Handedness and Sleep

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Abbreviations

EHI	Edinburgh Handedness Inventory (score)
absEHI	Absolute value of Edinburgh Handedness Inventory score
BMI	Body Mass Index
RH	Right-hander, right-handed
LH	Left-hander, left-handed
CH	Consistently-handed, consistent handedness
ICH	Inconsistently-handed, inconsistent handedness
CRH	Consistently right-handed
CLH	Consistently left-handed
TIB	Time in bed
SOL	Sleep onset latency
TST	Total sleep time
SD	Sleeping duration
SE	Sleep efficiency
Nwake	Number of times participants woke for more than 5 min during each night
WASO	Amount of time spent awake after sleep onset
PSQI	Pittsburgh Sleep Quality Index
D-MEQ	Morningness-Eveningness-Questionnaire, German version
ESS	Epworth Sleepiness Scale

1 Introduction

1.1 Handedness

1.1.1 Defining and measuring handedness

Handedness is defined as the tendency or preference to use one hand rather than the other. The percentage of right- and left-handed individuals in a given population has been topic of many studies throughout decades. It is however not straightforward to evaluate, as handedness is a matter of definition.

Handedness is commonly thought of as a dichotomous trait labelling individuals as either left- or right-handed (LH or RH).[1] Using this approach, around 10% of humans are LH.[2] Research has used three categories: RH, LH and inconsistently-handed (ICH), also called mixed-handed individuals. Further approaches on categorizing handedness have grouped RH and LH together as consistently-handed (CH) as opposed to ICH.[3] More recent concepts avoid partitioning at all treating handedness as a continuum with two qualities: *degree* (meaning CH vs ICH) and *direction* (meaning RH vs LH).[4]

The most commonly used tool to assess handedness is the Edinburgh Handedness Inventory (EHI) Scale.[5] The Score developed by Oldfield et al. in 1971 produces real numbers ranging from -100 for consistently LH (CLH) to +100 for consistently RH (CRH) individuals. It is based on a set of questions regarding hand preference in different motor activities such as writing, striking a match, opening a box and throwing. Additionally, an extra set of questions determines hand use consistency in each of these activities. Notably, *degree* and *direction* of handedness are connected: while most of the RH are CH, most LH are little lateralized or ICH.[5] Ageing influences handedness, with the *degree* of lateralization increasing with age especially for RH.[6]

1.1.2 Determinants of handedness

Why handedness as a phenomenon arises and why RH seems to represent the standard has been subject of extensive research. Over time, different theories have been proposed. One obvious assumption is a genetic determination. A variety of genes such as *PCSK2*,[7] *MAP2*[8] or *LRRTM1*[9] have been associated with handedness.

Genetic variation, however, can only explain a limited part of handedness' distribution with as little as 4.35% heritability of left-handedness.[10] In line with that, a twin study on handedness suggests genetic mechanisms may only explain 25% of the variance of handedness in twins with the remaining 75% on account of other effects.[11] Next to genetic factors also epigenetic mechanisms may play a role, thus being able to shape handedness without altering DNA sequence and going unnoticed in traditional genetic studies. This field, however, remains to be understudied.[12]

Another popular approach to unravel origins of handedness is research on endocrine differences such as sex hormones. This approach is sustained by findings, that testosterone levels can influence asymmetries of the brain, both prenatally and during puberty.[12,13] For example, language lateralization[14] and mental rotation[13] were found to be associated with testosterone levels. Adding to that, the development of left-handedness has been suggested to be influenced by androgen levels in utero.[15,16] Although more recent studies could not find an association of sex hormone exposure with the *direction* of hand preference,[17] it was reported that "in females, high levels of prenatal testosterone were associated with weaker lateralization of hand skill, and high levels of prenatal estradiol were associated with weaker hand preference".[17] This could emphasize the influence of sex hormones on *degree* rather than *direction* of lateralization.

Early life factors, such as "being part of a multiple birth, not being breastfed, having lower birthweight, being born in a more recent year, and being born in summer", were identified in a large-scale population study to be associated with a higher probability of being left-handed.[10] Generally, increased gestational stress has been linked to ICH or LH in offspring.[18]

The theory of implicit role model learning, as a way to shape children's handedness, has been devaluated by several studies.[12] Such it was shown that children´s handedness is neither related to the *degree* of lateralization of their stepparents[19] nor adoptive parents.[20]

Research additionally suggests culture and society to be a main influence of handedness distribution. In traditional societies, the frequency of LH is highly variable with numbers ranging from 26% in the Eipo to 3.3% in the Inuit.[21]

As there is a "difference in heritability between industrialized and non-industrialized countries"[22] and a "geographical variation of throwing and hammering" can account for the abundance of handedness types,[23] it is likely that handedness is connected with Darwinian fitness and entails a selection advantage that is dependent on the abundance of atypical handedness in a given population (see below, chapter 1.1.3).

1.1.3 Handedness over time and cultural aspects

Laterality and preference of the right hand,[1] foot,[1] ear,[1] eye[1] and even head position whilst kissing[24] is not only common in humans. It reaches as far as to the order of the insects. An example is the earwig (*Labidura riparia*), who has two penises with 90% of the earwigs preferring the "right-handed penis" of the two.[25]

Sundry forms of handedness have coexisted in the human population for at least ten thousand years,[26] with non-RH always being in minority.[27] It has been proposed many times, that left-handedness might entail a fitness-disadvantage or evolutionary cost,[28] as the frequency in the population has never been remotely close to 50%.[21,23]

Interestingly, especially the level of violence in a given population was associated with the percentage of non-RH.[29] Hence, the fighting hypothesis as an evolutionary explanation postulates, that "left-handers, being in the minority because of health issues, are still maintained in the population since they would have a greater chance of winning in fights than right-handers due to a surprise effect".[30] Obviously, such a surprise effect is necessarily linked to a minority position of non-RH.[29] Although this theory "remains intuitively plausible",[30] it has been challenged and more research is crucial.[30] Nonetheless, it was found that the frequency of LH in interactive sports, such as fencing and tennis, can be as high as 40 - 50% compared with non-confrontational sports, such as gymnastics, where it mirrors the general population. This corroborates the fighting hypothesis.[31,32]

A field of research, which is perhaps understudied, is that of social stigma and violence against LH and the psychological consequences thereof. "For centuries, prejudice and superstition have stigmatized left-handers"[33] and prominent examples can be found in many languages and cultural practices (find more details in Kushner HI 2013).[34] Various languages until today use references to left-handedness as a negative connotation or to communicate unwanted traits like dishonesty (German: "gelinkt werden"), clumsiness (French: "avoir deux mains gauches", German: "linkisch", "zwei linke Hände haben", Spanish: "tener dos manos izquierdos", Hungarian: "kétbalkezes", Polish: "mieć dwie lewe ręce"), bad luck (Spanish: "levantarse con el pie izquierdo") or illegal behavior (Russian: "налево").

Moreover, the practice of forcing children to switch handedness (framed as "curing" left-handedness) was until recently common all over the world and still is in many countries.[33-36] Examples of violent behavior (such as placing the left hand in boiling hot water or hitting it with a stick) against children in order to make them not use their left hand have been reported abundantly.[34,37] This practices have been reinforced by religion, with traces of stigmatization against left-handedness present in "holy texts of Judaism, Christianity, and Islam".[34] Until this day, the extent of harm on the psychological well-being of former "converted" LH is not clear. However, there are hints of detrimental consequences of forced switching with the most prominent being its association with stuttering.[38]

1.1.4 Handedness and health

Health-related biological characteristics and their association with handedness have been studied abundantly. It was reported that diseases connected with the immune system like Crohn's disease,[39] ulcerative colitis,[39] coeliac disease,[39] rheumatoid arthritis,[39] diabetes[39] and allergies[40] were associated with LH or ICH. Moreover, cardiovascular risk factors such as "circulation problems",[40] heart disease[40] or high blood pressure[40] have been linked to non-RH. The same was proposed for neurological and psychiatric conditions like epilepsy,[40] schizophrenia,[41] autism spectrum disorder,[42] bipolar disorder,[43] smoking[44] and alcoholism.[45] Many of these conditions are connected with sleep.[46,47] Apart from chronic diseases, also the frequency of accidents and injuries has been repeatedly reported to be associated with non-RH.[48,49] Left-handedness was suggested to be a risk factor for head injuries[50] and LH were shown to be more likely to need medical attention after an accident.[51]

Not surprisingly, considering the heightened susceptibility for health threats mentioned above, non-RH was reported to be associated with a reduced life expectancy.[52,53] Social history suggests that older age-groups were more frequently taught to switch to right-handedness,[54] thus being the reason for a lower prevalence of LH in older age groups.[55] This theory was shown to be only partly true, as it was found that this dynamic is due to LH having a shorter life expectancy independent of social-historic factors.[56] It was further shown that numbers of LH decrease with age in men and women alike, with the earliest deaths in the subgroup of little lateralized LH suggesting *degree* and *direction* to be of importance.[52]

1.1.5 Handedness and brain architecture and function

Although no clear-cut lateralization[57] that is "simply based on a mirrored organization of hand motor areas"[58] is apparent, a number of anatomical and functional differences can be observed in dependence of handedness.

