To spindle or not to spindle: A replication study into spindling excessive beta as a transdiagnostic EEG feature associated with impulse control

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1. Introduction

Beta spindles or ‘spindling excessive beta’ (SEB), conceptualized as “High frequency beta with a spindle morphology, often with an anterior emphasis” (Johnstone, Gunkelman, & Lunt, 2005 p. 101), have not yet been thoroughly studied. An early study by Kubicki and Ascona (1983) described the presence of beta bursts over the frontal areas with a frequency ranging between 25 and 35 Hz and a maximum amplitude of 30 μV, and suggested these were reflective of sub-vigil beta or hypoarousal. A later study identified the presence of frontal excess beta in children diagnosed with ADHD and considered these to reflect an atypical ADHD group. The authors found that the group presenting SEB is characterized by higher levels of moodiness and proneness to temper tantrums (Clarke, Barry, McCarthy, & Selikowitz, 2001). Studies suggest that SEB occurs in 13–20% of ADHD patients (Chabot & Serfontein, 1996; Clarke et al., 2001), although similar percentage rates of individuals with frontocentral SEB have been reported in children with and without ADHD (Arns, Gunkelman, Breteler, & Spronk, 2008). Interestingly, high beta activity has usually been associated with hypervigilance. For example, it has been reported that individuals with complaints of insomnia show elevated levels of beta activity (based on absolute or relative power) around sleep onset (Perlis, Merica, Smith, & Giles, 2001; Perlis, Smith, Andrews, Orff, & Giles, 2001), possibly explained by central nervous system hyperarousal (Perlis et al., 2001). Also, individuals with insomnia as their primary complaint showed higher beta/gamma power at non-rapid eye movement (NREM) stages of sleep, whereas individuals who reported no sleep issues, or individuals whose complaints of insomnia were secondary to depression, showed no such increases (Perlis et al., 2001). This suggests that beta activity is positively associated with arousal, such that increased beta translates to increased arousal. Yet, some studies have reported findings that challenge this view. Strijkstra, Beersma, Drayer, Halbesma, and Daan (2003) found a positive association between frontocentral beta-2 (23–29 Hz) power and subjective sleepiness. Also, a study by Greeneche et al. (2008), in which...
EEG was measured during a 24-hours sustained wakefulness period, found that individuals with Obstructive Sleep Apnea (OSA) had increased waking delta, theta, and beta power compared to healthy controls. Interestingly, only in healthy individuals a negative association between alertness and beta power (among other bands) during this time period was found (Greneche et al., 2008). Another study (of which the sample consisted only of males) that focused on EEG changes in response to sleep deprivation reported increased beta power at central sites and, remarkably, beta power correlated positively with hours of wakefulness (Lorenzo, Ramos, Arce, Guevara, & Corsi-Cabrera, 1995). This leaves the question of whether different types of beta serve different purposes; it has been suggested that desynchronized beta is related to hyperarousal and synchronized SEB is related to hypoarousal (Arns, Swatzyna, Gunkelman, & Olbrich, 2015). This distinction can also be seen in a study on children diagnosed with ADHD and excess beta who present a degree of hypoarousal similar to excess theta (Clarke et al., 2013). A similar observation can be made in drug symptomatology. Benzodiazepines increase beta activity and are also known for their sedating effect (Blume, 2006). A recent animal study also highlighted that higher beta oscillations (15–35 Hz) behave differently depending on the animal’s state (active wake or quiet wake) in which they are observed (Gronli, Rempe, Clegern, Schmidt, & Wisor, 2016). Challenging the view that beta has a unidimensional relationship with arousal, these findings open up doors to a more dynamic interpretation of beta activity.

Some studies suggest a genetic contribution of beta activity. A link between GABA-A receptor genes and beta power (subdivided in different frequency bins) was previously reported (Porjesz et al., 2002). Also, Zietsch et al. (2007) found support for the heritability of power across different frequency bands, including beta, in a twin study. Given these findings, genetics may also influence the presence of SEB. A genetic component to the presence of SEB has been proposed by Kubicki and Ascona (1983), and Vogel (1970) observed potential support for an autosomal dominant mode of inheritance in family studies.

