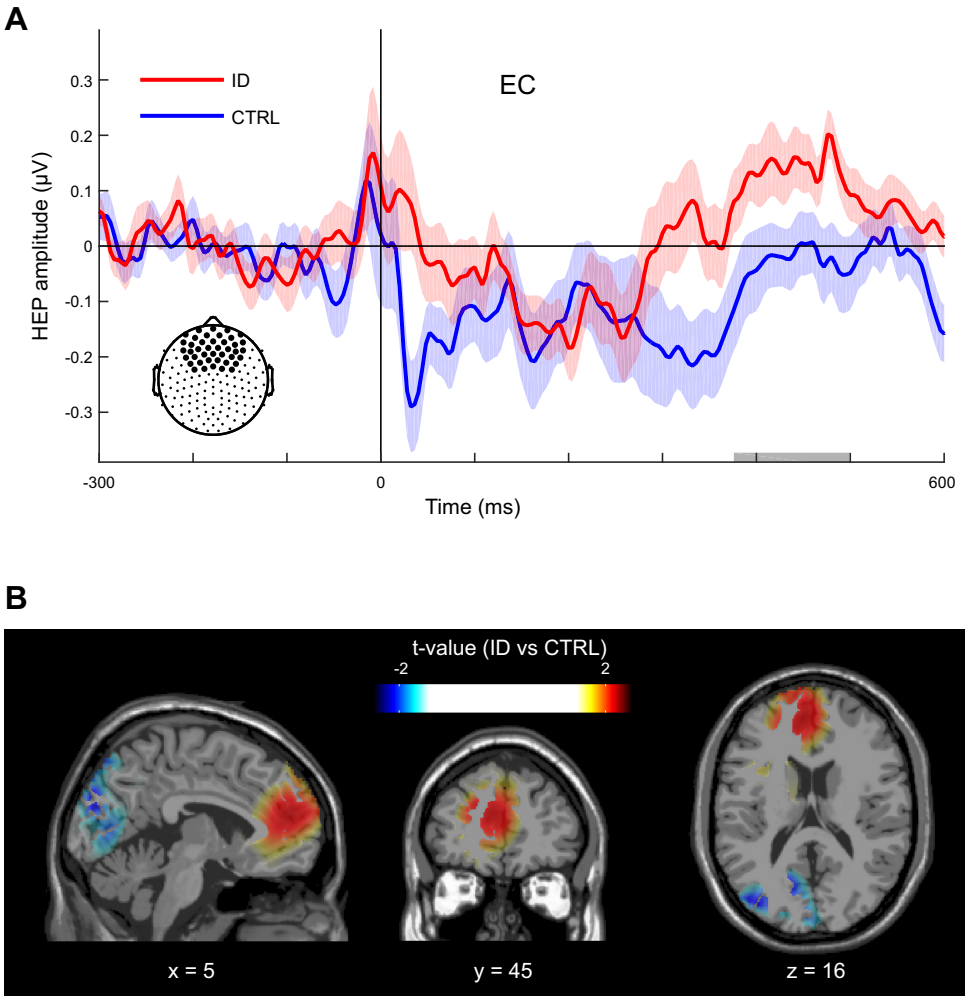

FIGURE 4. Late component in the heartbeat-evoked potential (HEP) in insomnia. *A*: waveforms show the frontal dynamics of the HEP during the eyes-closed (EC) resting state in people with insomnia disorder (ID) and control participants (CTRL). People with insomnia show a significant late amplitude within the 376–500-ms time window (gray bar) that is not present in controls without sleep complaints. Shaded areas indicate one SE. *B*: 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 Ref. 69.]

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 (68, 88).

3.2.5. EEG response to stimuli.

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 investigate the response of the brain to incoming stimuli. As reviewed by Feige et al. (80), 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. (80), 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** and **FIGURE 5** from references (89) and (69)]. Given the MRI findings that suggest involvement of the salience network in the vulnerability to insomnia (sect. 7), it is noteworthy that the insular cortex interacts with the amygdala to transform novel stimuli into familiar stimuli (90).

While on the one hand, sleep can be assessed with the increasingly advanced methodologies of HD-EEG recording and analysis, sleep can on 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., Ref. 91). Sleep estimation from activity signals is based on the low probability that extended periods of time without movement can occur during wakefulness.

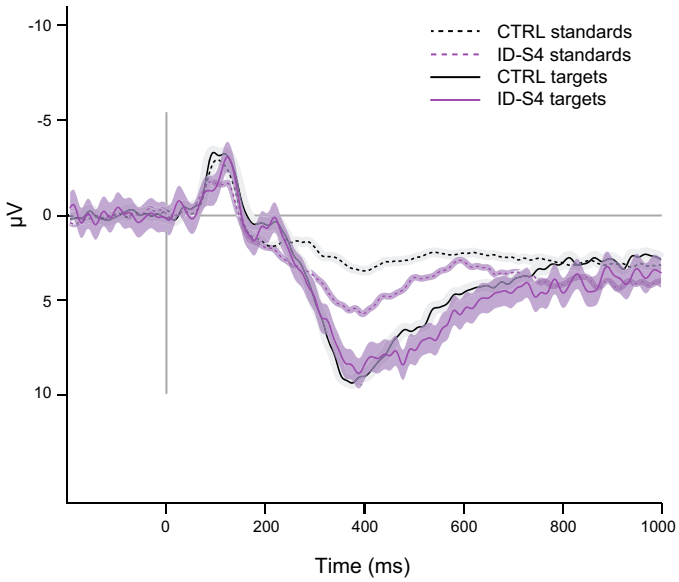

FIGURE 5. Enhanced late components in the auditory oddball event-related potential in the reactive insomnia subtype. Auditory event-related potentials (ERPs) for frequent standard tones (dashed lines) and infrequent deviant target tones (solid lines), recorded during an auditory oddball task in 13 people 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 SE. 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 least 1,000 ms after standard tones were played. This 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 Ref. 89.]

3.2.6. Actigraphy.

Although objective sleep estimates are not required (neither via PSG nor actigraphy) for the diagnosis of ID, it has been suggested that actigraphy aids in recognizing sleep state misperception or paradoxical insomnia (92). As discussed above, these namings may not be optimal if insomnia would involve 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 (93), 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 (94). Interestingly, night-by-night variability, as assessed using sleep diaries (95) or the combination of sleep diaries and actigraphy (96), have suggested subtypes of insomnia and of sleep state misperception.

Natale et al. (97) evaluated the use of actigraphy to distinguish people with insomnia from people without sleep complaints. 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 5 min. Using a different type of actigraph; however, Natale et al. (98) found other variables to distinguish insomnia best. The discrepancy indicated the need of device-independent algorithms that use the raw accelerometry data (99).

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 (100). The meta-analysis concluded as well that actigraphy did not always provide sufficiently reliable sleep estimates and could fail to detect intervention effects on sleep that were established by polysomnography. Thus, Smith et al. (100) echoed a conclusion reached 15 years earlier 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" (101). To improve this situation, progress has been made in optimizing actigraphy specifically for use in insomnia (102).

3.3. *Discrepancy between Subjective and Objective Sleep: Misperception?*

3.3.1. What determines sleep quality?

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. (103) extensively investigated the determinants of subjective sleep quality. It was notable that the top three 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 a good mood during the day. Thus, subjective poor sleep quality primarily reflects a failure of overnight brain processes that promote waking up feeling good.

3.3.2. Misperception or memory of mentation?

Compared with 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 (104–106) or actigraphy does so (107, 108). 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 (3, 104). As stated above (sect. 3.1), we consider it possible that people with insomnia consolidate ongoing mental content during NREM sleep better—and thus wake up at night or in the morning full of memories of thoughts and ruminations (75). As for determinants of the subjective experience of a bad night's sleep by Ramlee et al. (103), Hebert et al. (109) 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 with worse mood on awakening. Thus, sleep state misperception also seems to reflect a failure of overnight brain processes that promote waking up feeling good.

3.3.3. Ruminating during restless sleep.

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. (110) suggested that difficulty to maintain consolidated NREM sleep 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 (14, 111). Riemann et al. (78) 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, nonrestorative sleep (14, 77, 78). Restless REM sleep is also a biomarker of the vulnerability to MDD in symptom-free probands (112, 113).

3.4. Vulnerability to Subjective and Objective Sleep Features Characteristics 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 with 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 *preexisting restless sleep* in people vulnerable to developing insomnia.

3.4.1. Genetic variants relate to restless sleep.

What we can learn of genetic variants that increase the risk of insomnia will be addressed in detail in sect. 5. 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, genetic variants may result in preexisting altered EEG during wake and sleep, pre-sleep arousal and fragmented sleep already before 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 (65) are seen in *SNCA* mouse mutants (114). Altered expression in mice changes *DNM1*, which encodes the synaptic protein dynamin 1, which is increased in *BTBD9* mutant mice (115) and mediates the sleep-disruptive effect of pre-sleep arousal (116). BTBD9 mouse mutants moreover show fragmented sleep (117). Of note, *BTBD9* is the top gene associated with insomnia (118).

3.4.2. Childhood adversity contributes to restless sleep.

How early-life stress increases the risk of insomnia will be addressed in detail in sect. 6. It suffices here to mention that childhood adversity could contribute to the characteristic sleep features of ID described above in the current section. Notably, childhood adversity may result in preexisting altered EEG during wake and sleep, pre-sleep arousal, and fragmented sleep already before any clinical diagnosis of ID. As concisely reviewed by Insana et al. (119), abused children have difficulty initiating sleep and have twice as many nocturnal arousals than nonabused control children (120, 121). People that retrospectively report parental emotional abuse during childhood have worse sleep quality at advanced age (122). Also, once people have been diagnosed with ID, childhood adversity leaves its lifetime trace in sleep, indicated by a higher number of arousals (123, 124). With respect to the general hypothesis that will be developed in this review, it is

important to note that the strongest late effects were seen in REM sleep. Both in humans and in animal models, REM sleep was more fragmented and restless in proportion to the early-life stress experienced (119, 125–128). The lifetime impact of early-life stress on sleep may, thus, be best noticeable during REM sleep.

4. DAYTIME CHARACTERISTICS OF INSOMNIA

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

4.1. Subjectively Experienced Daytime Cognitive and Emotional Functioning

The diagnosis of ID is strictly based on subjective sleep complaints and does not 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 impairments cause marked personal distress or interfere with functioning in work or personal life (129, 130).

4.1.1. Fatigued but not sleepy.

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 (89). Compared to controls without sleep complaints, a highly distressed insomnia subtype suffers on average almost two standard deviations more, while moderately distressed subtypes suffer about one standard deviation more, and low distressed subtypes about half a standard deviation more (89). *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.

4.1.2. Hyperarousal.

Hyperarousal is commonly mentioned as the key subjective complaint experienced by people with ID, contrasting to the hypoarousal that can be induced by sleep depriving people without intrinsic insomnia complaints. Hyperarousal resembles the state of acute anxiety or other emotional distress. Hyperarousal is, however, only one of many persistent, trait-like characteristics that can be experienced subjectively. An extensive survey of personality and affect traits by means of validated questionnaires shows that people with insomnia can experience the following: a lack of action control, lack of agreeableness, lack of extraversion, neuroticism, lack of behavioral activation, fatigue, response to stress and life events, more negative affect, and a lack of positive affect, perfectionism, lack of positive rumination, dampening of positive moods, hyperarousal, rumination, lack of subjective happiness, and lack of experiencing pleasure (89, 131). These characteristics are not equally present in all people with insomnia. Different subtypes of insomnia can be defined on the basis of the profile of the presence and severity of each of the characteristics. Interestingly, these non-sleep-related subtypes are very robust and stable over time. This stability contrasts markedly with some previously proposed unstable subtype classifications that were based on sleep characteristics like “sleep onset insomnia” (132) or on specific predisposing, precipitating, and perpetuating processes [e.g., psychophysiological insomnia (133)]. These earlier subtypes were abandoned from the major nosologies due to a lack of reliability and validity (134).

