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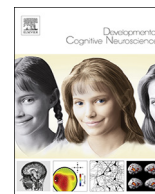
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From swing to cane: Sex differences of EEG resting-state temporal patterns during maturation and aging

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ABSTRACT

While many insights on brain development and aging have been gained by studying resting-state networks with fMRI, relating these changes to cognitive functions is limited by the temporal resolution of fMRI. In order to better grasp short-lasting and dynamically changing mental activities, an increasing number of studies utilize EEG to define resting-state networks, thereby often using the concept of EEG microstates. These are brief (around 100 ms) periods of stable scalp potential fields that are influenced by cognitive states and are sensitive to neuropsychiatric diseases. Despite the rising popularity of the EEG microstate approach, information about age changes is sparse and nothing is known about sex differences. Here we investigated age and sex related changes of the temporal dynamics of EEG microstates in 179 healthy individuals (6–87 years old, 90 females, 204-channel EEG). We show strong sex-specific changes in microstate dynamics during adolescence as well as at older age. In addition, males and females differ in the duration and occurrence of specific microstates. These results are of relevance for the comparison of studies in populations of different age and sex and for the understanding of the changes in neuropsychiatric diseases.

1. Introduction

1.1. Age and sex differences in brain structure and function

Knowledge about maturation, aging and sex specific trajectories of structural and functional brain networks is critical for understanding the emergence of neurodevelopmental and neurodegenerative disorders. Structural imaging studies show that brain regions that are responsible for higher order cognitive processes, are amongst the last to mature, long after the maturation of primary sensory cortices (Gogtay et al., 2004). During aging, structural changes such as white matter hyperintensities, reduced grey and/or white matter volume, and cortical thinning have been reported (Raz and Rodrigue, 2006). These processes are evolving spatially in a selective and differential manner with most evidence suggesting an anterior to posterior direction (Raz and Rodrigue, 2006; Davis et al., 2009; Bartzokis et al., 2004), where anterior cortices are most vulnerable to aging.

While functional imaging studies using resting-state fMRI approaches indicated changes of specific resting-state network

connectivity during development (Zielinski et al., 2010; Fair et al., 2007; Uddin et al., 2011; Ferreira and Busatto, 2013; Tomasi and Volkow, 2012), and general decreased connectivity between networks during aging (Chan et al., 2014), these studies have to be considered with caution since head motion variability between different age groups might have contaminated the results (Power et al., 2012; Satterthwaite et al., 2012).

Concerning sex differences, it is relatively well accepted that males and females differ in terms of brain volume (Ruigrok et al., 2014), grey/white matter ratio (Gur et al., 1999), and regional cerebral blood flow (Amen et al., 2017). In terms of functional connectivity, females have more within-network connectivity while males display more between-network connectivity in regions within the attention, auditory, memory retrieval and default mode networks (Satterthwaite et al., 2015). An important question to ask is whether these functional and structural maturation trajectories explain the differences in cognitive performance between males and females. For example, females outperform males in tasks relying on selective attention, verbal fluency, conductive and non-verbal reasoning, and emotion identification (Christakou et al., 2009;

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Anderson, 2001; Klenberg et al., 2001; De Luca et al., 2003; Schaie, 1994). Males, however, perform better in tasks involving visual-spatial processing, motor speed, language accuracy and mental rotation (Christakou et al., 2009; Anderson, 2001; Klenberg et al., 2001; De Luca et al., 2003; Schaie, 1994). Few studies investigated age by sex interactions of functional connectivity while participants performed a task. Rubia and colleagues found that during different cognitive control tasks, male's performance was associated with enhanced parieto-temporal activation, and female's performance was related to enhanced activation in fronto-striatal regions (Rubia et al., 2010). Taken together, these results seem to suggest that there is a sex specific pattern of brain functional and structural organization, which accounts for preferences in cognitive strategies and ultimately behavior.

1.2. Temporal dynamics of cognitive networks

Relating age and sex differences in fMRI resting-state networks to variations in cognitive strategies is only possible if one assumes that resting-state networks correspond to different functional domains (Yeo et al., 2011; Glasser et al., 2016). However, there are several arguments that question this correspondence, such as the fact that different brain regions are co-activated during rest and during task, that certain brain regions can be implicated in several cognitive functions and that their activation depends on task performance (Davis et al., 2017; Campbell and Schacter, 2017). But most relevant in the context of this study is the fact that the haemodynamic response is too sluggish to follow the fast dynamics of cognitive mental activity. Large-scale neuronal networks reorganize on a sub-second time scale in order to rapidly adapt to momentary thoughts (Bressler, 1995; Bressler and Kelso, 2001). In order to explore such fast brain dynamics and relate them to cognitive functions, recent studies focused on exploring resting-state networks with EEG or MEG. Important work using such methods relies on the notion of EEG microstates, reported for the first time by Lehmann and co-workers (Lehmann et al., 1987). EEG microstates are characterized by short periods of time (80–120 ms) during which the global scalp potential map shows a stable topography (for reviews see (Lehmann et al., 2009; Michel and Koenig, 2017; Lehmann and Michel, 2011; Koenig et al., 2005; Khanna et al., 2015)). Given that these periods of stability are in the time range of cognitive processes, it has been argued that EEG microstates are the electrophysiological manifestation of the continuous stream of conscious thoughts that is parcelled into short metastable states, and that their occurrence and temporal dynamics define the quality and content of the mental processes (Lehmann, 1990; Lehmann et al., 1998; Changeux and Michel, 2004); for discussions see (Meehan and Bressler, 2012; Betzel et al., 2012; de Pasquale et al., 2017). Interestingly, only a few prototypical potential map configurations define these states, repeatedly observed in different studies. Their appearance, duration and sequence are selectively influenced by different mental states such as sleep (Brodbeck et al., 2012), hypnosis (Katayama et al., 2007), hallucinations (Kindler et al., 2011) and meditation (Lehmann et al., 2006). They have been attributed to different mental states such as visual vs. abstract imagery (Lehmann et al., 1998), object and spatial visualization vs. verbalization (Milz et al., 2016), somatic awareness (Pipinis et al., 2017), and traits such as personality (Schlegel et al., 2012) and fluid intelligence (Santarnecchi et al., 2017). Many different studies showed selective changes of temporal dynamics of EEG microstates in psychiatric and neurological diseases such as schizophrenia (Tomescu et al., 2014), dementia (Kanda et al., 2013), panic disorders (Kikuchi et al., 2011), multiple sclerosis (Gschwind et al., 2016), narcolepsy (Drissi et al., 2016) and stroke (Zappasodi et al., 2017). Successful treatment of schizophrenic symptoms with medication or brain stimulation goes along with normalization of the abnormal EEG microstates (Kikuchi et al., 2007; Sverak et al., 2017). Thus, these studies indicate that EEG microstates might be closely related to changes in mental activity during rest, even though further studies are needed to clarify the functional role of each of them.

