Continued Evaluation of Environmental Stimuli in the Absence of Consciousness suggests the Human Brain is Standing Sentinel during Sleep

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Funding
CB is supported by the Konrad-Adenauer-Stiftung e.V. and CB, MW and DPJH are supported by a grant from the Austrian Science Fund FWF (Y-777). CB, RdG, MW and DPJH are also supported by the Doctoral College ''Imaging the Mind'' (FWF; W1233-G17).

Abstract

While it is well-known that subject's own names (SON) or familiar voices are salient during wakefulness, we investigate stimulus processing during sleep including N3 and REM sleep. Additionally, we investigate how sleep EEG patterns (i.e. sleep spindles and slow oscillations [SOs]) relate to stimulus processing. Using 256-channel EEG we studied stimulus processing by means of event-related oscillatory responses (de-/synchronisation, ERD/ERS) and potentials (ERPs). We varied stimulus salience by manipulating subjective (SON vs. unfamiliar name) and paralinguistic emotional relevance (familiar vs. unfamiliar voice, FV/UFV). We show that evaluation of voice familiarity continues during all NREM sleep stages and even REM sleep suggesting a 'sentinel processing mode' in the absence of consciousness. Especially UFV stimuli elicit larger responses in a 1-15Hz range suggesting they are salient. Unlike previously suggested sleep spindles and the negative slope of SOs do not uniformly inhibit information processing but inhibition seems to be tuned to stimulus salience.

Keywords: sleep, sleep spindles, slow oscillations, high-density electroencephalography, auditory stimulation

Introduction

Cognitive processing and task performance are well-known to vary with time of day (Dijk, Duffy, & Czeisler, 1992; Santhi et al., 2016; Wyatt, Cecco, Czeisler, & Dijk, 1999). Behaviourally, it can readily be observed with major variations in performance paralleling the sleep-wake cycle. Beyond these within-state studies that investigated wakefulness only, we lately studied cognitive processing during the fading of consciousness, which we here define as behavioural responsiveness, that is across vigilance stages from waking to light NREM sleep (Blume et al., 2016). Specifically, we compared processing of subjectively relevant vs. irrelevant stimuli (i.e. subject's own names [SONs] vs. unfamiliar names [UNs]) during wakefulness and non-rapid eye movement (NREM) sleep stages N1 and N2 during a nap and additionally varied the emotional prosody of the stimuli (i.e. stimuli spoken by an angry vs. a neutral voice [AV vs. NV]). Interestingly, we found evidence for preferential processing of salient stimuli (i.e. SONs and AV stimuli) not only during wakefulness, but also during light NREM sleep with these findings suggesting not only continued processing of external stimuli, but a 'sentinel processing mode' of the brain during states of decreased consciousness and naturally occurring unconsciousness, that is N1 and N2 sleep, respectively. Moreover, this initial preferential processing of salient stimuli seemed to be accompanied by a subsequent inhibitory sleep-protecting process during N2 sleep that was reflected by a K-complex-like response.

In the present study we sought to replicate our previous findings on the interaction between 'global brain' or vigilance states (i.e. wakefulness, N1 and N2 sleep) and stimulus characteristics and expand them to deep N3 as well as rapid-eye-movement (REM) sleep during a full night. Beyond this, we aimed at investigating the interaction between stimulus characteristics and 'local brain states' in more fine-grained analyses. In particular, we were interested in the interaction between stimuli and sleep-specific electroencephalogram (EEG) phenomena, that is sleep spindles and slow oscillations. Sleep spindles are considered the hallmark of N2 sleep albeit they also occur during sleep stage N3. They are defined as bursts of oscillatory activity in the sigma range (11-15Hz) with a characteristic waxing and waning shape

and a duration of 0.5-3s. Slow oscillations (SOs), on the other hand, are defined as large delta (0.5-3Hz) waves with a first negative going wave that is followed by a positive going deflection. They occasionally occur during N2 sleep already, where they may appear as isolated K-complexes, but their probability of occurrence strongly increases with sleep depth also being a criterion for the definition of deep N3 sleep.

While it is well-established that the brain is not completely shut off from the environment during sleep but continues to process external stimuli (e.g. Bastuji & García-Larrea, 1999; Blume et al., 2016; Perrin, Garcia-Larrea, Mauguiere, & Bastuji, 1999; Strauss et al., 2015), studies also suggest that sleep-specific oscillatory patterns, that is sleep spindles as well as SOs, can significantly alter stimulus processing. Generally, it has been suggested that during spindles the thalamus acts as a sensory filter inhibiting sensory transmission to the forebrain (Steriade, 1991). The negative or positive going slope of SOs on the other hand has been associated with changes in the probability of synaptic release at the cortical level, which could affect stimulus processing (Massimini & Amzica, 2001). In a combined EEG and functional magnetic resonance imaging (fMRI) study Schabus et al. (2012) found that responses to simple tones during NREM sleep were comparable to responses during wakefulness except for when tones were presented during a spindle or the negative going slope of a slow oscillation thereby also confirming previous findings (Dang-Vu et al., 2011; see De Gennaro & Ferrara, 2003 for an overview; Massimini, Rosanova, & Mariotti, 2003). Likewise, in a study that looked at event-related potentials (ERPs) Elton et al. (1997) suggested that sleep spindles inhibit processing of auditory stimuli and Cote, Epps, and Campbell (2000) additionally found the effect of sleep spindles on processing to be modulated by stimulus intensity. Specifically, they report that spindles co-occurring with more intense (i.e. louder) stimuli seemed to inhibit processing to a greater extent than it was the case with less intense stimuli. Regarding slow oscillatory activity on the other hand, a pioneering study by Oswald, Taylor, and Treisman (1960) already showed that SONs evoke more K-complexes (KCs) than do unfamiliar names. Beyond this, Massimini et al. (2003) showed that evoked somatosensory EEG potentials were strongly modified not only by the presence but also by the phase of the slow oscillation. In summary, these

findings strongly suggest that sleep spindles and slow oscillatory activity systematically alter stimulus processing during NREM sleep in a dynamic manner.

The aim of the present study was to investigate processing of more complex auditory stimuli (as compared to simple tones) in relation to (i) 'global' as well as (ii) 'local' states of the brain. Complex stimuli were first names that varied in salience on two dimensions, namely subjective relevance (SONs vs. UNs) and familiarity or paralinguistic aspects of emotional relevance. Specifically, stimuli were uttered by a familiar voice (FV) vs. a stranger's voice (unfamiliar voice [UFV]). Regarding the first aim, we studied stimulus processing during all 'global brain states' across the vigilance continuum (i.e. during wakefulness, N1, N2, N3 and REM sleep) irrespective of the 'local state'. Regarding 'local' states, we investigated between-stimulus differences in oscillatory activity when (i) a spindle was present during stimulus presentation, when a stimulus was presented during the (ii) positive slope of a SO, (iii) during the negative slope and when (iv) stimulus presentation evoked a SO. Processing was studied by comparing oscillatory brain responses evoked by stimulus presentation in each of these cases, that is event-related synchronisation (ERS) and desynchronisation (ERD) in the delta (1-3Hz), theta (4-7Hz), alpha (8-12Hz) and sigma (11-15 Hz) frequency range. Functionally, delta ERS has repeatedly been linked to attentional processes and the detection of salient or motivationally relevant stimuli (for reviews see Knyazev, 2007; Knyazev, 2012) while theta ERS has been suggested to indicate the encoding of new information as well as working and episodic memory involvement (for a review see Klimesch, 1999; Klimesch, Schack, & Sauseng, 2005). Alpha ERD on the other hand is thought to reflect task demands, attentional processes and memory retrieval processes (for a review see Klimesch, 1999; Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998). Importantly, all these interpretations have been established during wakefulness and it is likely that their functional roles are different during sleep. In a previous publication, we suggested that delta and theta ERS during sleep may mirror an inhibitory sleep-protecting response following initial processing of salient stimuli as has been suggested for sigma ERS (Blume et al., 2016).

