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Sex differences in neurodevelopmental and common mental disorders examined from three epidemiological perspectives

Short title: Alternative perspectives on sex differences in CMD

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Abstract

Sex differences in neurodevelopmental and common mental disorders are a ubiquitous, well-known, though poorly understood phenomenon. This study examined the issue from three epidemiological perspectives: congruence in age of onset, distribution of sex-ratios with respect to age of onset and similarity of comorbidity and risk factor patterns. The analysis was based on data from the population-based PsyCoLaus study (N=4,874, age 35-82 years). Congruence in age of onset and distribution of sex-ratios were examined with the Mann-Whitney test and cluster analysis. The similarity of comorbidity and risk factor patterns, which were represented by 35 variables, was assessed with the Jaccard coefficient and, after factor analysis, with Tucker's congruence coefficient. While age of onset parameters differed little by sex, the sex ratio varied markedly both in early and in late onset disorders. Moreover, the Jaccard coefficients for most disorders indicated that the similarity of comorbidity and further association patterns was low. Similarly, Tucker's congruence coefficient remained below the range of fair similarity in all factor combinations. In sum, sex differences in common mental disorders were impressively reflected by diverging sex ratios and comorbidity / risk factor patterns. This outcome supports the notion that most mental disorders need a sex-specific etiopathogenetic understanding.

Key words: mental disorders, neurodevelopmental disorders, sex differences, sex ratio, age of onset, similarity index

1. Introduction

Sex differences in neurodevelopmental (ND) and common mental disorders (CMD) represent basic and relevant information for researchers and clinicians. Nevertheless, this remains one of the least understood topics in psychopathology. If sex differences were strong, the implications would be far reaching. For instance, research on etiopathogenesis that failed to differentiate between male and female subsamples would have produced mostly noisy results. Also, many findings from animal-based research, which typically relies on male animals (Beery and Zucker, 2011), could not be generalized.

It is well known that the sex ratio in common mental disorders shows a higher prevalence in women than in men, whereas neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD), tend to be more prevalent in boys than in girls (Kessler et al., 2005). Researchers have tackled this contrast from different perspectives. Evolutionary psychology / psychopathology has associated sex differences with developmental challenges that are different in young males and females (Del Giudice, 2016; Ellis et al., 2012). Biological researchers have discussed the role of adrenal hormones (Byrne et al., 2017; Del Giudice et al., 2009) and sex hormones in the etiopathogenesis of ND/CMDs (Li and Graham, 2017; Lockshin, 2010). One CMD supporting this notion is depression: higher prevalence rates in women do not appear until puberty (Angold and Costello, 2006). However, the contrast might reflect too strong a simplification. The susceptibility period and the onset of most neurodevelopmental disorders with male preponderance (autism, ADHD, stuttering) are supposed to occur before the onset of adrenarche. Moreover, female preponderance in anxiety disorders paradoxically also occurs in disorders starting before puberty, e.g. separation anxiety (Silove et al., 2015), and girls were found to react more strongly than boys to threats of child abuse, which is a major risk factor for ND/CMD (Cooke and Weathington, 2014). Conversely, there are also disorders of young adulthood, such as schizophrenia, with a male preponderance. In the end, each

susceptibility period might imply sex-specific risk factors, sex-specific comorbidities and, possibly, sex-specific etiopathogenetic mechanisms in ND/CMD.

The aim of this study was to further scrutinize sex differences in ND/CMD using a comparative epidemiological approach. The study combined three basic parameters – sex-ratios, age of onset (AoO), and comorbidity / risk factor patterns of ND/CMD – as a novel aspect. As yet, a systematic comparison of sex-specific results using these different perspectives has not been conducted.

2. Methods

2.1. The PsyCoLaus sample

The database for this study stems from PsyCoLaus, a large population-based epidemiological study of mental health in the city of Lausanne (Switzerland). The survey methodology of PsyCoLaus has been detailed elsewhere (Preisig et al., 2009). Briefly, the cohort data were collected in 2003-2006 and, within a follow-up survey, in 2009-2012. The sample comprised 4874 participants (2264 men and 2610 women) within an age range of 35 to 82 years. Information on ND/CMD and other comorbidities and risk factors was collected using the French version (Preisig et al., 1999) of the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) in which the anxiety sections were enriched using information from the Schedule for Affective Disorders and Schizophrenia - Lifetime and Anxiety Disorder version (SADS-LA) (Endicott and Spitzer, 1978) for the French version (Leboyer et al., 1991). The figures represent lifetime prevalence data. Information on age of onset was provided for each disorder. Ages below three years or answers such as "ever since I can remember" were randomly assigned a value between three and five for the age of onset and then rounded.

