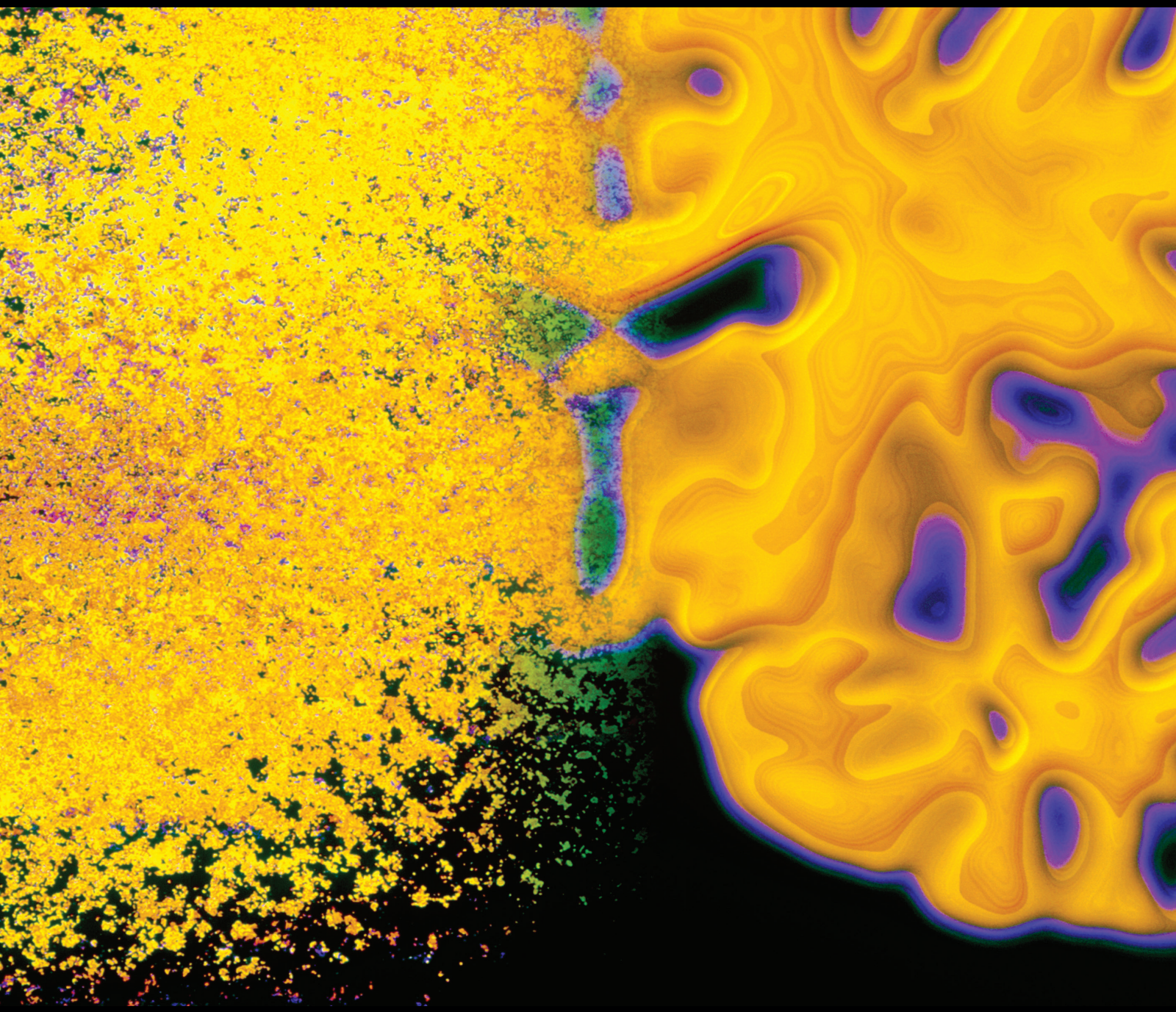
Behavioural Neurology

Sex Differences in the Study of Neurological Illnesses

Guest Editors: Hrayr Attarian, Jan Brandes, Rima Dafer, Elizabeth Gerard, and Barbara Giesser



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Editorial

Sex Differences in the Study of Neurological Illnesses

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There are clear sex based neurophysiological differences in brain structure and function. These impact both healthy individuals and those with neurological and psychiatric disorders. It is well documented that these diseases affect women differently from men. Many of these sex differences remain unknown and underrecognized. In addition, hormonal changes and fluctuations during a woman's lifespan are significantly more numerous and more complex than in men. These hormonal changes can impact the pathogenesis and the clinical presentation of neurological illness as well as a woman's response to treatment. There are definite sex and gender differences in prevalence of various neurological illnesses, in the incidence of psychiatric comorbidities, and in the therapeutic responses to various pharmacological and nonpharmacological interventions.

For instance, Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and other neurodegenerative illnesses have different prevalence and distinct presentation in women compared to men. Depression, both on its own and as a comorbid condition with neurological illnesses, has a gender specific presentation, impact, and therapeutic response. Antiepileptic drugs and other neurological medications can interact with hormonal contraception causing unplanned pregnancies. Hormonal contraception can impact risk of stroke, and migraine headaches fluctuate throughout the menstrual period. There are reports of MS symptoms fluctuating in response to different phases of the menstrual cycle. Sleep disorders increase in pregnancy and menopause and can affect the health of mother and fetus in the former and significantly reduce quality of life in the latter. There are also complex issues of managing specific disorders such as migraines, epilepsy, restless legs syndrome, and multiple sclerosis (MS) in pregnancy. Last but not least stroke, the third cause of death worldwide, has very unique sex and gender based symptomatology and semiology.

Despite these distinctions, there is a dearth of research in specific aspects of neurology as it relates to women's health. Often in clinical trials the data is not specifically separated by gender.

We invited authors to submit original research, case series, case reports, or review papers that address this disparity of research in women and look into neurologic and behavioral sex based changes in healthy individuals, the specific pathophysiology of neuropsychiatric illnesses in women, epidemiological and health based social disparities, and the differential effect of therapeutic interventions in women.

After rigorous peer review we decided to include eight papers in this special issue. These cover gender differences in neurodegenerative diseases like AD and PD as well as sex specific interface of cognitive function and mood disorders. We also included articles on gender specific burden of MS care, sex differences in childhood neuroborreliosis, and behavioral symptoms in Prader-Willi syndrome. Lastly two intriguing contributions were also accepted for publication and these are on the role of estrogen deficiency in subarachnoid hemorrhage and the role of gender in sociosexuality of infidelity after traumatic brain injury.

In summary this special edition of this journal includes a wide range of papers addressing the sex and gender differences in neuropsychiatric pathophysiology and care. We

hope it will increase awareness of these sex and gender based variations in the presentation of neurologic illness and care in the medical community.