4.1.3. Emotion: reactivity, regulation, and adaptation.

With respect to *subjective emotion*, Baglioni et al. (135) assessed ratings while exposing people with insomnia and controls to low-to-medium arousing pictures from the International Affective Pictures System, as well as to complementary sleep-related pictures. People with insomnia had enhanced emotional reactivity, especially to sleep-related pictures. In contrast, another study indicated that people with insomnia subjectively rate emotional faces as less emotionally intense (136). The latter finding, however, seemed driven by anxiety and depression rather than by insomnia severity, because individual differences in intensity ratings correlated four times stronger with anxiety and depression than with sleep efficiency. Wassing et al. (13) found that people with insomnia show a deficit in subjective overnight adaptation to a novel distressing experience. As a result, distress was more likely to last not only overnight but even up to weeks (14). Jansson-Fröjmark et al. (137) 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.

4.1.4. Comfort/discomfort imbalance.

A recent study employed the experience sampling (ES) method to evaluate current subjective mood across many time points on multiple days in naturalistic conditions (138). Overall, people with insomnia did not differ from people without sleep complaints on their ratings of commonly used positive and negative mood adjectives (139). Groups did differ, however, on questions that more directly tapped into wanting and liking, the two major discriminable dimensions of reward and hedonic processing (140, 141). A study on more than 3,500 volunteers showed that insomnia *really hurts:* while their nights of worst sleep increase next day's pain disproportionally, their relatively best nights bring less relief (454). In agreement with a previous laboratory study showing insufficient comfort sensing (142), and a home study indicating that people with insomnia do not judge their bed as comfortable as normal sleepers do (143), the findings indicate deficient hedonic and reward processing in insomnia.

4.2. Objectively Assessed Daytime Cognitive and Emotional Functioning

4.2.1. Unlike sleep deprivation: cognitive performance mostly intact.

Objective deficits in daytime *cognitive* functioning in people with insomnia have been systematically reviewed and meta-analyzed (144, 145). Widespread large deficits might have been expected, on the basis of both the subjective complaints of people with insomnia, as well as on the marked effects reported in sleep-deprived people without insomnia (146–148). 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 (149). 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 (150).

4.2.2. Stressed high achievers?

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 (151, 152), word fluency (153), mental flexibility (154), and across tasks (155). Successful intervention for insomnia may even result in a decrease in performance speed (151, 156). Interestin-gly, fast reaction times are associated with increased EEG power in the β- and γ-band (157). As discussed above in sect. 3 and below in sect. 4, high β-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 (158). Performing better instead of worse in stressful and dangerous situation makes perfect sense from an evolutionary perspective.

4.2.3. Overnight plasticity of skills and knowledge.

Only a few studies have compared people with insomnia with controls who sleep well, with respect to *overnight* effects on procedural and declarative memory. While animal studies mimicking aspects of insomnia consistently suggest disrupted sleep-dependent memory effects (20, 159–161), results are not that equivocal in actual patient studies. A first study reported that people with insomnia lacked the overnight explicit memory enhancement of learned associated word pairs that was seen in well-sleeping controls No group differences were seen in overnight changes on a procedural mirror-tracing task. A subsequent study, first reported as a pilot study (12), in contrast, reported results (11) that were dissociating double from those of Backhaus et al. (9). People with insomnia did not have a significantly deviating overnight change in verbal memory, but lacked the overnight improvement on a procedural motor task (mirror tracing) that was seen in fully rested controls. The difference, however, seemed driven mostly by a slow pre-sleep performance in controls: post-sleep performance was identical in people with insomnia and well-sleeping controls. Interpretation of the findings was, moreover, somewhat complicated by the use of a percentage-change score, which results in bias, given the baseline imbalance (162). The finding also contrasted with an

earlier report of a significant overnight improvement on the same mirror tracing task in a sample among whom 74% had insomnia (163). A study that used another procedural task (finger tapping) also found no deviations in insomnia with respect to overnight performance improvements, nor on unperturbed performance of a declarative word pair memory task (10). Interestingly, however, after subsequent interference, people with insomnia showed a stronger drop in declarative performance than good sleepers did in proportion to their individual sleep fragmentation. The study suggests that sleep fragmentation might weaken next day's memory stability and may be revealed only with the use of interference (10). In contrast to Griessenberger et al. (10), Cellini et al. (452), while using the very same procedural finger tapping task, did report an attenuated overnight performance improvement in people with insomnia. Finally, Wislowska et al. (164) reported unperturbed overnight consolidation of word pairs in insomnia and noted that overnight forgetting was mostly bound to occur to people with poor baseline performance. In summary, it remains quite equivocal whether people with insomnia show deviations in overnight changes on explicit and implicit tasks. Of note, all of the studies mentioned above used tasks without emotional relevance. A few more recent studies specifically addressed another type of *overnight* learning in insomnia: *emotional distress adaptation*, with consistent and remarkable findings, as will be discussed in detail in sect. 10 (13–16).

4.2.4. Overnight plasticity of emotional distress.

Relatively few studies objectified deficits in daytime *emotional* functioning in people with insomnia. Baglioni et al. (135, 165) report a stronger emotional reactivity, especially to sleep-related pictures: in facial electromyography, electrocardiography, and the functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) response of the amygdala. Wassing et al. (15) investigated the overnight adaptation in the fMRI BOLD response of the amygdala to a novel self-conscious emotional experience and found worse adaptation in subjects that had more fragmented REM sleep—a key characteristic of insomnia. They also compared responses to novel self-conscious emotional experiences and relived memories of such experiences from the distant past (16). While autonomic and BOLD responses to novel experiences were not altered in people with insomnia, they showed stronger autonomic responses to relived experiences, as well as stronger BOLD responses in the salience network circuit, including limbic parts, notably in the dorsal anterior cingulate cortex (ACC).

4.2.5. EEG and fMRI indexes of an alert brain.

Few studies have investigated deviations in insomnia in resting state EEG recorded during wakefulness. EEG differences between people with insomnia and controls are more consistently found during sleep than during wake (166). Wake-like activity during sleep may be easier to detect than "added" wake-like activity amidst the normal wake EEG activity, where ceiling effects are more likely. As reviewed by Colombo et al. (65), wake-EEG studies overall once more indicate most consistently increased power in the β-range, just as is the case during sleep. High-density EEG (HD-EEG) recordings have added spatial information to spectral findings. Both scalp-level topography and source estimates suggested widespread global rather than cortically localized increased β in people with insomnia (65), as is the case during sleep (68). In addition, wake α- band activity (8–12 Hz) was lower in people insomnia than in controls across the cortex (65), in contrast to their increased α-band activity specifically in sensory-motor areas during sleep (68). The contrasting lower α before sleep and higher α during sleep had been reported before using regular EEG (88). Both lower α and increased β before sleep indicate pre-sleep arousal (88). Wake hyperarousal is also supported by fMRI findings of predominantly salience network activation, as will be extensively discussed in sect. 8.

4.2.6. Autonomic indexes of an alert brain.

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 assumed in insomnia (167), deviations in heart rate and its variability are not unequivocally supported by actual findings (168). 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 (169). Twenty-four-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 (169). 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 posttraumatic stress disorder (170). A perturbation

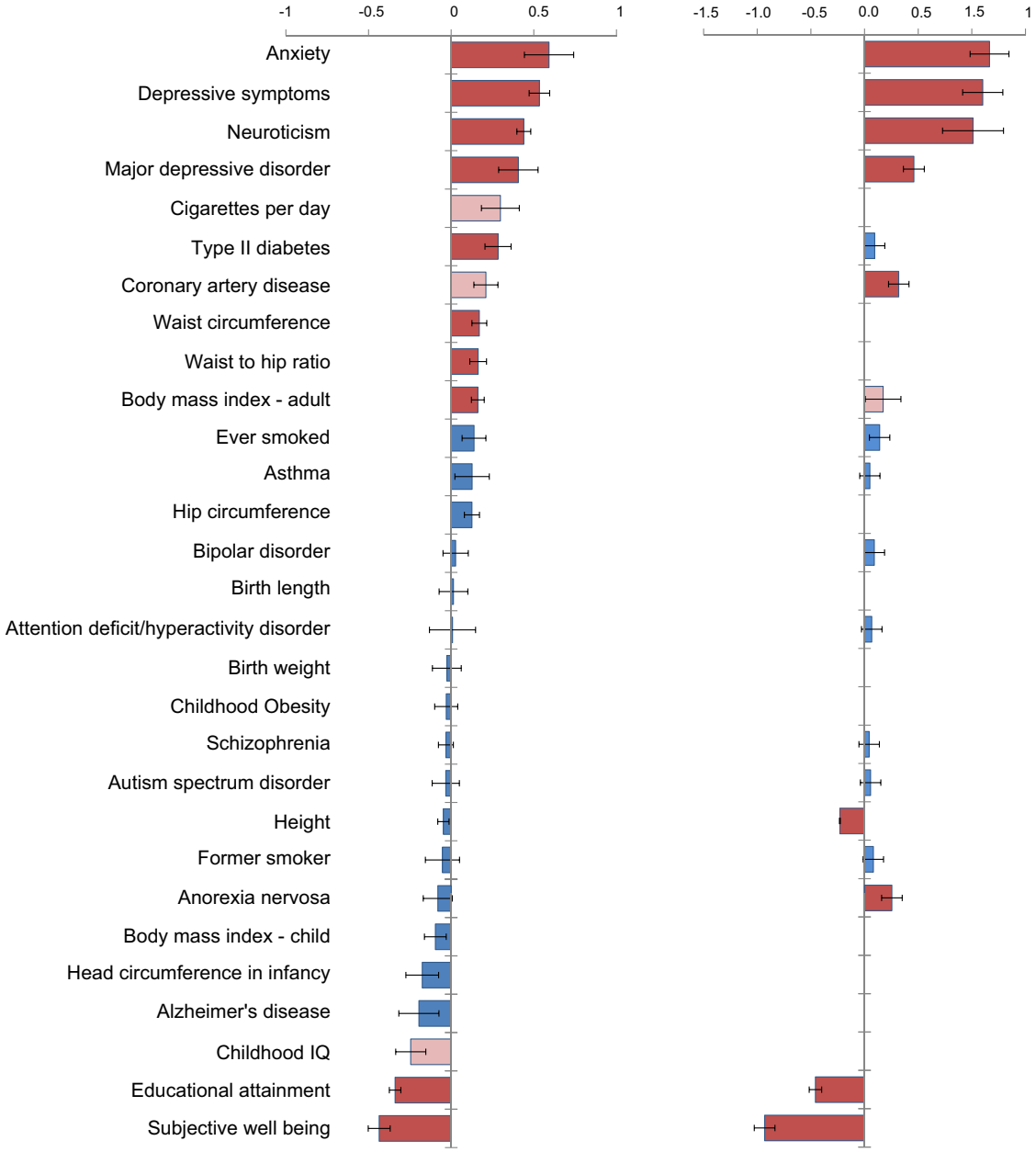

FIGURE 6. Genetic and phenotypic overlap of insomnia with other traits and disorders. Bars in the left panel show genetic correlations (r_g) between the frequency of experiencing trouble falling asleep or waking up in the middle of the night and various other traits and diseases. Error bars represent 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 (89, 131). Bars in the right panel show phenotypic overlap of insomnia with the same subject characteristics assessed in this independent sample. The profiles of genetic correlations and phenotypic effect sizes are strikingly similar. [Adapted from Ref. 32.]

approach seems even more powerful if it is repeated overnight (15).

