CONCLUSION

Chapter 9

Summary, general discussion and future perspectives

So why worry about insomnia? Total sleep deprivation leads to performance decrements, even after one night. But insomniacs are not totally sleep deprived every night. They do sleep. Insomnia, as we have shown and will further elaborate on, is not the same as sleep deprivation, where the environment defines whether we sleep or not. In insomnia, one or more factors *within* a person keeps him awake, when getting ample opportunity to sleep. And as is previously shown by others and now by us, patients with insomnia perform well on most cognitive tasks. In fact, compared to normal sleepers, performance is even better on some tasks. And from an evolutionary viewpoint: should we not be able to get by if our children keep us up at night for prolonged periods of time, or if our environment is not safe enough for us to sleep deeply at night?

Insomniacs do get by, but until a certain level, and, as will be shown in the following sections, at some cost. This cost can however be reduced and possibly even reversed by non-pharmacological sleep therapy. These viewpoints will be discussed in detail below, on the basis of the presented data and in the context of ongoing and new theories on insomnia. First, a summary is given of the data presented in the previous chapters. In the subsequent sections we will then focus on the different issues, conclusions and new questions raised by our results in the context of other studies. First cognitive performance in insomnia will be discussed, then the therapy effects for both behavioral and imaging data. We will then focus on the comparison between insomnia and experimental sleep deprivation, after which a new model is proposed to integrate all the information discussed in the previous sections. Clinical implications and future directions will be discussed in the last sections.

SUMMARY

In **chapter 3**, we showed that, compared to controls without sleep complaints, insomnia patients perform faster on a simple vigilance task, but slower on a more complex vigilance task. This interaction effect of insomnia with task difficulty may be related to the state of hyperarousal, known to be characteristic of insomnia. The effect normalized after sleep therapy but not after a waitlist interval, ruling out the possibility that this normalization could be attributed to possible learning effects of repeated measurements.

In **chapter 4,** we showed that when insomnia patients perform letter and category fluency tasks in fMRI, they show less activation in task-related prefrontal regions (inferior frontal gyrus, medial prefrontal cortex) than controls without sleep complaints do. Sleep therapy, but not waitlist control, results in partial recovery

of this hypo-activation. In spite of the initial hypo-activation, insomnia patients generate more words on both fluency tasks than controls do. After sleep therapy, but not after waitlist control, the number of words generated on the most complex task, the letter fluency task, increases even more. The high performance level on word production deserves further attention, especially its possible associations with perfectionism, with rumination and with 'running thoughts', which have all been reported as characteristics of insomnia.

In **chapter 5,** structural brain differences between insomnia patients and controls without sleep complaints were reported. Compared to controls, insomnia patients have a lower grey matter density in the orbitofrontal cortex and anterior and posterior precuneus. Of note, the orbitofrontal grey matter density shows a strong negative relation with insomnia severity, but not with subclinical depression or anxiety measures. The affected orbitofrontal region is involved in decision-making and in evaluating the affective value of stimuli, functions that have been related to insomnia. Insomnia patients do not show higher grey matter density in any brain region, nor did we find deviations in white matter density.

In **chapter 6,** we evaluated intracortical inhibition and facilitation using double pulse transcranial magnetic stimulation. Both after a single and a double pulse, the physiological motor response is higher for insomniacs than for controls, possibly due to hyperarousal. The intracortical facilitation effect after double pulse stimulation is lower for the insomniacs however, possibly due to the already higher baseline (single pulse) response. Group differences are not altered after sleep therapy. This attenuation appears specific to insomnia and has not been reported in previous experimental sleep deprivation studies.

In **chapter 7** we evaluated the effects of experimentally induced shallow sleep (selective slow wave suppression) in controls without sleep complaints in the same age range as our insomnia patients. By presenting an auditory stimulus when the participant enters slow wave sleep during the night, slow waves do not develop normally as indicated by a reduction in low frequencies in the power spectrum. Different from the usually applied total sleep deprivation, the method does not affect total sleep duration and other aspects of sleep macrostructure. Upon performing similar vigilance tasks as insomnia patients described in Chapter 3, controls show an increased number of lapses after slow wave suppression compared to performance after normal nights of sleep. This was independent of task (complex or simple vigilance).