In 2015, using a Research Domain Criteria approach (RDoC; Cuthbert & Insel, 2013), Arns and colleagues (2015) investigated SEB in relation to hyperactivity/impulsivity and sleep problems. It was found that problems with sleep maintenance and impulse control were higher in patients with frontocentral SEB. Importantly, the presence of SEB was not associated with having trouble falling asleep (Arns et al., 2015). The authors concluded that SEB may be regarded as a state marker, caused by sleep maintenance problems, and in turn associated with more hyperactivity/impulsivity complaints (possibly as a vigilance-autostabilization behavior related to low vigilance (Arns, Gunkelman, Olbrich, Sander, & Hegerl, 2011; Arns & Kenemans, 2014)). However, these results still require replication and elaboration, which are the main aims of this manuscript. First, it will be attempted to replicate the findings reported by Arns and colleagues (2015). This will be done using a mixed dataset, consisting of participants reporting primary sleep problems or symptoms of ADHD. It was hypothesized that the presence of SEB is associated with complaints regarding impulse control and sleep maintenance. It was also expected that this association would be transdiagnostic and thus would be equally present in both the insomnia and ADHD groups (Arns et al., 2015).

2. Methods and materials

For both datasets, the following assessments were conducted at baseline: ADHD-Rating Scale (ADHD-RS), Pittsburgh Sleep Quality Index (PSQI), Holland Sleep Disorder Questionnaire (HSDQ), and QEEG. Informed consent was obtained for all participants. Impulse control problems were operationalized identically to the original study using items from the ADHD-RS. In addition, neuropsychologically-defined impulse control problems, measured by the amount of false positive errors on a Continuous Performance Task (CPT), were analyzed. The PSQI and HSDQ were systematically collected (different from the measurements in the original study). These scales were chosen to refine the associations with sleep maintenance problems since these questionnaires are well-validated, in contrast to the three distinct items (part of the generic 300-item-screening questionnaire (CNC1020; EEG Professionals, The Netherlands)) used in the original study.

2.1. Dataset 1: insomnia

Baseline EEG and behavioral data were gathered for an ongoing naturalistic, open-labeled study investigating the effects of SMR neurofeedback on sleep. The study included only patients that had a primary sleep problem and excluded any participants with primary psychiatric comorbidities that explained the sleep problem. The sample included patients between 18 and 65 years of age with a primary insomnia problem expressed as a sleep onset problem (latency (SOL) ≥30 min), sleep maintenance problem (wake after sleep onset (WASO) ≥30 min), or sleeping ≤6 h per night. The sleep complaints should occur at least three times per week and be present for at least six months at the time of intake. Medication usage was allowed if stable during the treatment. Exclusion criteria were comorbid medical or psychiatric complaints (as assessed using the MINI), recent parenthood, night shifts, students, pregnancy, excessive alcohol or caffeine usage, and diagnosis of a primary sleep disorder other than primary insomnia.

2.2. Dataset 2: ADHD

The ADHD sample was previously published in Krepel et al. (2020) in an open-labeled, naturalistic multi-site study. Data were gathered at two different clinics specialized in neuromodulation treatment (neuroCare Group Nijmegen & neuroCare Group The Hague, The Netherlands).

2.3. QEEG

QEEG recording details were previously described elsewhere (e.g. Arns et al., 2016) and were performed in accordance with the standardized methodology developed by Brain Resource Ltd., of which reliability and validity are published elsewhere (Clark et al., 2006; Paul et al., 2007; Williams et al. 2005). In short, using a 26-electrode EEG cap recording was performed based on the 10–20 international system. Data were referenced to averaged mastoids with a ground at AFz. Horizontal and vertical eye movements were controlled for, and skin resistance was <10 kΩ for all electrodes. The sampling rate was 500 Hz. Prior to digitization, a low-pass filter of 100 Hz was applied. Data were corrected offline for EEG. Three tasks are recorded during the EEG: a 2-minute Eyes Open (EO), a 2-min Eyes Closed (EC), and a 6-min CPT. In the CPT, 125 letters were presented with an ISI of 2.5 s. Participants were asked to detect the occurrence of two consecutive identical letters. During the CPT, participants were asked to press the two buttons simultaneously (one under the left index finger and one under the right index finger).