The Institutional Ethics Committee of the University of Lausanne approved the CoLaus|PsyCoLaus study. All participants signed written informed consent forms after receiving a detailed description of the study's goal and funding.

The following disorders were excluded from the analysis because of their strong dependence on age-related environmental and cultural factors: post-traumatic stress, eating and substance use disorders. Moreover, few individuals had schizophrenia and other psychotic disorders, so these were also excluded. Specific phobias were categorized into three subtypes, namely animals,

other than animals and a mixed group with both an animal and another specific phobia (Ajdacic-Gross et al., 2016)

To determine sex-specific association patterns, 35 risk factors and comorbidities were included in the analysis. They comprised, in addition to ND/CMDs, the comorbidities stuttering, tics, migraine, ulcer, irritable bowel syndrome, urinary tract infections, hay fever, asthma, urticaria, eczema, drug allergies, fever blister (herpes simplex), acne, psoriasis, interparental violence, fear of punishment by parents and trauma before the age of 10.

2.2. Statistical analysis

AoO comparisons between men and women across ND/CMDs were conducted with the Mann-Whitney U test. A k-means cluster analysis was used to split the median AoOs into clusters. Odds ratios were used to represent the sex ratios (women:men). To assess the similarity of comorbidities and association patterns across sex, the Jaccard coefficient was applied to significant bivariate associations between each ND/CMD and other disorders / risk factors. This coefficient represents the proportion of joint hits across sex related to all hits (i.e., all comorbidities and associations found either in males or in females). Joint absences of hits are excluded from the calculation. A value of 1 indicates perfect similarity, whereas 0.33 is reached if one half of the associations in men and one half in women are shared (on condition that the number of significant associations in men and women is the same). Finally, the 35 risk factors and mental disorders were submitted to a factor analysis in men and women and the corresponding factors were compared with Tucker's congruence coefficient.

The analyses were conducted using SPSS (IBM, version 23). The factor analysis was carried out in Mplus (Version 7.4) with the EFA (exploratory factor analysis) procedure applied on

categorical variables. Tucker's congruence coefficient (CC) was calculated based on factor loadings after Promax rotation following the formula discussed in (Lorenzo-Seva and ten Berge, 2006).

3. Results

The distribution of the ND/CMDs across their AoO and sex ratios is shown in Table 1 and Figure 1. The median AoOs ranged from 5 years (y) for ADHD to 34 y for major depressive disorder. K-means analysis yielded a three-cluster solution for PsyCoLaus with centers at 6.7 y, 17.2 y and 29.2 y (see vertical lines in Figure 1). The large clusters were related to childhood onset (n=8) and adulthood onset (n=6), respectively, whereas an intermediate cluster (n=3) was related to adolescence onset.

The AoOs were mostly similar in men and women, although they were often slightly delayed in men. The Mann-Whitney U test yielded significant differences only for major depressive disorder (AoO 34:36 y in women:men) and mixed specific phobias (7:10 y).

(Table 1 about here)
(Figure 1 about here)

The sex ratios were highest in animal phobias, mixed specific phobias and agoraphobia (ORs~3), and lowest in conduct and bipolar 1 disorder (ORs<0.5). The heterogeneity of sex ratios appeared to be greatest in the early onset cluster, followed by the adulthood onset cluster; it remained small in the adolescence onset cluster (ORs in the range of 1.2-1.4).

In similarity analysis based on comorbidities with ND/CMD and associations with risk factors (see Figure 1), the Jaccard coefficients only exceptionally exceeded a high value (e.g., separation anxiety disorder, overanxious disorder, agoraphobia, depression). In most other disorders, the coefficients were around 0.33 or below, indicating more differences than similarities between the two sexes.

Finally, the ND / CMD and the risk factors were classified in factor analyses separately for men and women in order to calculate Tucker's CC. The factor loadings derived from the three-factor solution after Promax rotation are listed in Table 2. In both genders, these three factors are determined by the same variables: atopies, internalizing and externalizing disorders. The CC for the corresponding factors were 0.63 (F1(m) / F3(f)), 0.82 (F2(m) / F2(f)) and 0.76 (F3(m) / F1(f)), which is below the range of fair similarity (0.85-0.94) as determined by Lorenzo-Seva and ten Berge (2006).