In **chapter 8,** we investigated what the effect of slow wave suppression is on memory performance and brain activation in controls without sleep complaints. After slow wave suppression during the night, brain activation was measured the following day when encoding novel pictures. Participants showed reduced

hippocampal activation when encoding novel pictures compared to their scores after a normal night of sleep. The day after, their recognition memory was affected accordingly.

COGNITIVE PERFORMANCE IN INSOMNIA

We hypothesized, on the basis of previous studies that failed to find conclusive evidence of cognitive deficits in insomnia, that standard paper and pencil neuropsychological tasks may not be sensitive enough to show possibly subtle changes in performance or cognitive strategies in insomnia patients. In the current study, we therefore implemented (1) computerized vigilance tasks that were designed to measure more subtle cognitive performance changes that may remain undetected by standard neuropsychological tests and (2) two versions of a standard neuropsychological task while monitoring the underlying brain activation pattern using fMRI. The tasks we applied had different levels of complexity and duration, and tapped into different cognitive functions. Of the two fluency tasks evaluated, the category version requires memory functions and cognitive flexibility. The more complex letter version requires more cognitive flexibility and less memory functions. By implementing the fluency tasks in the MRI scanner, we could map cognitive correlates of insomnia both on a behavioral as well as on a brain activation level. One vigilance task measured simple reaction time while the second was slightly more complex in additionally requiring decision making. The simple vigilance task demands were limited to pressing whenever an asterisk occurred. In the complex vigilance task, participants were asked to press only if a 'p' was presented, but not if a 'd' was presented.

On the simple vigilance task, insomnia patients had shorter reaction times, i.e. responded faster, than controls. The shorter reaction times on the simpler form of vigilance task may be related to the hyperarousal phenomenon that has repeatedly been described in insomnia[1-4]. If task demands are low, performance may increase with arousal level – up to a certain extent[5]. With increasing task demand, similarly high arousal levels may attenuate performance, i.e. the typical Yerkes-Dodson inverted U-curve is shifted to optimal performance at a lower arousal level[5-11] (see figures 1 and 2). Indeed, insomnia patients had longer reaction times than controls on the more complex vigilance task. A 'go-nogo' type decision is required on this task before a response is generated, which could be considered as a simple form of decision making.

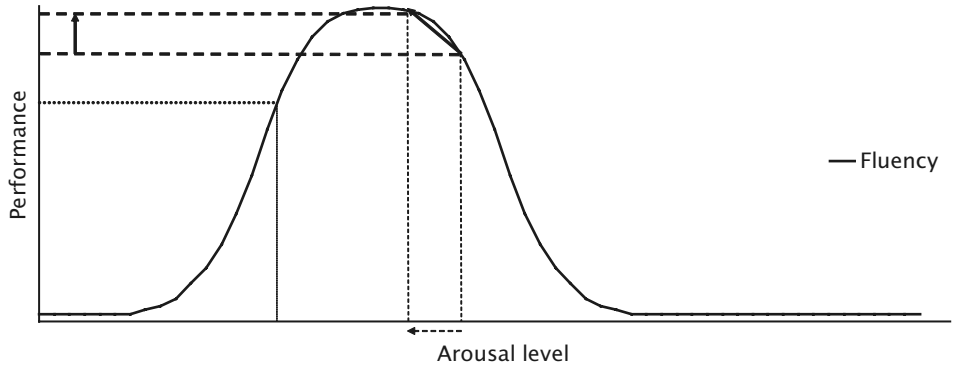

Figure 1. Level of arousal predicts performance level. On baseline, the high arousal group (insomniacs, striped line) performs better than the low arousal group (controls, dotted line). After sleep therapy reduces arousal and thus partly normalizes the arousal level (see arrow), performance is even higher. Indeed, the number of words generated increased for both category and letter fluency, but only significantly so for letter fluency.