Given the increasing emergence of clinical and experimental studies on EEG microstates, it is important to understand their evolution during development and aging and evaluate potential sex differences. However, only one previous study using low-density EEG recordings (19 channels) investigated the temporal changes across development (Koenig et al., 2002). The strongest differences were found during adolescence and early adulthood (16–21 years), characterized by an increase in duration and frequency of occurrence of class C and a decrease in these parameters of class D. The authors proposed that developmental trajectories of the EEG microstates reflect an adaptive biological mechanism that selects the brain functional states that are optimal for age-specific learning and behavior. But are these trajectories different between males and females? Answering this question might not only be important to extend the knowledge about sex dimorphisms in brain network maturation but it might also be essential for sex specific prognosis, and to better understand prevalence and risk of several developmental and neurodegenerative diseases. With this aim, we investigated sex and age interactions of temporal structure and transition dynamics of microstates using high-density EEG recordings (204 channels) in a large dataset of 179 subjects.

2. Methods

2.1. Participants and data acquisition

This study included 179 participants (90 females) in the age range of 6–87 years from two centers in Switzerland, Geneva and Basel. The studies which provided the data for this study were approved by the local ethical committees, in accordance with the declaration of Helsinki. Participants and parents of children younger than 18 years provided written informed consent for their participation. In Basel, participants (N = 73) were recruited at the Department of Neurology, University Hospital Basel. In Geneva, participants were recruited at the Department of Psychiatry (N = 76), the Neurology Department (N = 11), and the Department of Fundamental Neuroscience (N = 19). As these data were recorded to form control groups for different clinical studies, the exclusion criteria included neurologic and psychiatric symptoms.

Across the age groups, there was no significant difference in the distribution of sex (Pearson Chi-square, $\chi^2 = 10$, $p = 0.26$) (Table 1).

In both centers, the EEG data were acquired in a darkened, electrically shielded room using a 256-channel HydroCel Geodesic Sensor Net (Electrical Geodesics Inc, Eugene, USA), sampled online at 1 kHz between DC and 100 Hz with a vertex reference. Participants sat in a comfortable, upright position and were instructed to stay awake, as calm as possible, to keep their eyes closed and to relax for five minutes without falling asleep.

2.2. EEG data processing

The EEG datasets were band-pass filtered offline between 1 and 40 Hz and electrodes on the cheeks and nape were excluded. The remaining 204 electrodes were kept for further analysis. EEG periods of movement contamination or other artifacts were excluded from the

Table 1

Demographics. Description of the study sample with each age group, number of individuals (N) per group, mean and standard deviation (s.d.) of age, number of females and males.

age group	n	mean age (S.D.)	n females	n males
6–13	32	10.5 (2.68)	11	21
14–19	34	16.87 (1.62)	14	20
20–30	30	24.46 (4.2)	13	17
31–60	41	39.04 (9.63)	26	15
61–87	38	74.57 (6.37)	23	15

analyses. In order to remove the oculomotor artefacts such as saccades and eye blinks as well as the cardiac artefacts (ECG), we applied the Infomax-based Independent Component Analysis (ICA) (Jung et al., 2000). Bad or noisy electrodes were interpolated using a 3-D spherical spline (Perrin et al., 1989), and were recomputed to the common average-reference. The data were then down-sampled to 125 Hz for further analysis.

The local maxima of the Global Field Power (GFP) show an optimal signal to noise-ratio in the EEG (Pascual-Marqui et al., 1995). The EEG signal was extracted at the corresponding time frame of GFP peaks and only the time points of GFP peaks were submitted to a modified k-means cluster analysis (Pascual-Marqui et al., 1995; Murray et al., 2008) in order to identify the most representative classes of stable topographies.

The k-means clustering was performed in two steps. First at the individual level, and, in a second step, at the group-level by clustering all individual dominant topographies with varying number of clusters. In order to determine the optimal number of clusters at the individual and the group level, we used the criteria implemented in Cartool (a free academic software developed in the lab; <https://sites.google.com/site/cartoolcommunity/>), based on seven maximally independent criteria: Davies and Bouldin, Gamma, Silhouette, Dunn Robust, Point-Biserial, Krzanowski-Lai Index, and Cross-Validation (Pascual-Marqui et al., 1995; Milligan and Cooper, 1985; Krzanowski and Lai, 1988; Charrad et al., 2014; Brunet et al., 2011) (for details see (Custo et al., 2017)).