(Table 2 about here)

4. Discussion

This study examined sex differences in ND/CMD from three different perspectives: the AoO, the sex ratio across AoO, and the congruence of comorbidities and risk factor patterns. It obtained three different answers, each with different implications.

First, as in previous studies (Kessler et al., 2005; Lijster et al., 2017), there was a considerable variation in AoOs. Typically, the AoOs were slightly lower in women than in men, but these differences were mostly negligible. Thus, the AoO did not suggest any noteworthy sex differences. However, as represented by three AoO clusters in this study, the AoOs in ND/CMD mirror stages of sensitive developmental periods (Andersen and Teicher, 2008) and stages of critical brain development (Jones, 2013), i.e. in infancy and childhood as well as during and after puberty / adolescence.

Second, the sex ratios varied considerably across the whole AoO range, thus contradicting the preliminary impression from the AoO comparisons. Curiously enough, the greatest spread is in early onset disorders (ND and early anxiety disorders), that is, before the onset of major hormonal changes in adrenarche and early puberty. This challenges the most common interpretations of the sex ratios, which refer to the impact of hormones (Byrne et al., 2017; Del Giudice et al., 2009; Kaestle, 2015; Li and Graham, 2017; Rubinow and Schmidt, 2019). Thus, the sex ratios indicate that explanatory concepts should also be considered that are not – or only indirectly – associated with hormonal changes.

Third, the sex-specific dissimilarities were additionally accentuated when comorbidity and risk factor patterns were explored. The similarity indicator yielded mostly modest coefficients. Given that most of the ND/CMDs represent heterogeneous entities, these coefficients tend even to overestimate the similarity of male and female patterns. Dissimilar sex-specific comorbidity

and risk factor patterns suggest that the etiopathogenetic mechanisms in ND/CMDs in men and women are predominantly incongruent for most disorders. Up to now, this perspective has gained too little attention, even though sex-differences have been discussed for many disorders (Rutter et al., 2003).

Not only the brain (Kaczkurkin et al., 2019; Nelson and Lenz, 2017; Schwarz and Bilbo, 2012) but also other systems relevant to ND/CMDs, such as the immune, hormonal and metabolic systems, develop in a sex-specific manner. Thus, sex differences in ND/CMDs cannot be viewed as a surprise, but they do call for appropriate responses regarding future research. Dissimilar sex-specific comorbidity and risk factor patterns thus suggest that the understanding of the pathogenesis of ND/CMDs should start with the basic assumption that most mechanisms are sex-specific, although some may not be (Darnall and Suarez, 2009). If the differences actually were small or negligible, it would be easy to unify theoretical concepts, pool research data, apply adjustment instead of stratification in statistical analysis.

This study has several limitations. While PsyCoLaus relies on a large epidemiological sample, the data analyzed in this study were collected retrospectively. Thus, the study shares the limitations of studies based on self-reporting data, including recall-bias and telescoping effects (Kaestle, 2015). The concept of telescoping effects suggests that recalling tends to shift recent events more towards the past, whereas remote events tend to be shifted more towards the present time. Thus, the AoO might have been displaced by up to three years higher than the real age of onset (Bright and Soulakova, 2014). Furthermore, women tend to report symptoms and diseases more frequently than men (Ajdacic-Gross et al., 2006), so that the sex ratios with a female preponderance might be overrated to some extent. Due to limited recall in very early childhood, the lower range of the age of onset was limited to three years (Bauer, 2015). Finally, recall outcomes are assumed to differ according to the severity and duration of symptoms.

Disorders depending on environmental and cultural factors (post-traumatic stress, eating and substance use disorders) and disorders with small Ns (schizophrenia and other psychotic disorders) were excluded from the analysis. As to the comorbidities, the selection included the most frequent neurodevelopmental and mental disorders. As to risk factors, the selection was limited on the one hand by the life-time perspective on ND/CMDs and, on the other, by the range of self-reported information covered in the DIGS. Notably, the range of psycho-social risk factors was limited. Among other potential risk factors that were not considered in this analysis are obesity and metabolic syndrome markers, life events and social rejection, to name but a few.

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Conflict of interest

None.