Compared with RH, LH were shown to have less morphological asymmetry and lateralization of the brain structure in general.[15] This was confirmed as regional cerebral blood flow was shown to have less lateralization in LH during verbal and spatial tasks.[59]

Connecting both hemispheres of the brain, the size of the corpus callosum is dependent on the *degree* but not the *direction* of handedness, with ICH having a bigger corpus callosum than CH.[60] Functional studies revealed a different extent of activation of brain regions implicated in hand movements between RH and LH "including the primary and secondary sensorimotor and premotor cortices, thalamus, dorsal putamen, and cerebellar lobule IV".[58]

More differences could be found in a diverse spectrum of cognitive, psychological or behavioral features. Across a wide variety of tasks, ICH "is associated with superior memory performance" and "increased flexibility and diversity of thoughts and beliefs".[4] Psychopathy scores were found to be higher in ICH[61] and they were found to be more easily persuaded, presumably due to interhemispheric interaction and belief updating.[62] Moreover, ICH "is associated with more accurate and adaptive body image representation" as well as "increased loss aversion and sensitivity to risk".[4]

Non-RH is associated with more "atypical" brain organization with regards to the speech dominant hemisphere of the brain. This is defined as the hemisphere holding language representation, also known as the Broca area. Commonly accepted as the "Broca rule", the left hemisphere was thought to be dominant in RH and vice versa for LH. True for RH, this is not the case for LH. Left-hemispheric dominance of language representation is highly correlated with all handedness groups, however highest in RH (96%).[63] Right-hemispheric dominance is increasing with left-handedness but the prevalence is low (15% in ICH and 27% in LH).[12,63,64]

In terms of origin, modern research believes handedness to be independent of speech development.[57] In line with that, the "*degree* of hand-preference does not mirror the *degree* of language lateralization".[65]

1.1.6 Handedness, lateralization and sex

Handedness appears to be sex-dependent with 10% of the males and 6% of the females being left-handed, if a laterality score <0 is taken as an indicator for left-handedness.[5] This greater male tendency towards left-handedness was found to be both significant and robust in a meta-analysis of k = 262 databases, totaling N = 2,396,170 individuals, however, with great heterogeneity among datasets.[2,27]

In adults, both lateralization and handedness (see above, chapter 1.1.2) are affected by sex hormones. Although hemispheric asymmetries are likely not initially triggered by sex hormones, they have "been shown to be able to profoundly shape them."[12] For instance, women during their reproductive years are experiencing a constant change of functional cerebral asymmetry (FCA) in dependence of their hormonal cycles. This was observed in functional magnetic resonance imaging (fMRI)[66,67] and electroencephalogram (EEG).[68]

During the follicular phase of the cycle estradiol levels are on the rise and functional asymmetries are reduced, whereas during menses FCA is most pronounced.[66] Thus, "a powerful neuromodulatory action of estradiol on the dynamics of functional brain organization in the female brain" was proposed.[66] Correspondingly, lateralized behavioral patterns, such as spatial attention and figure recognition, are modified by cycle phase and hormonal status.[12,69]

Later in life during menopause, differences in relation to handedness can be found as well. Concentrations of circulating sex hormones in the blood were found to be significantly different, depending on handedness. LH women were shown to have higher levels of luteinizing hormone and follicle stimulating hormone (FSH) with lower levels of prolactin, estradiol and progesterone than RH women during menopause.[70] In a large group of 1985 women between the ages of 55 and 65 years, LH women experienced menopause earlier together with a shorter menopause transition time,[71-73] although also non-supportive studies exist as well.[74,75]

In adult men, testosterone levels have been associated with brain asymmetries in terms of cerebral laterality for language.[76]

Not only connected with biological sex, lateralization is associated with human sexuality and gender as well. Atypical handedness patterns (meaning non-RH) have been found in male and female homosexuals, with 39% greater odds of homosexual persons to be non-RH.[77] Further, ICH was discussed as a "biomarker of variation in anal sex role behavior and recalled childhood gender nonconformity among gay men".[78] Focusing on transsexualism, a variety of studies revealed non-RH to be more abundant in both, male-to-female and female-to-male transsexual persons.[79-81]

With the not yet fully understood importance of sex hormones in terms of handedness in mind, one focus of the following study was on differences between women and men while analyzing their respective sleep.

1.2 Sleep

Restorative and sufficient sleep is crucial for cognitive[82], emotional[83] and behavioral[84] performance and general human well-being.[85] Additionally, the "economic costs associated with sleep disorders are substantial".[86]

Sleep is influenced in its quality and quantity by many factors and inter-individual differences are pervading. Among the most well-studied influences are sex, body mass index (BMI) and age.[87] Another factor possibly shaping sleep is handedness.[88]

1.2.1 Sleep, sex and sex hormones

Like handedness, sleep varies significantly between sexes. Among other parameters women generally show longer total sleep time (TST) and less sleep onset latency

(SOL) than men.[89] However, women constantly report a subjectively lesser quality of sleep.[90-92]

Divergence of sleep in women and men is partly rooted in the influence of sexual hormones. In women during their reproductive years, changes in circadian rhythm and sleep architecture were found to be connected with follicle stimulating hormone (FSH), luteinising hormone, oestrogen and progesterone, which causes women to have more problems with their sleep during the week before and during menstruation.[90] During menopausal transition, a reduction of sex hormone levels is associated with sleep problems in 40 - 56% of women, with 26% even "experiencing severe symptoms that impact daytime functioning".[93] Accordingly, when applied exogenously to post-menopausal women, progesterone was shown to reduce wakefulness and to have sleep-promoting effects.[94-96] Additionally, also estradiol influences women´s sleep, however, by contributing to the regulation of sleep stages.[97]

Men's sleep too seems to be influenced by sex hormones, particularly low testosterone levels were shown to be associated with compromised sleep.[98,99] Decreasing levels of testosterone during aging have been linked to lower sleep efficiency on the one hand,[100] on the other hand sleep is a main influence on maintaining endocrine regulation including regulation of testosterone levels in men.[100,101] Thus, sleep deprivation is linked to a significant decrease of testosterone levels.[101]

1.2.2 Sleep and handedness

Handedness' influence on sleep has been studied with different approaches using objective techniques like polysomnography[102], actigraphy[102-105] or (electroencephalography) EEG[106-111] and subjective questionnaires[1,102,112-116], dream journals[113,115] and surveys.[117] Findings remain controversial, as most studies had a very limited amount of participants and were almost exclusively conducted with young adults.

1.2.2.1 Subjective sleep and handedness

Different aspects of the interaction between handedness and subjective sleep have been studied. Notably though, out of seven studies, all[1,102,112-116] but one[117] have been working with young adults under the age of 30. Out of these, "two studied *degree* of handedness,[114,115] two *direction*[1,102] and two both[112,113]".[118]

Regarding subjective estimation of time intervals, a longer total sleep time (TST)[112] and a shorter sleep onset latency (SOL)[114] were associated with a higher *degree* of handedness. Correspondingly, one study using *direction* instead of *degree* of handedness found LH to be associated with shorter reported TST.[115] However, also studies which could not find any differences between the handedness groups regarding TST or time spent in bed exist.[113]

In terms of perceived quality of sleep, a higher *degree* of handedness was associated with desirable features such as less awakening during the night[114] and less "trouble returning to sleep after an awakening".[114] The same was found to be true for *direction* of handedness, with RH found to have less "trouble falling asleep"[1] and to wake less frequently during the night.[1]

The single study addressing seniors (participants with age above 65 years) was restricted to the question whether they felt they obtained "enough rest and sleep" and revealed no differences between handedness groups.[117] Additionally, one study working with children aged 8-12 years focused on associations between *direction* of handedness and sleep in 23 non-gifted and 35 gifted children. Although gifted children showed more left-hand bias combined with a trend "toward experiencing more sleep disturbance" the association between the two was not explored further.[116]

Taken together, these studies tend to suggest a better subjective sleep to be associated with either right-handedness or a higher *degree* of handedness. It might be the same effect visible in each setting, as *degree* and *direction* of handedness are connected, meaning RH tend to have a higher *degree* of lateralization.[5,119]

Another field of research with connection to subjective sleep is dreaming. There seems to be an association between right-handedness and a better ability to remember dreams.[113] However, no difference in the number of dreams reported per week became apparent in adults.[115] In adolescents too, this association between right-handedness and better dream recall was found, with RH and ICH also reporting to have a higher number of dreams than LH.[120]

1.2.2.2 Objective sleep and handedness

The most commonly used approach to study objective sleep parameters such as TST, sleep efficiency (SE) or SOL with regards to handedness is actimetry, as was used in all four studies available,[102-105] with one of them additionally employing polysomnography and self-report.[102] The data available is solely based on small groups of participants (10 to 41 individuals), all of which were young adults (mean ages 20.5 to 22.4 years).