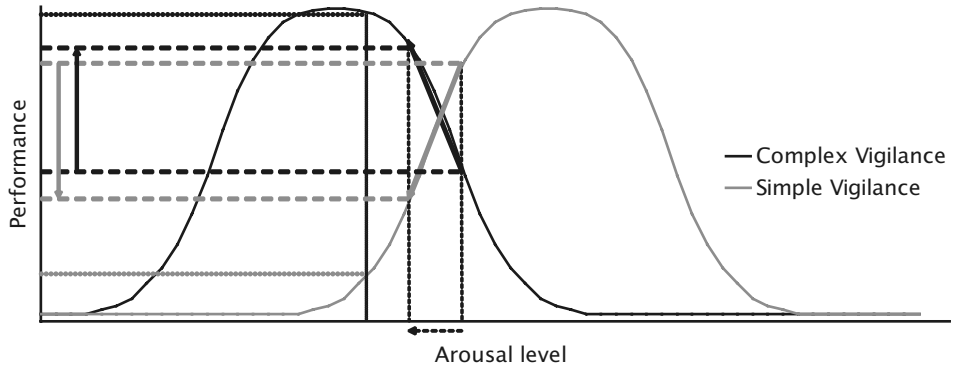

Figure 2. Performance and arousal levels are task-dependent. On baseline, performance on the complex vigilance task (black curve) is low for insomnia patients (black striped line) due to high arousal levels. After reduction of these arousal levels through sleep therapy, performance shifts to a higher level (left black arrow parallel to y-axis) and closer to - but not yet equal to - the arousal level and performance of controls (dotted line on top of curve), performance levels after sleep therapy are more similar to performance levels of controls. The performance versus arousal curve for the simple vigilance task (grey curve) shows that optimal performance can be reached at a higher arousal level for a simple task. In this case the same reduction of arousal in insomniacs shifts them to a lower performance level (left grey arrow parallel to y-axis), again closer to the arousal level and performance of controls.

Elevated arousal may also underlie our finding that insomniacs generate more words on the verbal fluency tasks than controls do; more significantly so on the relatively simple category version than on the more complex letter version. Although fluency task performance is affected in neurological deterioration[12-15], the task is not considered to be highly demanding for healthy participants. Hyperarousal, which could account for the higher performance levels in insomniacs, would therefore not be counteracted by the demanding nature of the task. This could, however, be the case with a more difficult task and, moreover, depend on the cognitive functions examined, such as the more complex form of the vigilance task requiring decision making (see figures 1 and 2). Hyperarousal could also play a role in the increased motor evoked potential to both single and double pulse stimulation after TMS. The fact that this deviation does not normalize after sleep therapy suggests that hyperarousal may not normalize completely at all levels of brain functionality, and may in part be a trait leading to an increased risk of more generalized hyperarousal and insomnia. Preliminary findings show that insomnia patients have reduced brain levels of the inhibitory and sleep promoting neurotransmitter GABA, which could quite well be related to this increased motor response[16]. Reduced levels of GABA can lead to increased levels of glutamate[17], which may in turn increase corticotrophin-releasing hormone (CRH)[18,19]. CRH plays an important role in arousal[20,21] and promotes wakefulness. An important but complex role for CRH in the onset and maintenance of insomnia has been suggested[22,23].

A region particularly important for decision making is the orbitofrontal cortex, where we found insomnia patients to have lower grey matter density than controls (**Chapter 5**). Of note, the orbitofrontal grey matter density was strongly related to the severity of insomnia. This finding could, in addition to the shifted inverted-U hypothesis, provide a second reason for the selectively attenuated performance on the complex vigilance task that required decision making. A third possible reason why we could demonstrate attenuated performance on this task, while previous studies in insomnia failed to find consistent deficiencies, could be the prolonged duration of the vigilance tasks. It is conceivable that adverse effects of chronic insomnia on task performance may initially be compensated during the first minutes of a task, and show only if the task lasts long enough. Compensatory effort is particularly likely in insomniacs, given their above-average level of perfectionism[24,25].

In conclusion, cognitive performance may be affected in insomnia in a subtle and complex way. Our findings suggest that at least three mechanisms may be involved. First, the typical elevated arousal may favor performance on simple tasks. This arousal-related advantage is reduced, lost or even reversed for more

demanding, complex tasks. Second, tasks involving the orbitofrontal cortex, e.g. tasks including a decision making component, may be more sensitive to insomnia-related cognitive alterations. Third, compensatory mechanisms are likely, and insomnia-related performance deficits may surface only on tasks of prolonged duration.