In the first part of the microstate analysis only GFP peaks were submitted to the k-means clustering. However, in the second part of the analysis, during the fitting process of the microstates, the entire EEG of participants was used, excluding only the marked artefact epochs. A temporal smoothing (window half-size 3 (24 ms), Besag factor of 10 (Murray et al., 2008)) and a rejection of small time frames (when < 3, i.e. 24 ms) was applied. Subsequently, in order to quantify the temporal parameters of microstates, every time point of the individual data was assigned to the microstate cluster with which it correlated best (Murray et al., 2008).

This fitting process enabled the determination of the mean duration and the occurrence of each microstate in each subject. The mean duration represents the average amount of time (in ms) that a given microstate map was present without interruptions, i.e. the mean duration during which the subject remained in a certain state. The mean duration is one of the most commonly used parameters of the temporal structure of microstates and has repeatedly been shown to be associated with different vigilance conditions and symptoms of neuropsychiatric disorders (Khanna et al., 2015). The mean occurrence of a microstate is independent of the duration. It indicates the rate at which a given microstate occurred, i.e. how many times per second the subject enters a certain state.

In addition to these two temporal parameters for each microstate, we also analyzed the transition between microstates: for each subject and transition pair we computed the number of transitions and normalized them by all between-class transitions as in Lehmann et al. (2005).

The free academic software Cartool (<https://sites.google.com/site/cartoolcommunity/>) was used for the analysis (Brunet et al., 2011).

2.3. Statistical analyses

Normality of the distributions was tested using the Shapiro-Wilk's test. Four subjects were found to be outliers and were excluded from the sample based on the interquartile range rule of 2.2 multipliers according to Hoaglin and Iglewicz (Hoaglin and Iglewicz (1987)). This concerned three females from the 20–30 years group and one male from the 61–87 years group.

For both microstate temporal parameters (mean duration and occurrence), a three-way repeated measures ANOVA with the factors age group (6–13, 14–19, 20–30, 31–60, 61–87), sex (females and males)

and classes of microstates (A–D) was performed. All post-hoc *t*-tests were corrected for multiple comparisons applying the Bonferroni correction by adjusting the corresponding *p*-value to the number of comparisons (alpha level after correction: sex*microstate $p = 0.006$, age*microstate $p = 0.002$, sex*microstate $p = 0.005$, sex*age*microstate $p = 0.001$). The same statistical procedure was applied to the transition probabilities with transition pairs (12), sex (2) and age groups (5) (alpha level after correction: sex*transition $p = 0.002$, age*transition $p = 0.0008$). To further compare maturational trajectories of males and females, we assessed separate one-way ANOVAs for those microstates that revealed sex effects in the 3-way ANOVA, as well as sex differences for each group.

In order to establish the distance between the observed transition probabilities and what could be expected given the occurrence of the four states, we used randomization tests to test the significance of this distance using the procedure described in Lehmann et al. (2005).

3. Results

The k-means clustering of the individual subjects resulted in a number of optimal clusters varying between 4 and 12 (mean: 7.1 ± 1.8). These maps were submitted to a second k-means clustering across all individuals. This analysis revealed that, as reported in previous studies, 4 clusters best described the topographical variance in the data using the set of optimization criteria described in the Method section. These 4 microstates explained 71.3% of the total global variance of the individual data. Microstate 1 had a left posterior-right anterior orientation, whereas microstate 2 had a right posterior-left anterior orientation, microstate 3 had a central anterior-posterior orientation and microstate 4 had a central maximum. Their topographies were very similar to the four canonical microstate maps previously described in the literature and were thus labeled as microstates A–D in accordance with these studies, (Fig. 1) (Tomescu et al., 2014; Koenig et al., 2002; Lehmann et al., 2005; Koenig et al., 1999; Strelets et al., 2003; Britz et al., 2010; Tomescu et al., 2015).

3.1. Microstate temporal parameters

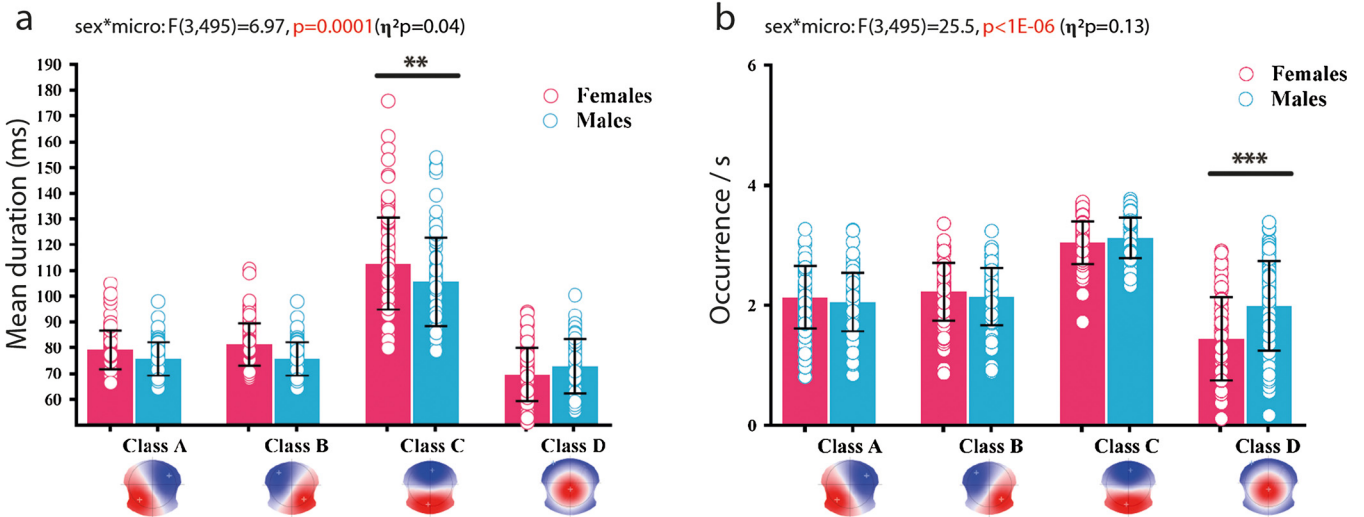
Table 2 summarizes the effects of the three-way repeated measure ANOVAs (microstate x sex x age groups).