Results were contradicting. While longer[102] or shorter[104] TST was found to be associated with right-handedness, other studies could not find an association at all.[105] Also a higher SE was found to be associated with right-handedness,[102] a lower *degree* of handedness[103] or not to be associated.[104]

Regarding sleep stages, a higher *degree* of handedness was associated with more time spent in REM sleep[103] and a higher number of REM periods.[103] This was confirmed for the *direction* of handedness, as consistently-RH individuals were shown to have a higher number of REM periods in their sleep.[105] Moreover, upon awakening, ICH were found to wake from NREM sleep more often than from REM sleep with no difference apparent in CH.[103]

Other handedness-studies focused on additional EEG variables during sleep to address lateralization. For example, it was shown that interhemispheric EEG coherence, a measure of functional interactions between neural systems, is higher for LH during the wake phase as well as during REM sleep and stage 2 sleep phases.[106] Moreover, the EEG amplitude seems to be time- and handedness-dependent: whilst amplitudes drop in both hemispheres during the course of the night in RH, the amplitude remains the same in LH.[107] Accordingly, four separate studies, in which left- and right-handed individuals were woken from REM and N-REM sleep and presented with different cognitive tasks, revealed a transient post-awakening shift of cognitive asymmetry only in RH. This shift was especially prominent in females.[108-111]

Although very interesting associations between handedness and sleep have been proposed, no clear picture on the relationship between handedness and sleep, especially objective sleep, has arisen from the literature.

1.3 Rationale for the study and hypotheses

With the importance of sufficient sleep and the lack of research on non-RH individuals in mind, the aim was to add knowledge to the complex relationship between handedness and sleep by analyzing a large sample of individuals from the general public, namely the LIFE-study (Leipzig Research Center for Civilization Diseases).[121] A special focus was put on differences between sexes, as both, handedness and sleep, have been linked to sex hormones. Moreover, objective sleep, determined by actigraphy, and subjective sleep were both analyzed and handedness used in terms of *direction* as well as *degree*.

With a research field as prone to only small effect-sizes as sleep, conducting large population-based studies is both appropriate and necessary for detecting also smaller effects. Especially so, as the prevalence of non-RH is low and the *degree* of lateralization in this group is highly variable, highlighting the need for big sample sizes.

Considering the strong bias which science has for RH, with many studies exclusively enrolling right-handed individuals,[122] studying differences of brain functions like sleep between handedness groups might contribute to elucidate how the human brain works.

Since large scale studies investigating the association between handedness and both subjective and objective sleep are lacking, this study fills a gap by determining objective and subjective sleep in 1764 participants. Moreover, this study is the first to include participants with a wide age-span delivering data from the general population.

While the nature of this study has been exploratory, we expected left-handedness to be associated with impaired sleep and more daytime sleepiness. In addition, we expected different associations in pre– and postmenopausal women.

2 Publication

Title	Non-Right Handedness is Associated with More Time Awake After Sleep Onset and Higher Daytime Sleepiness Than Right Handedness: Objective (Actigraphic) and Subjective Data from a Large Community Sample
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ORIGINAL RESEARCH

Non-Right Handedness is Associated with More Time Awake After Sleep Onset and Higher Daytime Sleepiness Than Right Handedness: Objective (Actigraphic) and Subjective Data from a Large Community Sample

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Purpose: Handedness has been linked to various physiological and pathological phenomena including memory function and psychiatric disorders. Also for sleep, several studies have reported associations. However, large-scale studies including a broad age span of participants and studies analyzing women and men separately are lacking.

Methods: Therefore, objective sleep data were determined using at-home actigraphy from 1764 healthy participants (18 to 80 years, 908 women), averaging five consecutive nights. In addition, subjective sleep-related data were captured by self-report diaries, the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS) and the Morningness-Eveningness-Questionnaire (MEQ). Handedness was determined with the Edinburgh Handedness Inventory (EHI) providing information on the *direction* (left vs right) and the *degree* of handedness (strong vs weak). To address the potential endocrine effects, premenopausal women (≤45 years) and postmenopausal women (≥55 years) were analyzed separately. This was also done for men.

Results: The degree and direction of handedness were correlated with "wake after sleep onset" (WASO) in the total sample and all women (the more right-handed/lateralized the shorter WASO). In postmenopausal women, additionally, time in bed (TIB) and total sleep time (TST) were correlated. There were no other significant associations between an *objective* sleep variable and handedness. In both premenopausal women and >55-year-old men *subjective* quality of sleep (PSQI) was correlated with direction and degree of handedness (the more right-handed/lateralized the better). In the total sample and postmenopausal women, the degree and direction of handedness were negatively correlated with daytime sleepiness. The chronotype was not associated with handedness in any group.

Conclusion: While associations were not consistent in all groups, overall, right-handedness tended to be associated with better sleep and less daytime sleepiness. Handedness and sleep seemed to be differentially associated in women and men, being in line with endocrine interactions.

Keywords: handedness, sleep, daytime sleepiness, menopause, actigraphy

Introduction

Restorative and sufficient sleep is essential for human well-being.[1] Factors affecting quality and quantity of sleep include sex, age, body mass index (BMI) as well as other health- and lifestyle-related factors.[2] Another factor probably affecting sleep is handedness.[3] Handedness was formerly used as a dichotomous characteristic labelling individuals as either left- or right-handed (LH or RH).[4] Using this concept, about 90% of the human population are RH.[5] Research has moved on

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to see at least three categories: RH, LH, both termed consistently handed (CH) and inconsistent-handed (ICH).[6] More modern approaches tend to avoid partitioning altogether and regard handedness as a continuum, which has two qualities: degree, meaning CH vs ICH, as well as direction, meaning RH vs LH.[7]

So far, handedness was inconsistently and in part contradictory reported being associated with several objective and subjective sleep parameters. Overall, lower degrees of lateralization were associated with objectively better sleep including a shorter sleep onset latency (SOL),[8] a higher sleep efficiency (SE)[8] and more N-REM sleep.[8,9] Elsewhere, left-handedness was associated with longer[10] or shorter total sleep time (TST)[11] and lower SE.[11] In contrast to objective sleep characteristics, lower degrees of lateralization were associated with subjectively impaired sleep, eg a shorter TST[12] or more awakenings.[13] Similarly, left-handedness was associated with more awakenings[4] and lower TST.[14] Most studies had limited sample sizes and a small range of ages of the participants, namely college students. Only a single study with solely over 65-year-old participants exists.[15] Moreover, the majority of these studies only used self-report for analyses.[4,12–14,16] Those using objective measures, ie actigraphy or polysomnography, recorded only a single night or lack of diversity of age or hand preference.[8–11]

Therefore, rational for our study was to add knowledge on the association between handedness and sleep. Compared to the right-handed majority, altered sleep in non-right-handed individuals could be caused by both, reactively, ie a more stressful life in a world designed for right-handers or a partly differing cortical sleep regulation.

While there is no clear cut lateralization in handedness,[17] which is "simply based on a mirrored organization of hand motor areas",[18] the extent of activation of brain regions involved in hand movements has been shown to differ between right and left handers.[18] In addition, handedness has been linked to different kinds of brain lateralization, such as language lateralization, eg "more atypical (right hemisphere) lateralization in left handers".[19,20]

There is evidence that sex hormones affect lateralization in women (eg during the menstrual cycle[21,22] and after estrogen replacement therapy[23]) as well as in men.[24,25] In addition, sex hormones also affect sleep in both women[26,27] and men.[28] Therefore, we analyzed the association between handedness and sleep separately for men and women, dividing the cohort into ages for pre- and post-menopause.