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Research Article

Gender Differences in the Behavioral Symptom Severity of Prader-Willi Syndrome

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Objectives. This study measured gender differences in Prader-Willi syndrome (PWS) in regard to the severity of behavioral symptoms. *Methods*. The Food Related Problem Questionnaire (FRPQ), the Aberrant Behavior Checklist Japanese Version, the Childhood Routines Inventory, the Pervasive Developmental Disorders Autism Society Japan Rating Scale, and Japanese ADHD-RS were administered to PWS patients (45 males aged 6 to 58 and 37 females aged 6 to 45). To examine the effects that gender and genotype have on the severity of each symptom, two-way ANOVAs were conducted. *Results*. Significant interactions were found only in regard to FRPQ scores, such as FRPQ total score ($F(1, 78) = 8.43$, $p < 0.01$). The FRPQ of male deletion (DEL) individuals was higher than that of female DEL and male mUPD. The FRPQ of male maternal uniparental disomy (mUPD) was lower than that of female mUPD. *Conclusions*. In terms of problem behaviors, routines, autistic behaviors, and hyperactivity, no significant differences were found. Food-related behaviors in DEL were more severe in males, although those in mUPD were less severe in males.

1. Introduction

Prader-Willi syndrome (PWS) is a genetic disorder caused by a loss of expression of the paternally derived genes on chromosome 15q11-13. The causes of this disruption include paternal deletion (DEL) of 15q11-13 and maternal uniparental disomy 15 (mUPD, when both copies of chromosome 15 are maternally inherited) [1]. As a neurodevelopmental disorder, PWS is associated with neonatal hypotonia, hypogonadism, hyperphagia, progressive obesity, and mild to moderate mental retardation [2]. The physical manifestations of PWS include short stature, small hands and feet, hypopigmentation, and craniofacial anomalies. Based on epidemiological surveys, the birth rate is estimated at around 1 in 25,000 [3].

The behavioral manifestations of this syndrome include hyperphagia [4, 5], temper tantrums [6], obsessive-compulsive behaviors [7, 8], repetitive and ritualistic behavior [9], self-injurious behavior [10, 11], autistic behaviors [12, 13], hyperactive/impulsive behaviors [14, 15], and psychiatric disorders [16]. Due to lack of specific drugs in controlling PWS-related behaviors, pharmacological treatment should

only be used with caution and in combination with behavioral management and psychiatric support [17].

In terms of population prevalence for people with Prader-Willi syndrome, the gender ratio is close to 1 : 1 [1, 18–20], including non-Western countries [21]. So far, however, there has been little research into gender differences in individuals with PWS in relation to behavioral symptom severity. One piece of data was presented by Dykens [22], who found that females are more inclined to pick their skin than males. Such gender difference in terms of skin picking was also found in individuals with nonspecific mental retardation [23]. When food-related behaviors were analyzed by both gender and genotype, female mUPD patients were found to be less severely affected than female DEL patients in terms of length of gavage feeding and a later onset of hyperphagia. This difference between mUPD and DEL was not found in male patients [24].

Aside from Prader-Willi syndrome, certain mental disorders show marked gender differences in the diagnosis rates. For example, unipolar depression is twice as common in women. In contrast, the prevalence of alcohol dependence is more than twice as high in men than in women [25]. The diagnosis of antisocial personality disorder is more than three times as high in men than in women. On the other hand, severe mental disorders such as schizophrenia and bipolar disorder are associated with no pronounced gender differences in terms of the prevalence rate [25]. Among neurodevelopmental disorders, autism spectrum disorders (ASD) have consistent male predominance ranging from 2.5 : 1 to 4 : 1 in individuals with autistic disorder and 9 : 1 in individuals with Asperger disorder [26–28]. Attention deficit hyperactivity disorder (ADHD) is more commonly diagnosed in males than females, with male-to-female ratios ranging from 4 : 1 to 9 : 1 [29]. Eating disorders, which are one of the most important psychiatric categories of the behavioral aspects of PWS, are more common among females than males in both anorexia nervosa and bulimia nervosa [30, 31]. Equally important is the fact that the reverse pattern of gender disparity is found in "subthreshold binge eating disorder" (0.6% women and 1.9% men) and that roughly comparable gender distribution is observed in the prevalence of "any binge eating" in women (4.9%) and men (4.0%) [32].

In terms of problems behavior in individuals with non-PWS mental retardation, findings regarding gender differences in Williams syndrome have been divided. Leyfer et al. [33], Pérez-García et al. [34], and Klein-Tasman et al. [35] did not find gender differences in psychiatric and problem behaviors. However, Porter et al. [36] found greater externalizing, somatic, affective, and conduct problems in girls. Also, Dykens [37] found that fearfulness was higher for girls than for boys. In the Down syndrome sample, problem behavior was more prevalent in boys than in girls [38]. By contrast, psychosis was predominantly seen in females with Down syndrome [39].

This study aims to explore gender differences in PWS in regard to the severity of behavioral symptoms. There are three inherent advantages in this study. Firstly, this is the only study of its kind in regard to gender differences in behavioral aspects of PWS, based on a large sample of the rare genetic disorder. Secondly, all subjects were recruited from a single institution and confirmed genetically with PWS using fluorescence in situ hybridization or the methylation test. Thirdly, all subjects with PWS were assessed by a single clinical psychologist (H.O.). Hence, the psychometrical data of this study can avoid the risk of interrater variability caused by participants being assessed by multiple assessors. At the same time, it should be noted that this single-center study has not only strength, but also weakness, because of sample selection bias and a small sample size.

2. Subjects and Methods

This study started upon receiving approval from the ethics committee of Dokkyo Medical University Koshigaya Hospital with which the authors were affiliated. After obtaining informed consent, the neurocognitive and behavioral assessment of each participant was carried out.

2.1. Subjects. Participants were 82 Japanese individuals with PWS recruited from a single location. The Department of Pediatrics, Dokkyo Medical University Koshigaya Hospital, was used for this purpose. All patients were diagnosed with PWS using fluorescence in situ hybridization or the methylation test. The participants consisted of 45 males (aged 6 to 58) and 37 females (aged 6 to 45), including 34 males and 25 females confirmed as having DEL involving 15q11-13 and 11 males and 12 females confirmed as having mUPD of chromosome 15 (Table 1). Psychotropic medications were prescribed to 16 out of 45 males and 9 out of 37 females.

2.2. Methods

The Assessment of Behavior. An extended battery of behavioral assessment was employed. In all cases, the psychologist (H.O.) involved in collecting data was blind to the genetic status of each patient.

2.3. Measures

2.3.1. Intellectual Ability. To measure intellectual ability, a Japanese version of the Wechsler Intelligence Scale [40–43] was administered.

2.3.2. Food-Related Behaviors. To assess the severity of food-related behaviors, the Food Related Problem Questionnaire (FRPQ) was administered. This is an informant-based questionnaire to assess eating behaviors in people with PWS, consisting of 16 items, with three subscales (preoccupation with food (P), impairment of satiety (S), and other food-related negative behaviors (N)). Examples of the questions are as follows: "How often does the person compare the size or content of their meal with others?" (P); "After a normal sized meal, how often does the person say they still feel hungry?" (S); and "If given the opportunity, how often would the person "help themselves" to food which they should not have?" (N). As Russell and Oliver [44] presented, the FRPQ has sufficiently robust psychometric properties to appraise the food-related problems in individuals with PWS.