For the mean duration of the microstates, a significant main effect was observed for the factors 'microstate' and 'age group'. The main effect of the factor 'microstate' was due to a generally longer microstate C and shorter microstate D duration compared to the three other microstates (Fig. 1.1a), an observation replicating several previous studies (Tomescu et al., 2014; Koenig et al., 2002). The main effect of 'age group' was due to a general tendency for increased duration of the microstates with age, with the exception of microstate C, leading to a significant age x microstate interaction. Results of the post-hoc *t*-tests of microstate C are shown in Fig. 1.2a and will be discussed separately below.

While the main effect of 'sex' was not significant ($p = 0.18$), there was a significant sex x microstate interaction ($F(3,495) = 6.98$, $p = 0.0001$, $\eta^2p = 0.04$) due to a difference between males and females in microstate C duration (post-hoc *t*-test, $p = 0.0001$, $d = 0.3$, see Fig. 1.1a below).

For the occurrence of the microstates, the three-way ANOVA also revealed a significant main effect of the factor 'microstate'. This was again due to an increased occurrence of microstate C and decreased microstate D occurrence compared to the other microstates (Fig. 1.1b). Also, the factor 'age group' showed a significant main effect due to a tendency of decreased occurrence of microstates with increasing age. However, microstate class D showed an opposite effect (an increased occurrence with age). A significant age x microstate interaction was also found. Results of the post-hoc *t*-tests of microstate D are shown in Fig. 1.2b and will be discussed separately below. The main effect of the

1. Sex by microstate interaction



2. Age by microstate interaction & sex trajectories

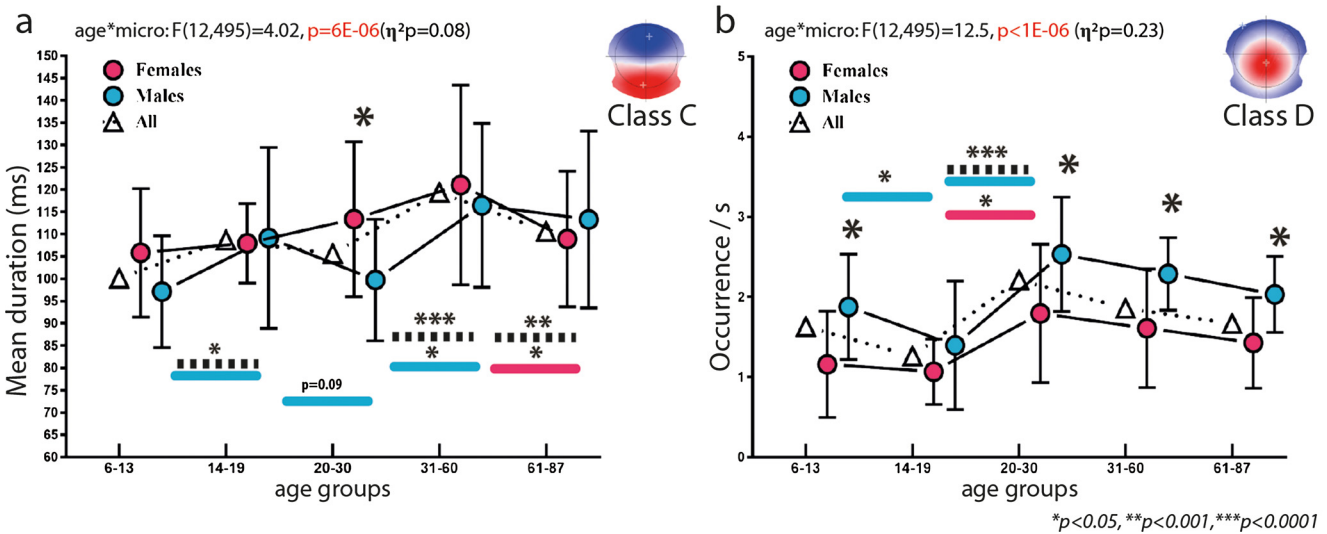


Fig. 1. (1) Results of the sex x microstate class ANOVAs for mean duration (a) and occurrence (b). Significant post hoc *t*-tests are indicated by asterisks above horizontal black bars. Vertical bars represent standard deviations (SD). (2) The two graphs depict the age- and sex differences of microstate C duration (a) and D occurrence (b). The results for microstates A and B can be found in the Supplementary Fig. S1. Significant post-hoc *t*-test results between age groups are marked above the horizontal bars (red: females, blue: males, black: both sex). Asterisks above the SD bars depict the significant sex differences for each age group (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

factor ‘sex’ was significant ($p = 0.049$), as well as the sex x microstate interaction, which was mainly due to an increased occurrence of microstate D ($p < 1E-06, d = 0.7$) in males compared to females, independent of age (see Fig. 1.2b). In summary, the global analysis showed significant differences between age groups and sex for the duration of microstate C and the occurrence of microstate D. These two effects are considered in more detail in the following post-hoc analyses.

The results of the randomization tests comparing the observed and the expected transitions given the occurrence of the four states (using the procedure described in Lehmann et al., 2005) show that over all age and sex groups, the observed transition probabilities were significantly different than the expected ones $p < 0.0001$. Thus, the structure of the observed transitions in this data set is not explained by the occurrence of the four states.