Thus, the aim of this study was to examine the association between handedness and objective and subjective sleep, addressing potential age and sex differences in a broad cohort of 1764 participants with ages ranging from 18 to 80 years. While the nature of this study has been exploratory, we expected left-handedness to be associated with impaired sleep and more daytime sleepiness. In addition, we expected different associations in pre– and postmenopausal women.

Materials and Methods

Participants and Experimental Procedure

For this study, we used data from the "LIFE-Adult" study (Leipzig Research Center for Civilization Diseases); for details see.[29] "LIFE-Adult" is a population-based study with 10,000 participating adults (age range: predominantly 40 to 79 years, 400 participants with an age range of 18 to 39 years). Participants were randomly recruited from the city of Leipzig, Germany. The LIFE participants took part in a baseline examination, during which various physical examinations (including blood sampling) were carried out, and interviews and questionnaires on various health topics were completed (including sociodemographics, medical history, medication intake). As part of an optional additional examination, a subgroup took part in a 1-week actigraphy examination to record physical activity and sleep behavior. The LIFE study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of the University of Leipzig (registration number: 263-2009-14122009). All participants gave written informed consent.

For the sub-cohort studied here, inclusion criteria comprised actimetry completed for a minimum of 4 out of 5 nights, recording of subjective sleep characteristics using scales and a sleep diary, as well as questionnaires on daytime sleepiness, chronotype and handedness (see below). The following exclusion criteria were defined, potentially affecting sleep: a medical history of stroke, Parkinson's disease or multiple sclerosis; current diagnosis of depression or cancer or treatment during the previous year. To address undetected depression, the Centre for Epidemiologic Studies – Depression Scale (CES-D) was measured, and participants with a score higher than 22 were excluded.[30] Furthermore, precluded were participants using sleeping drugs more than once per week during the preceding month (according to item 7 of

Pittsburgh Sleep Index, PSQI) or taking drugs with sleep-altering effects including hypnotics, tranquilizers, antipsychotics, anxiolytics, opioids and first-generation antihistamines (according to medication anamnesis interview). In addition, in order to minimize the inclusion of participants with otherwise disturbed sleep, only participants who slept more than 4 hours, objectively (according to actigraphy) as well as subjectively (PSQI item 4), were analyzed. In addition, shift workers or participants on parental leave were excluded from analyses.

Sleep was objectively measured using actigraphy (see below) in 2788 participants. Of these, 1024 participants were excluded for not meeting in- or exclusion criteria (see Figure 1). Thus, the resulting study population comprised 1764 persons (908 women and 856 men). Mean (± SD) age was 57.8 (± 12.2) years, mean BMI was 27.1 (± 4.3) kg/m^2. Women had a mean age of 56.8 (± 12.1) years, men had a mean age of 58.8 (± 12.2) years. Women had a mean BMI of 26.8 (± 4.8) kg/m^2, men had a mean BMI of 27.5 (± 3.7) kg/m^2. The most diagnosed and reported illnesses were hypertension, elevated blood lipids, thyroid disease, arthrosis, disc prolapse, acid reflux, herpes zoster, 'other skin diseases' (than psoriasis or atopic dermatitis), hay fever and 'other kidney diseases' (than renal insufficiency).

Objective Measurement of Sleep Using Actigraphy

Actigraphy recordings were performed using SenseWear Pro 3 devices (BodyMedia Monitoring System, Bodymedia, Pittsburgh, Pennsylvania, USA). Participants were instructed to wear them for a total of seven consecutive days and nights. During this study period, participants were asked to keep a sleep-log, in which they documented their bedtimes and wake-up times, among other things.

Actigraphy data was analyzed using the SenseWear Professional software package version 6.1 (BodyMedia Monitoring System, Bodymedia, Pittsburgh, Pennsylvania, USA), which scores each recording minute as laying down (yes/no) and sleep (wake vs sleep). The algorithms used are based on multiple sensor parameters (galvanic skin response, skin temperature, 2-axis body acceleration, heat flux) with an off-arm detection in place to note the removal of the device. Validated successfully when compared with PSG, the SenseWear was shown to accurately detect total sleep time, wake after sleep onset and sleep efficiency.[31–35] Many studies indirectly validated measurements of time in bed, meaning lying duration, by accurately assessing energy expenditure in relation to different activities.[36–38] Lying duration assessed via this algorithm has been used in studies before.[39,40] It was also shown that the SenseWear armband performs equally well in comparison with another well-established wearable tool called Actiwatch.[31,35,41]

Afterwards, data was exported to a Microsoft Excel template with customized Visual Basic for Applications (VBA) macros. The Excel tool was used to customize analysis windows to the specific day-night-cycles of each participant, as no fixed time-window was used for night sleep analyses. Based on the bedtime and wake-up information provided in the sleep log, the respective night sleep episodes were identified manually. Then, the following sleep parameters were calculated for each:

Time in bed (TIB = sum of all minutes classified as lying down)

Total Sleep Time (TST = sum of all minutes classified as sleep)

Sleep onset latency (SOL = sum of all minutes classified as lying down before first time falling asleep)

Sleep efficiency (SE = ratio of TST to TIB)

Number of waking episodes (Nwake = amount of nocturnal waking episodes ≥ 5 minutes)

Wake after sleep onset (WASO = sum of all minutes classified as wake between sleep onset and awakening).

For greater reliability, only data from nights during the week was used. Values were averaged across the 5 nights prior to work days (Sunday to Thursday night). Only participants with analyzable data from at least 4 nights were included in the analyses.

Subjective Assessment of Sleep and Sleep Quality

Subjective sleep characteristics and sleep related variables were captured during the baseline visit of the LIFE study using the following self-report questionnaires: The Pittsburgh Sleep Quality Index (PSQI) is a self-rating scale to assess the subjective quality and quantity of sleep during the past four weeks. It consists of 19 individual items, creating 7 components, producing a global score, ranging from 0 to 21 points with higher scores reflecting greater sleep problems.[42–44] For the analysis of *subjective* sleep, we used items 1 (usual bedtime) and 3 (usual get up time) to