2.4. Statistics

To determine the presence of SEB, the QEEGs of all participants were visually examined by the first and last author of this manuscript (NK and MA), blinded to diagnosis and behavioral scores. SEB presence was determined consistent with the definition proposed by Johnstone et al. (2005): “High frequency beta with a spindle morphology, often with an anterior emphasis” (Johnstone et al., 2005 p. 101) as well as the morphology published by Clarke et al. (2001). Both the raw EEG and quantitative EEG were inspected for SEB presence and, if applicable, peak frequency and maximum site of SEB were identified. The raw EEG was used for initial inspection, and the quantitative EEG was used to verify SEB presence using the following criteria: SEB should (a) be in excess based on Z-scores, (b) be present in the beta band (confined to 15–40 Hz), (c) match the site of the observed SEB to the topography of the deviating Z-scores. Then, participants were divided according to SEB...
presence: Category 0 (no SEB present), Category 1 (fast synchronous beta regularly present without a clear spindle morphology), or Category 2 (SEB present). These categories are in line with Clarke et al. (2001), consisting of normal amplitude excess beta, high amplitude excess beta, and excess beta with frontal beta spindles. Examples of these three groups can be found in Fig. 1.

Using the ADHD-RS, an impulsivity (IMP) scale was created, consisting of item 19 (Blurt out answers), 21 (Difficulty waiting my turn), and 23 (Interrupt others), in line with Arns et al. (2015). Note that the IMP scale is a subscale of the ADHD-RS (which is composed of the hyperactivity/impulsivity (HYP) and Inattention (ATT) scale). However, it is calculated differently from the ATT and HYP scale, thus IMP cannot be compared to ATT or HYP. Also, given that the IMP scale is part of the HYP scale, HYP was not considered in this study. Behavioral differences were evaluated using a GLM Univariate, with a behavioral measure as a dependent variable, and SEB (No-SEB and SEB) and Sample (Insomnia and ADHD) as between-subject factors. The objectively measured CPT, False Positives (FP; a response was given when no response was required), and False Negatives (FN; no response was given when a response was required) were investigated in extension to the self-rated ADHD-RS, where specifically FP were considered to be indicative of impulse control problems. Other self-rated scales were used to investigate sleep problems. These included the PSQI including its components (Subjective Sleep Quality (SSQ); Sleep Latency (SL); Sleep Duration (SDu); Habitual Sleep Efficiency (HSE); Sleep Disturbances (SDi); Use of Sleep Medication (USM); Daytime Dysfunction (DD)) and the HSDQ and its components (insomnia, parasomnia, Circadian Rhythm Sleep Disorder (CRSD), hypersomnia, Restless Legs Syndrome/Periodic Limb Movement Disorder (RLS/PLMD), Sleep Breathing Disorder (SBD)). The $p$-value was set at 0.05. In case of non-normality, potential results were confirmed using a nonparametric Mann-Whitney U, using SEB as an independent variable, and if applicable, separated by Sample. Effect sizes are reported using Cohen’s $d$.

Analyses were performed using Category 0 ($n = 47$) and 2 ($n = 32$) only, confined to frontocentral SEB and adults in line with Arns et al. (2015). Eight participants with SEB at other sites were excluded. Two participants were excluded because of EMG contamination in the EEG. Descriptive statistics can be found in Table 1. Sample differences in frontocentral or SEB presentation were tested using Chi-square. Frontocentral SEB representation did not differ between Samples ($\chi^2(1, n = 79) = 1.440, p = .230$).