The statistical results of the observed probability of transitions of the $2 \times 5 \times 12$ (transition pairs) ANOVA revealed a significant main effect of age group ($F(4, 165) = 5.3, p = 0.0004, \eta^2p = 0.11$), and a significant interaction of age group and transition pair ($F(44,$

$1815) = 10.6, p < 1E-06, \eta^2p = 0.20$). In addition, we found a significant interaction between sex and transition pair ($F(11.1815) = 22.7, p < 1E-06, \eta^2p = 0.12$). The results of the post-hoc analyses are presented in Fig. 2 and in the following sections.

3.2. Microstate C

As Fig. 1.2a illustrates, females show a different trajectory of the duration of microstate C across the life span than males. Females show a constant increase in microstate C duration towards adulthood (from 6 to 13 years to 31–60 years, $p = 0.01, d = 0.7$); and from 14–19 years to 31–60 years, ($p = 0.02, d = 0.7$). Conversely, in males we found a trend of a decreased duration from adolescence to young adulthood ($p = 0.09, d = 0.5$), but also significant increases from childhood to adolescence ($p = 0.02, d = 0.7$), and later on from 20–30 to 31–60 years ($p = 0.006, d = 1.07$). These opposite developmental trajectories between females and males led to a significant difference between males and females in the age group 20–30 years ($p = 0.02, \eta^2p = 0.17$).

Table 2

The results of the two separate statistical analyses (3-way ANOVA) for mean duration and occurrence. Significant results are highlighted in bold.

	F(df)		p	η^2p
Mean duration				
<u>main effects</u>				
Sex	F(1, 165)	1.78	0.18	0.01
Age	F(4, 165)	32.4	< 1E-06	0.43
Microstate class	F(3, 495)	390.5	< 1E-06	0.70
<u>2-way interaction</u>				
Sex *Microstate class	F(3, 495)	6.98	0.0001	0.04
Age *Microstate class	F(12, 495)	4.02	6E-06	0.08
Sex *Age	F(4, 165)	2.45	0.04	0.05
<u>3-way interaction</u>				
Age*Sex *Microstate class	F(12, 495)	1.14	0.32	0.02
Occurrence				
<u>main effects</u>				
Sex	F(1, 165)	3.9	0.049	0.02
Age	F(4, 165)	5.4	0.0003	0.1
Microstate class	F(3, 495)	266.9	< 1E-06	0.61
<u>2-way interaction</u>				
Sex *Microstate class	F(3, 495)	25.5	< 1E-06	0.13
Age *Microstate class	F(12, 495)	12.5	< 1E-06	0.23
Sex *Age	F(4, 165)	1.97	0.10	0.04
<u>3-way interaction</u>				
Age*Sex *Microstate class	F(12, 495)	0.74	0.71	0.01

F(df) = F-test (degrees of freedom), p = p-value, η^2p = partial eta square.

In the oldest age group the duration of microstate C significantly decreased in females ($p = 0.016$, $d = 0.6$). While the decrease was not significant in males alone, it was significant when merging both groups ($p = 0.0001$, $d = 0.4$).

We also looked at the transition probabilities of all microstates from and to microstate C. As illustrated in Fig. 2.2, the probability of a transition from microstate B to microstate C was increased in females as compared to males ($p = 0.00001$, $d = 0.5$), independent of the age group. The same was true for transitions from A to C ($p = 0.00005$, $d = 0.7$), C to A ($p = 0.00004$, $d = 0.5$) and C to B ($p = 0.00001$, $d = 0.5$). With age, and across both sexes, these transition probabilities decreased from adolescence to adulthood (see Fig. 2.1). Concerning aging, there was a significantly decreased transition from microstate C to D between adults and seniors ($p = 0.00004$, $d = 0.6$). The same was true for transitions from D to C ($p = 0.000002$, $d = 0.6$; see Fig. 2.1).

3.3. Microstate D

Fig. 1.1b shows that microstate D occurs much more often in males than females independent of the age group.

This result is further confirmed by the results of a separate statistical 5 (age groups) \times 2 (sex) ANOVA analysis performed only on microstate D occurrence. We found a significant sex effect ($F(1, 165) = 35.39$, $p = 1E-08$, $\eta^2p = 0.17$; males > females, $p = 1E-07$) without a significant interaction between age group \times sex ($F(4, 165) = 0.52$, $p = 0.71$). Furthermore, simple one-way ANOVA's between males and females for each age group showed significant occurrence differences in the following age groups: 6–13 years ($F(1,30) = 8.5$, $p = 0.006$, $\eta^2p = 0.22$), 20–30 years ($F(1,28) = 6.5$, $p = 0.01$, $\eta^2p = 0.19$), 31–60 years ($F(1,39) = 10.2$, $p = 0.002$, $\eta^2p = 0.2$) and finally between 61–87 years ($F(1,36) = 11.6$, $p = 0.001$, $\eta^2p = 0.24$).

The transition probabilities towards and from microstate D were also different between males and females. As indicated in Fig. 2.2, this was due to an increased transition probability from microstates C to D ($p = 1E-10$, $d = 0.6$), but also from D to C ($p = 8.6E-11$, $d = 0.5$) in males. With age, and across both sexes, the maturational trajectories of D–C and C–D transition pairs show a significant increase in transition probability from adolescence to adulthood (Fig. 2.1).

