code : 77323
Research proposal

Research question
Could we significantly reduce REM sleep time without adverse consequences on cognitive processes?

Introduction
In the review [1] about sleep role in memory, authors concluded that, although, previously it was believed that REM sleep is very important for memory consolidation, today we have controversial evidence that REM sleep reduction leads to impairments in declarative, procedural or motor memory performance. Furthermore, many depressed people could live almost normal lives with antidepressant drugs, which significantly reduce REM sleep time [1, 2]. Lavie et al. [3] reported the case study about the man, whose REM sleep was significantly reduced after brain injury. Nevertheless, he could live a near-normal life in several years after the incident. In a randomized and controlled experiment [4], overall daytime sleepiness was tested after significant REM sleep reduction. No significant increase in daytime sleepiness was found. In a double-blind, randomized and controlled experiment [2], motor skills consolidation and word-pairing were tested in healthy individuals after REM sleep suppression with drugs. No effect was found. Some researchers [5] believe that REM sleep is important for early childhood development, as it significantly higher both in percentage and in absolute amount during the first years of life. Then it remains in adults as an effective mechanism of energy saving: it is easy to wake up and check whether the surroundings are safe and also it is only the brain which works during that stage. All these pieces of evidence mean that for now we do not know exactly what for do we need REM sleep. Or, even more radically, do we really need it?

We think that all previous studies about REM sleep reduction have the one core problem — short-term duration (just several days of an experiment). Our idea is to run the case study (see 1st plan), the remote quasi-experiment (see 2nd plan) and the randomized, double-blind and controlled experiment (see 3rd plan) to check whether the long-term REM sleep deprivation affects cognitive processes. However, firstly, we should think why no one else tried to do this before. We came to the following possible explanations: (1) ethical issues — maybe it is not really safe to deprive subjects with REM sleep for a long time period; (2) high costs of long-term, big sampled, controlled experiment in a sleep laboratory. Let us discuss these issues in more details.

Safety: First of all, we think that if adverse consequences due to REM sleep deprivation take place they should first appear as impairments in core cognitive functions and only then proceed with real health problems. So that, we should determine the thresholds on cognitive tests results, which show as when it is time to stop an experiment if it is not safe anymore. Secondly, we are going to propose three designs but insist on starting with the single-subject case study (see 1st plan). This first subject will be under control all the time, so we hope it significantly reduce risks that something dangerous happens with her mental or general health. And if it will be safe for the first REM-deprived subject, we could proceed with two other experiments, considering our stop thresholds. Moreover, as anecdotical evidence, we know that lots of newborns' moms and dads sleep with interruptions for a long time after their babies appearance. And it seems as they have no serious problems with their mental or general health.

High costs: To be honest, we realize that the idea to prove the safety of REM sleep deprivation is high-risk one. That is why we are going to start with one subject case study in a sleep laboratory (see the 1st plan), which should not be extremely costly. In case of success, we proceed with remote quasi-experiment (see 2nd plan), and only then start a really expensive randomized, double-blind and controlled experiment in a sleep laboratory (see 3rd plan).

Moreover, we believe that possible implications (of course, if we find that REM sleep deprivation does not lead to adverse consequences on cognitive processes) outperform possible risks. It is shown that total sleep time is reduced with REM sleep deprivation [4, 6], as REM takes 15-25% of total sleep time in adults [7]. So that, people could gain approximately 1.5 extra hours per day. Is not this a true life extension?

Hypothesis
Long-term REM sleep reduction does not lead to cognitive impairments

Timeline
The timeline is unified for all three designs.

7-day pre-test stage — with sleep and daytime measurements but without sleep intervention: (1) we need this stage to make subjects familiar with tests we are going to use further for cognitive impairments assessment. So that, to decrease the probability that performance is due to learning or predictability effects during the main stage. (2) And also we need this stage as subjects should adapt to sleep measurements;

21-day pre-test stage — with sleep and daytime measurements but without sleep intervention: to collect baseline measurements for each subject (we need such a long pre-test phase to determine safety thresholds);

28-day main test stage — with sleep and daytime measurements and with sleep intervention for target subjects;

7-day recovery stage — with sleep and daytime measurements but without sleep intervention: we need this stage (1) to track subjects recover and (2) to measure possible delayed effects.