We hypothesised that oscillatory responses would mirror salience of SONs as well as FV stimuli (compared to UNs and UFV) during wakefulness. Moreover, we expected responsiveness to stimuli to vary with the 'global brain state', that is a decrease in responsiveness from wakefulness to N3 sleep. Regarding the 'local brain state' we expected that when stimulus-presentation co-occurs with sleep spindles and slow oscillations the differential brain response elicited by stimulus salience would vanish. This should specifically be the case when stimulus onset coincided with the negative slope of the slow oscillation or stimulus presentation largely overlapped with a sleep spindle.

Results

Wakefulness

Analyses in the delta band (1-3Hz) yielded a significant effect of *name* (see Fig. 1A). Specifically, analyses revealed that SONs led to stronger ERS at 2Hz in a frontocentral and a parieto-occipital cluster (p = .01 and p = .02, respectively) with an effect size of d = 1.11. This effect was also visible in the ERP with SONs giving rise to a stronger P3 component than UNs (d = .5, see Fig 1B). Analyses did not indicate a significant effect of *voice* or a *name* × *voice* interaction (*voice*: *ps* > 0.37; *name* × *voice*: *ps* > .35).

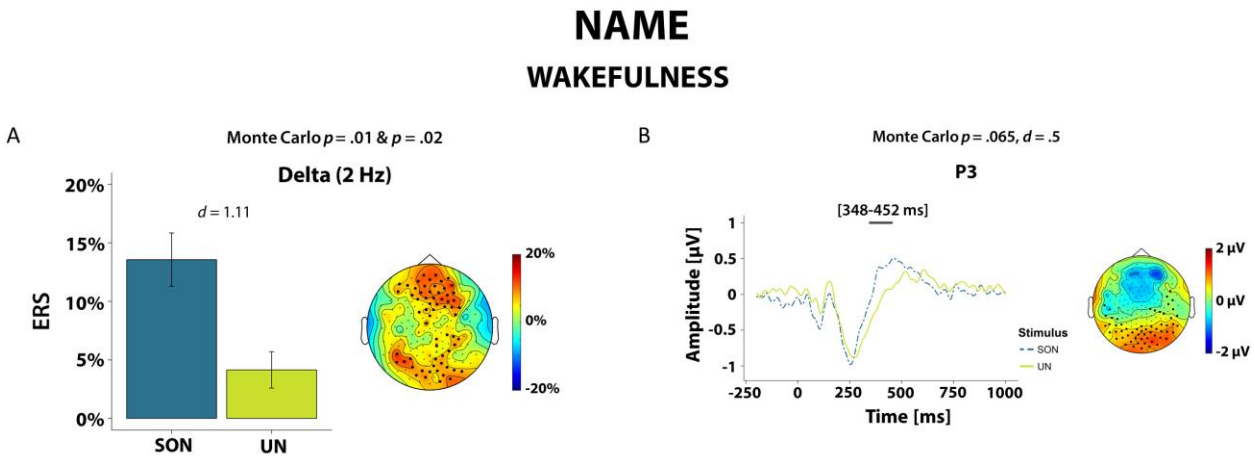


Fig. 1: Event-Related Responses during Wakefulness. (A) Responses in the delta (1-3Hz) range. Bar plot for the effect of *name* (left) and corresponding scalp plot of differences in ERS between SONs and UNs (right).

Large black dots indicate the electrodes that are part of the significant clusters at 2Hz. Error bars indicate ±1 standard error of the mean. Please note that for illustration purposes we show the effects at a representative frequency (i.e. 2 Hz) although significant clusters may have comprised a larger frequency range (see main text). **(B)** Event-related P3 response. Left: Grand average of the ERP elicited by SONs and UNs during wakefulness at all electrodes that were part of the cluster (see scalp plot). The horizontal grey line represents the time window during which the effect was significant (348 to 452ms). Right: Scalp plot of the difference in the ERPs evoked by SONs and UNs. Large black dots indicate electrodes that were part of the marginally significant cluster and *d* is Cohen's *d* for the significant clusters. SON = subject's own name, UN = unfamiliar name. Analyses and figures are based on data from $n = 17$ participants.

In the theta, alpha and sigma bands (4-15Hz), the analyses yielded no significant effects (*voice*: *ps* > 0.62; *name*: *ps* > 0.24; *name* × *voice*: *ps* > 0.4).