### Table 1
Descriptive statistics of the sample considered in this study. The total ($n = 79$) sample consisted of adult participants with ($n = 32$) and without ($n = 47$) frontocentral SEB. A significant difference between samples was found for Sex ($\chi^2(1, n = 79) = 6.495, p = .011$). No significant difference between samples was found for frontocentral SEB representation ($\chi^2(1, n = 79) = 1.440, p = .230$).

| Metric | Total ($n = 79$) | ADHD ($n = 48$) | Insomnia ($n = 31$) | $p$ |
|--------|-----------------|----------------|--------------------|-----|
| Males ($n$ (%)) | 37 (46.8) | 28 (58.3) | 9 (29.0) | .011 |
| SEB ($n$ (%)) | 32 (40.5) | 22 (45.8) | 10 (32.3) | .230 |

### 3. Results
A One-Way ANOVA showed no significant age differences between participants with SEB (2) and No-SEB (0) ($F(1,77) = .099, p = .754$). SEB age range (yrs): 18–62, with average age: 38.7 (SD 13.2). SEB age range (yrs): 20–58, with average age: 37.8 (SD 12.0)). Therefore, age was not considered as a covariate in the analyses. There was a significant Sex difference between the two samples ($\chi^2(1, n = 79) = 6.495, p = .011$).
Sex (An overview of GLM Univariate analyses using a behavioral measure as dependent variable, and Sample (Insomnia and ADHD) and SEB (No-SEB and SEB) as between- 

Subject factors. Significant (p < .001) main effect of Sample was also found. No significant interactions between SEB and Sample were observed. FP were non-normally distributed, therefore non-parametric analyses were used to confirm the result. A Mann-Whitney U confirmed the result for the total sample (U(105,SEB = 42, nSEB = 28) = 410.00, z = -2.293, p = .022). Spearman’s correlation showed no association between IMP and FP on the CPT (r(68) = 0.214, p = .079, r² = 4.6%).

Differences for SEB on sleep parameters were also examined (Table 2). PSQI (SDi) most closely resembles the sleep maintenance problems reported before (albeit in the original study sleep maintenance problems were defined as awakenings accompanied by having trouble falling back asleep, whereas items on PSQI (SDi) solely reflects awakenings). No differences between SEB and No-SEB were observed on the total sample (F(1,71) = 1.131, p = .291, d = -.20) and results were in the opposite direction as in the original study. For ADHD only, a significant effect of SEB on IMP was observed (F(1,44) = 8.787, p = .005, d = -.87).

4. Discussion

The current study reports a clear association between the presence of SEB and impaired levels of impulse control. This was found on both a self-rated as well as a neuropsychologically-defined scale. These effects were found in both an ADHD and an insomnia group, demonstrating that SEB represents a transdiagnostic feature related to impulse control problems. The current results replicate and extend on the earlier report (Arns et al., 2015). The effects observed concerned large effect sizes, and while the association held for the two different operationalizations of impulse control (self-reported and FP errors), the correlation between these two operationalizations was not significant. However, the association between SEB and sleep maintenance problems could not be conceptually replicated, possibly due to the use of different sleep questionnaires. (Table 3).

An important additional finding in the current study was that the presence of SEB reflects a transdiagnostic EEG property (reflected by a lack of Sample and SEB interactions visualized in Figs. 2 and 3). Remarkably, SEB presence was also related to more false positives errors on a CPT (d = .55). This means that SEB was associated with impulse control problems on a subjective as well as an objective scale. These results are found consistently across different disorders and pose the suggestion that SEB may be considered an RDoC (Insel et al., 2010), given the relation between SEB and impulse control problems seems to reflect a neurobehavioral correlate without being confined to a specific diagnosis. Yet, the association between impulse control problems and sleep maintenance problems was not apparent in the current study. Specifically, participants showing SEB did not experience more sleep disturbances. An important note to this null-finding is that the questionnaire items in the current sample did not identically match the measures that showed to be significantly different in the original study, therefore, an accurate replication on this aspect could not be performed. No significant effects on sleep parameters were found, apart from SOL. In ADHD only, participants showing SEB reported having fewer problems with falling asleep, yet for Insomnia as well as full sample there was no significant difference between participants with and without SEB on SOL. These results are in line with the original study (Arns et al., 2015), specifically, the authors found that individuals with SEB did not differ from individuals showing no SEB on SOL. This is important because it is known that 70–80% of patients with ADHD have a delayed SOL, which may be related to their ADHD symptoms (Arns, Feddema, & Kenemans, 2014; Bijlenga et al., 2013; Bijlenga, Vollebregt, Kooij, & Arns, 2019; Konofal, Lecendreux, & Cortese, 2010). This suggests that a qualitatively different subgroup in ADHD can be identified in which impulse control problems are related to SEB, but not to SOL. Of note, although there seem to be some differences between subjective and objective measurements of sleep quality, SOL is a metric that is different between ADHD and controls on subjective as well as objective measurements (Cortese, Faraone, Konofal, & Lecendreux, 2009; Diaz-Roman, Mitchell, & Cortese, 2018). In the current study, SOL problems were pronounced in ADHD (on average 35.6 (SD 24.2) minutes before falling asleep) and