5. 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 the underlying mechanism of the disorder. The current and next sections (sects. 5 and 6) 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 (171, 172). The same

heuristic model can be 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 current and next sections will, therefore, systematically review risk factors along the developmental axis, starting with heritability and genetic variants (sect. 5), followed by prenatal stressors, adverse childhood experiences (ACEs), major life events, and trauma (sect. 6), and current stressors from disease and the socioeconomical and physical environment (sect. 6).

5.1. Heritability

Can people be "born" with a risk to develop insomnia? Family and twin studies, indeed, suggest that this is the case. As scholarly review by Lind and Gehrman (173) found 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 the part accounted for by genetics requires twin studies. The heritability estimates reported for specific insomnia phenotypes ranged from 0.28 to 0.59 (240) and the most recent meta-analyzed average estimate is 0.44 (208). Two particular estimates, 0.59 for women and 0.38 for men seem most representative for trait-like, persistent insomnia vulnerability, because they were found in a longitudinal repeated-measures study (174). A higher heritability of insomnia for females than for males was found before (0.55 vs. 0.43, respectively; Ref. 175), and it resembles their higher heritability for depression (0.40 vs. 0.29, respectively; Refs. 176, 177). Not only insomnia itself has shown to be partly heritable. Heritability has also been documented for the traits that have been associated with insomnia, as shown in Supplemental Table 1 of Blanken et al. (89).

The heritability of insomnia seems at least as pronounced as the heritability for anxiety, depression, and neuroticism, arguably the three traits that are most closely related to insomnia (see **FIGURE 6**). Meta-analytic and large-scale studies provide heritability estimates of 0.32 for anxiety disorder (178), 0.38 for major depression (177, 179), and 0.39 for neuroticism (180). Accordingly, one could expect at least as much statistical power to find loci for insomnia in molecular genetics studies as there has been in studies on anxiety, depression, and neuroticism risk genes.

5.2. Genetic Variants

The heritability of insomnia indicates that variants of specific genes could increase its risk. Involved genes can be found by comparing cases and controls with respect to the presence of DNA base pair differences at specific locations, known as single nucleotide polymorphisms (SNPs). DNA differences can also occur in the number of repeats of short 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 is 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. Therefore, more recent work has 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 to its perpetuation, or *chronicity*, as has been suggested for PTSD (181).

5.2.1. Candidate gene studies.

CGS on insomnia have been reviewed in Lind and Gehrman (173). Insomnia has been associated with polymorphisms in genes implicated in other psychiatric disorders. Examples are genes involved in the transport (*5-HTTLPR*) (182, 183) or metabolism (*MAO-A*) (184) of serotonin. One study found an increased probability of insomnia in carriers of the *Apoε4* allele (185). Overall sleep disturbance measured with the Pittsburg Sleep Quality Index (PSQI) showed no significant association with 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* (187), *PER3* (188), *CLOCK* and *BMAL1* (189), and PGC-1α, a gene involved in both clock mechanisms and metabolism (185).

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

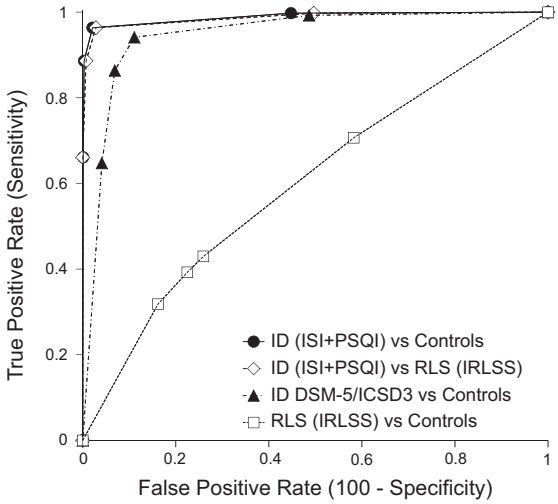

FIGURE 7. UK Biobank insomnia phenotype validation. Receiver operating characteristic curve shows excellent accuracy of the UK Biobank question on insomnia to discriminate insomnia (defined with two different methods in an independent sample) against controls and restless legs syndrome (RLS) in an independent sample. Two questions on trouble falling or staying asleep were assessed in the Netherlands Sleep Registry (89, 131), along with the Pittsburgh Sleep Quality Index (PSQI), the Insomnia Severity Index (ISI) and Diagnostic and Statistical Manual (DSM)-5+ International Classification of Sleep Disorders 3 (ICSD3) and International Restless Legs Syndrome Scale (IRLSS) diagnoses obtained in a structured interview. The five markers (some markers are hidden due to overlap at the origin) from left to right on each curve indicate answers from two questions on trouble falling or staying asleep with very severe, with severe, with moderate, with mild, or with none of either. Solid line with solid circles denote people with probable insomnia disorder (ID), according to ISI+PSQI criteria versus controls. Dashed line with open diamonds denote people with probable ID (ISI+PSQI) vs. RLS (IRLSS). Dash-dotted line with solid triangles denote ID (DSM-5+ICSD3 criteria) versus controls. Dotted line with open squares denote 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 ID, validating its usefulness for genome-wide association studies.

are genetically predisposed to be late chronotypes will experience difficulties with sleep onset if they try to adhere to a societally desirable clock times. However, this is not the same as insomnia. Likewise, although it is valuable to find genetic variants related to daytime sleepiness (190) or stress reactivity (191, 192), these genes may not necessarily be specific to the risk of insomnia disorder. Genetic variants associated with insomnia-related traits have been reviewed in Table S2 from Blanken et al. (89).

5.2.2. 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. Although samples of more than a million have become available and help to overcome the first issue, there is no sizable cohort with a detailed clinical diagnosis of insomnia disorder.

Hammerschlag et al. (32), 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 (131), 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 from reference (32).

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. (193) found significant associations of insomnia with *MEIS1, TMEM132E*, and *CYCL1* across sexes and one additional gene in both 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 (118). 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

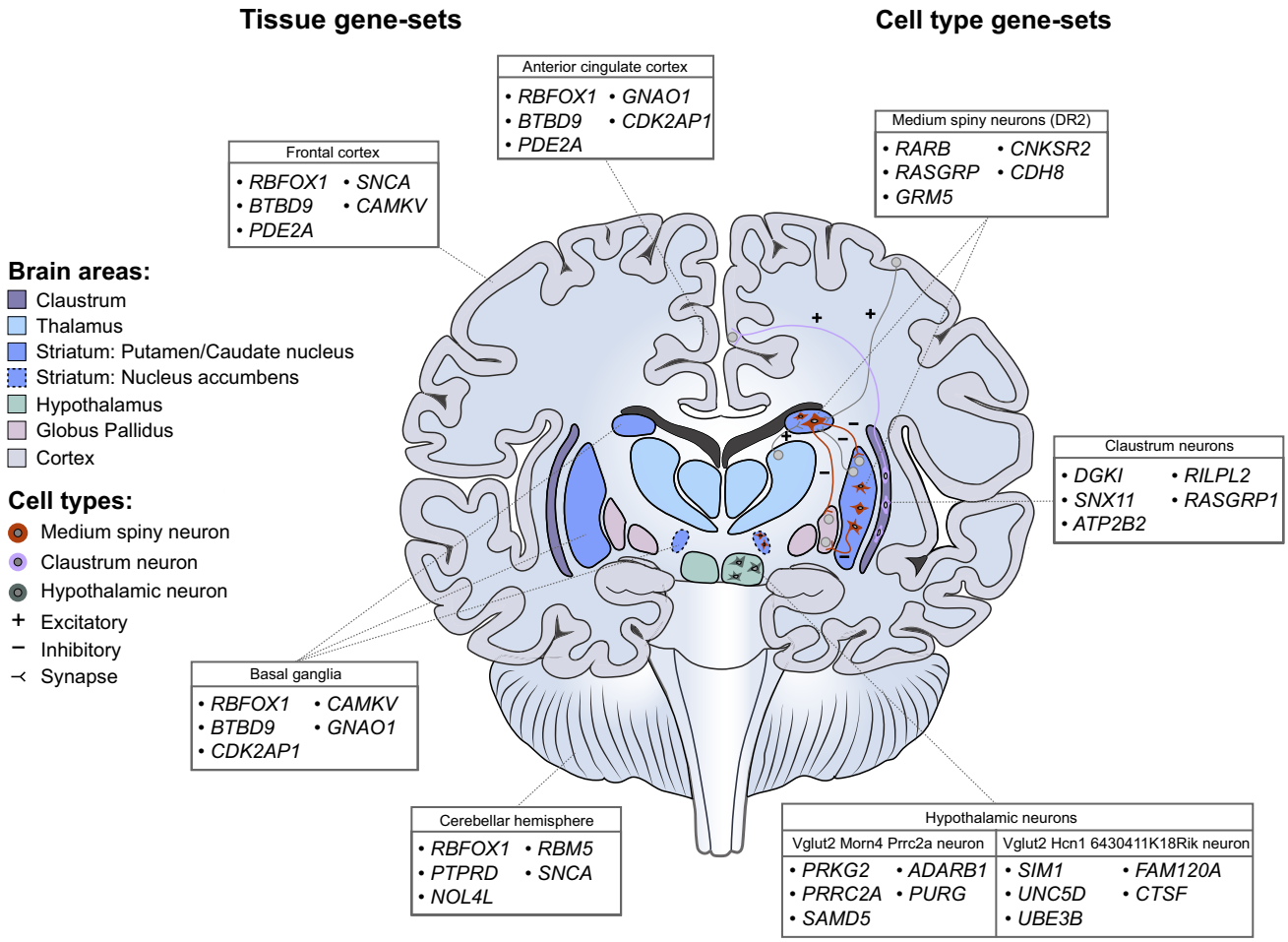

FIGURE 8. Brain tissues and cell types associated with genetic vulnerability of insomnia. Genes with a genome-wide significant association with insomnia were found in a genome-wide association studies in 1,331,010 individuals. Gene-set analyses subsequently identified genes that significantly converged in tissue- or cell-specific gene expression. [From Ref. 118.]

al. (118) 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 (115, 116). *BTBD9* mouse mutants also show altered plasticity, resulting in a stronger fear memory (115) and other phenotypes that match findings in insomnia (117), like increased restless, more fragmented sleep, and altered thermal sensitivity (142, 194).

5.2.3. Variance explained by GWAS.

So far, GWAS have explained only a very small percentage of the phenotypic variation of insomnia: 2.6% in the largest GWAS to date (118). Theoretically, if all genetic variants affecting insomnia were known and if all their effects were estimated correctly, the maximal variance explained could equal the heritability, which meta-analysis estimated to be 44% (195). The large difference between the variance explained by GWAS versus heritability estimates is common for complex traits and is known as the "missing heritability" (196, 197). 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 Refs. 196–198).

While limitations of genetic methodology received the most attention in explaining the missing heritability, phenotypic measurement issues contribute significantly as well (for a review, see Ref. 196). Although diagnostic nosologies present insomnia is as a clear-cut disorder (1, 3), the actual presence of the disorder may fluctuate during a lifetime, and GWAS cohorts may be heterogeneous with respect to established robust subtypes of insomnia (89). 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. One GWA study that extensively validated the UK Biobank insomnia phenotype using an independent deep-phenotyped cohort (89, 131) demonstrated its excellent properties to discriminate cases with probable insomnia disorder [see **FIGURE 7** and Figures S1 to S4 in Hammerschlag et al. (32)].

One may question the value of GWAS if missing heritability remains large in spite of an 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 as to involvement of specific biological functional pathways, tissues, and cell types. Of note, any suboptimal function in these substrates does not necessarily only have to result from genetic variants but could of course also emerge during one's lifetime due to other causes than genetic make-up, thus diluting the variance explained by GWAS. These substrates will be discussed in the paragraph below.