THE EFFECTS OF NON-PHARMACOLOGICAL SLEEP THERAPY IN INSOMNIA: COGNITIVE PERFORMANCE AND BRAIN ACTIVATION RESULTS

We have demonstrated that sleep therapy normalizes the performance deviations of insomniacs on the simple and complex vigilance tasks; they become faster on the complex, and slower on the simple vigilance task. Thus, the performance ratio on the complex vs. simple version of the task becomes more comparable to controls without sleep complaints. This finding is compatible with a reduction in hyperarousal. We did not find normalization, i.e. an attenuation, of performance on fluency performance. Instead, sleep therapy resulted in an increase of the number of words generated, particularly on the most complex, letter version of the fluency task.

To explain the seemingly divergent effects of sleep therapy on the two types of tasks, we have to consider our findings on brain activation during the fluency tasks before and after sleep therapy. As described above, insomniacs have better rather than worse fluency performance compared to controls. Still, at baseline, insomnia patients show deviant brain activation patterns during the fluency task. In particular, they show hypoactivation in task-related prefrontal regions. This finding suggests that hyperarousal, perfectionism or compensation makes insomniacs perform better in spite of the fact that they have difficulty activating the most appropriate prefrontal brain areas to perform the task. The result corresponds to earlier studies showing prefrontal hypoactivation during the day[3]. After sleep therapy, the prefrontal hypoactivation in task-related regions partly recovers (see **Chapter 4**). Thus, additional resources, notably prefrontal areas optimally suited for fluency performance, become available upon sleep therapy and may elevate performance even further above the already high level insomniacs may have due to perfectionism, compensation or hyperarousal. In conclusion, short term sleep therapy can lead to normalization of performance on simple and complex vigilance tasks and to normalization of brain activation patterns on fluency tasks. The findings are compatible with the explanation that a sleep-therapy-induced attenuation of hyperarousal may selectively normalize the vigilance and decision

making functions, while its effect on prefrontal brain regions further enhances fluency performance, not affecting factors that cause these high performance levels on fluency tasks.

INSOMNIA COMPARED TO EXPERIMENTAL SLEEP DEPRIVATION

In **chapter 3** and **chapter 7** we show that vigilance performance in insomnia does not resemble the typical findings on vigilance performance after experimental sleep deprivation. In the present study we did not find insomnia to be associated with an increase in the number of lapses or errors, which are known to occur after total sleep deprivation[26-28]. The faster performance on one but slower performance on the other task may point to a dysbalance in brain processes – possibly related to the inverted-U effects of hyperarousal on performance - rather than an overall affected task performance, as is usually found after sleep deprivation. Insomniacs did not differ from controls with respect to the number of lapses or false positive responses during the complex task.

In our attempt to experimentally induce an insomnia-type of sleep in a better way than total sleep deprivation, we applied SWA suppression in matched controls without sleep complaints. This procedure did not produce the reaction time profile seen in insomniacs. SWA suppression did not affect reaction times, yet caused the percentage of vigilance lapses to increase from 3.4% to 6.5%, irrespective of type of vigilance task.

As shown in **chapter 8**, even a mild sleep disruption like the one we induced using this SWA suppression technique, has an immediate effect on both hippocampal activation and memory performance in controls. The effects on hippocampal activation and memory performance resemble total sleep deprivation effects in younger adults[29].In contrast, memory performance deficits have not characteristically been found for insomnia patients in previous studies applying a similar task[30-34]. Our functional imaging study on fluency also did not reveal deviations in hippocampal activation in insomniacs, which is part of the expected fluency task activation; the method was however sensitive enough to reveal prefrontal alterations.

In summary, the performance and brain activation effects of slow wave suppression in older controls without sleep complaints differs from the performance and brain activation profile typical of insomnia, but do resemble the effects of total sleep deprivation in younger adults.

UNDERLYING MECHANISMS OF INSOMNIA: STATE OR TRAIT?