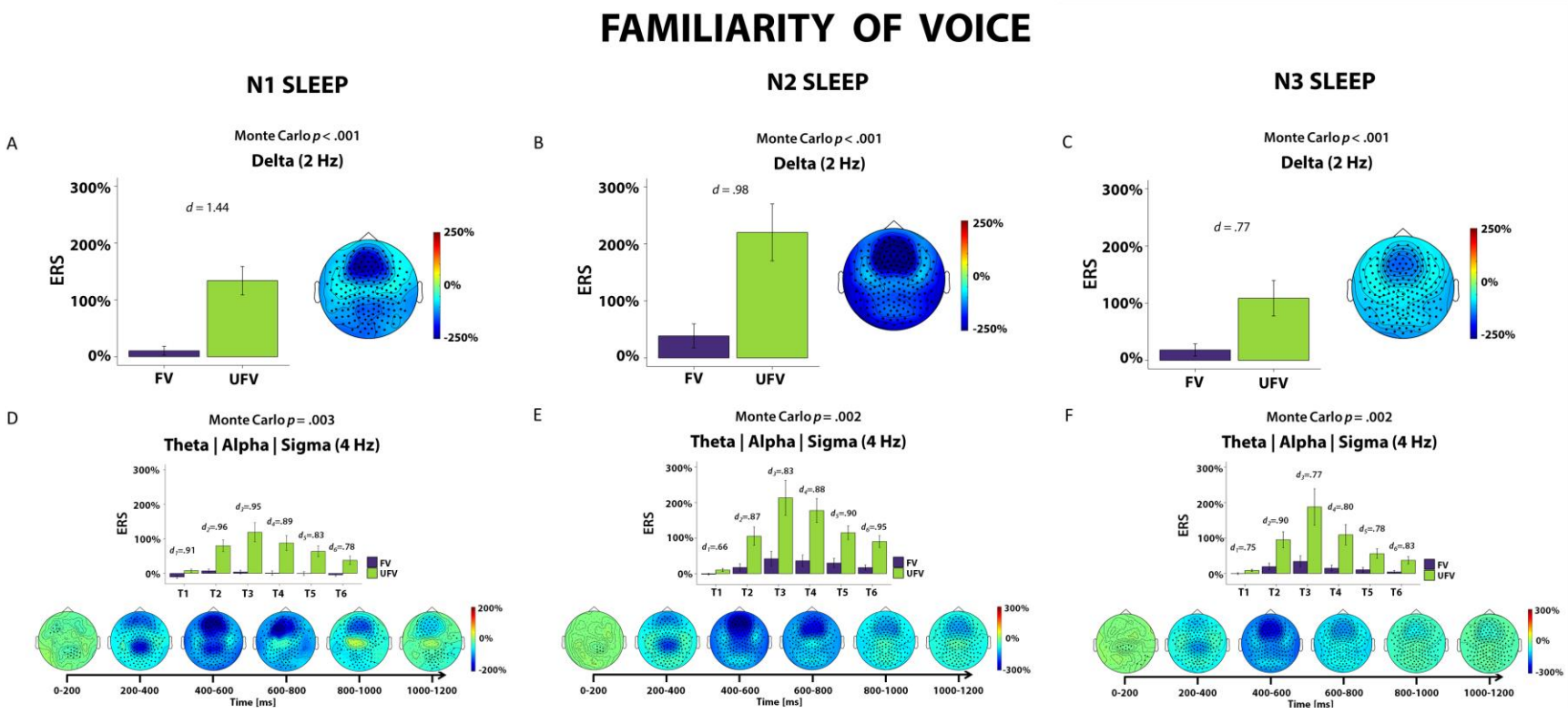
Sleep

Analysis of the sleep staging results revealed that the median of the total sleep time (TST) during the experimental night was 430.5 minutes (range 300-481.5 min). Wakefulness after sleep onset (WASO) had a median of 20 minutes (range 3.5-110 min). The total number of awakenings varied between 5 and 25 with a median of 15. SOL to N2 was characterised by a median of 20 minutes (range 10-107.5 min), and SOL to REM had a median of 92.5 minutes (range 68.5-228 min). Regarding sleep architecture participants had a median of 7.2% N1 sleep (range 2.7-13.7%), a median of 37% N2 sleep (range 23-54.4%), a median of 34.2% N3 sleep (range 16.5-46.1%) and a median of 18.9% REM sleep (range 12.2-45.1%).

"Global Brain State" Analyses

N1 sleep

166 During light N1 sleep, analyses yielded significant stimulus-induced differences in delta (1-3Hz)
167 ERS for the effect of *voice* ($p < .001$). Here, UFV stimuli elicited stronger delta ERS than FV stimuli in a
168 cluster that spanned large areas of the scalp with a frontal-central focus (see Fig. 2A). There were no
169 further significant stimulus-induced differences in the delta range (*name*: $p > .21$; *name* × *voice:* no
170 significant clusters). Analyses of responses in the theta, alpha and sigma bands (4-15Hz) also yielded a
171 significant effect of *voice* ($p = .003$, see Fig. 2C). Here, UFV stimuli elicited considerable ERS in the
172 theta through sigma frequency range in all time windows analysed (T1-T6: 4-15Hz). Analyses did not
173 show a significant effect of *name* (*ps* > .26), but a marginally significant *name* × *voice* interaction ($p =$
174 .055) with UFV stimuli eliciting stronger ERS irrespective of the name that was presented, i.e. SON or
175 UN thus confirming the main effect of *voice*. The effects of *voice* were also confirmed by ERP analyses
176 with a stronger positive (92-428ms) and negative component (440-996ms) for UFV as compared to FV
177 (see Suppl. Fig. 2A).



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179 **Fig. 2: Event-related responses during NREM sleep. (A, B, C)**: Event-related responses in the delta range (1-3 Hz) during N1, N2 and N3. Bar plots

180 for the effect of *voice* (left) and corresponding scalp plots of differences in ERS between FV and UFV (right). **(D, E, F)** Event-related responses in the

181 theta/alpha/sigma range (4-15Hz) during N1, N2 and N3. Bar plot for the effect of *voice* during the six time windows (top) and corresponding scalp plots of

182 differences in ERS/ERD between FV and UFV stimuli (bottom). Large black dots indicate the electrodes that are part of the significant clusters and *d* is Cohen's *d*

183 for the significant clusters. Error bars indicate ±1 standard error of the mean. Please note that for illustration purposes we show the effects at representative

frequencies (i.e. 2 and 4 Hz) although significant clusters may have comprised a larger frequency range (see main text). FV = familiar voice, UFV = unfamiliar voice. Analyses and figures are based on data from n = 17 participants.

N2 sleep

Analyses in the delta range yielded a significant effect of *voice* ($p < .001$) with a cluster covering the whole scalp. Specifically, UFV stimuli elicited stronger delta ERS than FV stimuli for all frequencies between 1 and 3Hz. The (fronto-central) topography was comparable to the N1 effect of *voice* in the delta range (see Fig. 2A and 2B). Analyses did not yield an effect of *name* or a *name* × *voice* interaction (*ps* > .18 and *no clusters*, respectively). In the theta to sigma range (4-15Hz), analyses also revealed a significant effect of *voice* ($p = .002$). Here, again UFV stimuli elicited strong ERS between 4 and 15Hz following about 200ms while FV stimuli elicited much less ERS (T1: 4-7 & 15Hz; T2-T6: 4-15Hz). The topography and time course was comparable to the N1 effect (see Fig. 2D and Suppl. Fig. 1D). Besides this, analyses showed no effect of *name* (*ps* > .16) and no *name* × *voice* interaction (*ps* > .34). The effects of *voice* in oscillatory analyses were also confirmed by ERP analyses (see Suppl. Fig. 2B).

N3 sleep

During N3 sleep, analyses in the delta range (1-3Hz) revealed a significant effect of *voice* ($p < .001$). UFV stimuli gave rise to stronger delta ERS than did FV stimuli in a cluster covering large areas of the scalp. Again, the topography was comparable to the results obtained in N1 and N2 (see. Fig. 2A, Fig. 2B and Fig. 2C). Analyses did not reveal any stimulus-induced differences for the *name* effect (no clusters) or the *name* × *voice* interaction (no clusters) in the delta range. Analyses in the theta to sigma range (4-15Hz) revealed a significant effect of *voice* ($p = .002$; T1: 4-9 & 15Hz; T2-6: 14-15Hz). Here, UFV stimuli elicited stronger ERS than did UFV stimuli, an effect that was especially pronounced between about 200 and 1200ms following stimulus onset in a cluster that spanned more or less the whole scalp. Also here, the time course and topography was comparable to the results obtained during N1 and N2 (cf. Fig. 2D, Fig. 2E and Fig. 2F). Analyses did not yield any other significant effects (*name*: *ps* > .23; *name* × *voice*: *ps* > .31). Analyses of ERPs confirmed the effects of *voice* (see Suppl. Fig. 2C).

REM sleep

Analyses during REM sleep yielded a significant effect of *voice* in the delta range (1-3Hz, p = .018, see Fig. 3A). As during N1-N3 FV stimuli were associated with stronger delta ERS between 1 and 2Hz than were UFV. There were no further stimulus-induced differences in delta ERS/ERD (*name*: *ps* > .18; *name* × *voice* interaction: *ps* > .17). Analyses in the theta to sigma range (4-15Hz) yielded a significant *voice* effect (p = .006, see Fig. 3B). Here, UFV stimuli elicited stronger ERS than FV stimuli following about 200ms. The effect mainly covered the alpha through sigma range (T1: 5Hz; T2: 4-15Hz; T3: 5-6 & 12-15Hz; T4/5: 8-15Hz; T6: 9-15Hz) and was most pronounced at central and centroparietal electrodes. Generally, effects during REM were much less pronounced and delayed compared to the NREM sleep stages. Analyses did not yield any further significant effects (*name*: *ps* > .37; *name* × *voice:* *ps* > .32).