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Legends

Figure 1:

Age of onset and sex ratios of neurodevelopmental and mental disorders in PsyCoLaus (with frequencies and the Jaccard coefficient in brackets); vertical lines indicate the centers of the three age-of-onset clusters

Abbreviations:

ADHD: attention deficit hyperactivity disorder; SAD: separation anxiety disorder; OAD: overanxious disorder; ODD: oppositional defiant disorder; CD: conduct disorder; SOC: social phobia; SPPa: specific phobia / animals; SPPo: specific phobia / other than animals; SPPm: specific phobia / mixed animals and other subtypes; OCD: obsessive compulsive disorder; GAD: generalized anxiety disorder; AGO: agoraphobia; PAN: panic; DYS: dysthymia; MDD: major depressive disorder; BIP1: bipolar disorder type 1; BIP2: bipolar disorder type 2

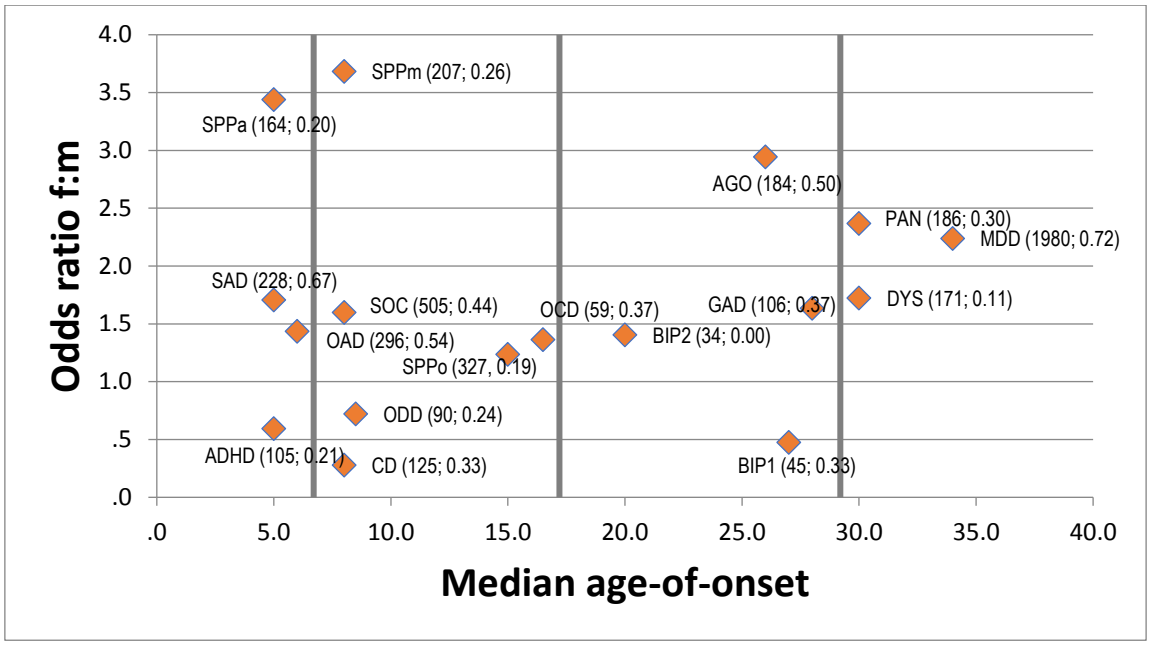
Odds ratio f:m
Median age-of-onset
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
.0
.0
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
SPPm (207; 0.26)
SPPa (164; 0.20)
AGO (184; 0.50)
PAN (186; 0.30)
MDD (1980; 0.72)
SAD (228; 0.67)
SOC (505; 0.44)
OCD (59; 0.37)
GAD (106; 0.37)
DYS (171; 0.11)
OAD (296; 0.54)
BIP2 (34; 0.00)
SPPo (327, 0.19)
ODD (90; 0.24)
ADHD (105; 0.21)
CD (125; 0.33)
BIP1 (45; 0.33)

Table 1:

Neurodevelopmental and common mental disorders in PsyCoLaus: frequencies, sex ratios, median age of onset (AoO), Jaccard coefficients for similarity of comorbidity and association patterns; sorted by median AoO

	frequencies			odds ratio	median AoO			M-W test	Jaccard
	total	men	women	f:m	all	men	women	p-value	coefficient
ADHD	105	62	43	0.6	5	5	5	0.88	0.21
separation anxiety disorder	228	78	150	1.7	5	5	4	0.24	0.67
pure animal specific phobia	164	34	130	3.4	5	6	5	0.28	0.20
overanxious disorder	296	113	183	1.4	6	7	6	0.08	0.54
conduct disorder	125	94	31	0.3	8	8	8	0.63	0.33
social phobia	505	183	322	1.6	8	8	7	0.81	0.44
mixed specific phobia	207	41	166	3.7	8	10	7	0.01	0.26
oppositional defiant disorder	90	49	41	0.7	8	9	8	0.67	0.24
pure other specific phobia	327	136	191	1.2	15	15	13.5	0.28	0.19
obsessive compulsive disorder	59	23	36	1.4	16.5	19	15.5	0.51	0.37
bipolar II	34	13	21	1.4	20	20	20	0.70	0.00
agoraphobia	184	43	141	2.9	26	29	25	0.14	0.50
bipolar I	45	29	16	0.5	27	26	31.5	0.41	0.33
generalized anxiety disorder	106	37	69	1.6	28	30	28	0.77	0.37
panic	186	51	135	2.4	30	35	30	0.07	0.30
dysthymia	171	58	113	1.7	30	29	31	0.87	0.11
major depression	1980	688	1292	2.2	34	36	34	0.01	0.72

Table 2:

Factor analysis: loadings after Promax rotation, by sex

	men			women		
	factor 1	factor 2	factor 3	factor 1	factor 2	factor 3
stuttering	0.201	0.036	0.173	0.277	-0.023	0.177
tics	0.007	0.236	0.127	0.186	0.108	0.223
ADHD	0.132	0.294	0.208	0.515	0.213	-0.137
conduct disorder	0.066	-0.148	0.779	0.516	-0.023	-0.088
oppositional defiant disorder	-0.016	-0.160	0.841	0.428	0.141	-0.065
separation anxiety disorder	-0.128	0.413	0.194	0.113	0.437	0.042
social phobia	-0.051	0.478	0.022	0.075	0.375	0.086
overanxious disorder	0.004	0.471	0.241	0.185	0.423	0.090
specific phobia (only animals)	-0.172	0.150	-0.097	-0.068	-0.003	0.213
specific phobia (mixed form)	-0.190	0.394	0.029	0.044	0.401	0.119
specific phobia (no animals)	0.090	0.308	-0.141	0.083	0.233	0.030
OCD	0.061	0.464	-0.039	0.417	0.317	-0.158
agoraphobia	-0.073	0.703	-0.092	-0.192	0.878	-0.072
generalized anxiety disorder	-0.053	0.665	-0.130	0.214	0.376	-0.010
panic disorder	-0.016	0.656	-0.017	-0.113	0.831	-0.086
PTSD	-0.004	0.309	0.190	0.442	0.304	0.044
bipolar 1 disorder	-0.179	0.163	0.276	0.633	-0.369	0.177
bipolar 2 disorder	-0.287	0.092	0.057	0.578	-0.338	0.044
major depression disorder	0.155	0.491	0.056	-0.094	0.525	-0.001
dysthymia	0.020	0.050	0.084	0.111	0.151	-0.099
migraine	-0.061	0.216	0.036	-0.028	0.290	0.169
interparental violence	0.028	-0.058	0.690	0.742	-0.022	-0.115
fear of parental maltreatment	0.122	0.082	0.717	0.761	0.083	-0.051
trauma below age of 10	-0.156	0.138	0.263	0.557	0.006	0.062
peptic ulcer	-0.215	0.208	0.088	0.254	0.052	0.145
irritable bowel syndrome	0.160	0.365	-0.129	0.067	0.221	0.246
urinary tract infection	0.038	0.406	-0.108	0.091	0.054	0.268
hay fever	0.664	-0.004	0.099	-0.093	-0.167	0.667
asthma	0.712	0.038	0.054	-0.116	-0.063	0.701
eczema	0.238	0.179	0.072	-0.026	0.036	0.445
urticaria	0.233	0.195	-0.078	0.001	0.012	0.645
drug allergy	0.145	0.188	0.069	-0.005	-0.013	0.404
fever blisters	0.021	0.231	0.028	0.008	0.126	0.161
acne	0.073	0.303	-0.196	0.067	-0.011	0.141
psoriasis	-0.139	0.129	0.085	0.133	0.083	0.011

Note:

ADHD: attention deficit hyperactivity disorder, OCD: obsessive compulsive disorder, PTSD: post-traumatic stress disorder