Table 1: Patient characteristics.

	Total	Male	Female	DEL	mUPD	p value (t-test)	
						Gender groups	Genotype groups
Number (patients)	82	45	37	59	23		
IQ (mean ± SD)	49.3 ± 9.6	49.9 ± 9.3	48.2 ± 10.3	49.7 ± 9.8	44.6 ± 6.5	0.44	0.001*
IQ range	39–84	39–79	39–84	39–84	39–62		
Age (mean ± SD)	18.6 ± 9.4	19.7 ± 10.2	16.9 ± 8.0	19.0 ± 9.5	15.4 ± 7.6	0.11	0.017*
Age range	6–58	6–58	6–45	6–58	6–36		

* $p < 0.05$.

2.3.3. Aberrant Behaviors. To assess the degree of problem behaviors in individuals with PWS, the Aberrant Behavior Checklist Japanese Version (ABC-J) [45] was applied. It is a 58-item checklist which takes about 10–15 minutes to complete. There are five subscales: (a) irritability and agitation, (b) lethargy and social withdrawal, (c) stereotypic behavior, (d) hyperactivity and noncompliance, and (e) inappropriate speech. It was found that the ABC identifies salient features of mental illness in individuals with mental retardation [46], including autism spectrum disorder [47], and is an effective tool in measuring treatment response [46, 48].

2.3.4. Routine Behaviors. To measure the extent of routines, the Childhood Routines Inventory (CRI) was administered. This is a parent-report checklist of commonly occurring children's routines [49], consisting of 19 items, including 5 items for "just right behavior" and 5 items for "repetitive behavior." An example of the former is "Prefers to have things done in a particular order" and that of the latter is "Prefers the same household schedules or routines." It was found that the CRI is an effective tool in measuring the severity of routine behaviors in normal young children [49] and children with Down syndrome [50].

2.3.5. Autistic Symptomatology. Autistic symptomatology was assessed using the Pervasive Developmental Disorders Autism Society Japan Rating Scale (PARS) [51, 52]. This scale is a behavior checklist, developed as a screening questionnaire to determine pervasive developmental disorders (PDDs). When assessing adolescents and adults, 33 items for adolescents, partially shared by those for children, are applied for the evaluation of current autistic states. The PARS for adolescents is made up to five clinical subscores consisting of interpersonal skills (6 items), communication (7 items), obsession (6 items), problematic behaviors (11 items), and hypersensitivity (3 items).

2.3.6. Inattention and Hyperactivity/Impulsivity. The Japanese ADHD-RS [53] was administered to all participants. The ADHD-RS [54] obtains parent ratings regarding the frequency of each ADHD symptom based on DSM-IV criteria. The scale consists of 2 subscales: inattention (9 items) and hyperactivity/impulsivity (9 items). Parents are asked to state the degree to which they best describe the child's behavior over the previous 6 months. All items are scored on a 4-point Likert scale from 0 ("rarely or never") to 3 ("always or very often"), with higher scores reflecting higher degree of inattention and hyperactivity/impulsivity. The reliability and the validity of the Japanese ADHD-RS have already been established [53].

By means of a numerical coding system, all data were guarded under strict confidentiality and anonymity. The data were analyzed by SPSS 20.0J for Windows. The results are expressed as mean (SD and range). To examine the effect that gender and genotype have on the severity of behavioral symptoms, two-way analyses of variance (ANOVAs) were conducted. The two gender groups (male versus female) and the two genotypes of PWS (DEL and mUPD) were used as independent variables, and the behavioral scores were used as dependent variables.

3. Results

As Table 1 shows, the mean IQs in both males and females were slightly less than 50, with no statistical difference between both groups. These scores are more than 50 points under the normative population score of 100, indicating a considerable impairment in intellectual abilities. As far as genotypes are concerned, a statistically significant difference was found between DEL and mUPD, with higher scores in the DEL group [15, 55].

Table 2 shows the results in regard to the degree of behavioral symptoms of PWS individuals. In order to examine the effects that genders and genotypes have on the symptom's severity, two-way ANOVAs were conducted. The two gender groups and the two genotypes of PWS were used as independent variables, and the scores of the FRPQ, the ABC-J, the CRI, the PARS, and the ADHD-RS were used as dependent variables.

Statistically significant interactions between genders and genotypes were found only in regard to FRPQ scores: FRPQ total score ($F(1, 78) = 8.43$, $p < 0.01$), FRPQ-P ($F(1, 78) = 6.66$, $p < 0.05$), FRPQ-S ($F(1, 78) = 7.74$, $p < 0.01$), and FRPQ-N ($F(1, 78) = 4.04$, $p < 0.05$). On finding this, a Bonferroni procedure was performed to test the simple main effects.

In terms of the FRPQ total score, it was found that the score of male DEL was higher than that of female DEL ($F(1, 78) = 4.22$, $p < 0.05$); on the contrary, the score of male mUPD was lower than that of female mUPD ($F(1, 78) = 4.56$, $p < 0.05$). Besides, the FRPQ score of male DEL was found

Table 2: The FRPQ, ABCJ, CRI, PARS, and ADHD-RS scores and the results of two-way ANOVA using the two gender groups and the two genotypes.