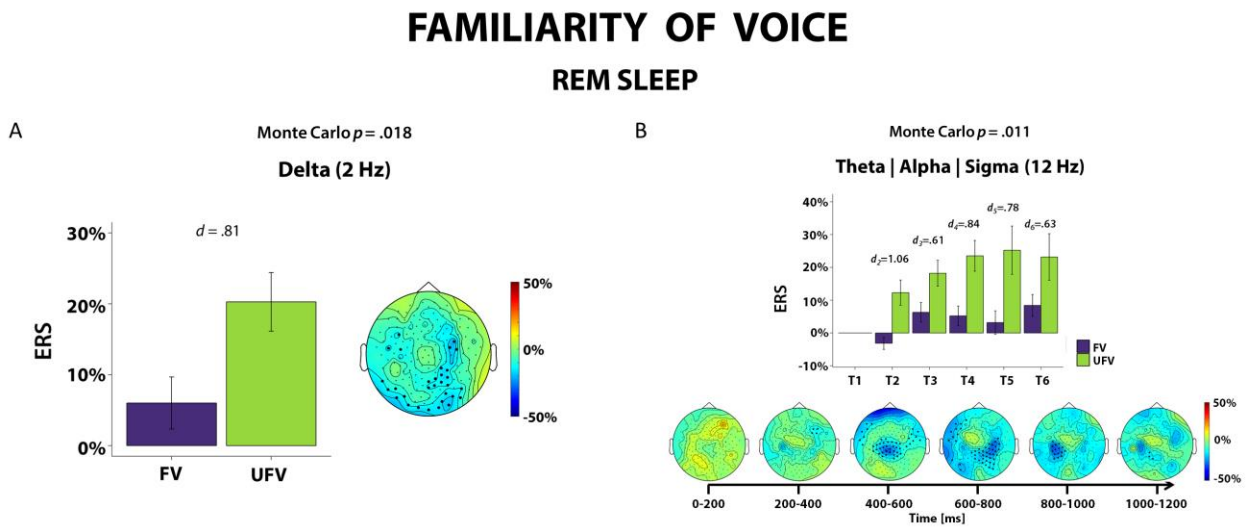

Fig. 3: Event-related responses during REM sleep. (A) Event-related responses in the delta (1-3Hz) range. Bar plot for the effect of *voice* (left) and corresponding scalp plot of differences in ERS between FV and UFV (right). Large black dots indicate the electrodes that are part of the significant cluster at 2Hz. **(B)** Event-related responses in the theta/alpha/sigma (4-15Hz) range. Bar plot for the effect of *voice* during the six time windows (top) and corresponding scalp plots of differences in ERS/ERD between FV and UFV stimuli (bottom). Large black dots indicate the electrodes that are part of the cluster at 12Hz and *d* is Cohen's *d* for the significant clusters. Error bars

indicate ±1 standard error of the mean. Please note that for illustration purposes we show the effects at representative frequencies (i.e. 2 and 12 Hz) although significant clusters may have comprised a larger frequency range (see main text). FV = familiar voice, UFV = unfamiliar voice. Analyses and figures are based on data from *n* = 17 participants.

"Local Brain State"- Analyses

Sleep Spindle vs. No Spindle

In both conditions, analyses of ERD/ERS revealed significant effects of *voice* in the delta range ("spindle" condition [S+]; $p = .03$; 1-2Hz, see Fig. 4A and "no spindle" condition [S-]: $p = .028$; 1-3Hz, cf. Fig. 4B) with UFV stimuli eliciting stronger delta ERS than FV stimuli. Besides, post hoc analyses indicated that stimulus presentation elicited more ERS in the S- compared to the S+ condition ($p = .073$). There were no further effects in the delta range in either condition (S+: *name:* $p = .40$; *name* × *voice*: no clusters; S-: *name*: no clusters; *name* × *voice*: *ps* > .26). In the theta to sigma range (4-15Hz) there were also significant effects of *voice* in both the "spindle" and the "no spindle" conditions (S+: $p = .033$, T1: 15Hz; T2: 4 & 8-15Hz; T3/4: 4-15Hz; T5: 8-15Hz, T6: 6-15Hz, see Figs. 4C and E; S-: $p = .016$, T1: not part of the cluster; T2: 4-12 Hz; T3: 4-14Hz; T4/5: 4-15Hz: T6: 4-9Hz, see Figs. 4D and F). Interestingly, the topography and time course of the effects in the "no spindle" condition were only comparable to the results in the "spindle" condition in the slower frequencies up to about 9Hz. While in the slower frequencies UFV stimuli elicited stronger ERS than FV stimuli, in the faster frequencies (10-15Hz), FV stimuli were specifically associated with a marked ERD in the "spindle" condition only (Condition differences: $p < .001$, diamonds in Figs. 4E and F indicate time windows with sign. differences). Analyses did not yield any further significant differences in the theta to sigma range (S+: *name: ps* > .12 and *name* × *voice: ps* > .10; S-: *name*: *ps* > .22; *name* × *voice*: *ps* > .24). ERP analyses showed a significant effect of *voice* that corresponded to the effects in the oscillatory analyses only in the "spindle" condition (see Suppl. Fig. 3).