Our findings on the structural correlates of insomnia **(Chapter 5)** provide a basis for a new view on mechanisms involved in insomnia. We found a relation of the orbitofrontal cortex grey matter density with insomnia severity. Careful selection and matching of participants in our study excluded possible confounding by factors known to have an effect on orbitofrontal grey matter, notably depression and anxiety[35,36]. None of the regions where insomnia patients have a low grey matter density showed a relation with insomnia duration. This provides some support for the idea that grey matter differences may have existed prior to the onset of insomnia, and possibly may have been involved in the risk of developing insomnia. This assumption, and the exclusion of psychiatric factors from the data, could lead to the following model for insomnia:

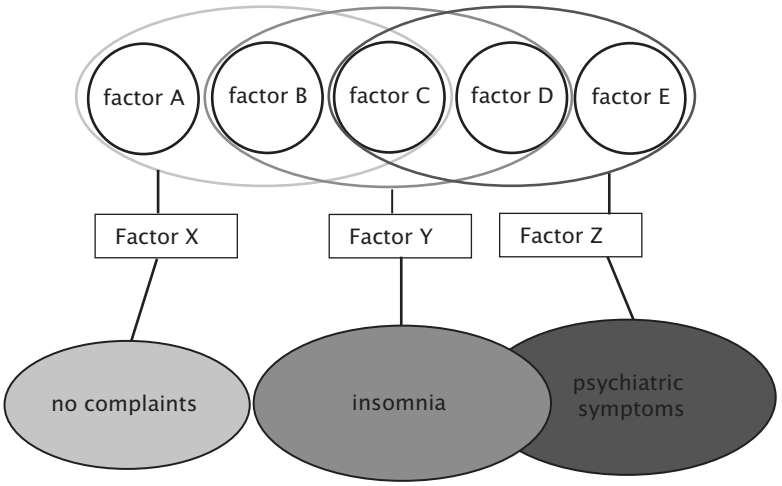

Figure 3. Insomnia model explaining how a combination of precipitating factors can lead to insomnia or psychiatric symptoms through secondary factors and, in some patients, to both. A minority of patients may have no complaints.

Factor A, B, C, D and E in the model are unchangeable factors, e.g. genotypes. Such factors have been identified to e.g. predict diurnal preference[37,38], patterns of brain structure and function[39,40] and psychiatric conditions[41,42]. These genetic factors can thus for instance represent a personality profile related to a vulnerability for rumination, but also be related to the grey matter differences in the orbitofrontal

cortex and precuneus. Since the prefrontal cortex has an inhibitory role on the HPA-axis[43], structural or functional changes in the prefrontal cortex could further lead to increases of CRH and cortisol, which could in turn promote sleep disturbances. Relatively low levels of GABA may also enhance CRH. Genetic studies may pay special attention to genes involved in prefrontal development and the regulation of GABA.

Factors X, Y and Z depict secondary vulnerability factors that define the manifestation of either psychiatric symptoms or insomnia, or result in no complaints. Factor Y could for instance represent events such as work stress, night shifts, a bad sleeping child or spouse, or hormonal changes. Factor Z could for instance be a severe psychological trauma promoting psychiatric symptoms.

In some persons, both insomnia and psychiatric symptoms may develop, even enhancing each other. In particular depression can lead to sleep disorders, while insomnia can lead to depression[44]. The same genetic factor D could in combination with different other factors lead to either insomnia or depression, or both. Recent recommendations for simultaneous treatment of both a mental disorder and a sleep disorder are in line with this idea[45]. This model is further supported by the clinical findings that insomnia could occur before a psychiatric or physiological disorder occurred and not only vice versa, which lead to the 2005 National Institute of Health resolution of the United States of America, in which the term 'secondary insomnia' was replaced by 'comorbid insomnia'[46]. Indeed, the beneficial effects of cognitive behavioral therapy are not only shown for primary, but also for comorbid insomnia[47].

Support for the involvement of traits that increase the risk for developing insomnia is given by the part of our results which shows that some features of insomnia are not sensitive to (non-pharmacological) intervention. Performance levels on the fluency task did not normalize, nor did the abnormal intracortical facilitation demonstrated by TMS. Fluency performance may be sensitive to the hyperarousal typical of insomnia, increasing number of words generated. These and other functions may stay intact and even 'benefit' from insomnia, making it possible to function on a seemingly normal level or even superior on tasks with low demands, but worse on more complex tasks.

Primary factors such as factor B, C or D could also be related to an emotion regulation disturbance, which, according to the Harvey model[48], leads to hyperarousal, which in turn can lead to insomnia. If the emotion regulation disturbance and the consequential hyperarousal are considered as factor C, it would be interesting to investigate factor X and the 'no complaints' group. Factors that prevent this group from either developing insomnia or psychiatric symptoms may be e.g. upbringing or treatment for subclinical psychological complaints.