**Table 2**

An overview of GLM Univariate analyses using a behavioral measure as dependent variable, and Sample (Insomnia and ADHD) and SEB (No-SEB and SEB) as between-subject factors. Significant (p < .05) Sample effects are indicated with *. Significant (p < .05) Sample X SEB interactions are indicated with #. Significant main effects of SEB can be found in IMP (F(1,72) = 15.899, p < .001, d = 0.87; Fig. 2) and FP on the CPT (F(1,66) = 4.051, p = .048, d = 0.55; Fig. 3). For IMP (F(1,72) = 14.578, p < .001, d = 1.02) a main effect of Sample was also found. No significant differences between SEB and Sample were observed. FP were non-normally distributed, therefore non-parametric analyses were used to confirm the result. A Mann-Whitney U confirmed the result for the total sample (U(105,SEB = 42, nSEB = 28) = 410.00, z = -2.293, p = .022). Spearman’s correlation showed no association between IMP and FP on the CPT (r(68) = 0.214, p = .079, r² = 4.6%).
even more pronounced in Insomnia (on average 47.0 (SD 33.6) minutes before falling asleep).

The current study confined analyses to frontocentral SEB, as did the original study (Arns et al., 2015). When broadening the analysis to include all SEB irrespective of site, results tended to be less pronounced or even disappear, which was also reported by Arns et al. (2015), thus suggesting site specificity for this association. Frontocentral SEB may be associated with impulse control problems, whereas SEB located elsewhere may have other behavioral correlates. A meta-analysis by Hart, Radua, Nakao, Mataix-Cols, and Rubia (2013), investigating fMRI studies in inhibition and attention in patients with ADHD, showed that for inhibition, lower activity in the right inferior frontal cortex, supplementary motor area (SMA), anterior cingulate cortex (ACC), and striato-thalamic areas was observed. Lower activity in these areas suggests a potential thalamo-cortical network that may be related to impulse control. Interestingly, another fMRI study found that, in boys, the right ventromedial prefrontal cortex (vmPFC) was a significant predictor of parent- and teacher-reported impulse control ratings. The authors also found a trend-level effect for the right ACC and a negative correlation between impulse control ratings and right vmPFC volume (Boes et al. 2009). Future studies should investigate this further by combining CPT with neuroimaging methods such as fMRI or MEG, such that the objectively measured impulse control problems may be linked to a (dys)functional network involving the areas previously described.

Also, given the current transdiagnostic results, future studies should investigate the presence of SEB in disorders that are characterized by impulse control problems, such as pathological gambling, kleptomania, skin picking, and compulsive-impulsive shopping (Dell’Osso, Altamura, Allen, Marazziti, & Hollander, 2006; J. E. Grant & Potenza, 2004). The earlier study reported increased moodiness and temper tantrums in children with SEB (Clarke et al., 2001), both of which seem to be in agreement with the underlying concept of impulse control problems. Hypothetically speaking, if SEB shows to be a transdiagnostic RDoC, as the current results seem to suggest, SEB and its relation to impulse control problems would be similar in various disorders. An association between impulse control disorders and obsessive-compulsive disorder has also been studied (Dell’Osso et al., 2006) and another study that investigated the responsiveness of OCD patients to rTMS found that
individuals with OCD showed increased levels of sleep disturbances. More so, individuals who did not respond to rTMS showed even higher levels of sleep disturbances compared to responders. Also, a model based on Circadian Rhythm Sleep Disorder (CRSD) could accurately predict rTMS non-response, whereas a model based on insomnia could not (Donse, Sack, Fitzgerald, & Arns, 2017). This further underlines the possible association between sleep and impulse control problems in a relevant subgroup.