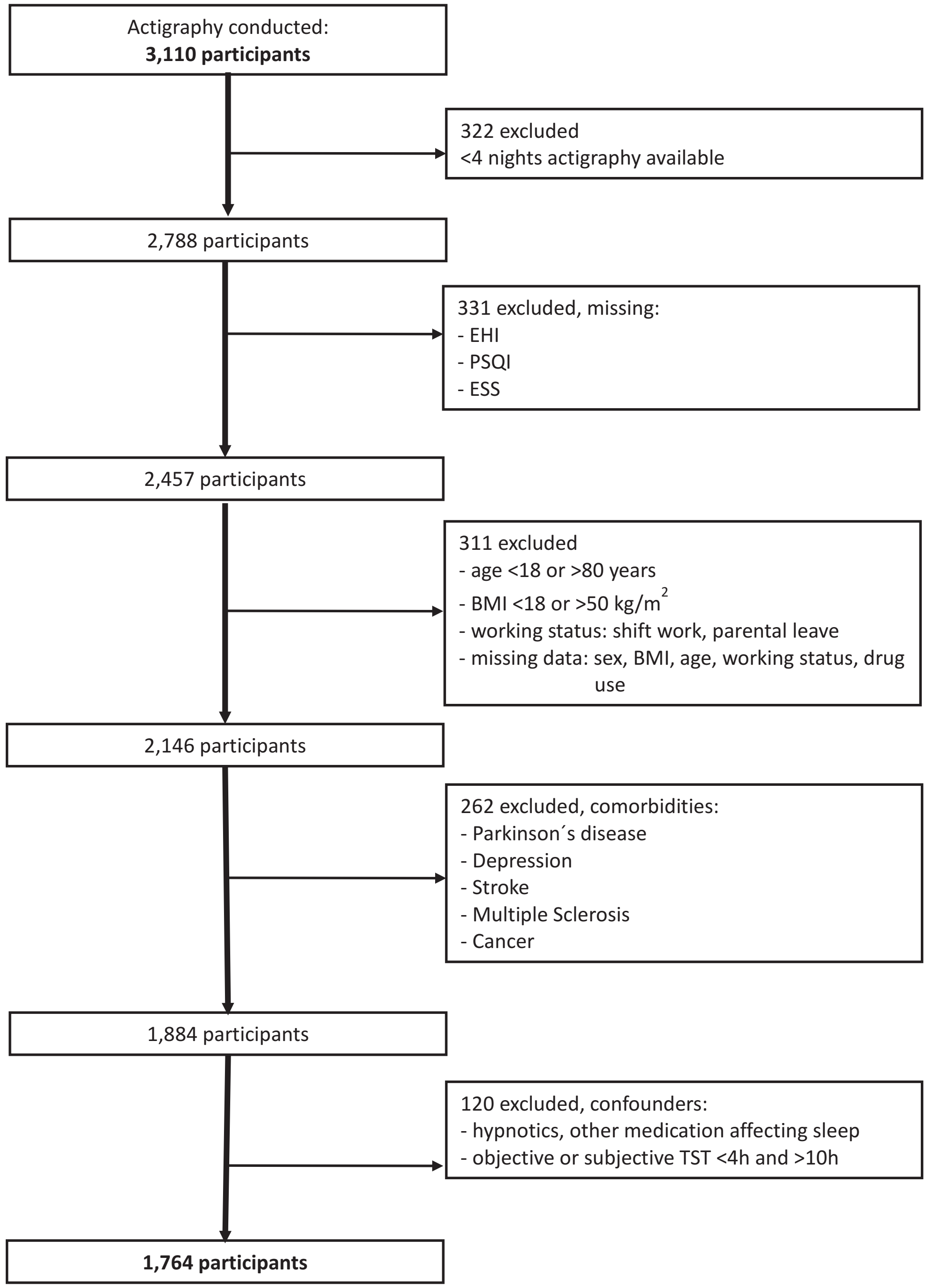

Figure 1 Flowchart illustrating the inclusion and exclusion criteria.
Abbreviations: BMI, body mass index; EHI, Edinburgh Handedness Scale; TST, total sleep time; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale.

calculate time in bed (TIB_{PSQI}), item 2 (typical sleep onset latency; SOL_{PSQI}) and 4 (usual sleep duration, SD_{PSQI}) and calculated subjective sleep efficiency ($SE_{PSQI} = SD_{PSQI}/TIB_{PSQI}$).

Determination of Daytime Sleepiness and Chronotype

To determine daytime sleepiness, the Epworth Sleepiness Scale (ESS) questionnaire was used. This self-rating instrument assesses the probability of falling asleep in 8 different everyday situations, thus addressing subjective sleepiness and hypersomnias.[45,46] The ESS ranges from 0 to 24 points, with higher scores reflecting greater daytime sleepiness.

The chronotype was assessed using the German version of the 19-item Morningness-Eveningness-Questionnaire (D-MEQ), identifying individual circadian phase and preferences.[47,48] The DMEQ ranges from 16 (definitive evening type) to 86 points (definitive morning type).

Determination of Handedness

Handedness was assessed using the Edinburgh Handedness Scale (EHI).[49] We used the modified German version of the scale comprising questions regarding hand preference in 10 different motor activities (eg writing, throwing, lighting a match) and additionally 10 questions targeting consistency of hand use regarding each of these 10 activities. The EHI score provides real numbers ranging from −100 (CLH, consistently left-handed) to +100 (CRH, consistently right-handed). As we regarded handedness as a continuum, we used metric values of the score for analyses. The EHI-Score (EHI) was used to determine the *direction of handedness*. The absolute value of the EHI-Score (absEHI, range 0 to 100) was used to determine the *degree of handedness*.

Determination of Other Variables

Sex, age, comorbidities, medical history, medication and social economic parameters were assessed via self-report.

Statistical Procedure

Only data recorded during the week was considered for analysis since sleeping patterns on the weekend are less reliant. Then, people engage in different activities, bending their sleeping schedules either to stay up especially late for festivities or to sleep longer to lessen the sleeping debt they may have accumulated during the week.

To control for age and menopausal status, a subgroup-analysis with restricted age ranges was performed. Participants between the ages of 18–45 years were grouped together to constitute a pre-menopausal group, while ≥55 year-olds were grouped together to build a post-menopausal group, considering that the mean age of menopause is about 50 years.[50] The cohort was further stratified for sex, leaving four subgroups: young females (N = 190), young males (N = 137), female seniors (N = 511), and male seniors (N = 519).

Subgroups were compared using *t*-test; if variances were not equal, corrected t-values were used. Correlations between sleep parameters and handedness were calculated using Spearman rank correlations. All statistical testing was performed using SPSS Statistics version 24 (IBM Corp., Armonk, New York, USA). *P*-values <0.05 were considered to be statistically significant. We did not use the Bonferroni correction for multiple testing in this exploratory study aiming at identifying effects worthy of further being studied. Thereby, we minimized the risk of type 2 errors (ie not detecting a true effect) and accepted the risk of type 1 errors (ie detecting a false effect). Type 2 errors are of particular concern in our sample since the absolute number of predominantly left-handed participants is low despite the large sample due to the small proportion. We believe that this approach is in line with both statistical recommendations[51] and current practice.[52–54]

Results

Objective and Subjective Sleep

Differences between sexes are shown in Table 1. Regarding *objective* sleep, women spent more time in bed (TIB), slept more (TST) and had a higher sleep efficiency (SE) with fewer awakenings (Nwake) and less time awake (WASO). In contrast, women *subjectively* reported to sleep less (shorter SD_{PSQI}), to require more time to fall asleep (longer SOL_{PSQI}) and therefore to sleep less efficiently (lower SE_{PSQI}) than men. Also, their subjective quality of sleep (PSQI score) is worse than in men. However, men score higher regarding daytime sleepiness (ESS score).

Distribution of Handedness

Mean EHI-Scores were 82.41 (SD = 39.45), with most participants (91.0%) being classified as right-handed (RH), according to their EHI-Score. N = 84 (4.8%) participants were classified as left-handed (LH) and N = 74 (4.2%) were classified as ambidextrous. While most RH showed extremely high lateralization (ie EHI-Score = +100), all other individuals were widely spread in their distribution of hand preferences. Strongly lateralized LH (EHI-Score = −100)

Table 1 Handedness, Objective and Subjective Sleep Parameters, Daytime Sleepiness and Chronotype Across the Cohort Separated by Sex

	Female N=908		Male N=856			
	Mean	**SD**	**Mean**	**SD**	**t**	**p**
EHI-Score	82.48	40.60	82.32	38.21	−1.889[Z]	0.059
Absolute EHI score	90.09	18.30	88.59	19.70	−2.037[Z]	**0.042**
Objective (actigraphy)						
TIB (h)	7.59	0.93	7.42	0.93	−3.770	**<0.001**
TST (h)	6.40	0.92	6.11	0.91	−6.610	**<0.001**
SE (%)	84.43	6.89	82.57	8.05	−5.209	**<0.001**
SOL (min)	9.91	8.16	9.41	6.73	−1.415	0.157
Nwake	2.71	1.34	2.91	1.51	2.949	**0.003**
WASO (h)	1.00	0.59	1.09	0.67	2.890	**0.004**
Subjective (questionnaires)						
TIB_{PSQI} (h)	8.08	1.06	7.97	1.10	−2.103	**0.036**
SD_{PSQI} (h)	6.76	1.15	6.92	1.06	2.873	**0.004**
SE_{PSQI} (%)	84.39	13.54	87.47	12.06	5.061	**<0.001**
SOL_{PSQI} (min)	22.26	23.67	16.54	17.71	−5.761	**<0.001**
PSQI score	5.40	3.21	4.39	2.54	−7.318	**<0.001**
ESS score	7.44	3.48	8.27	3.30	5.182	**<0.001**
D-MEQ score	59.42	8.53	59.72	8.31	0.724	0.469

Notes: Time in decimal values. [Z]Z-Values, Mann–Whitney-*U*-Test was used. Significant differences are shown in bold.
Abbreviations: TIB, time in bed; TST, total sleep time; SE, sleep efficiency (TST/IB); SOL, sleep onset latency; Nwake, number of awake periods of more than 5 min during night sleep; WASO, time spent awake after sleep onset. Subjective questionnaire-based sleep parameters; TIB, time in bed; SD, sleep duration; SE, sleep efficiency (SD/TIB); SOL, sleep onset latency; EHI, Edinburgh Handedness Scale; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; D-MEQ, Morningness-Eveningness-Questionnaire (chronotype).

were very rare with most LH being only mildly lateralized. It is apparent that handedness is a continuum rather than discrete categories.

Degree and direction of handedness for both men and women are depicted in Figure 2. Handedness scores were comparable for women (EHI = 82.48; absEHI = 90.09) and men (EHI = 82.33, absEHI = 88.59), yet the Mann–Whitney-Test reached significance for absEHI (Z = −2.037, p = 0.042). There were slightly less left-handed men than women (4.1% vs 5.4%), while there were less ambidextrous women than men (3.6% vs 4.8%).