4. Discussion

The findings of this study are in line with the developmental changes shown by Koenig and colleagues (Koenig et al., 2002) and extend it by revealing sex-specific trajectories of the duration of microstate C and the occurrence of microstate D. In summary, microstate D occurred more frequently in males than in females, whereas the duration of microstate C was prolonged in females compared to males. When looking at sex differences for each age range, we found that the increased occurrence of microstate D in men was significant for all age groups except during adolescence (14–19). Concerning microstate C, we found a particular development trajectory in males showing two stages of increased duration, from childhood to adolescence, and from young to mid adulthood. Interestingly, the duration of class C decreased from adolescence to young adulthood in males but not in females. This opposite effect led to the significant sex difference in microstate C duration in young adulthood (20–30). Conversely, microstate D became more frequent in adulthood for both sexes. Furthermore, sex differences were also observed by changes in the pattern of their transitions. Independent of age, females exhibited a transition pattern to and from state C in relation to A and B, whereas males showed more C–D and D–C transitions than females. Finally, at older age (61–87 years), the duration of microstate C decreased, which was particularly pronounced in females.

The pattern of transitions from one microstate to another also changed with brain maturation and aging. While the C–A, A–C and C–B, B–C transitions decreased from adolescence to adulthood, the transitions from D–C, C–D increased. Moreover, a significantly decreased probability was noted with aging, for the D–C and C–D transition pairs.

Microstate classes A and B did not significantly differ between males and females (see Fig. 1 and Supplementary Fig. S1). Combined EEG-fMRI as well as EEG source imaging studies suggested that these two classes of microstates are related to temporal and occipital activities, respectively, areas that are more involved in sensory processing (auditory and visual) (Custo et al., 2017; Britz et al., 2010; Milz et al., 2016). These networks are expected to reach maturation significantly earlier than higher order cognitive networks (Gogtay et al., 2004). Thus, one possible explanation why we did not find any sex difference in these two microstates could be that most maturational changes of the underlying networks occurred before the age of 6, the minimum age of participants here.

The functional significance of the microstates and the possible interpretation of these findings are discussed separately for microstate C and D in the following sections.

4.1. Microstate C

A combined EEG-fMRI study showed correlations of the time course of microstate C with BOLD activation in the dorsal anterior cingulate cortex, the bilateral inferior frontal cortices, and the insula (Britz et al., 2010). Functional MRI resting state studies attributed activation of these areas to the salience network which plays an important role in switching between central-executive function and the default mode resting state (Sridharan et al., 2008). Seeley and colleagues suggested that it's functional role consists in the integration of the internal (visceral, autonomic) and external sensory information to assess the homeostatic relevance of internal and external stimuli (Seeley et al., 2007). Other authors attributed these brain areas (anterior insula/frontal operculum, anterior cingulate) to the cingulo-opercular system implicated in maintaining alertness for salient stimuli (Coste and Kleinschmidt, 2016). Several studies indicated that the development of structural and functional connectivity within this network is associated with better cognitive performance (Squeglia et al., 2013; Dwyer et al., 2014; Smith et al., 2014; Blakemore, 2008).

If we attribute these putative functional roles to microstate C, our finding that the duration of microstate C was increased in females might