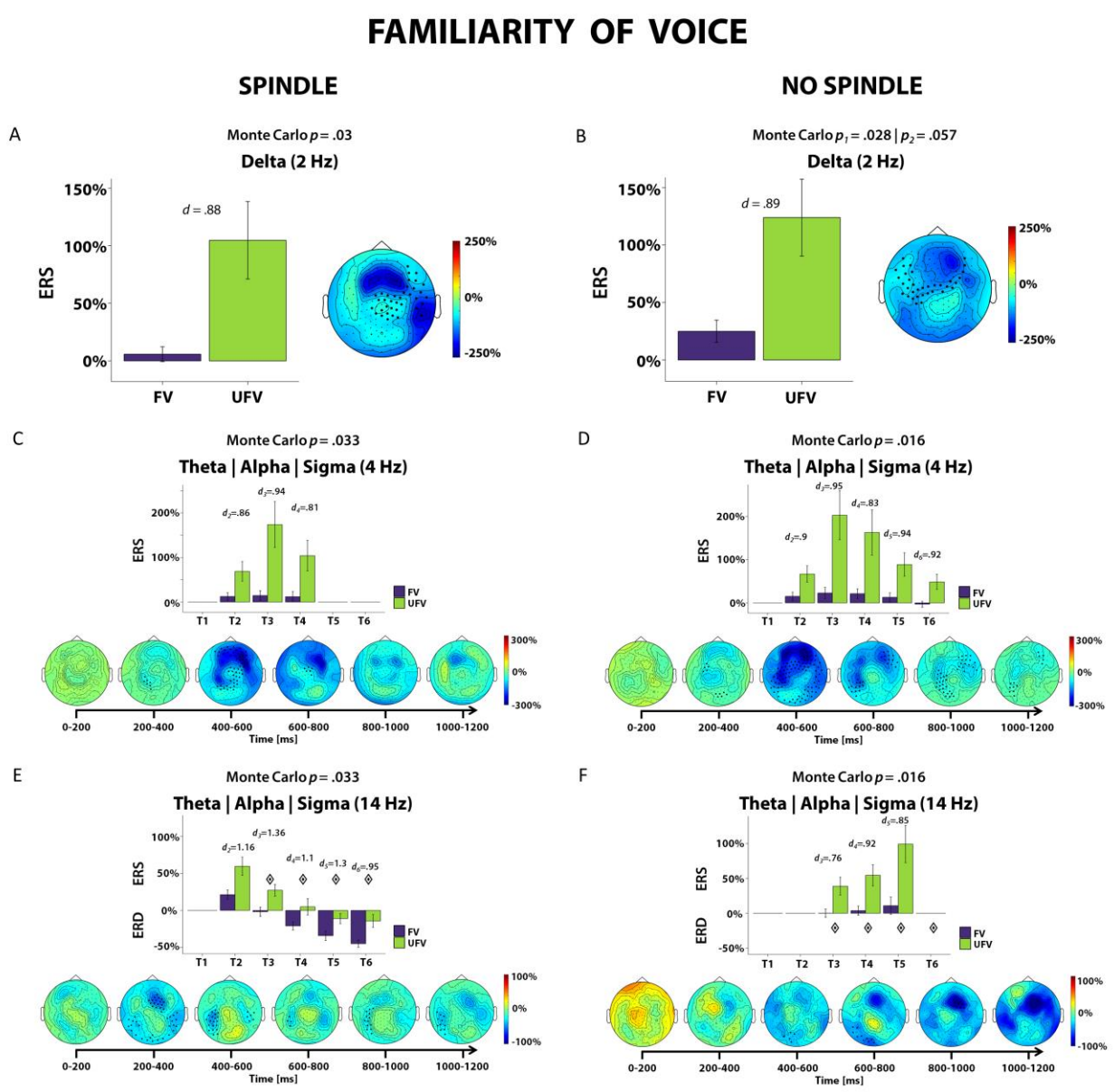

Fig. 4: Event-related responses during N2/N3 sleep depending on the presence/absence of sleep spindles. (A, B) Event-related responses in the delta (1-3Hz) range. Bar plots for the effect of *voice* (left) and corresponding scalp plot of differences in ERS between FV and UFV (right). **(C, D)** Event-related responses in the theta/alpha/sigma (4-15Hz) range at 4Hz and **(E, F)** responses at 14Hz. Bar plots for the effect of *voice* during the six time windows (top) and corresponding scalp plots of differences in ERS/ERD between FV and UFV stimuli (bottom). Diamonds in figures E and F indicate the time windows with significant differences between S+ and S- conditions at 14 Hz. Large

black dots indicate the electrodes that are part of the clusters at 2Hz, 4Hz or 14Hz, respectively. Error bars indicate ±1 standard error of the mean and *d* is Cohen's *d* for the significant clusters. Please note that for illustration purposes we show the effects at representative frequencies (i.e. 2, 4 and 14 Hz) although significant clusters may have comprised a larger frequency range (see main text). FV = familiar voice, UFV = unfamiliar voice. Analyses and figures are based on data from $n = 10$ participants.

Stimulus Presentation along Slow Oscillation Positive vs. Negative Slope

Irrespective of the slope of a SO during which a stimulus was presented, analyses yielded significant effects of *voice* (pos. slope: $p < .001$, $d = .70$ see Fig. 5A, neg. slope: $p = .003$, $d = .67$, see Fig. 5B) in the delta range. Specifically, like in the other conditions UFV stimuli elicited stronger ERS than did FV stimuli between 1 and 3Hz in clusters spanning large parts of the scalp. There were no differences in delta ERS between positive and negative SO slope ($p = .18$) and no further effects were evident in the delta range (pos. slope: *name*: no clusters; *voice* × *name:* $p > .1$; neg. slope: *name*: $p = .18$; *voice* × *name:* $p > .16$). In the theta to sigma range (4-15Hz) analyses also revealed significant effects of *voice* in both conditions (pos. slope: $p < .001$, see Fig. 5C; neg. slope: $p = .008$, see Fig. 5D) with UFV stimuli eliciting stronger ERS than FV stimuli following about 200ms in a broad frequency range comparable to the effects in the other conditions regarding topography and time course (pos. slope: T1: 9Hz; T2-6: 4-15Hz; neg. slope: T1: not part of the cluster; T2-6: 4-15Hz). There were no differences in the theta through sigma range between positive and negative SO slope (*ps* > .72). The effects of *voice* were also confirmed by ERP analyses (pos. slope: see Suppl. Fig. 4B; neg. slope: see Suppl. Fig. 4C). There were no further effects in the theta through sigma range (pos. slope: *name*: *ps* > .27 *name* × *voice:* *ps* > .31; neg. slope: *name*: *ps* > .40; *name* × *voice*: *ps* > .48).