5.2.4. GWAS provides clues on cell types and tissues involved in insomnia.

Insomnia risk genes are likely to sort their effect by altering brain function. Jansen at al. (118), 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 anterior cingulate cortex. The cerebellar hemisphere was enriched as well. Three striatal basal ganglia structures (nucleus accumbens, caudate nucleus, and putamen) showed gene expression that was highly similar to that of the cortical areas ($r > 0.96$) but fell just below the significant threshold for enrichment. Concertedly, the tissue gene-set findings suggest 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 MSNs 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 mediolateral 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** (from Ref. 118) 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 it predisposes people to become vulnerable to insomnia.

5.2.5. Comorbidity: a role for the MEIS1 gene in insomnia, RLS, and PLMS?

Across the few large studies on insomnia risk genes, a consistent significant association was found with *MEIS1*. A closer study of its 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) (199–201). Thus, it is 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 that they *usually* have trouble falling asleep at night or wake up in the middle of the night. "Usually" is more often than would 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 (202). 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) (203). In fact, only a minority of RLS patients (13%) experience restless legs symptoms more than three times a week (204). In contrast, experiencing sleep problems at least three times a week is a defining characteristic of insomnia disorder. Indeed, Hammerschlag et al. (32) 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**; see also Figures S1 to S4 in Hammerschlag et al. (32)]. 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 complex and severe cases that report to sleep centers specializing in RLS. Hammerschlag et al also provided detailed additional analyses to demonstrate that *MEIS1* shows pleiotropy for insomnia and RLS: the same genetic variant can manifest itself in different phenotypes. In addition, different loci within the gene may differentially increase the risk of one or the other phenotype, as has been suggested for involvement of *MEIS1* in RLS and PLMS as well (199).

5.2.6. Mapping genetic variants across sensory, motor, and cognitive restlessness?

If we consider the conceptual hallmarks of RLS, PLMS, and ID, there is a striking link of hyperarousal, restlessness, or agitation: *sensory* restlessness in RLS, *motor* restlessness in PLMS and *higher-order* restlessness (cognition, consciousness) in ID. This "tripartitioning" may be too strict: the disorders show high comorbidity, and biomarkers and underlying mechanisms may overlap in several ways. For example, trouble falling asleep in RLS relates to similar EEG power abnormalities, as found in insomnia (205, 206). In *MEIS1* mouse mutants, hyperactivity, which is most characteristic of insomnia, has even been used as a readout for *RLS* rather than for insomnia (207). In conclusion, it appears worthwhile to investigate how known functions *MEIS1* could be relevant to close in on the enigmatic mechanisms underlying individual differences in vulnerability to insomnia.

5.2.7. Mapping genetic variants across emotional restlessness?

Several animal studies addressed the involvement of *MEIS1* in developmental biology. The gene encodes a protein that activates and regulates transcription that is essential for normal development of the central nervous system (207–209). The early recognition of *MEIS1* involvement in RLS may have promoted a focus on *MEIS1* mutation consequences specifically for the motor system (207). However, *MEIS1* has longer been known to be involved on other functions. A relevant example is the regulatory role of *MEIS1* in the expression of substance P, both in the subset of medium spiny neurons that project to the substantia nigra (210) and in the human amygdala (211). This is an interesting lead, 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** from (32)]. In support of suboptimal amygdala functioning in insomnia, fMRI studies revealed that people with insomnia show an enhanced amygdala responses to insomnia-related stimuli (165) and a lack of overnight attenuation of the amygdala response to emotional stimuli (15). A more detailed discussion of the link between insomnia, mood, and anxiety will follow in sects. 7 and 10.

6. 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 (212). 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.

6.1. 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 have 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 (213). 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 (214). A systematic review suggests effects of prenatal stress on infant sleep duration and architecture (215). 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 (215), suggest that prenatal stress alters sleep in adulthood, as indicated by less slow-wave sleep and increased REM-sleep pressure (216, 217). Somewhat more animal studies demonstrated effects of prenatal stress on adult hypothalamus-pituitary-adrenal (HPA) axis functioning and sympathetic reactivity (215). Indeed, stress reactivity lasting into the night and disrupting

sleep increases the risk of developing insomnia (218–220).

One virtually unexplored possible prenatal stressor concerns the maternal sleep problems that are experienced by about 10% of pregnant women (221). Studies on the effects of maternal sleep on fetal outcomes are limited and often conflicting (222). An intriguing hypothesis is that maternal fatigue, depression, and hormonal changes induced by sleep problems during pregnancy impair the mother-infant relationship (223), which could, in turn, increase the odds of insomnia in adulthood, as described in the next paragraph.

6.2. Adverse Experiences

Not only prenatal stress, but also stress during early childhood can lead to persistent consequences for adult stress sensitivity and regulation (215). These persistent changes in the stress system can increase the risk of 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?

6.2.1. 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 by Palagini et al. (215). Some earlier samples from small- to medium-sized studies, indeed, suggested that childhood adversity could increase the risk of insomnia in adulthood (124), in adolescence (224), and in early adulthood (225, 226). Koskenvuo and colleagues (226) were the first to report on 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 experiences, including parental divorce, prolonged financial difficulties, serious conflicts, frequent fear of a family member, poverty, and illness or alcoholism of a family member. Of the different adverse events, frequent fear of a family member and serious conflicts increased the odds most strongly. Worst off were those that experienced more than two adversities and additionally had a poor relationship with their mother [odds ratio (OR) 10.4] or father (OR 5.4).

A critical question is whether ACE increases insomnia only secondarily, as a complaint strictly due to other conditions, like depression. In the study of Koskenvuo et al. (226), adjustment for current depressive symptoms changed the results only modestly, indicating that the effect of childhood adversity on sleep complaints is not simply secondary to its known effect on the risk of developing depression in adulthood. Notably, the odds of having poor sleep are much higher than the odds of for depression (OR 4.4), as well as the majority of other adverse health sequelae, as recently meta-analyzed (227). Interestingly, adjustment for recent life events did not considerably change the odds for poor sleep after childhood adversity either (226).

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

6.2.2. Does the kind of ACE matter?

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

This question has been posed previously for the risk of other disorders. For example, neglect has been suggested to be the strongest predicting ACE subtype for depression (228). However, as reviewed by Negele et al. (229), studies that tried to map specific types of ACEs to specific mental disorders yielded quite equivocal results. In their own study that aimed to map specific types of ACEs to features of depression, multiplicity rather than specificity of adversities predicted symptom severity, and the more chronic the ACEs, the higher the lifetime prevalence of depression (229).

In insomnia, it has been reported that childhood adversity among people suffering from insomnia disorder most markedly concerns emotional neglect (124). Insomnia complaints in the elderly have been linked primarily to childhood emotional abuse (122). As is the case for depression, it may be the number and categorical multiplicity that primarily drives increasing severity of insomnia. A large ($n \sim 17{,}000$) epidemiological study (230) showed that trouble falling or staying asleep increased with the *number* of adversities people had experienced during childhood. A proportional increase of the risk of current insomnia has also been seen with an increasing *diversity* of childhood adversities, both in adolescents (224) and in elderly people (122).

In summary, the findings provide further indirect support for the involvement of early learning "not to be safe". Early-life learning of being unsafe and of the need to stay *watchful* will engrave a stronger memory trace if such learning occurs repeatedly and *across multiple*

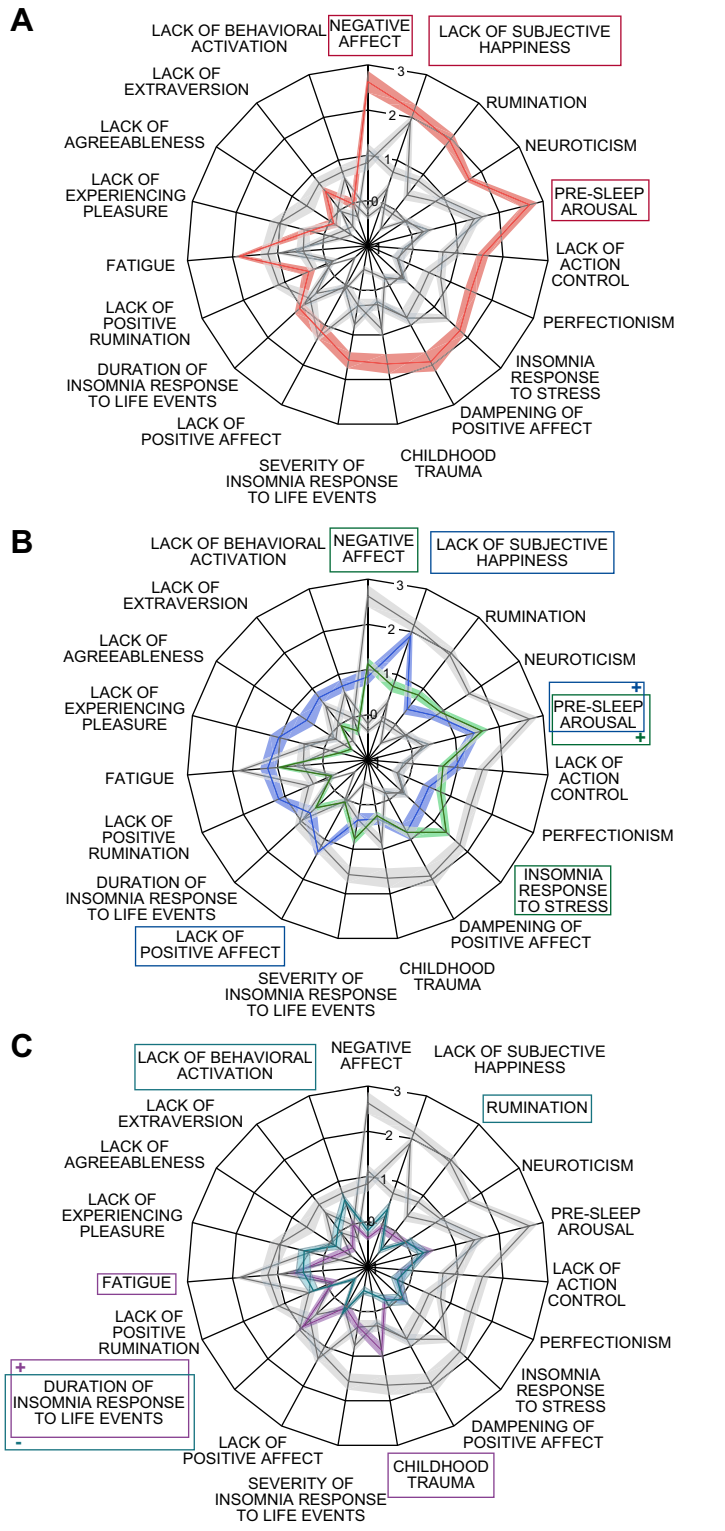

FIGURE 9. Multivariate profile plots of insomnia subtypes. Data are scaled subtype group means [95% CIs (confidence intervals)], in which *Z* scores have been standardized to the mean and SD of controls for each characteristic, with the subtype-explained variance, ranked clockwise from the top. *A*: 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 (e.g., subjective happiness) were reverse-coded and renamed (e.g., lack of subjective happiness), 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 Ref. 89.]

contexts. Indeed, the increased risk of insomnia after childhood adversity is mediated by neuroticism (231), which has been defined as a general sensitivity to negative information. It is tempting to suggest that early-life learning of being unsafe and of the need to stay watchful could result in lasting alterations in brain circuits effectuating a lifelong inclination for hypervigilance (122, 232), that could even continue into sleep.