This could lead to changes in their emotion regulation system and reductions of hyperarousal before insomnia or psychiatric symptoms can develop.

The emotion regulation disturbance and the consequential hyperarousal could also lead to the tendency for perfectionism[24] and the worry and negative cognitions about sleep[25,49]. Worry about sleep predicts subjective sleeplessness in longer duration but not in shorter duration insomnia[25] , which suggests that the longer insomnia lasts, the more worry it will cause and the more negative cognitions will be formed about sleep. Worrying and ruminating then further enhances the insomnia. Reversing these negative cognitions in CBT is effective for resolving insomnia; in fact, Edinger et al. found a positive relation between severity of negative sleep-related cognitions and effectiveness of CBT[49].

Alternatively, insomnia features that were not responsive to sleep therapy in our evaluation after 6 weeks, such as response rates on the fluency tasks, decreased facilitation after TMS and possibly also lower grey matter density in prefrontal and parietal regions may all be reversible features that show normalization only after longer duration sleep therapy or long term follow-up measures.

CLINICAL IMPLICATIONS

Cognitive behavioral therapy has proved its effectiveness in comparison to placebo and medication in earlier studies, particularly when measuring long term effects and particularly in the elderly. Now we additionally show that normalization occurs on the level of brain activation in insomnia, even with a short duration intervention. We also show normalization of performance on simple and complex vigilance tasks. This further confirms the effectiveness of non-pharmacological CBT in insomnia, which calls for the wider availability of this therapy to insomnia patients. Awareness of the severity of this condition, related to lower prefrontal grey matter density, hypoactivation in prefrontal regions and hyperarousal, and resulting in high direct and indirect care costs, may lead to policy changes for general practitioners. This could result in increased referrals to sleep clinics for differential diagnosis of sleep disorders. On the basis of our current results and our clinical impression, this is very important for the following reasons.

First, we received hundreds of responses on each of our recruitment advertisements of persons with sleep complaints that stated sleep medication or any other intervention available to them was not effective (anymore), and their general practitioner could not help them (anymore). Most of them had never been referred to a sleep clinic and/or had never received non-pharmacological sleep therapy, or knew of its existence. In our experience, compliance of these insomnia

patients in our study was very high because of their despair to be treated; none of the patients finally included in our study refused participation at any stage, despite the highly demanding protocol. Many patients were excluded by us however, because their screening and questionnaire scores or interview outcomes showed indications they suffered from a different sleep disorder (mostly sleep apnea or restless legs). In particular with restless legs, sleep questionnaires did not always detect the problem; additional foot actigraphy or PSG did. In our opinion, more frequent referral to a sleep clinic may improve differential diagnosis of sleep disorders or other (psychiatric) disorders and improve treatment frequency of these disorders, with beneficial consequences for health costs and traffic and industrial accident frequency.

Second, patients referred to a sleep clinic and diagnosed with primary insomnia should have CBT treatment more readily available to hem. Where effective medication and treatment options exist for apnea and restless legs, these treatment options are known to general practitioners, and reimbursement is provided by health insurance, the same does not count for non-pharmacological sleep therapy for primary insomnia. Treatment of primary insomnia can, just as treatment of other sleep disorders, result in a reduction of direct and indirection health costs. Next to that, and in particular in insomnia, productivity at work can possibly be increased and absence days can be reduced. In the elderly, quality of life of the insomnia patient and its partner can be improved, prefrontal functioning can be improved, and natural prefrontal changes may be slowed or stabilized longer. Non-pharmacological treatment is further preferred over pharmacological treatment since the adverse effects of sleep medication can, particularly in the elderly, lead to cognitive impairment (in particular anterograde amnesia), daytime sedation, motor incoordination and increased risk of traffic accidents and falls[50].

Third, further differential diagnosis within the group of insomnia patients is needed. We specifically chose to select insomnia patients with both subjective and objective insomnia. We therefore excluded many participants that would perhaps fulfill the criteria of insomnia on the basis of subjective measures only. A criticism to our setup could be that the group of insomnia patients we investigated is not representative for the group of people in the general population suffering from sleeping problems not explained by other sleep disorders or medical conditions. To allow for conclusions about the meaning of brain activation and cognitive measures however, homogeneous groups are required. Further research is needed to define the different subtypes of insomnia and its underlying mechanisms, including insomnia based on subjective measures only.