Handedness and Objective Sleep Parameters

In the total sample, time spent awake after sleep onset (WASO) was correlated with handedness. The same was true for the sample of all women (Table 2). In postmenopausal women, in addition to WASO, also time in bed (TIB) and total sleep time (TST) were correlated with handedness. In this subset, right-handedness was associated with longer TIB, longer TST and less WASO (Table 2). Other associations between handedness and objective sleep parameters could not be found. This applies to all other groups looked at: all men, premenopausal women and men stratified for age groups

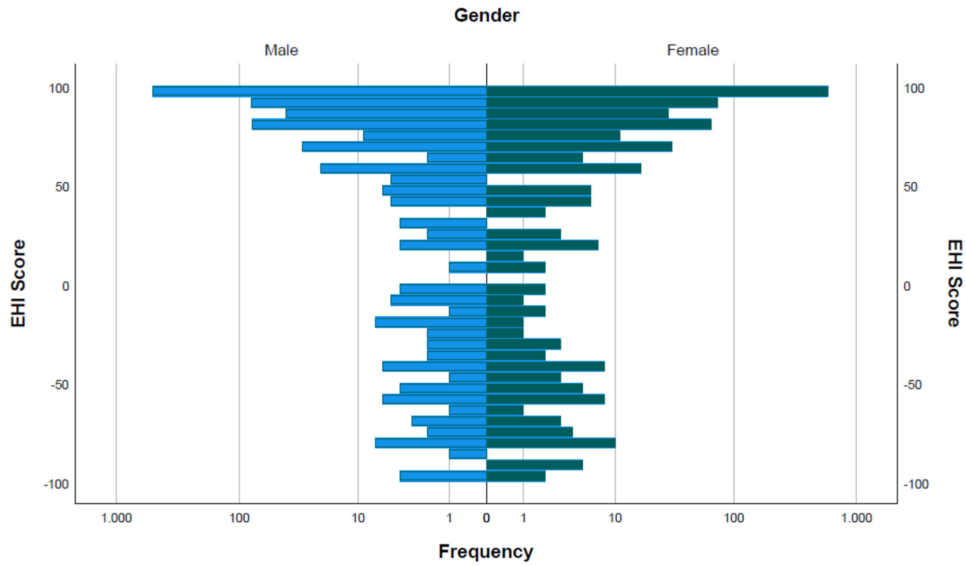

Figure 2 Frequency of the Edinburgh Handedness Scale (EHI)-Score in female and male participants.
Notes: EHI-Score 100 = consistently right-handed. EHI-Score −100 = consistently left-handed.

(Table 2). All significant correlations existed for both EHI and absEHI, meaning that direction and degree of lateralization were correlated with sleep parameters in the same way.

Handedness and Subjective Sleep Parameters

There was no significant association between handedness and a *quantitative* sleep parameter as assessed with the PSQI (eg SOL) in any group. In terms of *quality* of sleep, however, right-handedness was associated with a lower PSQI score in premenopausal women and older men, indicating better sleep quality (Table 3). All significant correlations existed for both EHI and absEHI, meaning that direction and degree of lateralization were correlated with sleep parameters in the same way. In the following groups, neither quantitative nor qualitative PSQI measures were associated with handedness: total group, all women, all men, younger men and postmenopausal women.

Daytime Sleepiness and Chronotype

In the total group and in postmenopausal women, right-handedness was associated with a lower ESS score, ie less daytime sleepiness (Table 3). The chronotype (D-MEQ score) was not associated with handedness in any group.

Discussion

To our knowledge, this is by far the largest study investigating the association between handedness and objective and subjective sleep. Key findings are:

First, the more right-handed/lateralized the participants were, the less they were awake after sleep onset. This was true for the total sample, all women and postmenopausal women. The latter also spent more time in bed and slept more. Secondly, in contrast to these associations with *objective* sleep variables, there was no significant association with any *subjective quantitative* sleep parameter in any group. Thirdly, however, the more right-handed/lateralized premenopausal women and >55-year-old men were, the better their *subjective quality* of sleep was. Fourthly, the more right-handed/lateralized the participants were, the less sleepy they were at daytime. This applied to the total group and postmenopausal women. Thus, overall, while associations were not consistently found in all groups, right-handedness tended to be associated with better sleep and less daytime sleepiness. Overall, associations were weak, though. The finding that direction (EHI) and degree (absEHI) of handedness showed similar correlations is plausible since the vast majority of participants were right-handed and showed a high degree of lateralization.

Table 2 Spearman's Rank Correlation of Direction of Handedness (Mean EHI) and Degree of Handedness (Absolute EHI) with *Objective* Sleep Parameters Separated by Sex and Age Group

	Total Sample	Female	Male	Female Age 18–45	Female Age ≥ 55	Male Age 18–45	Male Age ≥ 55
N	1764	908	856	190	511	137	519
Mean EHI-Score							
TIB	0.022	0.004	0.034	−0.099	**0.087***	0.049	0.014
TST	0.028	0.026	0.021	−0.031	**0.096***	−0.029	0.027
SE	0.033	0.053	0.007	0.090	0.065	−0.039	0.017
SOL	0.021	0.005	0.041	0.025	0.007	0.141	0.081
Nwake	−0.025	−0.052	0.007	−0.079	−0.051	0.016	−0.024
WASO	**−0.049***	**−0.087****	−0.008	−0.101	**−0.101***	0.041	−0.048
Absolute EHI-Score							
TIB	0.016	0.002	0.023	−0.090	**0.087***	0.048	0.005
TST	0.026	0.027	0.016	−0.015	**0.096***	−0.021	0.023
SE	0.035	0.054	0.010	0.097	0.062	−0.029	0.019
SOL	0.022	0.003	0.046	0.018	0.010	0.157	0.074
Nwake	−0.029	−0.053	−0.001	−0.083	−0.047	−0.011	−0.026
WASO	**−0.054***	**−0.090****	−0.016	−0.110	**−0.099***	0.028	−0.050

Notes: *The correlation is significant at the 0.05 level (two-sided); **The correlation is significant at the 0.01 level (two-sided).
Abbreviations: TIB, time in bed; TST, total sleep time; SE, sleep efficiency (TST/IB); SOL, sleep onset latency; Nwake, number of awake periods of more than 5 min during night sleep; WASO, time spent awake after sleep onset.

So far, there are only 11 studies on the association between handedness and sleep. Four of them used objective measuring techniques (actigraphy[8–11] with one study additionally comparing with polysomnography and self-report[11]) while seven only used self-reports.[4,12–16,55]

Studies capturing *objective* sleep variables were rather small (10 to 41 participants) and included only young participants with mean ages ranging from 20.5 to 22.4 years. Results were inconsistent: One study reported right-handedness to be associated with longer total sleep time (TST) and higher sleep efficiency (SE).[11] Another study reported left-handedness to be associated with longer sleep duration with no significant differences in sleep onset latency (SOL) or SE.[10] Propper et al reported in a first study, investigating sleep depending on the *degree* of handedness, a higher degree of handedness (ie consistently handed individuals) to be associated with longer SOL and lower SE in women.[8] In a second study, addressing *direction* of handedness, they compared sleep in 5 consistent LH (4 females) and 5 consistent RH (5 females). Here, the only significant finding is a higher number of REM periods in consistent LH.[9] Thus overall, no clear picture has arisen from these studies. Our findings also do not show a homogenous picture. Overall, however, direction and degree of handedness (the more right-handed and the more lateralized) were associated with better objective sleep, being roughly in line with the results of one of the studies[11] but not of the others.[8,10]

Research focusing on the association between handedness and *subjective* sleep is limited as well. Except for one[15] out of seven, all studies included young participants with mean ages 16–29 years.[4,11–14,16] Two studied the degree of handedness,[13,14] two direction[4,11] and two both.[12,16] The one study in elderly (older than 64 years) included 1277 participants but was (regarding sleep) limited to the question "can get enough rest and sleep" in consistent-handed and non-consistent-handed (mixed-handed) participants.[15] A further recent study compared subjective sleep parameters and direction of handedness in 35 gifted and 28 non-gifted children between 8 and 12 years.[55]

Also, in terms of *subjective* sleep, findings were not uniform but less contradictory: Among young adults, a higher *degree* of handedness was found to be associated with longer sleep duration,[14] lower SOL,[13] less awakenings[13] and less