6.2.3. Objective indices of disturbed sleep after trauma.

Childhood adversity predisposes to fragmented REM sleep (119), a key feature of chronic insomnia (14, 77, 78). Among people suffering from insomnia disorder, those that reported childhood adversity specifically show more awakenings and movement arousals in both polysomnographic and actigraphic recordings of their sleep, while other sleep variables did not differ (124). 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 α-oscillations in the sleep-EEG—a marker of insomnia (233).

6.2.4. Memory traces of ACEs hidden in gene expression.

ACEs can have a persistent impact on gene expression and behavior through epigenetic mechanisms (234). For example, ACEs increase DNA methylation in the promoter region of the serotonin transporter gene (SERT) (235, 236). This epigenetic effect alters SERT expression and stress reactivity throughout life. This mechanism could be relevant for at least one subtype of insomnia (see sects. 8 and 10 and **FIGURE 9**) that is, indeed, characterized both by ACEs and by more severe and longer-lasting effects of recent life events on insomnia symptoms (89).

"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 (237). 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* (235, 238) and *FKBP5* (238). Polymorphisms in *SLC6A4* increase the risk of insomnia (239). Moreover, in interaction with ACEs, polymorphisms in both *SLC6A4* (240, 241), and *FKBP5* (242) specifically promote hyperarousal symptoms, which are most characteristic of insomnia as well.

6.2.5. 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 (226, 243). 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 posttraumatic 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 (119).

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 (219, 220, 244). Indeed, current poor sleep is among the strongest risk factors for future insomnia (OR = 11.07) (245). 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 (244).

Stressful life events, for which someone perceives as being responsible, are more likely to result in insomnia than events that are beyond one's control (246). This finding indicates that studies on emotion processing in insomnia could be most sensitive if they address *self-conscious* emotions like guilt, shame, and embarrassment, rather than the basic emotions that are usually studied, e.g., using the International Affective Picture System (247). Indeed, strong findings recently emerged in a series of studies on overnight dissolving of self-conscious emotional distress in insomnia (13–16). A more detailed discussion of the deficiency in overnight dissolving of self-conscious emotional distress in insomnia will follow below in sects. 7 and 10.

7. 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 (248). Somatic conditions of which the risk increases are for example obesity (249), Type 2 diabetes (249), and cardiovascular disease (250). Insomnia, however, most notably increases the risk for mental disorders, including anxiety disorders, major depressive disorder, bipolar disorder, and post-traumatic stress disorder (251–254). A cross-mental disorder meta-analysis reported that insomnia most significantly predicts onset of anxiety disorders (six studies, OR 3.23) and depression (10 studies, OR 2.83) (255). Only studies on the risk of depression that did not find insomnia have not included it as a possible predictor (e.g., Ref. 256). Males and females do not differ with respect to the risk of depression conveyed by insomnia disorder (257). The risk of inflammation-induced depressive symptoms can, however, be stronger in mildly sleep-disturbed women than men (258).

Preexisting insomnia is also key to whether or not a traumatic experience elicits PTSD (259, 260), as well as to the persistence of PTSD (260). Indeed, good-quality sleep may be protective against poor emotion regulation and anxiety in veterans with PTSD (261). Interestingly, the most characteristic polysomnographic findings of disturbed sleep in PTSD are virtually indiscriminate 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 (262, 263). Both arousal and eye movement density have been linked to experiencing continuing thoughts during sleep in insomnia, and to insufficient overnight adaptation to emotional distress, which may accumulate to chronic hyperarousal (14).

Across psychiatric brain disorders, insomnia is probably the most common and burdening co-occurring symptom. While this is generally recognized for major depressive disorder (264), it may hold for other disorders of mood or distress regulation as well. Zhou et al. (265) found that four out of five of generalized anxiety disorder (GAD) patients have comorbid insomnia disorder. Sleep studies have also shown that these subjective complaints have their objective counterpart in sleep EEG recordings. On the basis of similar polysomnographic sleep features in primary insomnia and major depression, Hein et al. (266) suggested a common underlying pathophysiology. Restless sleep was also found in people with high trait anxiety (267), PTSD (119, 268, 269), and GAD (270). 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, is more likely to develop disorders of mood or distress regulation (244). Insomnia aggravates the disease state, worsens the prognosis, impedes treatment response, and promotes relapse after recovery (271–273).

Importantly, interventions for insomnia also ameliorate depressive symptoms (274–279) (for meta-analysis, see Ref. 280). Although it has been demonstrated that insomnia is, indeed, an independent risk factor contributing to *first-onset* depression (281), a 6-mo 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 (277). 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.

8. 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 Refs. 282–284). Findings do not converge robustly at the voxel level (285). Here, we 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 (282, 283). For magnetic resonance spectroscopy (MRS) studies to assess concentrations of neurotransmitters, including glutamate GABA, we refer to Kay and Buysse (282), 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 (285). 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 total sample size and the sample size of individual studies are 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 has shown highly significant differences in the overnight changes in brain activation between people with insomnia and those without sleep complaints. Fourth, differences in recruitment strategies and inclusion criteria make it highly likely that the samples included in the meta-analyzed studies differed considerably in the proportion of each of the different subtypes of insomnia that have been identified (89). These subtypes are distinguished by specific profiles of traits, which were mostly selected on the basis of being associated with specific brain structural- and brain functional characteristics. Brain structural correlates of insomnia-related traits have been reviewed in Table S3 of Blanken et al. (89). Subtypes are likely to differ with respect to their *distributed deviations* of brain characteristics (286). Moreover, even within an individual, dysfunction may not necessarily relate to the same voxels across time. Metaphorical examples can be given to explain this. A brain structural metaphor would be the white-matter intensities in multiple sclerosis that may disappear from one location and later appear at another location. A brain functional metaphor would be that a slow car *anywhere* on a crowded highway can result in a queue that increases the time it takes to reach one's destination.

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

8.1. Volumetric and Voxel-Based Morphology Studies

As mentioned above, meta-analysis did not reveal consistently affected voxels in insomnia (285). At the extremes, poor sleep quality has been related to both cortical atrophy (287, 288) and hypertrophy (289). However, some consistency exists for more localized differences between people with insomnia and controls without sleep complaints. Quite a few volumetric and voxel-based morphology studies suggested that deficiencies anywhere in the orbitofrontal cortex could increase the risk of insomnia. The orbitofrontal cortex is strongly implicated in hedonic evaluation (290, 291), which, indeed, is compromised in people with insomnia (138, 142, 292). People with a low gray matter density in a part of their orbitofrontal cortex are vulnerable to early morning awakening (293), insomnia (294–296), fragmented sleep (297), and low perceived sleep quality (298). In contrast, people with a high orbitofrontal gray matter density succeed to habitually sleep longer than they consider strictly necessary (299). Some of these studies located low orbitofrontal gray matter, especially at the border of the insula, the part that is strongly implicated in the salience network (293, 294). Of relevance to insomnia and emotion regulation (see sects. 4 and 10) is that the orbitofrontal cortex (OFC) is implicated in downregulating and reappraising emotional distress (300, 301).

8.2. Structural Connectivity

Structural connectivity of white matter can be assessed by diffusion tensor imaging and probabilistic tractography. Several studies reported associations of sleep quality and quantity in areas that are also suggested by other methods discussed in this section. Jespersen et al (302) used network-based statistics to compare people with insomnia and controls without sleep complaints to reveal a particular reduction in the connectivity in a network with the insula as a key node. Khalsa et al. (303) 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. Findings from a connectome analysis once more included compromised connectivity of the orbitofrontal-anterior insula and anterior cingulate cortex in people with insomnia (304).

Probably the most consistent findings on white matter alterations in insomnia concern the anterior limb of the capsula interna (305–308). 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 (309). Fronto-subcortical networks subserved by the anterior limb of the capsula interna show functional and structural network connectivity alterations in insomnia (302, 310, 311).

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 network. Wei et al. (312) 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.

8.3. 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. (313). The findings did not show robust convergence, yet they 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 (314, 315); and the dorsomedial nucleus of the thalamus (316). 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 before 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 (317). Further support of its robust involvement in insomnia was demonstrated by using a different methodology to assess resting state dynamics; i.e., quantifying EEG microstates also pointed to the involvement of the salience network (70). Within the salience network, especially the insula shows enhanced activation in people with insomnia, in proportion to their EEG γ-band activity and negative mood (318). In addition to the voxel-based morphometry and volume studies mentioned above, several functional connectivity studies support the involvement of the orbitofrontal cortex in altered salience network functioning in insomnia (319). Reduced gray matter density in the orbitofrontal cortex was found to attenuate its efferent functional connectivity to head of the caudate nucleus (320). Lee et al. (321) 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 relevance to insomnia is that the head of the caudate nucleus is implicated both in distinguishing pleasantness (322) and suppressing cortical excitability (see Ref. 320).

Resting state fMRI may also be studied under different pharmacological conditions. Although not specifically targeted at insomnia, one study is particularly worthwhile mentioning, given the hypothesis developed in the current review. Song et al (323) assessed locus coeruleus connectivity while pharmacologically suppressing its activity using an agonist of inhibitory autoreceptors on noradrenergic cells. Silencing of locus coeruleus activity particularly affected its connectivity with multiple regions that have previously been shown to functionally or structurally deviate in insomnia, notably, the anterior cingulate cortex (16), insula (302) precuneus (294), thalamus (307), and caudate nucleus (320).

Dynamic functional connectivity (DFC) of resting-state fMRI is a method that has somewhat higher sensitivity to detect distributed dysfunctions that are only subtle. Only one study so far has investigated DFC in insomnia (324). The study included 65 people with insomnia and 65 controls without sleep complaints. In support of the sensitivity of the method, the study showed that while none of the average between-network functional connectivity strength deviations in insomnia reached significance, people with insomnia did show significantly less variability in functional connectivity between the anterior salience network and the left executive control network. The finding suggests less flexible interaction between the salience network and the executive control network during resting state in people with insomnia.

The salience network interacts with other networks. It modulates activation of the default-mode network and the executive-control network (325). Reduced dynamic FC of the salience network could compromise switching between networks in response to changing environments and needs. fMRI during demanding cognitive tasks provides some support for this idea. They reported hypoactivation of the left inferior frontal gyrus, which is part of the executive-control network (153), and a failure to deactivate the default-mode network (326) in people with insomnia. The salience network also strongly interacts with the amygdala. A study with a small sample size reported altered functional connectivity between the

insula and the amygdala in people with insomnia (327), as previously reported for generalized anxiety disorder as well (328). Interestingly, altered insula connectivity seems key in the exaggerated interoceptive and exteroceptive processing in people at risk of anxiety due to a polymorphism in the *ADORA2A* gene (329), which alters the function of the receptor for adenosine, the key molecule involved in homeostatic regulation of slow-wave sleep (330, 331). Transdiagnostic involvement of the areas here discussed in both sleep and mood complaints is also reported by a study using the large human connectome sample (332). Both of these types of complaints were associated with altered functional connectivity in several of these areas, including the orbitofrontal, insula, and anterior cingulate cortices and the amygdala.

8.4. Brain Activation during Tasks

Surprisingly, few studies have evaluated differences between people with insomnia and controls without sleep complaints in task-related brain activation. As mentioned in this section, fMRI during demanding cognitive tasks suggest hypoactivation of the left inferior frontal gyrus, which is part of the executive-control network (153), and a failure to deactivate the default-mode network (326) in people with insomnia. As mentioned in sect. 4, a few studies have assessed fMRI during emotional tasks. Baglioni et al (135, 165) report a stronger reactivity of the amygdala to sleep-related pictures. Moreover, Wassing et al. (15) found insufficient overnight adaptation of the amygdala in subjects with fragmented REM sleep, a key characteristic of insomnia. They also reported stronger activation in the salience network circuit, including the limbic parts, notably in the dorsal anterior cingulate cortex in people with insomnia, while reliving emotional memories from the distant past (16). Seo et al. (333) 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.