FUTURE DIRECTIONS

Future studies focusing on the cognitive and neural correlates of insomnia and therapy effects should first focus on the long term effects of non-pharmacological sleep therapy. The current results show partial normalization of prefrontal activation after a 6-week intervention. Long term follow-up, either after long term sleep therapy or after termination of successful sleep therapy, could show more profound normalization effects. Of particular interest would be follow-ups of six months and more: short term sleep therapy has shown to remain effective on sleep parameters[51] and reduce presleep arousal and dysfunctional beliefs about sleep[52] after follow-ups of 3, 6 and 8 months. In particular on the fluency task, long term follow-up measures may indicate whether number of words generated may normalize, due to further reduction of hyperarousal, or whether the fluency task taps into functions that represent more stable factors of insomnia, insensitive to therapy interventions. Such stable factors were also detected in the facilitation differences between insomnia patients and controls on TMS stimulation, which were insensitive to therapy interventions. The reversibility of the grey matter density differences between insomnia patients and controls, found in the VBM study, may also be further investigated. Previous findings have indicated that even relatively brief learning episodes (three months) can lead to changes in grey matter density[53]. This suggests that normalization of grey matter density is possible. Of particular interest also is the comparison of results attained with non-pharmacological sleep therapy versus pharmacological sleep therapy.

Furthermore, the grey matter density differences in orbitofrontal cortex call for more investigation on decision making functions in insomnia. Insomnia has been related to problem solving deficits, but the direct relation with decision making needs to be explored. In and outside the MRI scanner, decision making can be further investigated on many levels: from real-life situations (what house to buy, what job or school to choose) to reward/punishment situations and gambling scenarios which allow for variance in levels of reward, loss or punishment. Decision making and ruminaton questionnaires could become part of the intake procedure in future insomnia studies. In particular, the Melbourne Decision Making Questionnaire[54], the Gambling Expectancy Questionnaire[55] and the Dickman Impulsivity Inventory DII[56] would be feasible questionnaires to investigate these functions. Social decision making can be tested by scenarios such as the prisoners' dilemma[57]. Higher neuroticism is related to poorer decision making performance in the elderly but not in younger adults, as measured by the Iowa Gambling Task[58]; what role insomnia plays in this process needs to be investigated. On a very basic level, we investigated decision making in our more complex vigilance task: depending on the stimulus

('p' or 'd'), a decision had to be made whether a button should be pressed. This was one of the few tasks where we did find an effect on performance in the insomnia group. Decision making is also affected in experimental sleep deprivation[59].

Future studies of insomnia may also focus on emotion regulation. According to the 3P model of Spielman[60], insomniacs tend to show internalization of emotions. Questionnaires such as the Regulation of Emotions questionnaire[61] could be used to further measure these abilities in future insomnia studies. Emotion-evoking stimuli particular for insomnia, such as pictures of well-rested or fatigued persons or sleeping people, but also angry, sad or stressed faces may directly provoke differential emotional reactions in insomniacs compared to controls. An emotional attentional bias for sleep-related items on the emotional Stroop task was recently found for insomniacs but not for a control group of sleep experts[62].

Future studies could also include a clinical interview by a psychiatrist as part of the screening procedure, as well as more precise psychiatric questionnaires. Psychiatric symptoms such as anxiety and depression but also rumination and obsessive compulsive symptoms need to be determined in more detail in insomnia, to determine their precise role as predisposing, precipitating and perpetuating factors. A longitudinal study focusing on a sample of the general population with and without sleep complaints may give more insight into what factors determine the onset, development and perpetuation of insomnia.

Further research should also focus on menopause as an insomnia onset factor. A majority of insomnia patients is female and menopause was indicated as a precipitating factor in a majority of our participants. A recent study reported that 62% of a group of 206 menopausal women suffered from insomnia, which was unrelated to hot flashes or incidence of chronic disease[63]. Hormonal changes may play an important role in the onset of insomnia. After menopause and its direct symptoms are over, insomnia may last, as happens after other life events. Direct treatment of insomnia during or directly after menopause may therefore be important to prevent the development of chronic insomnia[64].

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