Operationalization
Independent and dependent variables are unified for all three designs, however, the ways to manipulate an independent variable and to measure dependent variables differ between the designs.

We are going to manipulate REM sleep duration, as an independent variable. REM-deprived subject will be woken up for 2 minutes each time she tries to start REM sleep phase, during this time she will be asked general questions to fix her from returning back to sleep. This procedure was proposed by Rosales-Lagarde et al. [6] with the following example: “name the days of the week ”. Subject from the control group[1] will be paired with REM-deprived one. She will be woken up for 2 minutes (if she is not in the REM stage) each time when her REM-deprived pair tries to start REM sleep phase [4].

We are going to measure overall sleepiness as an aggregated indicator of sleep deprivation consequence [4]. We will also use two groups of tests, which evaluate cognitive performance. The first group reflects our intuition combined with existing results [8,9,10] about the main cognitive impairments, which could appear due to nonspecific sleep deprivation. So the first group tests will be attention and working memory tests. The second group of tests reflects impairments, which are usually reported due to REM deprivation: declarative memory and procedural memory [1], and emotional response [6, 11]. You could find specifications of these tests further:

* *Sleepiness*: Multiple Sleep Latency Test (MSLT) [4] will be conducted every day during the study to assess overall sleepiness. A subject will have three 20 min napping periods per day, starting from four hours after night sleep awakening and with 3 hours intervals between napping periods over a day. The time between the start of the napping period and falling asleep is measured and averaged across three napping periods for one day for one subject.

* *Attention*: We are going to measure simple attention (or reaction time) with Psychomotor Vigilance Test [9] for 5 min every day. Subject has to press the button each time the visual stimulus appears on the screen. Reaction time will be measured.

* *Working memory*: Delayed match-to-sample task [8, 9] is often used to assess sleep deprivation impact on working memory. Visual pattern is presented for a short period of time, then it

[1] Note that control group will be used only in 2nd and 3rd plans

disappears and after a short delay, several different visual patterns are presented. Subject has to find the initial visual pattern among these patterns. We are going to conduct this test for 7 minutes every day[2]. Reaction time and percent of the right answers will be measured.

* *Declarative memory*: We are going to use a declarative paired associate task as was proposed by Rasch et al [2]. 40 semantically connected word pairs from the list 1 are sequentially presented to the subject. Then, during the learning stage, the first word from the pair appears and the subject is asked to name the second word. The correct answer is presented in several seconds. This procedure continues with a random order of words until the subject reaches 60% accuracy. Next day the retrieval phase starts: the subject again should name the second word from list 1 when the first word is presented. Accuracy is measured. Then, later this day, the test is repeated with word pairs from the list 2. This test will be conducted every day with different word lists. (For further clarification, please, see Supplementary materials[3] of the original paper [2] page 4).

* *Procedural memory*: We are going to use a finger sequence tapping task as again was proposed by Rasch et al [2]. The subject is presented with a 5-slot sequence for tapping on a keyboard with the fingers of her non-leading hand (for example, 5-3-2-4-1). She is learning this sequence for the nine 30 sec trials and then gets two averaged learning scores on the last three trials (1 — how many corrected sequences were tapped during 30 sec; 2 — percent of wrongly tapped sequences among all tapped sequences during 30 sec). Next day the retrieval phase starts: subject has three more three trials, average retrieval scores are assessed. The difference between retrieval and learning scores is measured. Then, later this day, this test is repeated with a new tapping sequence. This test will be conducted every day with different tapping sequences. (For further clarification, please, see Supplementary materials[4] of the original paper[2] page 4).