8.5. 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 (334) and concertedly affect consciousness, sleep, and arousal. All three areas are also involved in sensing pleasantness (335, 336). The pontine brainstem locus coeruleus receives extensive direct inputs from the anterior cingulate cortex (ACC) and OFC reflecting contextual relevance (337). The LC thus monitors activity in the salience network to adapt its activity accordingly (337). Animal studies showed that lesions of the anterior insula affect sleep through strong reciprocal connectivity with wake and sleep-regulating hypothalamic and brain stem regions (338) and that electrical stimulation of orbitofrontal cortical areas can induce EEG and behavioral manifestations of sleep (339). The anterior insula and the subcortical claustrum that it lines are important parts of a network that subserves consciousness (340). Of note, several of these structures, including the claustrum and the anterior cingulate cortex that it activates during REM sleep (341, 342), as well as the caudate nucleus, are significantly implicated in the genetic vulnerability of insomnia, as shown in **FIGURE 8** (118). 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. Alterations in gray and white matter associated with poor sleep may emerge early in development, as indicated by their establishment at the age of 7 years (343). Although minor and/or distributed alterations anywhere in this circuit could result in a suboptimal functioning and predispose individuals to develop insomnia, the stringent correction for multiple testing that is required for whole brain voxel-based analysis impedes their detection unless massive sample sizes are available. Moreover, as discussed, alterations are likely to be different depending on the subtype of insomnia (89). Future studies may reduce unexplained variance by subtyping their participants (89) and increase statistical power even more by evaluating a predefined network rather than the whole brain.

9. TOWARD MECHANISMS UNDERLYING INSOMNIA VULNERABILITY: SLEEP REGULATION?

In search of mechanisms, the name “insomnia”, which translates as “no sleep”, would suggest a primary involvement of brain circuits involved in the circadian and a homeostatic components of sleep regulation (344, 345). The so-called “two-process” model has been extended to allow for a better description of ultradian processes (346–348), of sleep inertia (349), and of sleep-permissive external conditions (350, 351). While deviations in circadian and a homeostatic regulation are certainly likely to compromise sleep quality, the converse of this statement does not hold. In fact, there is

surprisingly little support for insomnia being primarily caused by circadian or homeostatic dysfunction.

9.1. Circadian Sleep Regulation?

With respect to the circadian component of sleep regulation, in only a few people with insomnia, complaints are primarily due to trying to initiate sleep at an inappropriate circadian phase (352). In a constant routine laboratory study to assess circadian rhythms in cardiovascular parameters, cortisol, and body temperature, no deviations could be found (353). Likewise, in a field study, no deviations could be found in activity rhythms (98). 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* (32, 118). As far as we know, other support for the possibility that insomnia would primarily be caused by circadian dysfunction is also lacking.

9.2. Homeostatic Sleep Regulation?

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 (354). Surprisingly few studies aimed to investigate the homeostatic process in insomnia disorder. In an early study, Bonnet (355) concluded that the restorative function of sleep operates efficiently in people suffering from insomnia. Besset et al. (356) sleep-deprived seven patients with insomnia and seven controls for 21 h. During subsequent recovery sleep, slow-wave activity (SWA) was assessed as a measure of build-up sleep pressure. Relative to the baseline night, SWA increased both in people with insomnia and in controls, be it somewhat less. The authors concluded that the homeostatic process was operating, but it was weaker in people with insomnia. While some other studies have also suggested homeostatic deficiencies in insomnia (357, 358), others could not confirm this (359), and all conclusions were based on studies that did not apply the strict deprivation protocols and analyses required to allow for any conclusion on homeostatic sleep regulation (354). Altered slow wave sleep may or may not exist in insomnia, but it is not sufficient to derive any conclusion about a homeostatic deficiency.

The molecule thought to play a key role in sleep homeostasis is adenosine (330). Indeed, functional genetic variations in its regulation alter the duration and intensity of slow-wave sleep in humans (331). Interestingly, the same variations predispose people to anxiety (360, 361). Recent GWAS studies did, however, not reveal a predominance of variants in genes involved in the regulation of adenosine. Analyses did not reveal even a hint of significance of the gene sets involved in adenosine deaminase activity ($P = 0.64$) or the adenosine A1 ($P = 0.47$), A2a ($P = 0.84$), A2b ($P = 0.65$), or A3 ($P = 0.30$) receptor (32, 118).

9.3. Sensitivitity to Sleep-Permissive and Wake-Promoting Conditions?

It has recently been suggested that the two-process model may have to be extended even more, to include sleep-permissive factors (350, 351). People fall asleep more easily after closing their eyes (362) in a dark environment (363), in a lying posture (364), and with a sleep-permissive comfortable skin temperature profile. A recent study systematically manipulated posture, light, and temperature in people with insomnia and matched healthy controls without sleep complaints while assessing elicited effects on cognitive and autonomic nervous system variables of relevance to sleep. Overall, people with insomnia showed comparable sleep-compatible cognitive and autonomic responses to *physical* sleep-permissive conditions (B. H. W. Te Lindert et al., unpublished data). 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 (365, 366). The unaltered threshold to *external* stimulation is in strong contrast to the increased density of *spontaneous* arousals and awakenings (77, 78), and the *intrinsic* tendency to transition from deeper sleep stages to more superficial sleep stages (83). N3 is the only sleep stage that seems “safe”; once people with insomnia reach this state, they do not 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 is a disorder of homeostatic sleep regulation.

9.4. Local or Simultaneous Sleep and Wakefulness?

An interesting new perspective on the subjective sleep complaints from people with insomnia is the possibility that sleep and wakefulness occurring in a nonintegrated 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 et al. (367, 368)

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 from 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 (369–371). 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 (67, 85, 372–374). It should be noted, however, that the concept of "local islands of wakefulness" (374) 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 very 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 suggests 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 (309). 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 Ref. 65).

9.5. Summarizing Involvement of Sleep-Regulating Factors

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.

10. TOWARD 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 (375–378) that may intrinsically interfere with sleep.

10.1. 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 (sect. 4). In contrast, polysomnography (sect. 3), epidemiology (sect. 2) and recent GWAS studies on genetic vulnerability (sect. 5) 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 (350). There can be emotional and motivational reasons to promote wakefulness and resist giving in to sound sleep (376, 378).

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 (379). The main intention of the current section is to explore whether such "watchfulness" could be involved in insomnia. The key questions addressed here are whether and how individual differences in the brain circuits involved in emotion and motivation could contribute to the vulnerability and expression of insomnia.

10.2. Sleep Reactivity and Emotional Reactivity

As mentioned in sect. 4, difficulties in emotion regulation have been found in people suffering from insomnia. Importantly, such difficulties *predict* incident insomnia

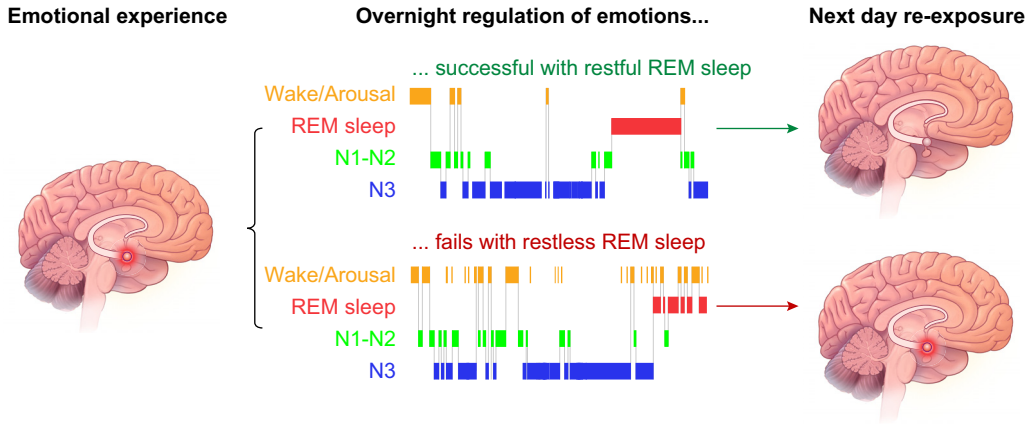

FIGURE 10. Restless rapid eye movement (REM) sleep impedes overnight emotion regulation. Schematic representation of how the amygdala response during an emotional experience changes overnight. Participants were presented with an upsetting stimulus during fMRI scans in the evening and again in the morning. 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 off without REM sleep. [Graphical representation of Refs. 13 and 15 kindly provided by Dr. R. Wassing, University of Sydney, Sydney, Australia.]

and its persistence, suggesting that altered emotion regulation rather seems a risk of insomnia, than to merely result from insomnia (137). Most of us are aware of how stressful and emotional experiences affect sleep (for reviews see e.g., Ref. 380). 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 (89, 131, 381). Drake et al. (381) 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

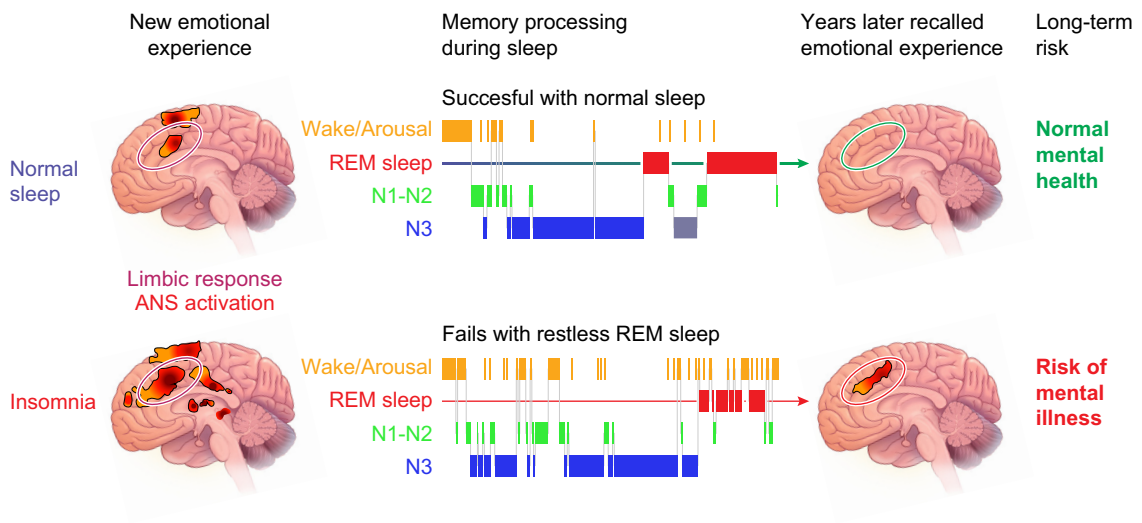

FIGURE 11. Long-term effects of insufficient overnight adaptation? Schematic representation of a functional magnetic resonance imaging (fMRI) study comparing brain activation during a novel shameful experience with brain activation while participants relived their most shameful experiences of decades 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 (*top*) and people with insomnia (*bottom*). 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 it had 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 is tempting to suggest that the deficiency also facilitates the development of anxiety disorders, major depressive disorder, and posttraumatic stress disorder. [Graphical representation of Refs. 14 and 16 kindly provided by Dr. R. Wassing, University of Sydney, Sydney, Australia.]

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 then conditionally to an occurrence, further ask about the severity and duration of experiencing insomnia due to the experience (89, 131). The scales are only modestly correlated (89) 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 (219, 220, 244) 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. Using the extended LES, Blanken et al. (89) showed that the *severity* and the *duration* of disrupted sleep in response to a major life event codefine specific insomnia subtypes. Concertedly, the studies on emotional reactivity suggest that altered emotion regulation seems rather to be a risk of insomnia than to result from insomnia.