4.1. Next steps

An important aspect of this paper is the detection of SEB, which currently can only be performed visually by expert ratings. This constriction poses some issues, and automatization of EEG feature detection may show to be a promising venture for the future. Although focused on clinical diagnoses rather than EEG feature detection, Gemein et al. (2020) explain in their report that the evaluation of clinical EEGs is often time-consuming, requires years of training, and the diagnostic accuracy is limited by several aspects. These limitations include a dependency of training and experience of the evaluator, consistency of rating over time, different filter settings (e.g., the definition of targeted frequency bands), and unclear potential changes thresholding criteria (Gemein et al., 2020). Additionally, a study investigating interrater reliability on clinical EEG interpretation found that agreement among experts was moderate (Grant et al., 2014). Automatization of feature detection in EEGs may help solve these limitations and contradictions. We propose that a similar case can be made for the detection of SEB, in that the current study can establish the foundation for future research and can suggest automatization of feature detection in EEGs. Given the initial results reported by Arns et al. (2015), the association between impulse control problems, sleep, and possibly other domains, may shed light on symptom presentation in disorders in which the SEB-impulse control mechanism seems to be a contributing factor. Automated SEB detection will reduce SEB detection time in comparison to current detection methods (i.e., manual scoring) which allows for multiple advantages. These could include the use of larger samples and examining SEB in other labs’ samples (possibly extending to multi-site findings), which are important factors in determining the replicability and robustness of a given finding (Maxwell, Lau, & Howard, 2015; Simons, 2014).

Fernandez and Luthi (2020) highlight some ways automatization of spindle detection can be improved. Although that paper concerns sleep spindles (which are confined to a lower frequency range and usually are visible in NREM sleep), Fernandez and Luthi (2020) explain that spindle detection can be automated using a fixed thresholding approach (using a fixed frequency range, amplitude threshold, and duration threshold), an adaptive thresholding approach (a similar approach as in fixed thresholding but adjusted for possible external influences), a time-frequency analysis (using continuous wavelet analysis for simultaneous frequency and temporal occurrence of spindles), and intracranial recordings (Fernandez & Luthi, 2020). Machine learning-based detection may also show to be of use in the future. Accurate sleep spindle detection using machine learning-based detection methods is relatively well represented in the literature (e.g., (Chambon, Thorey, Arnal, Mignot, & Gramfort, 2018; Kulkarni et al., 2019; Sokolovsky, Guerrero, Pajarsrisomsuk, Ruiz, & Alvarez, 2020))) and results are promising. Given the relative visual similarities between sleep spindles and SEB, future studies may consider machine learning as a way to automate SEB detection.

4.2. Limitations

While interpreting the results of this study one should keep in mind the following limitations. Both the ADHD and Insomnia studies were open-labeled, therefore potential non-specific influences cannot be ruled out. ADHD data were gathered naturalistically. Medication usage was not controlled. Benzodiazepines and barbiturates are known to increase the presence of beta (Blume, 2006), which may have potentially influenced the current results. However, this does not seem likely since when analyses were repeated on participants who were not using benzodiazepines or barbiturates, the results did not change. Furthermore, the scoring of SEB was limited insofar that some participants were categorized as synchronous beta or indefinite SEB presence (synchronous beta without spindle morphology). These participants were omitted from the current analyses. Future detection tools should aim to be developed so that doubtful cases can be accurately categorized into SEB or No-SEB.

4.3. Conclusion

This study has shown that participants exhibiting fronto-central SEB show higher levels of impulse control problems. This finding was apparent for a subscale of the self-rated ADHD-RS, as well as for performance on an objective CPT (measured by more false positive responses in participants showing fronto-central SEB). The relation between sleep parameters and fronto-central SEB presentation could not be established. The results partially replicate earlier results communicated by Arns et al. (2015). Future studies should aim to automate SEB detection and disentangle the association between fronto-central SEB, impulse control problems, sleep, and potentially other related factors.

Disclosures

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CRedit authorship contribution statement

MA and NK conceptualized the study and performed the SEB classification, NK managed the literature search, performed the analyses, and wrote the first draft of the manuscript. All other authors contributed, reviewed, and approved the final manuscript.

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