* *Emotional response*: For this test we need around 20x63 highly unpleasant and exciting pictures and around 20x63 neutral pictures on different topics (like in International Affective Picture System[5]), where 63 is a number of days of the study. However, we can not use IAPS itself as we need more pictures than it allows. So that, we are going to collect these pictures manually and to use Yandex.Toloka[6] to assess distributions of each picture pleasantness (on the nine-point scale from “highly unpleasant” = “-4” to “highly pleasant” = “+4”, “0” is neutral) and excitability (on the nine-point scale from “highly boring” = “-4” to “highly exciting” = “+4, “0” is neutral). During the main study, the subject will be sequentially presented with 40 pictures in a random order (20 pictures are highly unpleasant and exciting, others 20 are neutral) and asked to evaluate each picture pleasantness. Next day she is presented with the same set of pictures and asked to evaluate each picture pleasantness once again. The following metric (M) will be constructed M = (N1 — U1) — (N2 —U2), where U1 is an averaged pleasantness for 20 unpleasant&exciting pictures measured on day 1, U2 — an averaged pleasantness for the same 20 unpleasant&exciting pictures measured on day 2, N1 is an averaged unpleasantness for 20 neutral pictures measured on day 1, N2 is an averaged unpleasantness for the same 20 neutral pictures measured on day 2. We expect that M will be positive when the subject could effectively cope with emotions aroused by unpleasant&exciting pictures, which are presented on the second day (as (N1 — U1) will be bigger than (N2 —U2)). Then, later this day, this test is repeated with a new set of pictures. This test will be conducted every day. We were inspired by Rosales-Lagarde et al. [6] to use this procedure.

Tests order will be randomly chosen for each day (for all tests except sleepiness, as it needs specific time intervals).

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[2] http://www.cambridgecognition.com/cantab/cognitive-tests/memory/delayed-matching-to-sample-dms/

[3] https://media.nature.com/original/nature-assets/neuro/journal/v12/n4/extref/nn.2206-S1.pdf

[4] https://media.nature.com/original/nature-assets/neuro/journal/v12/n4/extref/nn.2206-S1.pdf

[5] https://www2.unifesp.br/dpsicobio/adap/instructions.pdf

[6] https://toloka.yandex.ru/tasks

Threshold determination
As we mentioned it is important to determine the thresholds to stop a manipulation if it appears to be dangerous for subjects' mental or general health. For each participant, we will have a baseline distribution of each measurement after a 21-day pre-test stage. So we are going to compute a joint distribution for the core measurements — we choose sleepiness, attention, and working memory — and we are going to stop our experiment if the joint measurement runs out 2.5% tails (so 5% for two-tailed distributions) for two sequential days.

1st research plan — case study
One healthy individual with usual bed habits will sleep in a sleep laboratory under a standard set of polysomnographic recordings: electroencephalography, electrooculogram, and electromyogram [2, 6, 11]. We are going to pay for participation in our study.

For the first 28 days (7-day and 21-day pre-test stages) we are going to make polysomnographic recordings and conduct daytime tests without any sleep intervention.

For the next 28 nights of the main stage, sleep laboratory operator will wake the subject up for 2 minutes each time she tries to start REM sleep phase (this moment will be detected with polysomnographic recordings). Subject's overall sleepiness and cognitive performance will be measured every day with tests described above (see operationalization). If the safety threshold will be reached, we terminate these procedures (see threshold determination).

Last 7 days (recovery stage) we are going to make polysomnographic recordings and conduct daytime tests without any sleep intervention.

We are going to consider this study as a safe one if safety threshold is not reached. However, it will be harder to decide whether this study does not refute the hypothesis, so that, we could proceed with the 2nd plan. For instance, overall sleepiness and cognitive performance could decline not due to REM deprivation but due to the awakening procedure. Thus, we need to add controls on this.

We based our ideas about REM duration manipulation and set of cognitive functions, which should be checked, on the most robust results from the previous studies of non-specific and REM sleep deprivation. Moreover, we tried to use the most popular and proven tests for sleep deprivation studies. Nevertheless, we realize that tests, which we propose here, could not fully reflect cognitive functions we want to track. (This statement is relevant for two other plans as well.)

As this is single-participant case study this is too far from the ideal experiment. We have poor generalizability, as we can not control that the effect occurs not due to the subject's certain characteristics, or not due to awakening procedure itself, or not due to subject motivation, or not due to experimenter expectations (but we could partly avoid these problems in the 2nd plan and mostly avoid these problems in the 3rd one). We also can not control lots of background events, which will happen during 9-week tests.

However, we still hope that this case study clarifies a significant part of the picture and shows us that it is safe and fruitful to proceed with the 2nd research plan.