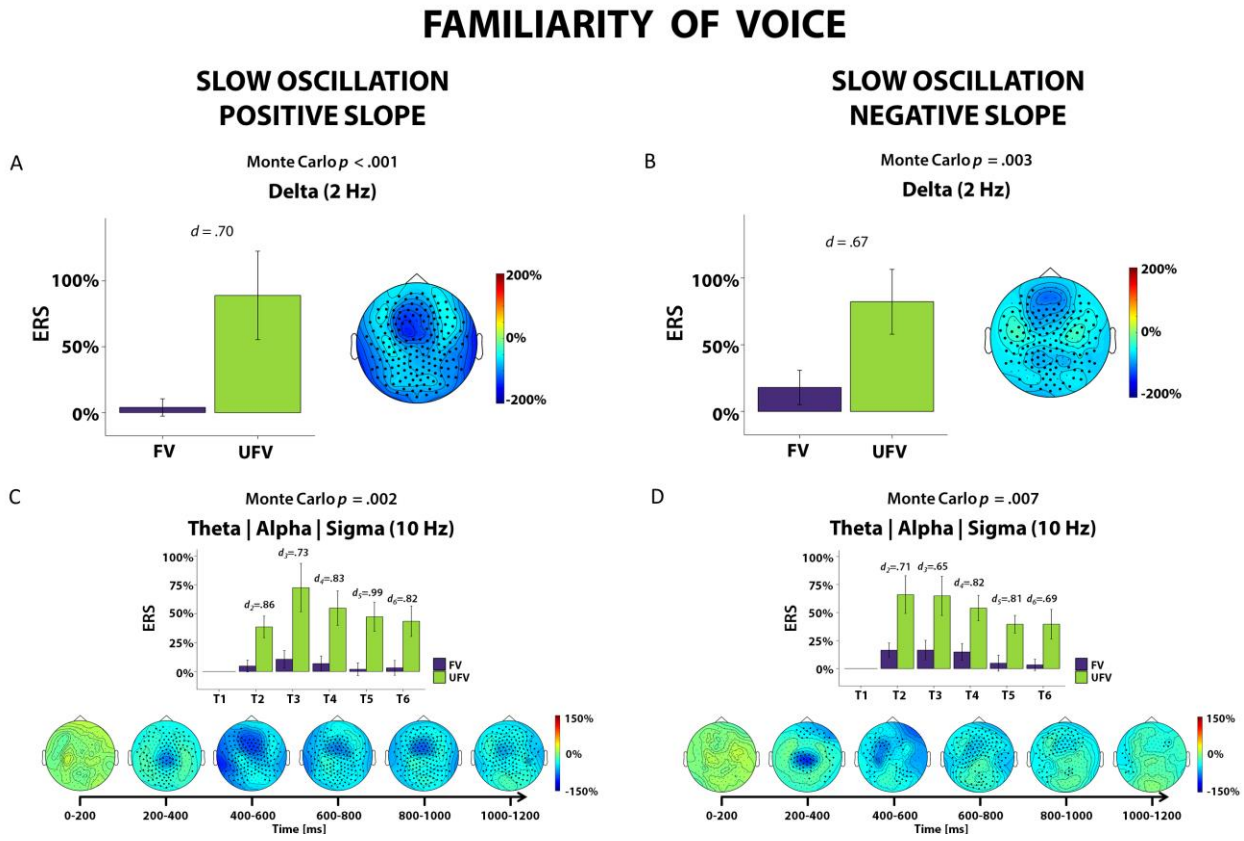

Fig. 5: Event-related responses during N2/N3 sleep when a stimulus was presented along the positive vs. negative slope of the SO. (A, B) Event-related responses in the delta (1-3Hz) range. Bar plots for the effect of *voice* (left) and corresponding scalp plots of differences in ERS between FV and UFV (right). **(C, D)** Event-related responses in the theta/alpha/sigma (4-15Hz) range. Bar plots for the effect of *voice* during the six time windows (top) and corresponding scalp plots of differences in ERS/ERD between FV and UFV stimuli (bottom). Large black dots indicate the electrodes that are part of the significant clusters and *d* is Cohen's *d* for the significant clusters. Error bars indicate ±1 standard error of the mean. Please note that for illustration purposes we show the effects at representative frequencies (i.e. 2 and 10 Hz) although significant clusters may have comprised a larger frequency range (see main text). FV = familiar voice, UFV = unfamiliar voice. Analyses and figures are based on data from *n* = 16 participants.

Discussion

In this study we show that especially processing of paralinguistic aspects of verbal stimuli such as the familiarity of a voice is even possible during fading and in the absence of consciousness during sleep. The findings add to existing evidence that the detection and evaluation of meaningful stimuli is still possible in these states (e.g. Perrin et al., 1999; Portas et al., 2000). Intriguingly, we do not only find that a differential response to familiar vs. unfamiliar voice (FV vs. UFV) stimuli persists during light NREM sleep stages N1 and N2 thus replicating previous results (cf. Blume et al., 2016; Perrin et al., 1999), but we extend this finding to deep N3 and intriguingly also REM sleep. Beyond this, we show that local brain states that have been suggested to alter sensory information processing during sleep, i.e. sleep spindles (Cote et al., 2000; Elton et al., 1997; Schabus et al., 2012) and slow oscillation down-states (Massimini et al., 2003; Schabus et al., 2012), do at least not uniformly, that is irrespective of stimulus characteristics, inhibit stimulus processing. Rather, their inhibitory function seems to be tuned to stimulus salience.

During wakefulness, SONs seemed to be salient when compared to UNs thus drawing more attentional resources. This was indicated by SONs eliciting stronger delta ERS than UNs across large areas of the scalp (Knyazev, 2007, 2012) and is well in line with the relatively larger P3 component evident in ERP analyses as well as results from earlier studies (e.g. Berlad & Pratt, 1995; Blume et al., 2016; Perrin et al., 1999). In an earlier study from our group, del Giudice et al. (2014) had also found stronger alpha ERD for SONs than for UNs, which we not could not replicate here. This may ultimately be due to methodological differences and the more conservative statistical analysis methods employed here. Somewhat surprisingly, no differences were evident between FV and UFV stimuli when participants were awake. However, we experience situations in which voices of varying degrees of familiarity are present along with unfamiliar voices every day and, in comparison to the SON, familiar voices do usually not draw attention automatically (cf. the "Cocktail Party Phenomenon"; Wood & Cowan, 1995). Probably, this were even maladaptive as the manifold familiar voices would constantly disturb orienting

and eventually allocation of attention. Thus, the lack of a differential response evoked by stimulus familiarity may well be considered adaptive.

During NREM sleep, that is from light N1 to deep N3 sleep, we consistently find that processing of FV vs. UFV stimuli gives rise to a differential response in the delta to sigma frequency range, an effect that is present in oscillatory analyses as well as ERPs. Most importantly, this provides support for the notion that processing of auditory stimuli and especially of paralinguistic stimulus aspects such as the familiarity of a voice is incessantly processed even in states where consciousness is absent. While this is well in line with earlier findings during light sleep stages N1 and N2 (e.g. Blume et al., 2016; Oswald et al., 1960; Portas et al., 2000), our results suggest that the same holds true even for deep N3 sleep. Thus, the findings also support the notion of a 'sentinel processing mode' of the brain during sleep, which we suggested in a previous publication (cf. Blume et al., 2016). Specifically, this mode describes the idea that (low-level) stimulus evaluation continues even when consciousness fades during sleep and the result of this evaluation may subsequently either trigger an inhibitory sleep-protecting response or awakening. In detail, we here find UFV stimuli to be associated with stronger ERS in the delta range than FV stimuli during all NREM sleep stages, an effect which was widespread across the scalp with the response being most pronounced above frontocentral areas. Adopting the interpretation of delta oscillations during wakefulness, the results suggest that UFV stimuli may become salient when consciousness fades (Knyazev, 2007, 2012). In particular, the presence of unfamiliar voices could challenge the impression of a safe environment that is necessary to 'let go of consciousness' and eventually fall and stay asleep, rendering them salient. However, an increase in delta ERS could also be related to a sleep-specific ERP, namely a K-complex-like response. K-complexes (KCs), whose peak frequency is in the delta range, have been suggested to serve cortical excitation and low-level information processing as well as the subsequent protection of sleep by neuronal silencing and they have been shown to be elicited by salient or high-intensity stimuli (Amzica & Steriade, 1997; Bastien & Campbell, 1992; Cash et al., 2009; Laurino et al., 2014). In line with the notion that KCs indicate ongoing cognitive processing, Vallat et al. (2017) have

recently reported a KC-like response during N2 sleep that was stronger for auditory stimuli that were followed by an arousal or awakening. The authors concluded that this reflects stronger reactivity of the brain to external stimuli, which in turn leads to stronger arousal. In accordance with this, ERP analyses of our data indicated that stimulus-induced differences in the delta range indeed reflected KC-like responses evoked by stimulus presentation with considerably larger amplitudes for UFV stimuli. In line with earlier ideas, we suggest that this ERP reflects increased (low-level) information processing of especially salient UFV stimuli (indexed by a larger positive wave), which is then followed by an inhibitory or sleep-protecting 'down-state' (indexed by a larger negative wave) that is likewise scaled to stimulus salience. Further support for this interpretation comes from analyses when stimulus presentation evoked an SO, with evoked SOs also seeming to be sensitive to stimulus salience. Also here, UFV stimuli were associated with stronger delta through sigma activity than FV stimuli and ERP analyses revealed that UFV stimuli were associated with a very slight positive-going wave, which was followed by a SO down-state that appeared much more pronounced for UFV stimuli (cf. Suppl. Fig. 4A). Besides the results obtained in the delta range, we also find that during all NREM sleep stages UFV stimuli are associated with stronger ERS in the theta through sigma range than FV stimuli, an effect which is most pronounced following about 200ms after stimulus onset. Most importantly, these findings are well in line with the delta results and they provide further convincing support for the notion that the brain is still able to process paralinguistic stimulus aspects even when consciousness fades and is absent. On a functional level, especially frequencies in the alpha and sigma range are thought to mirror an increase in arousal during sleep (cf. American Academy of Sleep Medicine & Iber, 2007). This suggests that UFV stimuli may be more arousing than FV stimuli during NREM sleep, an interpretation that, also given the observed KC-like response, is well in line with Vallat et al.'s results. As suggested above, the presence of unfamiliar voices may challenge the impression of an environment 'safe to sleep' and thus be arousing. Admittedly, our findings during N2 sleep partly contrast results earlier studies, where the brain also seemed to continue differentiating between UNs and SONs (e.g. Blume et al., 2016; Perrin et al., 1999).