10.3. 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 (382). 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 toward late retrieval, the engram or network activation shift from hippocampal to neocortical dominance (383). The progressive disengagement of the hippocampus and engagement of especially prefrontal cortical regions is strongly facilitated by posttraining sleep. Thus, sleep aids the bias for a stronger consolidation of emotional experiences than neutral memories (reviewed in e.g., Ref. 384). 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 (385). Recently, long-term effects of sleep were examined for the first time in a mouse model (386). 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 (386).

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. (387) assessed overnight changes in subjective valence and arousal when reexposed to emotionally negative, positive, and neutral pictures from the IAPS (247). 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.

10.4. 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 (388). 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 have suggested a dual role for sleep in memory and forgetting (389, 390); while sleep, indeed, adds to the consolidation of the declarative, contextual, or semantic aspects of an emotional experience, at the same time that it aids in separating these engrams from the emotional tone and somatic arousal, the emotional experiences originally elicited. In other words, postlearning sleep also has an impact on the functional connections of limbic areas with the network representing the declarative, contextual, or semantic engram.

10.4.1. Subjective distress.

Although several studies indicate that sleep supports the downregulation of emotional distress, findings are not unequivocal (reviewed in Ref. 391). A sleep-dependent decrease in subjective arousal ratings of the same stimuli

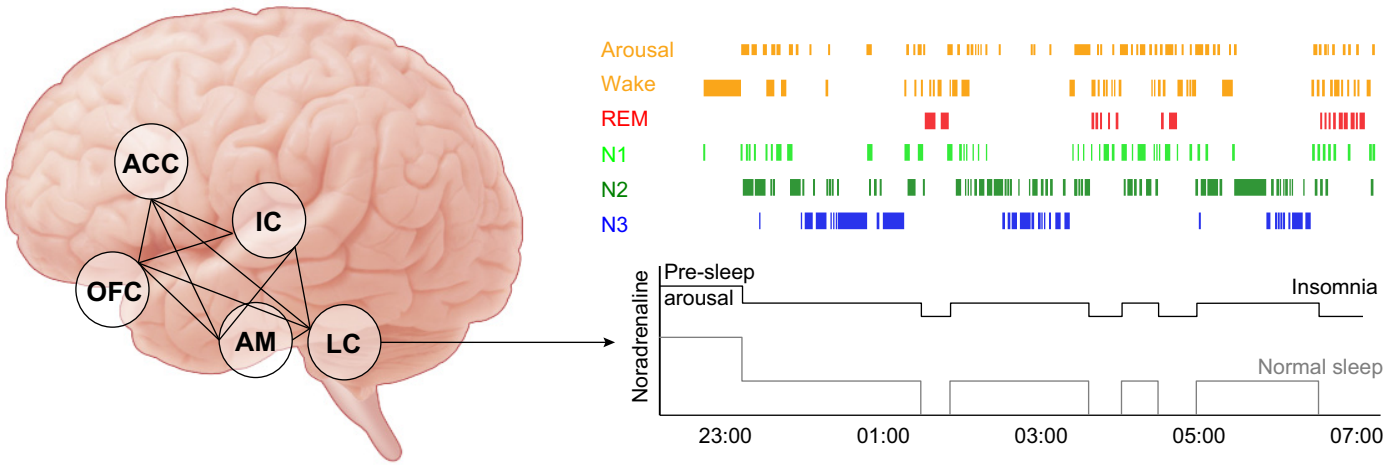

FIGURE 12. Insufficient silencing of the locus coeruleus during sleep. Model of lingering arousal during sleep in people with insomnia or a vulnerability to develop it. Distributed deviations in networks, including the salience network and the locus coeruleus may lead to a vulnerability to insufficiently silence the locus coeruleus during sleep. Pre-sleep arousal may aggravate the lingering of locus coeruleus activity. This may become problematic, especially during rapid eye movement (REM) sleep, the only state during which the brain has a "time-out" of noradrenaline (NA). 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 (20–22) during a time with extensive activation and reorganization of limbic circuits of the brain, including claustrum-induced activation of the anterior cingulate cortex (341, 342). Moreover, significant enrichment for insomnia risk genes has been found in these circuits (118), and their possible subtle functional consequences could further contribute to suboptimal overnight circuit adaptation. ACC, anterior cingulate cortex; AM, amygdala; IC, insular cortex; LC, locus coeruleus; OFC, orbitofrontal cortex. [Colored PSG graph kindly provided by Prof. D. Riemann, University of Freiburg, Freiburg, Germany.]

presented both before and after periods of sleep or wakefulness has not always been found (392). Also, an advantage of late sleep, rich in REM-sleep, over early sleep, rich in non-REM-sleep, has not systematically been found (393, 394). Both sleep-related enhancement and attenuation of subjectively experienced emotional intensity have been reported when comparing periods of sleep and sleep deprivation (395–397). In an early-sleep versus late-sleep protocol, REM-rich late sleep supported the "factual" recognition part of emotional stimuli better than NREM-rich early sleep did, while subjective valence and arousal ratings of emotional pictures were not differentially affected by REM or NREM-rich sleep (393). However, subjective valence and arousal ratings involve higher-order emotional appraisal, and they may be dissociated from brain and somatic reactivity (398). Indeed, a recent sleep study demonstrated brain activation in the salience circuit, as well as and correlated GSR amplitudes, in the absence of corresponding subjective emotional intensity ratings (16). Within subjective rating surveys, subscales that immediately address *somatic* reactivity seem most sensitive (13).

10.4.2. Objective measures.

Objective measures tend to give more consistent results: reexposure 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 (18, 399–401). In a series of studies, Wassing et al. (13–16) 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** and **FIGURE 11**).

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. (402) 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 reexperiencing* was less in participants with high REM θ-activity. Animal studies suggest that this EEG spectral signature is associated with low LC activity (20).

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.

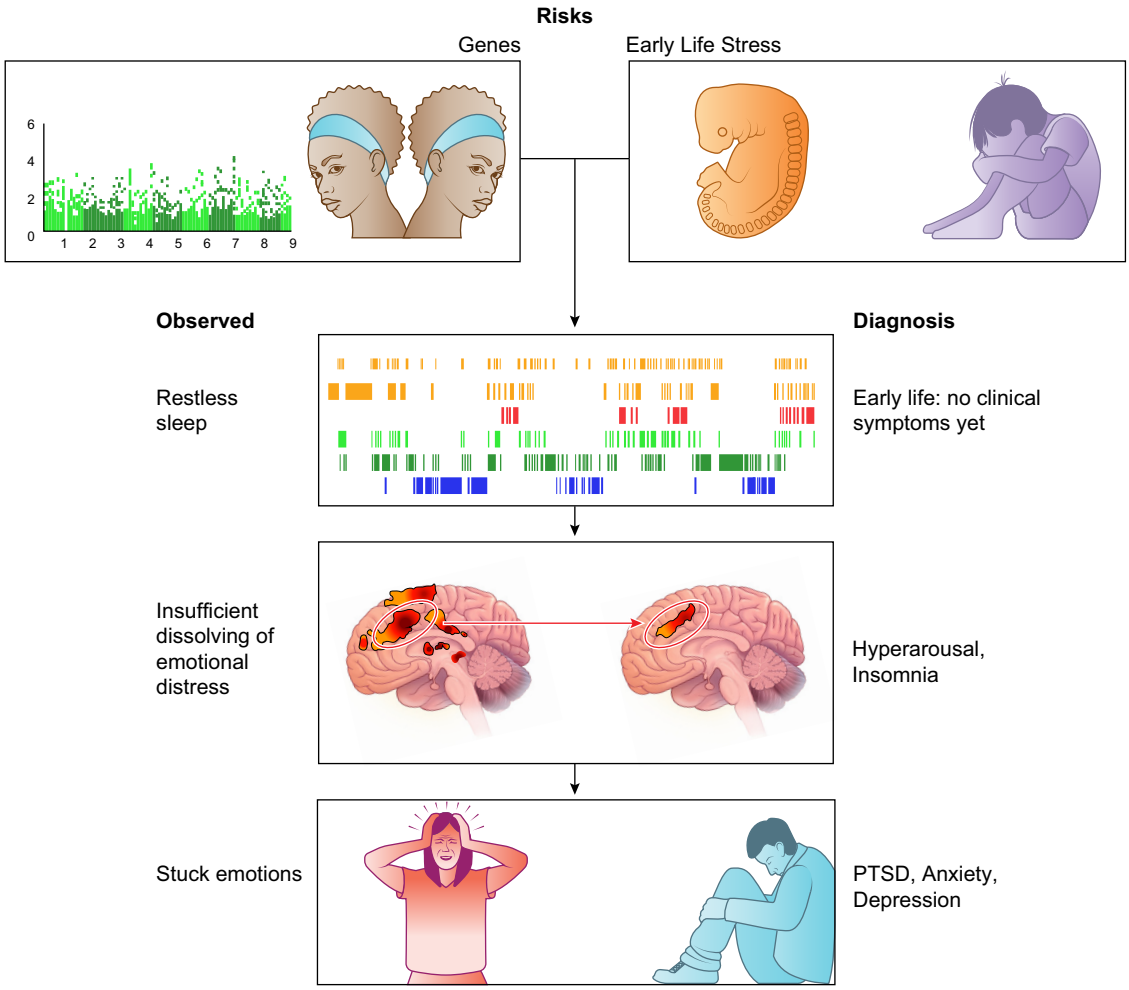

FIGURE 13. Developmental model linking the vulnerability to restless sleep, insomnia, and other mental disorders. It is proposed that genetic variants and early life adversity can make the locus coeruleus more sensitive to input from the salience network and related circuits, even during rapid eye movement (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 posttraumatic stress disorder.

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.

10.5. 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 (22, 389). The net result of this process is thought to favor the generation of semanticized memories, represented in distributed cortical connectivity biases (403). 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 (403). 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 (404). The decreased levels of norepinephrine during sleep, reaching complete absence during REM sleep, favor depotentiation and sleep-dependent synaptic downscaling (405–407), 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 (20). 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 (408). It can be hypothesized that malfunction results in *distributed deviations*, because there are only few brain areas that are not innervated by the LC (337, 409).

11. INSOMNIA BY INSUFFICIENT OVERNIGHT ADAPTATION TO EMOTIONAL DISTRESS?

Integrating all findings 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 posttraumatic 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** and **FIGURE 13** sketch the main components of the model.

11.1. Developing Vulnerable Brain Circuits

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 result from their significant expression of risk genes only. Other reasons include early devel-opmental influences on these tissues and cells. As extensively discussed in sect. 5, GWAS suggests vulnerability in several parts of the salience network and related structures that were also identified as relevant in MRI studies. These areas include the anterior cingulate cortex, caudate nucleus, and claustrum. Of note, the anterior cingulate cortex is one of the few areas activated during REM sleep, triggered by input from the claustrum (341, 342). In addition to tissues and cell types, genes also point to vulnerabilities detected in mouse mutant studies. Notably, the top-risk gene for insomnia, *BTBD9* and another identified gene *DNM1* are involved in the sleep-disruptive effect (increased sleep onset latency) of pre-sleep arousal (115, 116). *BTBD9* mouse mutants also show altered plasticity resulting in a stronger fear memory (115) and other phenotypes that match findings in insomnia (117), like increased restless, more fragmented sleep, and altered thermal sensitivity (142, 194). We posit that genetic vulnerability to insomnia, but also to the genetically strongly related anxiety and depression (32), is mediated by functional alterations that increase reactivity and sustained activity of the salience network, resulting in difficulties to reach a low level of arousal before sleep, and as a consequence, less deep sleep (410) with lingering arousal. Moreover, genetic vulnerability may be mediated by subtle changes in claustrum-initiated activation of the anterior cingulate cortex during REM sleep (341, 342). The genetic predisposition to arousal during sleep can additionally be boosted by childhood adversity (119, 124, 233). After genetic variants have set the stage for an increased risk of insomnia, early developmental conditions can impact their expression and later life consequences through epigenetic changes (212). Studies have proposed that early life epigenetic changes, as induced by early traumatization, determine whether or not risk variants evoke late-life disease vulnerability.