	Total	Gender		Genotype		ANOVA interaction	
		Male	Female	DEL	mUPD	F	p
FRPQ total	34.4 ± 15.0	35.6 ± 15.3	33.0 ± 14.8	37.3 ± 14.6	27.0 ± 13.6	8.43	0.005*
FRPQ-P	9.3 ± 4.4	9.5 ± 4.5	9.0 ± 4.3	9.8 ± 4.4	8.0 ± 4.2	6.66	0.012*
FRPQ-S	15.4 ± 6.3	16.0 ± 6.1	14.8 ± 6.5	16.3 ± 6.1	13.3 ± 6.3	7.74	0.007*
FRPQ-N	9.7 ± 6.9	10.1 ± 7.1	9.2 ± 6.7	11.3 ± 6.8	5.7 ± 5.3	4.04	0.048*
ABCJ total	33.2 ± 29.4	34.3 ± 30.8	31.8 ± 27.9	30.7 ± 27.0	39.8 ± 35.2	0.91	0.344
ABCJ excitement	11.3 ± 10.2	12.0 ± 10.2	10.4 ± 10.2	11.2 ± 10.1	11.6 ± 0.6	1.20	0.277
ABCJ apathy	7.1 ± 8.0	6.6 ± 7.3	7.7 ± 8.9	5.8 ± 6.3	10.6 ± 10.7	2.16	0.145
ABCJ stereotype	2.1 ± 3.2	1.9 ± 2.9	2.3 ± 3.6	1.7 ± 2.7	3.2 ± 4.2	0.93	0.337
ABCJ hyperactivity	8.6 ± 9.2	9.5 ± 10.6	7.4 ± 7.1	8.1 ± 8.7	9.9 ± 10.7	0.06	0.812
ABCJ inappropriate	4.0 ± 3.2	4.2 ± 3.2	3.8 ± 3.3	4.0 ± 3.3	4.2 ± 3.0	0.27	0.603
CRI total	3.1 ± 1.6	2.8 ± 1.5	3.3 ± 1.8	3.1 ± 1.7	2.9 ± 1.6	0.38	0.542
CRI Fre	9.3 ± 5.8	8.0 ± 5.1	10.7 ± 6.2	9.7 ± 5.8	8.5 ± 5.8	0.84	0.364
CRI Jr	0.8 ± 0.8	0.8 ± 0.9	0.7 ± 0.8	0.9 ± 0.7	0.5 ± 1.0	0.85	0.363
CRI JrFre	2.1 ± 2.6	2.2 ± 2.8	2.1 ± 2.5	2.3 ± 2.0	1.7 ± 3.6	0.51	0.480
CRI Re	0.7 ± 0.6	0.6 ± 0.6	0.8 ± 0.7	0.7 ± 0.7	0.8 ± 0.6	0.16	0.687
CRI ReFre	2.1 ± 2.1	1.5 ± 1.5	2.7 ± 2.5	2.1 ± 2.3	2.2 ± 1.8	0.03	0.868
PARS child	9.8 ± 7.0	10.2 ± 7.7	9.2 ± 5.5	9.4 ± 6.6	11.3 ± 8.0	0.00	0.972
PARS adolescent and adult	17.0 ± 9.2	16.9 ± 9.4	17.2 ± 9.2	15.9 ± 9.1	21.6 ± 8.8	1.06	0.307
ADHD-RS total	4.9 ± 5.9	5.3 ± 6.7	4.1 ± 3.8	4.6 ± 5.7	5.7 ± 6.6	0.02	0.902
ADHD-RS inattention	2.9 ± 3.4	3.1 ± 3.8	2.5 ± 2.3	2.7 ± 3.0	3.5 ± 4.3	0.02	0.877
ADHD-RS hyperactivity/impulsivity	2.0 ± 3.1	2.2 ± 3.5	1.5 ± 2.2	1.9 ± 3.3	2.3 ± 2.5	0.16	0.687

* $p < 0.05$.
FRPQ: Food Related Problem Questionnaire; FRPQ-P: preoccupation with food, S: impairment of satiety, N: composite negative behavior; ABC-J: Aberrant Behavior Checklist-Community Japan Rating Scale; CRI: Childhood Routine Inventory; CRI Jr: just right behaviors, Re: repetitive behaviors, Fre: frequency/intensity score; PARS: Pervasive Developmental Disorders Autism Society Japan Rating Scale; ADHD-RS: ADHD Rating Scale.

to be higher than that of male mUPD ($F(1, 78) = 17.43$, $p < 0.01$).

In regard to the FRPQ subscores, the FRPQ-P (preoccupation) score of male DEL was higher than that of male mUPD ($F(1, 78) = 8.79$, $p < 0.01$). The FRPQ-S (satiety) score of male DEL was higher than that of female DEL ($F(1, 78) = 4.43$, $p < 0.05$) and was higher than that of male mUPD ($F(1, 78) = 11.32$, $p < 0.01$). The FRPQ-N (negativity) score of male DEL was higher than that of male mUPD ($F(1, 78) = 15.84$, $p < 0.01$) (Figure 1).

4. Discussion

To our knowledge, this study is the first attempt to compare a wide range of behavioral features of PWS between male and female groups. To examine the effect that genotypes as well as genders have on the severity of behavioral symptoms, two-way analyses of variance (ANOVAs) were conducted. Two gender groups and two genotypes of PWS were used as independent variables. Apart from food-related behaviors, no significant statistical differences were found between male and female in regard to other behavioral features, such as problem behaviors, routines, autistic symptoms, inattention, and hyperactivity. As a whole, male and female PWS patients seem to be more similar than different regarding PWS-related behavioral symptoms. In this respect, our data accord with previous reports, which found similarities, rather than differences, in behavior between male and female [56–58].

The two-way ANOVAs to examine the interaction between gender and genotype, followed by the Bonferroni procedure to test the simple main effects, showed the following: food-related behaviors of male DEL were more severe than those of female DEL, and on the contrary food-related behaviors of male mUPD were less severe than those of female mUPD. Thus, the reverse pattern of gender disparity between the two genotypes was found.

These data contradicted the recent report of Jauregi et al. [58], who found female dominant scores in only two among the twenty-two items of the Developmental Behavior Checklist for Adults: "irritability" and "distress over small changes in their routine or environment." Aside from these items, they did not find significant differences between male and female behaviors. At the same time, they found significant differences between DEL and non-DEL, such as "increase in appetite" with a higher score in DEL. Indeed, Dykens et al. [59] showed the lack of significant relations between food-related behaviors and genetic status. However, as the results suggest, the relationship between hyperphagia