2nd research plan — remote quasi-experiment
For this remote quasi-experiment we need 60 healthy participants with usual bed habits. We are going to pay for participation in our study. There are 2 core requirements for these participants. The first is to have smart watches, which could accurately measure sleep stages and allow new apps to be installed. The second is to have a personal computer to take cognitive tasks remotely. We are going to program two apps: (1) for smart watches to wake subjects up while operator sends a command; (2) for computers to run cognitive tests remotely.

Participants will be randomly paired and randomly placed into one of two groups: the first participant — into target group (REM deprivation condition), the second one — into control group (subjects of this group will be also wakened up but not during REM sleep — see operationalization for more details).

For the first 28 days (7-day and 21-day pre-test stages) we are going to make sleep recordings (via smart watches) and conduct daytime tests without any sleep intervention.

For the next 28 nights of the main stage, the operator will wake up the subject from the REM deprivation group while REM sleep starting and paired subject from the control group if she is not in the REM stage (see operationalization). Subjects overall sleepiness and cognitive performance will be measured every day with tests described above (see operationalization), which will be passed remotely. If the safety threshold will be reached for either target or control group, we terminate these procedures (see threshold determination).

Last 7 days (recovery stage) we are going to make sleep recordings (via smart watches) and conduct daytime tests without any sleep intervention.

Two main improvements of this plan, compared to the 1st plan, are increased sample and additional control group. The increased sample could diminish the probability of the effect due to certain subjects' characteristics. Although, it still could be the case as our participants will be just volunteers with smart watches. Control group allows us to control different side effects, for instance, of the awakening procedure. Moreover, we diminish an experimenter influence, as this study is remote.

There is no doubt that polysomnographic recordings are much more accurate than smart watches' ones. Furthermore, we can not control anymore that daytime tests' procedure is unified for all participants. So we definitely lose accuracy of measurements due to remoteness. However, we still could control that subjects sleep only during the allowed time (as watches tracked this) and take tests on time (as results will be sent automatically after each test). And, what is more important, we could deal with all these 60 subjects at the same time as we do not need the sleep laboratory and this is a significant time and costs reduction.

3rd research plan — experiment
40 healthy individual with usual bed habits will sleep in a sleep laboratory under a standard set of polysomnographic recordings: electroencephalography, electrooculogram, and electromyogram. We are going to pay for participation in our study. Participants will be randomly paired and randomly placed into one of two groups: a first participant — into target group (REM deprivation condition), the second one — into control group (subjects of this group will be also wakened up but not during REM sleep — see operationalization for more details).

This experiment will be double-blind, as the first operator will track sleep recordings and send commands about wakening time to the second operators, who will wake up subjects. Another third group of operators will conduct daytime tests.

For the first 28 days (7-day and 21-day pre-test stages) we are going to make polysomnographic recordings and conduct daytime tests without any sleep intervention.

For the next 28 nights of the main stage, two groups of operators will wake up the subject from the REM deprivation group while REM sleep starting and paired subject from the control group if she is not in the REM stage (see operationalization). Subject's overall sleepiness and cognitive performance will be measured every day with tests described above (see operationalization). If the safety threshold will be reached for either target or control group, we terminate these procedures (see threshold determination).

Last 7 days (recovery stage) we are going to make polysomnographic recordings and conduct daytime tests without any sleep intervention.

This is a randomized, double-blind, controlled, long-term experiment, so it is quite close to the ideal one. However, we still have limited and biased to volunteers (who, nevertheless, will be paid)

sample of participants. We also realize that tests, which we propose here, could not fully reflect cognitive functions we want to track. Moreover, maybe other cognitive functions, which we do not include into these tests, will suffer from REM sleep deprivation. Since safety thresholds are established and checked on the 1st and 2nd plans, the main complaint about this experiment is its very high costs and long time (as usually sleep laboratory could not accommodate 40 participants at the same time).

Conclusion

Obviously, the 3rd plan would be the best one in the world without financial and time constraints, where we know everything about safety threats and where people care about high-risk projects. But it is not the case of the today world…So, as we have already proposed it seems as a good idea to start with the 1st plan, proceed with the 2nd one and if both these studies are successful, follow on with the 3rd plan.

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