Table 3 Spearman's Rank Correlation of Direction of Handedness (Mean EHI) and Degree of Handedness (Absolute EHI) with *Subjective* Sleep Parameters Separated by Sex and Age Group

	Total Sample	Female	Male	Female Age 18–45	Female Age ≥ 55	Male Age 18–45	Male Age ≥ 55
N	1764	908	856	190	511	137	519
Mean EHI-Score							
TIB_{PSQI}	−0.021	−0.053	0.007	−0.072	−0.011	−0.099	0.003
SD_{PSQI}	−0.012	−0.022	0.004	0.065	−0.011	−0.101	0.023
SE_{PSQI}	0.008	0.029	−0.005	0.070	0.020	−0.006	0.019
SOL_{PSQI}	−0.037	−0.042	−0.044	−0.129	−0.001	−0.077	−0.061
PSQI score	−0.028	−0.035	−0.035	**−0.168***	−0.011	0.059	**−0.092***
ESS score	**−0.049***	−0.055	−0.030	−0.016	**−0.094***	0.096	−0.074
D-MEQ score	0.013	0.039	−0.012	−0.033	0.071	−0.080	0.010
Absolute EHI-Score							
TIB_{PSQI}	−0.027	−0.052	−0.007	−0.037	−0.015	−0.120	0.000
SD_{PSQI}	−0.018	−0.027	−0.002	0.079	−0.023	−0.093	0.021
SE_{PSQI}	0.009	0.023	0.004	0.046	0.013	0.028	0.019
SOL_{PSQI}	−0.042	−0.041	−0.057	−0.108	0.004	−0.122	−0.067
PSQI score	−0.029	−0.033	−0.042	**−0.156***	−0.005	0.043	**−0.096***
ESS score	**−0.052***	−0.063	−0.027	−0.045	**−0.096***	0.102	−0.069
D-MEQ score	0.009	0.038	−0.021	−0.023	0.072	−0.069	0.012

Note: *The correlation is significant at the 0.05 level (two-sided).
Abbreviations: TIB, time in bed; SD, sleep duration; SE, sleep efficiency (SD/TIB); SOL, sleep onset latency; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; D-MEQ, Morningness-Eveningness-Questionnaire (chronotype).

"trouble returning to sleep after an awakening".[13] That means overall, a higher degree of handedness tended to be associated with better sleep. A study addressing *direction* of handedness reported right-handedness to be associated with less sleep problems.[4] Another study, mainly addressing dream recall, found that the sleep duration in left-, right- and mixed-handed individuals was comparable.[16] In elderly participants, the proportion agreeing on the question "can get enough rest and sleep" did not differ between consistent-handed and non-consistent-handed (mixed-handed) participants.[15] Piro et al showed gifted children to be significantly more left-handed, as well as showing a trend towards more sleep disturbances.[55] Thus, at least in adults, most studies point to better sleep in right-handed or consistent handed participants. These findings are in line with our result of a better sleep quality in pre-menopausal women and older men as assessed with the PSQI total score. Single subjective sleep measures derived from the PSQI (eg TIB) did not show correlations with handedness in our study, though.

Objectively measured TIB and TST were shorter than subjectively reported in our sample (Table 1), being a well-known finding[56] and a possible reason that associations between handedness and objective and subjective sleep, respectively, were not congruent.

In contrast to sleep, we are not aware of reports on the association of handedness and daytime sleepiness. The less right-handed/consistent handed participants were, the higher the daytime sleepiness was. This interesting finding is in line with the concept that it may be more stressful for left-handers or mixed-handers "to cope in a right-handed world".[10] Either, sleepiness could be "directly" induced by the higher effort required to manage the daily routine. Or, sleepiness could be caused by impaired night sleep since stress has been shown to impair sleep.[57–59] In line with that, stress reduction was repeatedly associated with improved sleep quality.[60,61] In addition or alternatively to those reactive mechanisms (to higher stress levels), higher sleepiness could also be linked to differences in brain structure or function.

While we did not find striking differences between women and men or between pre- and postmenopausal women, there are several indications that might suggest endocrine influences: For example, TIB and TST were positively correlated in postmenopausal women and negatively in premenopausal women. In the smaller premenopausal group, this did not reach significance, though. Of note, we did not analyze sex hormones so that this assumption ultimately remains speculative.

While handedness appears to be mainly, and sleep partly determined by genetic and epigenetic factors,[20,62] there is evidence that both lateralization and handedness as well as sleep are also affected by sex hormones. While sex hormones are 'likely not initially triggering hemispheric asymmetries', they have 'been shown to be able to profoundly shape them.'[20] For example in premenopausal women, functional cerebral asymmetry (FCA) constantly changes in dependence of their hormonal cycles as shown by the electroencephalogram (EEG)[63] or functional magnetic resonance imaging (fMRI).[21,64] During the follicular phase when estradiol levels are rising, FCA is lowest, and during the menses, lateralization is most pronounced.[21] Accordingly, the lateralized behavior (figure recognition or spatial attention) changed.[20,22] In men, salivary testosterone levels in adult men have been linked to cerebral laterality for language.[65] In addition, testosterone has been shown to affect brain asymmetries in terms of language lateralization[66] and mental rotation,[24] prenatally and during puberty.[24] Similarly, androgen exposure in utero has been suggested to influence the development of left-handedness.[67,68] A recent study found high prenatal testosterone concentrations in amniotic fluids to predict weak hand skill asymmetry scores and high prenatal estradiol to predict predicted weak hand preference in 15-year-old girls, thus overall also suggesting some influence of sex hormones on handedness.[69] An interplay between sex hormones and handedness in females is also suggested by reports that left-handedness is associated with earlier menopause[70,71] – yet, here also non-supportive reports exist[72,73] – and different sex hormone levels in left- and right-handed menopausal women.[74]

Sex hormones also affect human sleep. In women, sleep architecture was found to be dependent on luteinizing hormone (LH), follicle stimulating hormone (FSH), progesterone and estrogen, causing more sleep difficulties during the week before and during menses.[75] Later in life, reduced sex hormone levels during menopause are associated with sleep difficulties in 40–56% "with 26% experiencing severe symptoms that impact daytime functioning".[76] Consistently, progesterone showed sleep-promoting effects in postmenopausal women.[26,77,78] Furthermore, besides progesterone also estradiol contributes to the regulation of sleep stages.[27] In men, low testosterone levels were associated with impaired sleep.[79,80] While the decreasing sleep efficiency in men during aging has been linked to declining testosterone levels,[28] sleep, in turn, plays an important role in endocrine regulation, including maintaining male testosterone levels.[28,81]

Opposed to a large body of literature reporting non-right handedness to be more common in men, regardless of culture and century,[82] we did not find a relevant difference in our cohort in terms of direction. This might be due to our comparatively old study cohort: LH have a shorter life expectancy than RH with the earliest deaths in the group of only little lateralized LH.[83] In addition, men die younger than women do. Our finding of better *objective* sleep in women but better *subjective* sleep in men is in agreement with current knowledge.[56]

Strengths and Limitations

The main strength of this study is the large sample size comprising both subjective and objective sleep data. By stratifying the cohort according to sex and age, we controlled for the two main confounding factors in sleep regulation.[84] Additionally, we analyzed the mean values of five consecutive nights in their home environment; thus, the setting was as natural as possible.

It is a limitation that the age distribution was uneven since more participants that are elderly were included. Moreover, it would have been interesting to capture polysomnographic data in order to shed light on sleep stages. It is another limitation that participants with undiagnosed sleep disorders, including obstructive sleep apnea (OSA) and sleep movement disorders, could not be excluded because there were neither data from polysomnography nor from appropriate questionnaires allowing us to do so. Therefore, the study results should be interpreted very carefully. In terms of insomnia, at least in severe forms, we excluded those with an objective or subjective sleep duration of less than 4 hours.

Conclusions

While associations between sleep parameters and handedness were not consistent in all groups, overall, right-handedness tended to be associated with better sleep and less daytime sleepiness. Handedness and sleep seemed to be differentially associated in women and men, being in line with endocrine interactions.

Abbreviations

EHI, Edinburgh Handedness Inventory (score); absEHI, absolute value of Edinburgh Handedness Inventory score; BMI, body mass index; RH, right-hander; LH, left-hander; CH, consistently handed; ICH, inconsistently handed; CRH, consistently right-handed; CLH, consistently left-handed; TIB, time in bed; SOL, sleep onset latency; TST, total sleep time; SE, sleep efficiency; Nwake, number of times participants woke for more than 5 min during each night; WASO, amount of time spent awake after sleep onset; PSQI, Pittsburgh Sleep Quality Index; D-MEQ, Morningness-Eveningness -Questionnaire, German version; ESS, Epworth Sleepiness Scale.