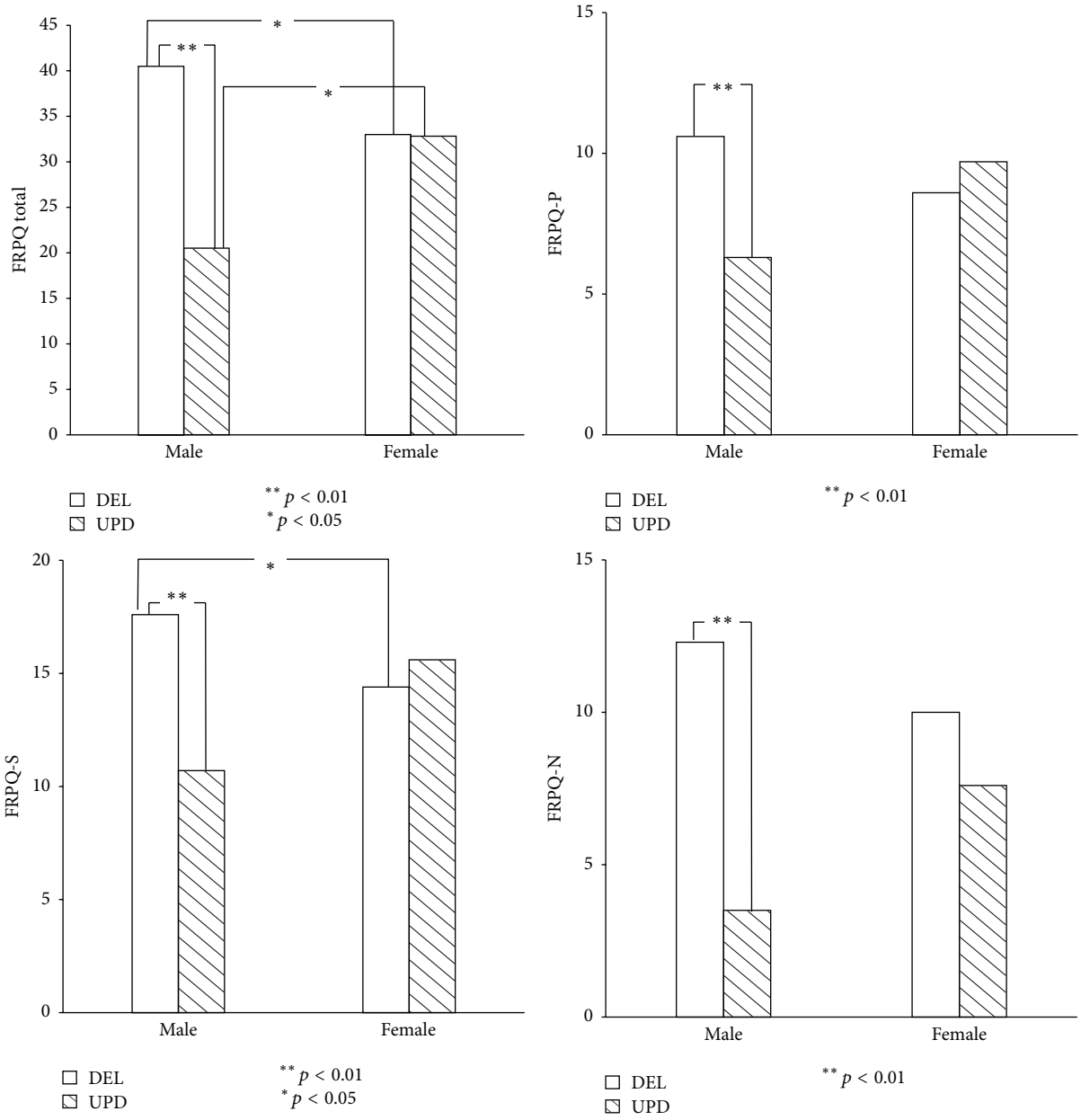

Figure 1: The effect of gender (male versus female) and genotype (DEL versus UPD) of PWS on the total score and preoccupation (P), impairment of satiety (S), and composite negative behavior (N) domains of FRPQ.

and genotype may be complicated by gender disparity. There seems to be a need for further investigation in terms of the impact of the gender differences on the relationship between genetic status, hyperphagia, and other behavioral symptoms.

It is evident that further methodological limitations exist in this study. First, the impact of biological changes in chronological adolescence was not considered. Unfortunately, the number of patients enrolled in this study was too small to analyze gender differences in the behavioral data in multiple age groups. According to Ogata et al. [15], there is a growing tendency for the autistic and impulsive behavioral problems, which are more severe in mUPD than in DEL that can manifest themselves later in adolescence. Likewise, gender differences in the behavioral symptom severity should take age, as well as genotypes, into consideration.

Second, this study did not encompass the entire range of psychiatric disorders relevant to gender differences in PWS. For example, it remains to be seen in regard to clinical categories whose rate is known to show striking gender differences. They include male-dominant disorders, such as alcohol dependence and antisocial personality disorder, and female-dominant ones, such as depression, anxiety, and somatic complaints [25]. Moreover, this study did not cover affective and psychotic disorders, in spite of the fact that

the PWS group was known to have higher rates of affective disorders with psychotic features [60]. Although little is known about gender differences, PWS individuals with a psychotic disorder showed a disproportionate number of mUPD patients [61]. A more comprehensive study is required to illuminate gender differences in the severity of various psychiatric categories in PWS.

Third, a future study should assess the influence of endocrinological factors including growth hormone therapy and diabetes on the behavioral aspects with PWS focusing on gender differences. Based on 35 Brazilian patients with PWS, Quaio et al. [62] demonstrated that growth hormone treatment considerably improved the control of weight gain and body mass index for female patients but no effect on either parameter in male patients. They suggested that in male patients the benefits of growth hormone treatment may have been overcome by other factors, such as food-intake behaviors. The relationship between the gender differences in the effects of growth hormone treatment and those in food-related behaviors is an area worthy of further exploration, because it could potentially throw a new light on the possibility of gender-specific hormonal treatment to PWS. Aside from food-related behaviors, another gender-specific hormonal treatment was conducted by Kido et al. [63]. They found that testosterone replacement therapy improved secondary sexual characteristics and body composition without adverse behavioral problems in male patients with PWS. Finally, due to a single-institution study that aimed at a rare genetic disorder, the size of sample is relatively small. For this reason, the male-female similarity regarding PWS-related behaviors in this study should be interpreted with caution.

Conflict of Interests

Kazutaka Shimoda has received research support from Shionogi & Co. Ltd., Eli Lilly Japan K.K., Yoshitomi Pharmaceutical Industries Ltd., Meiji Seika Pharma Co. Ltd., Eisai Co. Ltd., Pfizer Inc., GlaxoSmithKline K.K., Otsuka Pharmaceutical Co. Ltd., Daiichi Sankyo Co., and Takeda Pharmaceutical Co. Ltd. and honoraria from Kowa Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Meiji Seika Pharma Co. Ltd., Dainippon Sumitomo Pharma Co. Ltd., Ono Pharmaceutical Co. Ltd., GlaxoSmithKline K.K., and Eisai Co. Ltd. All other authors declare no biomedical or financial interests or potential conflict of interests directly relevant to the content of the present study.

Authors' Contribution

Masao Gito and Hiroshi Ihara managed this work and were equal contributors in writing the paper. Hiroyuki Ogata conducted the assessments. Masayuki Sayama drafted the figure. Nobuyuki Murakami, Toshiro Nagai, Tadayuki Ayabe, and Yuji Oto collected the samples. Toshiro Nagai is the leader of the PWS research project and Kazutaka Shimoda is the coordinator at department of psychiatry, Dokkyo Medical University School of Medicine.

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Research Article

Functional Performance and Associations between Performance Tests and Neurological Assessment Differ in Men and Women with Parkinson's Disease

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Background. Neurological assessment of a patient with Parkinson's disease (PD) is expected to reflect upon functional performance. As women are known to report more limitations even for same observed functional performance level, present study was designed to examine whether associations between neurological assessments and functional performance differ across genders. *Methods*. 14 men and 14 women with PD participated. Functional performance was assessed by measuring walking speeds on 10-meter walk test (10MWT) and by performing timed-up-and-go-test (TUG). Neurological assessment included Hoehn and Yahr Scale (HY), Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Schwab and England Activities of Daily Living Scale (S-E), and Mini Mental State Examination (MMSE). *Results*. In women with PD, Kendall's tau-b correlation analyses revealed significant correlations between functional performance tests and neurological assessment measures, with the exception in MMSE. No corresponding associations were found for men, although they demonstrated better functional performance, as expected. *Conclusion*. Men in similar clinical stage of the PD perform better on functional tests than women. Disease severity reflects upon functional performance differently in men and women with PD. Results indicate that when interpreting the assessment results of both functional performance and neurological assessment tests, the gender of the patient should be taken into consideration.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease diagnosed mainly based on clinical features. Several gender differences have been reported in symptomatology of PD. According to Haaxma et al. [1], women are older at the onset of the disease and are subject to tremor more often. Women experience nonmotor symptoms such as nervousness, sadness, depression, and constipation more often, whereas men suffer more from daytime sleepiness, drooling, and sex-related symptoms [2]. The information about symptoms is obtained in the form of a patient interview, questionnaires, and objective neurological assessments, which to date are generally not interpreted in a gender-specific context.