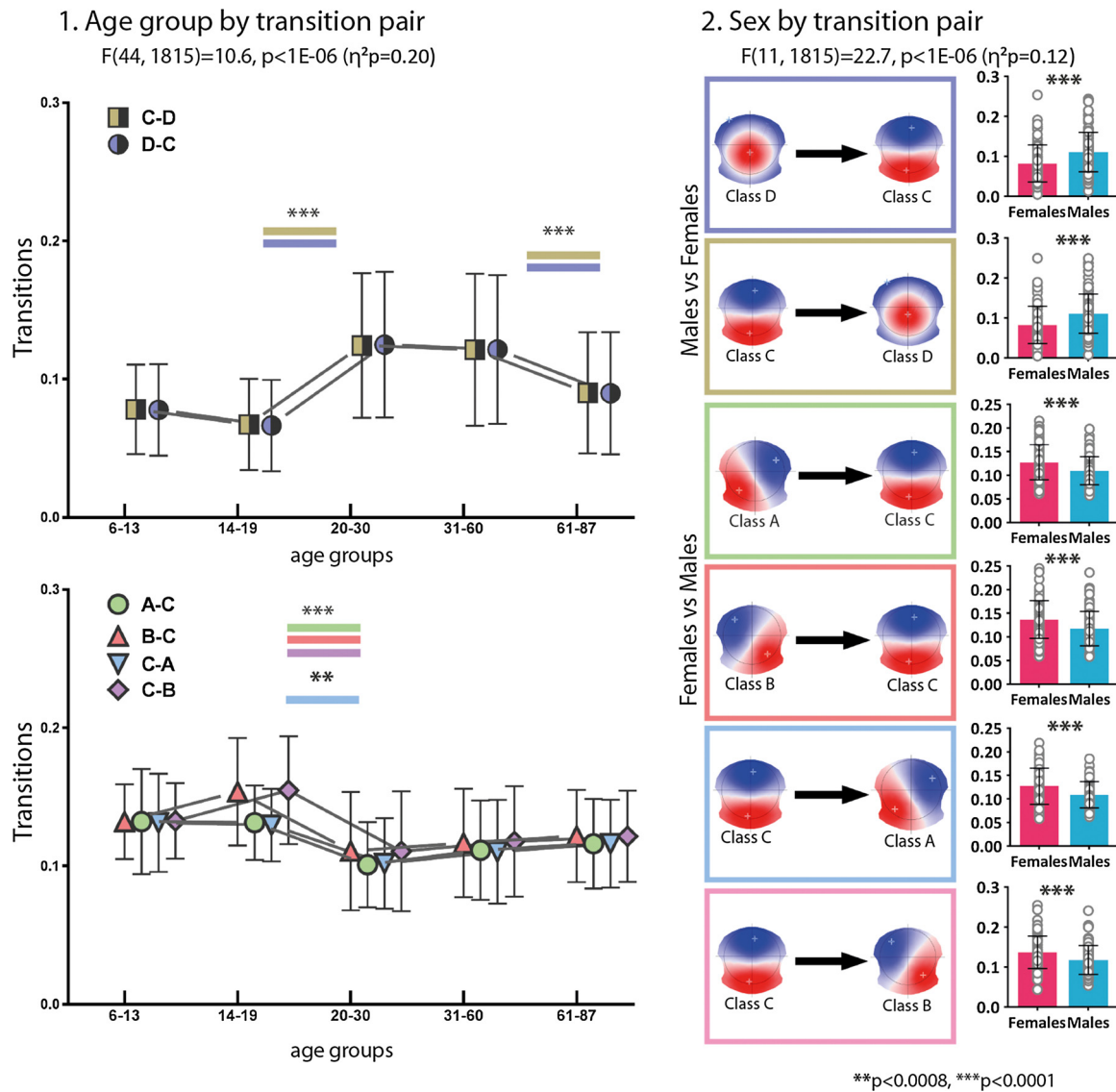


Fig. 2. (1) Age by microstate transition results are shown on left part of the graph. Asterisks above colored bars depict significant post-hoc *t*-tests. (2) The same transition pairs are shown in the right panel, this time indicating significant sex differences. Sex by microstate transitions and significant post-hoc *t*-tests results are depicted by asterisks above standard deviation bars.

indicate that females at rest spend more time in salience processing and/or maintaining alertness than males, particularly in the age range of 20–30 years. One might also expect that females would perform better than males in cognitive tasks, which rely more on salience processing/alertness. While these hypotheses remain to be investigated, it is rather well accepted that there is a certain degree of sex based cognitive specialization sustained by different neuronal mechanisms (Rubia, 2013). Moreover, different neuronal mechanisms might also account for a similar cognitive performance. There is evidence that for cognitive control tasks like attention switching and interference inhibition, the performance, although similar at the behavioral level, was associated with enhanced parieto-temporal activation in male participants while in females it was related to enhanced activation in frontostriatal regions (Christakou et al., 2009). Increased functional connectivity in frontal and temporal regions was predominant in women and connectivity in occipital and parietal regions was more significant in men (Rubia et al., 2010), suggesting a connectivity pattern which relies more on the frontal cortex in females, and more on the parietal cortex in males. Moreover, these sex differences were found to vary significantly with age (Christakou et al., 2009; Rubia et al., 2010; Marsh et al., 2006). In females, the patterns of cortical activation were relying

more on the inferior frontal regions and were positively associated with age, leading the authors to conclude that this is reflective of a more mature functional activation of these regions in females and in line with converging evidence of structural development processes taking place earlier in females (Campbell et al., 2005; Giedd et al., 1999; Giedd and Rapoport, 2010; Lenroot and Giedd, 2010). Interestingly, a recent study on cerebral perfusion found that, compared to males, females showed increases in many widespread regions of the prefrontal and limbic cortices (Amen et al., 2017).

Direct source localization of EEG microstates confirmed the implication of frontal brain regions in the generation of microstate C (Custo et al., 2017; Pascual-Marqui et al., 2014), regions that were attributed to the anterior parts of the default mode network defined in resting-state fMRI. Recent discussion of the functional significance of the default mode network indicate a separation into an anterior and posterior network with a distinct functional significance (Damoiseaux et al., 2008; Lei et al., 2014). Xu and colleagues (Xu et al., 2016) suggested that the anterior regions of the default mode network are associated with self-referential mental thoughts, while the posterior regions are associated with episodic memory retrieval. Attributing microstate C to the anterior default mode network would better explain the finding

that microstate C decreases during a serial subtraction task (Seitzman et al., 2017) and during visualization compared to rest (Milz et al., 2016). Thus, an alternative explanation would be that young (20–30 years) females at rest spend more time in self-referential processing than males.

An fMRI study by Weissmann-Fogel and colleagues (Weissmann-Fogel et al., 2010) claims that female's brains do not "rest" differently than male's brains in the SN, DMN and central executive network. The authors argue that the cognitive specialization between males and females might rather be related to the different strategies employed by each sex while solving cognitive task. However, the age ranges of both sexes in this study were grossly averaged from 21 to 50 years, thus, as our results demonstrate, important differences during maturation might have been overlooked, and might exhibit different temporal patterns of resting states at specific maturational stages. Our results are in line with many other studies showing evidence for sex differences in resting-state connectivity in regions such as the medial prefrontal cortex/orbito-frontal cortex (Jung et al., 2015), the amygdala (Dai et al., 2012; Kogler et al., 2016) and the insula (Li et al., 2012). In addition, females reveal stronger connectivity in anterior cingulate, fronto-temporo-cerebellar regions, and within cognitive control and memory related networks than males (Filippi et al., 2013).

With aging, a significant decrease of microstate C was found in females between 61 and 87 years. These results might reflect normal aging processes that involve degradation of functional and structural connections and might be also associated with cognitive functioning. A study looking at cognitive function in a population within the same age range shows that women perform better than men in cognitive speed and memory tasks (van Exel et al., 2001). Relatively few studies have shown that aging can differentially affect connectivity measures for the two sexes (Zuo et al., 2010; Agcaoğlu et al., 2015; Scheinost et al., 2015; Goldstone et al., 2016), however, the results of these studies might also be confounded by motion differences between males and females, young and old participants (Power et al., 2012; Satterthwaite et al., 2012).

4.2. Microstate D

In the combined EEG-fMRI study of Britz et al. (2010), microstate D was correlated with BOLD signal in the dorsal and ventral areas of frontal and parietal cortex of the right hemisphere. Hence, microstate D has been related with the attention network revealed by ICA analysis of the fMRI (Britz et al., 2010). Similar localization of the sources of microstate D has been found using EEG source localization (Custo et al., 2017). In addition, compared to females, males experienced increase in functional connectivity in parietal and occipital regions during resting (Filippi et al., 2013).