11.2. Vulnerable Brain Circuits Insufficiently Silence LC-NA Activity During REM Sleep

We next posit that entering sleep with lingering arousal means that locus coeruleus activity will not reach the low levels that can be expected during sound sleep (**FIGURE 12**). This may become problematic especially during REM sleep. Ground-breaking animal studies of others identified why restless REM sleep disrupts overnight adaptive processes (20–22). Sound REM sleep is the only state during which the brain has a "time-out" of noradrenaline (NA): the locus coeruleus (LC) is silenced. The NA time-out allows for a uniquely balanced potentiation and depotentiation of synapses, not found in any other state. Restless REM sleep, however, indicates insufficient LC silencing. The resulting lack of a NA-free REM sleep period disrupts synaptic plasticity (20–22).

11.3. Insufficient REM-Sleep LC-NA Silencing Affects Overnight Plasticity and Distress Adaptation

Indeed, we and others pinpointed specifically restless REM sleep to interfere with emotional adaptation. Restful REM sleep helps the limbic circuit of the brain to adapt overnight

(18), resolving the burden by making emotions milder and more tractable (19). Restless REM sleep, in contrast, does not work well. REM sleep that is fragmented by arousals indicates persistence of LC activity during a time window that should normally provide a NA-free period. Restless REM sleep impedes processes involved in overnight emotion regulation. The resulting distress "accumulation" is experienced as hyperarousal and resembles anxiety. Restless REM sleep interferes with restructuring of brain circuits involved in emotional memories and salience. People with insomnia, in particular, fail to disengage the anterior cingulate cortex. The anterior cingulate cortex is one of the few areas activated during REM sleep, triggered by input from the claustrum (341, 342). As mentioned earlier, our recent genome-wide analysis identified particular enrichment of these two regions for insomnia risk genes. These genes include *BTBD9*, involved in fragmented sleep, fear memory, and difficulties falling asleep following arousal (115–117).

Restless REM sleep can even invert beneficial effects of sleep on overnight adaptation to emotional distress, and become *maladaptive* (13, 15). It can not only impede overnight resolution of distress but even aggravate it (13). Adverse consequences leave traces in brain activation for decades, especially in the anterior cingulate cortex. Because of failing overnight plasticity, distress may not resolve sufficiently, linger for a long time, and contribute to the development of a generalized hyperaroused state, which, in turn, perpetuates insomnia (14) (see **FIGURE 10** and **FIGURE 11**).

11.4. The Transdiagnostic Perspective of Maladaptive Sleep

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 (411–413). Animal studies support the hypothesis that common neural substrates may underlie disturbed sleep and mental health. Already in early animal models for depression, coexpression of an insomnia phenotype was noted to be common (413–415). 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 (219, 220, 244). On the other hand, preexisting insomnia puts individuals at elevated risk of developing posttraumatic stress disorder when exposed to a traumatic event (259, 416). Likewise, postdeployment, sleep continuity disturbance co-determines whether combat exposure results in posttraumatic stress symptoms (417).

11.4.1. Better off without restless REM sleep?

Trouble distancing oneself from negative memories is not only found in insomnia, but also holds for people with depression or other mood disorders (418). Even before disease onset, sleep in people at risk of these disorders may be altered, as demonstrated for insomnia and posttraumatic stress disorder (119, 410). 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 does not resolve anxiety, tension, and sadness at all. They may even wake up worse than they were the night before (13, 15). A common distinguishing feature from the "occasional bad day" of a healthy subject is, thus, that people with anxiety, insomnia, depression, or posttraumatic stress disorder take their emotional distress to the next day. Night after night, sleep brings no relief. Although sound consolidated REM sleep might be beneficial for overnight adaptation to emotional distress, people with highly fragmented REM sleep may even be better off without, as previously proposed for depression (419) (see **FIGURE 10** and **FIGURE 11**).

11.5. Revisiting Insomnia Characteristics from the LC-NA Perspective

Many main features characterizing people with ID, according to the present review, are compatible with increased LC activity such as higher levels of arousal (420, 421); a strong expression of >20 Hz EEG (422); an increased probability to transition from sleep to wake that is especially prominent in response to stress (83, 244, 423–426); active cognitive task engagement (427, 428); sensitized salience detection (429); increased cortical excitability (65, 66, 453) and enhanced late potentials evoked by intrinsic and extrinsic stimuli (69, 286, 430).

12. RECOVERING RESTFUL REM SLEEP: A RESEARCH AGENDA

Restless REM sleep is one of the most distinguishing sleep characteristics of insomnia (64, 77, 78). 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 (80), 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-out that should accompany REM sleep might be off-label use of existing medication that either blocks NA receptors (e.g., β-blockers) or suppresses LC activity (e.g., guanfacin). Below, it is briefly discussed whether such pharmacological approaches would be feasible without, by themselves, disturbing mood or sleep.

12.1. Could LC-NA Activity be Controlled Without Disturbing Mood?

In the 1950s, the "monoamine hypothesis" proposed a role of the noradrenaline in depressive disorders. Findings and hypotheses include noradrenergic deficiency, as well as the opposite, a prolonged increased activity of the noradrenergic, and alterations of downstream receptor, sensitivity in response (431, 432). Seventy years later, the exact role of noradrenergic transmission has remained enigmatic, and it is relevant to consider whether the proposed nocturnal pharmacological suppression of noradrenergic activity during REM sleep using e.g., β-blockers could induce depression or disrupt sleep.

A meta-analysis, including 15 controlled trials with a total of more than 35,000 patients concluded that β-blockers did not increase depressive symptoms (433). A systematic review on β-blockers' side effects, including 13 controlled trials, even found less depression across the groups randomized to β-blockers than across the groups randomized to placebo (434). These overviews indicate that the risk of depression is no a priori reason to refrain from the proposed use of noradrenergic agents to mitigate restlessness of REM sleep.

12.2. Could LC-NA Activity be Controlled Without Disturbing Sleep?

Disrupted sleep by using β-blockers is more common. A concise review of the literature reveals that several β-blockers have undesirable effects like suppression of REM sleep rather than enhancing its consolidation, or worsening of sleep quality, possibly by suppressing melatonin release, which might be mitigated by exogenous melatonin (435–437). However, at least one β-blocker, Nebivolol, has been suggested to improve sleep quality (438, 439) and, moreover, had the desired safety and strong lipophilic profile, i.e., acting on the brain, so this would be a good candidate to start evaluating for the mitigation of restless REM sleep. No studies on insomnia disorder have been reported yet.

Downstream effects of noradrenaline may also be blocked using α_1-receptor antagonists. As reviewed Broese et al. (440), the α_1-receptor antagonist prazosin has a promising profile of actions, and they have proposed it for evaluation in the treatment of insomnia. The disturbed sleep in PTSD has been proposed to specifically involve enhanced responsiveness of α_1-receptors (441). Indeed, in PTSD patients, prazosin improved subjective sleep in three studies (442–444) and polysomnographically recorded sleep in one out of two studies (441, 442). Importantly, because mitigating restlessness of REM sleep would be preferable over complete suppression of REM sleep, one study found that prazosin increased both the continuity and total duration of REM sleep (441). The promise of these studies is somewhat moderated by a letter questioning the conclusion of one of the studies (445), and a more recent study reported, in fact, significant adverse effects of prazosin on sleep, as compared to placebo, in PTSD patients (446). No studies on insomnia have been reported yet.

12.3. Downstream Versus Direct Targeting of LC-NA Activity Control

While β-blockers and α_1-receptor antagonists could be used to prevent adverse postsynaptic downstream effects of a LC that is insufficiently silenced during REM sleep, a more direct approach would be to target inhibitory receptors on noradrenergic LC neurons. GABA-A receptors on LC neurons can be targeted directly and indirectly with the common sleeping pills, i.e., benzodiazepines and "z-drugs" like zolpidem and zopiclone. However, these GABA-A-targeting drugs have been reported to reduce REM sleep (for review, see Ref. 447), which may be a second-best solution, since mitigating restlessness of REM sleep would be preferable over suppression of REM sleep. Moreover, benzodiazepines have been reported to increase β-power in the sleep EEG (448, 449), which does not suggest an optimal natural arousal reduction. Broese et al. (440) proposed that the noradrenergic α_2-autoreceptor agonists could be evaluated to treat insomnia and discussed several drugs with different affinities for the α_2-receptor subtypes α_{2A}, α_{2B} and α_{2C}: clonidine, 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 (450). No studies on use of α_2-autoreceptor agonists in insomnia disorder have been reported yet.

12.4. A Fundamental Research Agenda

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 these novel approaches, the proposed model opens up the possibility for animal studies, thus catalyzing a neuroscience of insomnia, which is direly needed for better treatment of one of the most burdensome disorders.

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ACKNOWLEDGMENTS

This review was written thanks to a Fellowship of the Golestan Foundation and the Netherlands Institute for Advanced Study in the Humanities and Social Sciences, an institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands. I am grateful for the support of the following current and past team members and research collaborators, who all contributed to the development of a neuroscience of insomnia: Anne Albers, Ellemarije Altena, Rebecca Astill-Schutte, Jeroen Benjamins, Tessa Blanken, Tom Bresser, Denny Borsboom, Jessica Bruijel, Julie Christensen, Michele Colombo, Joris Coppens, Roy Cox, Kim Dekker, Bernd Feige, Jessica Foster-Dingley, Laura Goetze-Dekkers, German Gomez-Herrero, Anke Hammerschlag, Rikkert Hindriks, Simon Houtman, Savannah Ikelaar, Jacob Itzhacki, Philip Jansen, Kira Jespersen, Merel Kindt, Desi Kocevska, Morten Kringelbach, Oti Lakbila-Kamal, Jaap Lancee, Cathalijn Leenaars, Jeanne Leerssen, Klaus Linkenkaer-Hansen, Armand Mensen, Filippo Migliorati,† Sarah Moens, Els Møst, Joy Perrier, Giovanni Piantoni, Danielle Posthuma, Jennifer Ramautar, Roy Raymann, Joyce Reesen, Faya Reinhold, Dieter Riemann, Rixt Riemersma-van der Lek, Nico Romeijn, Lara Rösler, Ernesto Sanz-Arigita, Frans Schalkwijk, Kai Spiegelhalder, Angus Stevner, Diederick Stoffers, Dick Swaab, Enzo Tagliazucchi, Bart Te Lindert, Martijn Van Den Heuvel, Glenn Van Der Lande, Wisse Van Der Meijden, Sophie Van Der Sluis, Ysbrand Van Der Werf, Annemieke van Straten, Marije Vermeulen, Diego Vidaurre, Rick Wassing, Kyoko Watanabe, Yishul Wei, and many devoted interns.

GRANTS

Research leading to these results has received funding and support from the Golestan Foundation and the Netherlands Institute for Advanced Study in the Humanities and Social Sciences, an institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam; the European Research Council Advanced Grant 671084 INSOMNIA; the Netherlands Organization for Health Research and Development (ZonMw) Neuropsychoanalysis Fund 16.561.0001; the Bial Foundation Grants 253/12 and 190/16; and the Netherlands Organization of Scientific Research (NWO) Grant VICI-453.07.001.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

E.V.S. drafted manuscript; E.V.S. edited and revised manuscript; E.V.S. approved final version of manuscript.

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