There is limited evidence on gender differences in motor performance of PD patients. Hass et al. [3] reported that male participants walk significantly faster, produce larger steps and stride lengths, have a faster cadence, and spend a greater percent of the gait cycle in swing-phase than women. According to Solla et al. [4], women with PD have a higher UPDRS instability score, whereas some studies have reported higher incidence of balance disturbances (e.g., on gait) in men with PD. Augustine et al. [5] found no differences between men and women in motor symptoms or in daily living.

To date, previous research in this field has overlooked the associations between clinical neurological assessment scales and functional performance. For a clinician working with patients with PD, it is important to know whether neurological assessment results are linked to functional performance. Patients with more advanced stages of the disease are expected to perform worse in physical performance tests. This is compliant with the study of Hass et al. [3] which

showed that patients with more pronounced Parkinson's disability walked significantly slower. The gait speed of normal walking correlated highly with disease severity also in the study of Hausdorff et al. [6].

Physical tests are less influenced by cultural and educational background and are more beneficial in aspects of validity and reproducibility compared to indirect assessments [7]. Therefore, usage of functional performance tests in both a clinical setting and research could be advantageous. An extensive amount of studies that have included physical performance tests in their methodology has been published in recent years.

To our knowledge, the current research has not looked into the possibility that the associations between functional performance and neurological assessment might be gender specific in patients with PD. However, the population-based study of Rodrigues-Barbosa and colleagues [7] revealed that men (and younger people) had better physical performance. In a study by Baba et al. [8] women with PD demonstrated significantly worse Activities of Daily Living (ADL) capacity. Murtagh and Hubert [9] found also that reporting limitations, usage of assistance, and a greater degree of disability is more probable in women. Older women have been suggested [10] to be more likely to report a higher level of ADL limitation for the same level of observed physical performance compared to men. Buchmann et al. [11] reported men to have greater muscle bulk at all ages, also when looking at participants with a clinical diagnosis of PD.

The main aim of this paper was to evaluate whether the relationships between performance tests and neurological assessment measures differ in women and men with PD. As the neurological and functional assessment results of PD patients are rarely interpreted in gender-specific context, investigating possible sex differences in functional performance and differences in associations among neurological and performance tests were also of interest. Consequently, we hypothesize that male patients with PD have better functional performance and associations between neurological assessments and functional performance differ across genders in patients with PD. The latter might lead to false interpretations about functioning of the patient, which is reasoning behind our study design.

2. Materials and Methods

2.1. Subjects. Participants were randomly selected from the Estonian Parkinson Disease Epidemiology Database and were diagnosed according to the Queen Square Brain Bank (QSBB) criteria [12]. Inclusion criteria implicated the following: age under 80; disease severity according to modified HY stages 1.5–3.0; absence of dementia (MMSE score of 24 or higher); adequate vision and hearing. Patients with severe dyskinesia and long "off" periods, other neurological problems, acute medical problems, and conditions affecting mobility were excluded. The study was approved by the Ethics Committee of University of Tartu. An informed consent declaration was signed by all participants.

2.2. Clinical Assessment. Clinical assessment and measurements of functional performance were conducted on all participants. All assessments were performed while patients were receiving their usual medication and were in "on" state. Clinical evaluation included collecting demographic data, history of the disease, and information on current medications. Neurological assessment comprised HY, MDS-UPDRS, S-E, and MMSE and was performed by a movement disorder specialist. The means and standard deviations for each variable are presented in Table 1 for both genders.

HY is a simple clinical rating scale of PD that defines the motor impairment of patients with PD and is widely used for staging the disease [13]. MDS-UPDRS is a neurological assessment measure created to assess the manifestations of PD. It has four parts, which monitor the influence of PD on nonmotor and motor experiences of daily living; motor examination and questions on motor complications are also included [14]. The total score and the motor score (sum of items from part III in MDS-UPDRS) were used for data analysis. S-E estimates the ability of an individual to live with a disease relative to complete independence [15]. MMSE is used for tracking changes in cognitive functioning and to screen cognitive impairment [16]. Reliable diagnosis of dementia is found to be provided by a cut-off score of 24 (maximum 30) [17].

2.3. Functional Performance Assessment. Measures to assess functional performance included timed-up-and-go-test (TUG) and a 10-meter walk test (10MWT). The assessment was performed by three physiotherapists. Prior to conducting the test trials, each of the tests was explained and demonstrated. Patients were barefoot and no participant required an assistive device during functional testing. Patients' blood pressure was measured prior to and during functional performance tests to insure their safety.

Firstly, the 10MWT was carried out on a walkway 12 meters long and 1 meter wide. To indicate the start and stop line for 10MWT, one meter from both ends of the walkway was marked with a red stripe. Patients were instructed to walk from one red stripe to the other red stripe. The time to pass the intermediate 6 meters was measured to allow for acceleration and deceleration. For data analysis, an average of three trials was calculated.

Performing miscellaneous activities requires the ability to adapt walking speed, therefore we included in our study measurement of walking speed at three different speeds: comfortable, maximum, and fast motivated walking speed using motivational instruction. It has been shown that as a person ages the maximum gait speed declines more than the comfortable gait speed [18].

First, the comfortable walking speed was assessed. The test instruction to the participant was walk as he/she would normally walk. Next, the patient was instructed to perform three trials to walk as fast as possible, in order to measure maximum walking speed. Finally, fast motivated gait was measured, by instructing the patient to walk as fast as possible not to miss an imaginary bus in the end of the walkway. This additional motivational instruction was used according to

Table 1: General clinical and demographic characteristics of PD patients, subdivided for gender.

Variable	Total PD patients (n = 28)	Male PD patients (n = 14)	Female PD patients (n = 14)	p value
Age, years (SD)	70.1 (5.7)	68.2 (6.4)	71.9 (4.4)	0.085
Age at onset, years (SD)	61.5 (7.4)	60.3 (8.5)	62.8 (6.1)	0.379
Disease duration, years (SD)	8.7 (5.5)	8.5 (6.2)	8.9 (5.0)	0.395
HY stage (SD)	2.3 (0.5)	2.3 (0.5)	2.3 (0.6)	0.676
MDS-UPDRS total score (SD)	62.4 (19.6)	58.5 (10.7)	66.4 (25.5)	0.303
MDS-UPDRS motor score (SD)	38.6 (13.8)	37.8 (6.9)	39.4 (18.5)	0.760
S-E %	81.3 (7.4)	83.2 (4.6)	79.3 (9.2)	0.165
MMSE	27.2 (2.0)	27.4 (2.1)	27.1 (1.9)	0.703
Height, cm (SD)	167.3 (10.4)	175.7 (5.6)	157.9 (5.4)	0.000*
Body weight, kg (SD)	77.2 (15.1)	85.7 (10.3)	68.6 (14.5)	0.001*

PD: Parkinson's disease; n: number of patients; p value: statistical significance probability of t-test comparing men and women; SD: standard deviation; HY: Hoehn and Yahr stage; MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; S-E: Schwab and England Activities of Daily Living Scale; MMSE: Mini Mental State Examination; cm: centimeter; kg: kilogram.

Table 2: Motor performance of PD patients, by gender.