Furthermore, evidence of enhanced microstate D during attention allocation on a mental arithmetic task has been found when compared to rest activity (Seitzman et al., 2017). Additionally, microstate D has been shown to be reduced in mental states with reduced attention such as hypnosis (Katayama et al., 2007), sleep (Brodbeck et al., 2012) and acute periods of hallucinations (Kindler et al., 2011).

Our results show a significant increase of the occurrence of microstate D from adolescence to adulthood. The putative relation of microstate D to the attentional network fits well with evidence on developmental changes of attentional processes. For example, Rubia et al. (2010) showed that with increasing age, speed in a visual-spatial odd-ball task was traded for accuracy which was interpreted as indicative of more attentional and less impulsive activity in adult subjects (Rubia et al., 2010). This was associated with progressively increased activation in lateral fronto-striatal and temporo-parietal brain regions, typical areas of selective attention.

Here we found a general increased occurrence of microstate D in males compared to females and these results might be in line with the fMRI literature which consistently describes increased prefrontal

activation in females and increased parietal activation in males during cognitive tasks of working memory, mental rotation, cognitive switching and interference inhibition (Christakou et al., 2009; Bell et al., 2006; Garavan et al., 2006; Goldstein et al., 2005; Thomsen et al., 2000; Weiss et al., 2003). In addition, behaviorally, males outperform females in cognitive tasks that rely on visual-spatial processing, especially mental rotation tasks (De Luca et al., 2003; Weiss et al., 2003), tasks that have been shown to selectively activate parietal areas in the right hemisphere (Pegna et al., 1997).

4.3. Relevance of these findings and relation to clinical observations

The effect sizes of sex differences in cognitive abilities are moderate, and evidence from meta-analyses suggests that males and females have more psychological similarities than differences (Hyde, 2005). Similarly, sex differences found in this study on EEG microstates have rather moderate effect sizes for temporal parameters, despite the substantial number of subjects included in the study. Interestingly, larger effect sizes of sex differences were found on transition probabilities, pointing towards different patterns of information processing. However, an important aspect of sex differences was addressed here, namely how these differences behave with brain maturation and aging. While some of these differences were more stable during maturation (class D occurrence increased in males), the duration of microstate C was increased in females mostly during young adulthood. These results might be essential in better understanding sex specific prognosis, prevalence and risk of several developmental and neurodegenerative diseases.

Many studies investigated changes in EEG microstates in neuropsychiatric diseases (for a review see Khanna et al., 2015) such as schizophrenia, schizotypy, fronto-temporal dementia, Alzheimer's disease, depression, panic disorders or Tourette syndrome (Khanna et al., 2015). A recent meta-analysis on microstates in schizophrenia (Rieger et al., 2016) revealed that microstate C enhancement and microstate D reduction were most consistently affected in schizophrenia with considerable effect sizes. The opposite effects on microstate C and D indicate that these two states are in balance in the resting healthy brain and that part of the schizophrenic symptoms might be due to an imbalance between attentional and salience-related processes. Our study shows that these two microstates undergo significant changes between adolescence and young adulthood, in the age where the risk to develop schizophrenia is particularly high (Gogtay et al., 2011). In addition, the particular developmental trajectories of males going through different stages of microstate C duration maturation to young adulthood might be related to their enhanced risk to develop schizophrenia. State C abnormal temporal pattern dynamics were also observed in adolescents suffering from a genetically increased risk to develop schizophrenia (Tomescu et al., 2014; Tomescu et al., 2015). Moreover, recent studies show that these changes are reversible in schizophrenia patients by successful treatment of the symptoms either by antipsychotic medication (Kikuchi et al., 2007) or by intensive rTMS therapy (Sverak et al., 2017). In this recent study, rTMS was applied over the left dorso-lateral prefrontal cortex (DLPFC) in schizophrenia patients with successful downregulation of the symptoms and microstate C presence after stimulation.

The result of decreased class C microstate duration with healthy aging (mean age 71) found in this study might be important in understanding cognitive decline. One study showed that fronto-temporal dementia patients (mean age 68) show a greater decline of the same state, C, when compared with healthy aging individuals (Kanda et al., 2013). Moreover, the structural and functional deficiencies in fronto-temporal dementia are localized in the main nodes of the higher cognitive networks such as the default mode, salience and central executive network. For example, structural atrophy of the fronto-insular cortex as well the functional connectivity of these regions, as part of the salience network, were associated with severity of dementia symptoms (Zhou et al., 2010; Seeley, 2008).

4.4. Conclusions and future directions

This study conducted on a large dataset of subjects constitutes a normative base for future studies. Based on this dataset, we have shown that the temporal structure and dynamics of EEG microstates at rest undergo sex specific reconfigurations with brain development and aging that expand on the structural and functional connectivity results of the resting state literature. Moreover, this study provides further support on sex specific network activity patterns, which should be taken into account by future work.

Furthermore, the results of this study might be essential in better understanding sex specific prognosis, prevalence and risk of several developmental and neurodegenerative diseases. Future studies should include a longitudinal design and should also include a younger age group (neonates to 6 years), which is missing in the current study. An interesting question for future studies would be to investigate whether the modulation of sex hormone changes during development affects microstate parameters during rest. A study on processing of emotional words showed that pre-stimulus EEG microstates parameters vary with changes of sex hormone in women (Cacioppo et al., 2013). Finally, to better understand how these changes are related to cognitive development and aging, future work should include multimodal imaging (fMRI and EEG), as well as cognitive and behavioral measures in a larger sample across the lifespan.

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Appendix A. Supplementary data

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