The deviating findings could be due to methodological differences and/or participants sleeping during a whole night and not just an afternoon nap (cf. Blume et al., 2016) with differences in the homeostatic and circadian factors rendering it questionable whether a daytime nap can be considered a short night sleep equivalent.

In summary, results obtained during wakefulness and NREM sleep suggest that familiarity of a voice can be processed even during the fading of consciousness (N1) and in the full absence of (behavioural) consciousness (N2 and N3). For REM sleep, a paradoxical state characterised by (i) the return of 'altered consciousness', namely 'dreaming', (ii) enhanced brain metabolism (Maquet, 2000; Nofzinger, Mintun, Wiseman, Kupfer, & Moore, 1997) and (iii) an increase in higher frequency EEG power (Uchida, Maloney, & Feinberg, 1992), we also observed a relatively stronger increase in delta as well as alpha/sigma ERS elicited by UFV compared to FV stimuli, which may indicate continued processing and/or arousal of salient or potentially 'dangerous' UFV stimuli. This is especially interesting because REM sleep has been suggested to reflect a 'closed loop', that is a state in which the brain is rather occupied with intrinsic activity than processing of external stimuli (Andrillon, Poulsen, Hansen, Léger, & Kouider, 2016; Llinás & Paré, 1991; Wehrle et al., 2007) with our results challenging this notion. At the same time, while the oscillatory response pattern was generally similar to NREM sleep findings, REM responses were considerably weaker and markedly delayed by approx. 400ms. This underlines the idea that brain activity and processing of environmental stimuli during REM is qualitatively different although not generally precluded.

Beyond investigating stimulus processing across global brain states, i.e. wakefulness and different sleep stages, we were also interested in how stimulus presentation relates to 'local oscillatory activity', that is sleep spindles and slow oscillations (SOs), during N2 and N3 sleep. Generally, sleep spindles (Elton et al., 1997; Schabus et al., 2012) and the negative slope of slow oscillations (Schabus et al., 2012) have been suggested to inhibit processing of external stimuli. Here we find that this does not seem to be universally true but that brain responses are still tuned to stimulus salience suggesting that at least 'low-

level' processing is not precluded. More specifically, we find that when a sleep spindle overlapped with stimulus presentation UFV stimuli still elicited responses in the delta through lower alpha (i.e. up to about 9Hz) range that were similar to those obtained when not taking 'local oscillatory activity' into account. Intriguingly and unlike proposed earlier (Schabus et al., 2012; Steriade, 1991), this suggests that processing of external stimuli is not or at least not uniformly inhibited by the presence of a sleep spindle, i.e. spindles do not generally seem to act as a sensory filter at the thalamic level. Interestingly, this is well in line with recent findings in rodents where thalamocortical sensory relay was shown to persist even during sleep spindles (Sela, Vyazovskiy, Cirelli, Tononi, & Nir, 2016). Beyond this, above ≈9Hz the response pattern when a spindle was present was markedly different from the general NREM (see Fig. 2) and, most importantly, the 'no spindle' (see Fig. 4F) patterns with FV stimuli eliciting stronger ERD than UFV stimuli in the ≈11-15Hz spindle range (see Fig. 4C). We speculate that this could reflect a relatively stronger release of inhibition (reflected by 10-15Hz ERD) for seemingly less relevant FV stimuli by sleep spindles. Arguably, a selective mechanism that specifically filters information that is considered irrelevant, i.e. here FV stimuli, seems more adaptive than the uniform inhibition of all environmental stimuli. Following the idea of a 'sentinel processing mode' of the brain during sleep, spindles just as slow oscillations could thus reflect a sleep-protecting response that follows initial stimulus evaluation during N2 and N3. Besides sleep spindles, previous studies suggested that also the slope of a SO during stimulus presentation affects stimulus processing. In particular the negative slope has been found to be associated with decreased responses in studies using somatosensory stimuli and simple tones as compared to the positive SO slope. Surprisingly, in our study stimulus delivery during negative and positive slopes revealed similar responses with responses in both conditions being tuned to stimulus salience. Specifically, as during all other sleep stages UFV stimuli elicited stronger (delta to sigma) ERS than FV stimuli. These results were supported by ERP analyses indicating that UFV stimuli induced a more pronounced down-state that was preceded by an up-state. The findings thereby contrast earlier findings and suggest that also the negative slope of a SO does at least not uniformly inhibit information processing

and allows continued evaluation of stimulus characteristics. Likewise, the findings also suggest that during a positive SO slope the brain is not uniformly open to external stimulation.

In conclusion, this study shows that stimulus characteristics and especially the familiarity of a voice continue to be evaluated during all stages of NREM sleep and thus even in the complete absence of behavioural consciousness. Surprisingly, this is the case even during REM sleep with processing of external seeming to be slowed and decreased though. Our findings thereby provide support for the idea of a 'sentinel processing mode' of the brain during sleep, i.e. the continued processing of environmental stimuli even in the absence of consciousness that may then be followed by either an inhibitory sleep-protective response or awakening depending on the result of stimulus evaluation. Beyond this, it appears that even 'local oscillatory activity', i.e. sleep spindles and slow oscillations are sensitive to paralinguistic emotional stimulus characteristics. Furthermore, we provide novel evidence that even during spindles and the negative slope of a SO the brain reacts differentially to incoming information. In a wider context, our findings also suggest that using emotional stimuli such as familiar voices, or favourite sounds and music may be helpful in the medical and therapeutic context when patients are in states of reduced or altered awareness e.g. following severe brain injury.

Methods and Materials

Participants

We recruited 20 healthy individuals for the study. Three participants were excluded from the data analysis, one dropped out after the adaptation night and two had to be excluded due to technical problems during the acquisition. The remaining sample comprised 17 participants (three males) and had a median age of 22.6 years (*SD* = 2.3 years). Prior to the study, participants gave written informed consent. Ethical consent had been obtained from the ethics committee of the University of Salzburg and the study was in accordance with the Declaration of Helsinki (World Medical Association (WMA), 1964). For more details on the study sample please see supplementary material.