Variable	Total PD patients (n = 28)	Male PD patients (n = 14)	Female PD patients (n = 14)	p value
TUG time, s (SD)	8.56 (3.80)	6.89 (1.40)	10.22 (4.7)	0.023*
TUG velocity, m/s (SD)	0.78 (0.21)	0.90 (0.16)	0.66 (0.19)	0.001*
CWS, m/s (SD)	1.27 (0.30)	1.39 (0.25)	1.15 (0.30)	0.030*
FWS, m/s (SD)	1.73 (0.54)	2.06 (0.42)	1.40 (0.43)	0.000*
FMWS, m/s (SD)	1.97 (0.54)	2.29 (0.35)	1.65 (0.52)	0.001*
%CWS_FWS (SD)	35.2 (27.1)	50.0 (29.0)	20.4 (14.3)	0.003*
%CWS_FMWS (SD)	54.6 (25.5)	67.2 (27.1)	41.9 (16.5)	0.007*

PD: Parkinson's disease; n: number of patients; p value: statistical significance probability; TUG time: the average duration of timed-up-and-go-test; s: second; SD: standard deviation; TUG velocity: the velocity calculated based on duration of timed-up-and-go-test; m/s: meters per second; CWS: customary walking speed during 10 m walk test; FWS: fast walking speed during 10 m walk test; FMWS: fast motivated walking speed during 10 m walk test; %CWS_FWS: the percentage of difference in FWS compared to CWS; CWS_FMWS: the percentage of difference in FMWS compared to CWS.

a study by Nascimento et al. [19]. Their study on stroke patients suggested that modified verbal commands or demonstration strategies should be employed by physical therapists to ensure accurate information about maximal gait speed, as the usage of motivational instruction increased the maximal walking speed of the participants.

Secondly, TUG test was used to assess sit-to-stand performance and walking. This test also allows the making of estimations in relation to dynamic balance. The standard protocol of TUG measures the time it takes to stand up, walk a distance of 3 meters, turn, walk back, and sit [20]. The patient was instructed to walk at a comfortable and safe walking speed and the time in seconds was recorded from the command "Go" to the time when the patient was seated again.

Over which shoulder the test is performed is generally left to be decided by the examinee. In present study TUG performance was measured around both shoulders and the average of three trials of the faster performance was used for statistical analysis. In addition to the standard protocol, we included a calculation of walking speed of TUG performance.

2.4. Statistics. IBM SPSS 20.0 was used for the database and analyses. Variables across genders were tested for normality with Shapiro-Wilk test. One-way ANOVA was used to compare male and female participants. In addition, partial eta squared was calculated. For each variable Levene's test of homogeneity of variance was also performed. In case of unequal variance the Welch test was used to compare means. Further, the results of functional performance tests were height normalized and same statistical procedures were conducted.

Pearson's coefficient was used to analyze the correlations between functional tests. The relationships between measures of neurological assessments were examined with Spearman rho correlation analysis. Kendall's tau-b correlation analysis was used to assess possible associations between functional performance tests and neurological assessment. Value $p < 0.05$ was considered to be statistically significant.

3. Results and Discussion

3.1. Differences in Functional Performance of Men and Women with PD. Gait speed is commonly used in clinical research. Walking speed has been shown to be a predictor of a range of outcomes, including survival [21] and fall risk [22]. In present study, the speed of walking was significantly higher in men with PD at all the test conditions used (Table 2).

At the same time, male and female participants did not differ in means of PD stage, disease severity according to MDS-UPDRS, and cognitive function. The effect size (partial

eta squared) of gender was under 1% when looking at the results of neurological assessment tests, except for S-E (7%). Anyhow, the level of independence did not differ in male and female participants as indicated in Table 1. Still, in current literature women have consistently reported poorer health status [23, 24].

Significantly faster walking speed of male participants in our study is in compliance with a study by Samson et al. [25] which revealed that absolute values for walking speed are lower in women than men at all ages. Hass et al. [3] demonstrated also faster walking speeds in men compared to women, but the walking speeds in their study were considerably slower. For example, in their study, men in stages 2–2.5 (according to HY) walked on average with a speed of 1.02 ± 0.02 m/s. In comparison, the average speed of comfortable walking was 1.39 ± 0.25 m/s in the present study. This difference can be attributed to the present study excluding acceleration and deceleration as the walking speed was calculated for the intermediate six meters of the 10MWT (2 meters from either end).

Another explanation for the higher walking speeds found in present study might be the particular walkway used. In addition to the red stripes indicating the start and end line, there were black stripes marking every meter. The center of the walkway was also marked with a line running along the entire course of the walkway.

Possibly, the walkway served as a visual cue for the participants. The effect of visual cueing on gait speed and step length of patients with PD has been demonstrated in a number of publications [26, 27]. It is possible that the visual cues were more effective in increasing the walking speed of male participants. Jiang and Norman [28] showed in their study that using transverse visual lines enables a person with PD to start walking with longer steps and higher velocity. Results were most evident in the length of first and second step.

Step length of men is known to be longer [29] and since the distance used in the present study to assess walking speed was short, the impact of transverse lines increasing step length could have been determining these distinct differences in male and female participants. The possible sex differences in effects of cueing in patients with PD need to be examined and verified with further studies.

Differences in walking speed can to some extent be attributed to sex differences in anthropometry. It is well known that on average men are taller [30] and also have longer lower extremities. It is clear that the distance covered in a time unit should be longer for a taller person. It has been demonstrated that a high proportion of the variance in walking speed is accounted for by height in both men and women [31]. Therefore, we compared walking speeds also when walking speeds were normalized for height. Movement speed remained to be higher in men, except for comfortable walking speed. This result is similar to one of our previous works [32], where also no sex differences emerged in walking at a comfortable speed. We hypothesized that, despite lower muscle strength indices, female patients perform relatively better in movements they are more accustomed to.

Walking speed is associated with lower-limb muscle strength [33], which is higher in men [11]. The latter further explains better results of male participants in our study. Anyhow, after height normalization the effect size of gender to the found differences in functional performance tests was under 0.2, indicating a small effect.

The only exception was FWS, which demonstrated a moderate gender effect before (0.394) and strong one after (0.853) height normalization procedure. Possibly, in addition to previously pointed facts, this result could be associated with motivational aspects. Men are known to be more motivated to participate in sporting activities [34]. It can be assumed that male participants might have had higher motivation to physically strain themselves during 10MWT as the maximal walking speed was measured.

The latter assumption is confirmed when looking at the results describing to what extent the participants were able to increase their walking speed compared to comfortable walking speed. On 10MWT, the walking speed of men was significantly higher compared to comfortable walking speed when looking at FWS ($p = 0.003$) and FMWS ($p = 0.007$). On average, the maximal walking speed was 50% faster than comfortable walking speed in men and 20.4% in women. Compared to comfortable walking speed, the fast motivated walking speed was 67.2% faster in men and 41.9% in women. It is noteworthy that considerable variability was found in the ability to increase walking speed from customary to maximal in both men and women.