Ethics Approval and Informed Consent

The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of the University of Leipzig (registration number: 263-2009-14122009). All participants gave written informed consent.

Data Sharing Statement

Restrictions are applied to the availability of these data. Data was obtained from the Leipzig Research Center for Civilisation Diseases. All data and samples of LIFE are the property of the University of Leipzig and are subject to the Law for the Protection of Informal Self-Determination in the Free State of Saxony (Saxon Data Protection Act). Use of data can be requested through the LIFE office (https://life.uni-leipzig.de/).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest related to this work.

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3 Summary

Dissertation zur Erlangung des akademischen Grades

Dr. med.

Titel: Handedness and Sleep

eingereicht von Hilde Taubert

angefertigt an der Universität Leipzig, Klinik für Psychiatrie und Psychotherapie

betreut von PD Dr. med. Michael Kluge

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Introduction

Restorative sleep is crucial for cognitive, emotional and behavioral performance and general human well-being. Handedness has been discussed as one factor affecting sleep among various others including age, body mass index (BMI) and sex. Being the preferred use of one hand over the other, handedness has been linked to physiological traits like memory function and pathological conditions like psychiatric disorders. While several studies investigated potential associations between handedness and (mostly subjective) sleep, large-scale studies including a broad age span of participants and studies analyzing women and men separately are lacking. In addition, there are only few studies determining objective sleep. These studies provided inconsistent results.

Objectives

Therefore, the aim of this study was to examine associations between handedness and both objective and subjective sleep in a large cohort with a broad age range from 18 to 80 years. In addition, the aim was to address potential endocrine effects by

comparing associations in women and men as well as in premenopausal and postmenopausal women.

Methods

A subset of the approximately 10,000 participants from the population-based study "LIFE-Adult" (Leipzig Research Center for Civilization Diseases – adult group) was analyzed with regard to their handedness, objective and subjective sleep and important co-factors. Objective sleep data were determined using at-home actigraphy from 1764 healthy participants (18 to 80 years, 908 women), averaging five consecutive nights. 1024 individuals receiving acticraphy had been previously excluded for not meeting any of the in- and exclusion criteria. Only data collected in nights prior to work days were used. In addition, subjective sleep-related data were captured by self-report diaries, the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS) and the Morningness-Eveningness-Questionnaire (MEQ). Handedness was determined using the Edinburgh Handedness Inventory (EHI). The EHI provides information on the direction (i.e. left vs right) and the degree of handedness (i.e. strong vs weak). To address potential endocrine effects, premenopausal women (≤45 years) and postmenopausal women (≥55 years) were analyzed separately. This was also done for men, leaving four subgroups: young females (N=190), young males (N=137), female seniors (N=511) and male seniors (N=519) in order to compare pre- and postmenopausal age groups. Subgroups were compared using t-Test and correlations between sleep parameters and handedness were calculated using Spearman rank correlations.

Results

The degree and direction of handedness were correlated with "wake after sleep onset" (WASO) in the total sample and all women (the more right-handed/lateralized the shorter WASO). In postmenopausal women, additionally, time in bed (TIB) and total sleep time (TST) were positively correlated with right-handedness/higher lateralization. There were no other significant associations between an objective sleep variable and handedness. In both premenopausal women and >55-year-old men subjective quality of sleep (PSQI) was correlated with direction and degree of handedness, i.e. the more right-handed/lateralized the better. In the total sample and postmenopausal women, the degree and the direction of handedness were negatively correlated with daytime sleepiness, i.e. the less right-handed/lateralized the higher the daytime sleepiness. The chronotype was not associated with handedness in any group.

91% of participants were classified as RH with a very high *degree* of lateralization that was lower in non-RH participants. 5.4% of the women and 4.1% of the men were left-handed, 3.6% of the women and 4.8% of the men were ambidextrous as defined by the EHI-Score (EHI > 50 as RH, EHI < -40 as LH).

Discussion

To my knowledge, this is by far the largest study investigating the association between handedness and objective and subjective sleep. Most essential findings are, that right-handedness and higher lateralization both are associated with the following:

a) less WASO in the whole group, all women and postmenopausal women

b) more TIB and TST in postmenopausal women

c) better subjective quality of sleep in premenopausal women and >55-year old men

d) less daytime sleepiness in the total group and postmenopausal women

Thus, overall, while associations were not consistently found in all groups, right-handedness tended to be associated with better sleep and less daytime sleepiness. Overall, associations were weak, though. The finding, that *direction* and *degree* of handedness showed similar correlations, is plausible, since the vast majority of participants were right handed and showed a high *degree* of lateralization.

Results of this study are met by a relatively small body of literature, as only 11 studies were conducted on the association between handedness and sleep so far.

Out of these, four used *objective* measuring techniques on young participants exclusively (mean ages from 20.5 to 22.4 years), delivering a rather inconsistent picture. For example, while longer or shorter TST was found to be associated with right-handedness, other studies could not find an association at all. Also findings from our study do not show a homogenous picture. Overall, however, *direction* and *degree* of handedness (the more right-handed and the more lateralized) were associated with better objective sleep, being roughly in line with most of the studies. In contrast to these, however, our study is the first one to include participants over 30 years of age.

Comparably, out of the seven studies focusing on *subjective* sleep, all but one included participants younger than 30 years. Findings here mostly indicated, that right-handedness or higher lateralization are associated with better subjective sleep (e.g. longer TST, less WASO, fewer sleep problems). The only study targeting older participants did not find differences in the proportion of individuals agreeing to the question, whether they “can get enough rest and sleep”. Thus, our study is overall in line with the studies in younger adults.

Importantly, our study is the first to explore the relationship between handedness and daytime sleepiness. Here, right-handedness and higher lateralization were associated with less daytime sleepiness. This finding is in line with the idea that it may be more stressful and exhausting for non-RH coping in a right-handed world.

While we did not find striking differences between women and men or between pre- and postmenopausal women, several indications might suggest endocrine influences: For example, TIB and TST were positively correlated in postmenopausal but negatively in premenopausal women. Such findings warant further research on the influence of sex hormones on both handedness and sleep.

Conclusion

Although associations found in this study were not consistent in all subgroups, a trend towards right-handedness and higher lateralization being associated with aspects of better objective and subjective sleep as well as less daytime sleepiness became apparent. Seemingly differing associations between women and men are in line with endocrine interactions. *Degree* and *direction* of handedness seem to be equally important and should both be considered in future research.

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Erklärung über den wissenschaftlichen Beitrag der Promovendin zur Publikation.

Die Promovendin erbrachte folgende Beiträge zur Publikation „Non-Right Handedness is Associated with More Time Awake After Sleep Onset and Higher Daytime Sleepiness Than Right Handedness: Objective (Actigraphic) and Subjective Data from a Large Community Sample“:

- Literaturrecherchen
- Mitentwicklung der Fragestellung
- Auswahl der zu testenden Items
- Durchführung der statistischen Testungen
- Ergebnisinterpretation und Diskussion
- Anfertigung des Publikationsmanuskripts
- Beteiligung an den Revisionen

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Declaration of authorship

Erklärung über die eigenständige Abfassung der Arbeit

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbstständig und ohne unzulässige Hilfe oder Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Ich versichere, dass Dritte von mir weder unmittelbar noch mittelbar eine Vergütung oder geldwerte Leistungen für Arbeiten erhalten haben, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen, und dass die vorgelegte Arbeit weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde zum Zweck einer Promotion oder eines anderen Prüfungsverfahrens vorgelegt wurde. Alles aus anderen Quellen und von anderen Personen übernommene Material, das in der Arbeit verwendet wurde oder auf das direkt Bezug genommen wird, wurde als solches kenntlich gemacht. Insbesondere wurden alle Personen genannt, die direkt an der Entstehung der vorliegenden Arbeit beteiligt waren. Die aktuellen gesetzlichen Vorgaben in Bezug auf die Zulassung der klinischen Studien, die Bestimmungen des Tierschutzgesetzes, die Bestimmungen des Gentechnikgesetzes und die allgemeinen Datenschutzbestimmungen wurden eingehalten. Ich versichere, dass ich die Regelungen der Satzung der Universität Leipzig zur Sicherung guter wissenschaftlicher Praxis kenne und eingehalten habe.

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Publications

Taubert H., Schroeter M., Sander C., Kluge M.
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