Experimental procedure

Participants were advised to keep a regular sleep/wake rhythm with eight hours time in bed (TIB) for at least four days prior to their first visit at our sleep laboratory, which was verified with wrist actigraphy (Cambridge Neurotechnology Actiwatch ©). Participants slept in the sleep laboratory of the University of Salzburg for two nights, one adaptation night and one experimental night. The adaptation and experimental nights were comparable except for no auditory stimulation during sleep taking place during the adaptation night. On both nights and the following mornings participants were tested during wakefulness resulting in four wakefulness recordings per participant. The wakefulness part comprised a passive listening as well as an active counting condition, during which participants listened to the stimuli presented via in-ear headphones at a volume of approximately 65 dB. For the passive condition participants were instructed to listen attentively to the stimuli while in the active condition they were to count the number of presentations of one specific name (i.e. the target). The passive condition always preceded the active one. In this publication, we only present the results from the passive listening condition, in which participants were presented with their own name (SON) as well as two unfamiliar names (UNs) as it is the only condition that can be analysed meaningfully across 'global brain' or vigilance stages (i.e. wakefulness, NREM and REM sleep). Moreover, each name was uttered by a familiar and by an unfamiliar voice. The stimulus set was specific for each participant and all names of one stimulus set were matched regarding the number of syllables and the occurrence in the general population. During the wakefulness recording, each stimulus was presented 40 times and the interstimulus interval (ISI) was 2000ms. Following the wakefulness recordings in the evenings, participants went to bed for eight hours of sleep. During the experimental night, stimulation was continued and the volume was adjusted individually so stimuli were clearly audible, but participants felt they could sleep despite the stimulation. The auditory stimulation protocol was akin to the passive condition of the wake part, although during the night, the stimulus onset asynchrony (SOA) was jittered between 2.8 and 7.8 s in 500ms steps. SOA was jittered specifically in the sleep protocol as this was necessary to allow for an

investigation of stimulus processing in relation to various EEG sleep phenomena (i.e. sleep spindles and slow oscillations) independent of expectation effects. SOA was not jittered during wakefulness as this would have rendered the tasks lengthy and probably too fatiguing. During the night each stimulus was presented 690 times and had the same probability of occurrence as had each SOA. For more details on the experimental procedure please see the supplementary material.

Electrophysiological data collection and reduction

For EEG acquisition we used a 256 electrode GSN HydroCel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, Oregon, USA) and a Net Amps 400 amplifier.

Wakefulness data

EEG data were processed using the Fieldtrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2010) in Matlab (Mathworks, Natick, USA). First, the number of electrodes was reduced to 183 as the others contained a lot of 'non-neural' artefacts and high-pass filtered at 0.5Hz. Subsequently, eye movement artefacts were corrected using independent component analysis (ICA), data were segmented into 4s epochs (symmetrically to stimulus onset) and bad intervals were removed manually during visual data inspection. In the next step, the number of electrodes was further reduced to a final number of 173 electrodes now excluding 10 more electrodes that had initially been kept for the identification of eye and muscular artefacts. Bad channels identified during visual data inspection were interpolated and data were re-referenced to average reference. Subsequently, we randomly selected the same number of trials for each stimulus to account for imbalances in the stimulus set (only one SON, but two UNs were presented). We then applied a Morlet wavelet transformation (cycles = 3, 1-16Hz, 1Hz frequency steps) to each of the segments, which was followed by a baseline correction (baseline interval: -600 to 0ms relative to stimulus onset) and averaging across trials.

Sleep data

Sleep was scored semi-automatically by The Siesta Group© (Somnolyzer 24×7; cf. Anderer et al., 2005; Anderer et al., 2004) according to standard criteria (American Academy of Sleep Medicine & Iber,

2007). Spindles were detected automatically during NREM sleep stages N2 and N3 at central leads using the algorithm by Anderer et al. (2005). Slow oscillations (SOs) were also detected automatically on frontal electrodes using lab-internal Matlab routines (cf. Heib et al., 2013) based on the criteria by Massimini, Huber, Ferrarelli, Hill, and Tononi (2004). For more details on the detection of spindles and SOs please see supplementary material. Pre-processing for the sleep data was essentially the same as for the wakefulness data; but we refrained from an automatic eye movement correction in order to not remove REMs. Beyond investigating processing of different stimuli across 'global brain states', that is in each sleep stage, we also investigated stimulus processing with regard to 'local brain states', that is sleep spindles and SOs. To this end, we compared evoked oscillatory responses elicited by different stimuli when a spindle was present during stimulus onset (i.e. spindle offset min. 200ms after stimulus onset) or when there was a substantial overlap between a spindle and stimulus presentation (spindle onset 0-400ms after stimulus onset, i.e. spindle overlapping with at least half of the stimulus on average, cf. Suppl.Fig.1, A). Moreover, we were interested in stimulus-specific differences in the evoked slow oscillatory responses ("SO evoked"). More precisely, a SO was defined as "evoked" when the negative peak occurred between 300 and 600ms after stimulus onset (cf. Suppl.Fig.1, B1), that is the time range when the negative components of evoked K-complexes (i.e. N350 and N550) have been found to occur (Cote, De Lugt, Langley, & Campbell, 1999). Beyond this, we compared stimulus processing when stimulus onset was during the positive going slope of a SO (cf. Suppl.Fig.1, B2) to when stimulus onset coincided with the down-state (cf. Suppl.Fig.1, B3). For more details on data collection and analysis please refer to the supplementary material.

Event-Related Potentials

Although we focus on oscillatory activity in different frequency bands in the present manuscript, we provide results from event-related potential (ERP) analyses in the supplementary material (and Fig.1).

Statistical Analyses

Statistical analyses were performed using the cluster-based permutation approach to correct for multiple comparisons implemented in Fieldtrip that uses a Monte Carlo method for calculating significance probabilities (Maris & Oostenveld, 2007). Three tests were run for the main effects of *name* (SON vs. UNs), *voice* (FV vs. UFV) and the *name* × *voice* interaction with significant (or marginally significant) interaction clusters being followed by post-hoc tests. We ran a first set of tests for the delta range that included the dimensions electrode and frequency (1-3Hz in 1Hz frequency steps). In the delta range, values were averaged across time (0-1000ms after stimulus onset for the WAKE condition, 0-1200ms during SLEEP) as time resolution obtained with these low frequencies was considered insufficient for an analysis in the time dimension. A second test was then run for the theta, alpha and sigma ranges including the dimensions electrode, frequency (4-15Hz, 1Hz frequency steps) and time (0-1000ms, five time windows à 200ms each in the WAKE condition, 6 time windows from 0-1200ms during SLEEP). For the "spindle vs. no spindle" and "negative vs. positive SO slope" contrasts we calculated averaged values for FV/UVF for each condition, which we then compared. For all permutation tests the critical *p*-value for the *T*-statistic for dependent samples was set to 0.05 and 1000 randomisations were used. Spatial clusters were formed only if electrodes had a minimum of two neighbouring electrodes that were also significant. We report the Monte Carlo approximation for the estimate of *p*-values. Effects with (one-sided) Monte Carlo $p < .05$ are denoted significant, effects with $p < .1$ are denoted marginally significant. Critical *p*-values for post-hoc tests were adjusted for multiple comparisons using Bonferroni-corrected *p*-values. We report Cohen's *d* (*d* = mean difference in a significant cluster/standard deviation of the differences) as a measure of the effect size for all analyses. For more details on the statistical analysis please see the supplementary material.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgements

We thank Daniel Koerner and Adriana Michalak for their help with the data collection and pre-processing and Vincenzo Muto for his advice on the sleep staging. We also thank Wolfgang Klimesch for the valuable discussion about the results.

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