3.2. Differences in Associations between Functional Performance Test and Neurological Assessment of Women and Men with PD. The main aim of this study was to find out whether the relationships between performance tests and neurological assessment measures differ in women and men with PD. The results to answer the main study question are summarized in Table 3.

Results distinctly demonstrate that women with more advanced PD perform worse in functional tests. As PD is a progressive disorder [35], long considered to be a disease primarily causing motor disability [36], these results were expected. Altogether, functional performance is most convincingly associated with S-E and MDS-UPDRS motor examination score, which demonstrated significant associations with all the performance tests in women. As the motor examination part is an examiner rating of the motor manifestations of PD and S-E scale is used to provide an estimation of the patient's ability to function, rated by interviewing the patient [37], finding a relationship with performance tests is a likely outcome.

Comfortable walking speed demonstrated weaker correlation with neurological assessment measures than other performance tests, the associations being significant only with UPDRS-MOT and S-E. The latter supports the hypothesis from one of our previous works [32]: women with PD perform relatively better in movements they are more accustomed to. This aspect might be important to consider when interpreting test results. However, further investigation is needed to verify this aspect.

Table 3: Associations between assessed variables in women ($n = 14$) and men ($n = 14$) with PD.

	Parameter	UPDRS-MOT	MDS-UPDRS	HY	S-E
Women	TUG	0.552**	0.492*	0.530*	0.679**
	TUG_vel	−0.575**	−0.469*	−0.530*	0.653**
	CWS	−0.420*	−0.313	−0.398	−0.474*
	FWS	0.464*	−0.425*	−0.464*	0.576**
	FMWS	−0.530**	−0.469*	0.497*	0.602**
Men	TUG	−0.068	0.00	0.073	−0.090
	TUG_vel	0.124	−0.101	−0.091	0.225
	CWS	0.101	0.191	0.018	0.344
	FWS	0.045	0.260	−0.239	−0.241
	FMWS	0.169	−0.056	−0.347	0.225

PD: Parkinson's disease; *n*: number of patients; UPDRS-MOT: motor examination score of MDS-UPDRS; MDS-UPDRS: Movement Disorders Society Unified Parkinson's Disease Rating Scale; HY: Hoehn and Yahr stage; S-E: Schwab and England Activities of Daily Living Scale; TUG: the average duration of "timed-up-and-go-test"; TUG_vel: the velocity calculated based on duration of "timed-up-and-go-test"; CWS: customary walking speed during 10 m walk test; FWS: fast walking speed during 10 m walk test; FMWS: fast motivated walking speed during 10 m walk test; *correlation is significant at the 0.05 level (2-tailed); **correlation is significant at the 0.01 level (2-tailed).

Explicit differences in associations between neurological and performance tests were detected in men compared to women: in our study, widely used MDS-UPDRS scores, HY, and S-E did not correlate with actual functional performance in men with PD.

We provide some potential explanations for our results. The first relates to the possibility that the test environment was perceived as competitive by men since participants were asked to perform as fast as they possibly could (with due regard for safety), while timing with a stopwatch was openly conducted.

Men tend to be more competitive about sports than women [38]. Deaner et al. [39] also reported that there is substantial sex difference in sports interest. Shekhar and Devi also found differences in achievement motivation of men and women [40]. In a study of Godin and Shephard [41] with older individuals, men showed higher perceived physical self. Consequently, this can result in men being more motivated to strain themselves physically to a greater extent than women. This assumption is supported by found significant gender differences in improving walking speed compared to customary walking speed.

Another explanation for different relationships across genders could be a possibly higher withdrawal of women during performance. Ennis et al. [42] demonstrated that because older adults perceived cognitive efforts as comparatively harder, the level of withdrawal was significantly higher than for younger participants. Withdrawal at harder effort might also apply to physical effort and not be age specific. As men walked faster, FWS testing could have been less difficult for them and as a result men would have strained themselves to a greater extent, whereas women might have withdrawn.

Another possible explanation for sex differences in results might be caused by differences in physical activity. Older women are known to be less active and more sedentary [43]. The latter has been proved also for older adults with chronic diseases [44]. In the present study, eight men and seven women considered themselves to be physically active. Detailed information about physical activity was not collected; therefore the effect of potential differences in physical activity cannot be excluded.

Our results conflict with the previous results by Qutubuddin et al. [45] who found that lower scores on the Berg Balance Scale correlated with higher scores on UPDRS motor score in men with PD. At least to some extent this difference can be attributed to conceptually different assessment methods. The Berg Balance Scale rates balance and consists of 14 items. Each of these items is scored from 0 to 4 and they are added together for a total score between 0 and 56, with a higher score indicating better balance [46]. Although the Berg Balance Scale has been proved to be a reliable assessment measure of functional balance in community-dwelling older adults [47], assessing performance by scoring remains always somewhat subjective compared to objective registration of performance characteristics (duration, speed, strength, etc.).

We found no associations between MMSE and functional performance tests. Due to the relatively small sample size of our study and selection of patients with MMSE scores >24, the generalizations about the effect of cognition on functional performance cannot be made.

In addition to looking for associations between neurological and functional performance tests, we also analyzed the relationships within each: women, who were rated to be in more advanced stage of the disease, also received higher motor and total scores on MDS-UPDRS and had a lower level of independence according to S-E.

Similarly to female participants, MDS-UPDRS total score was associated with estimation of independence in men. On the other hand, in present study stage of PD according to HY was not associated with the other measure used to assess disease severity, MDS-UPDRS in men. Motor examination scores of MDS-UPDRS were associated with neither HY, S-E, nor MMSE in male participants.

Whilst no associations between neurological assessments and functional tests were found in men, the associations found among functional tests were also less clear for male participants than for their female counterparts. For example, a female participant, who walked faster at comfortable speed, also performed faster in the other functional tests (correlations were strong, correlation coefficient r being higher than 0.835 at all cases). For male participant CWS demonstrated significant associations only with TUG performance ($r = 0.537$).

The main limitation of our study was the relatively small study sample which limits the usage of several statistical methods, therefore hindering the possible generalizations of our results. However, our results indicate that the gender of the patient with PD influences functional performance and the associations between assessment measures differ across genders. Therefore, when interpreting assessment results, considering sex differences is important for both clinicians and researchers working with patients with PD.

4. Conclusions

Men with a similar clinical stage of PD perform better in functional performance tests than women. Functional performance is associated with neurological assessments in women, whereas it is not in men with PD. We recommend considering both neurological and functional assessment measures in a gender-specific context.

Possible sex differences in effects of visual cueing on patients with PD need further investigation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

The Effects of Gender Differences in Patients with Depression on Their Emotional Working Memory and Emotional Experience

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A large amount of research has been conducted on the effects of sex hormones on gender differences in patients with depression, yet research on cognitive differences between male and female patients with depression is insufficient. This study uses emotion pictures to investigate the differences of the emotional working memory ability and emotional experience in male and female patients with depression. Despite identifying that the working memory of patients with depression is impaired, our study found no significant gender differences in emotional working memory. Moreover, the research results revealed that memory effects of mood congruence are produced in both men and women, which may explain why the depression state can be maintained. Furthermore, female patients have more emotional experiences than male patients, which is particularly significant in terms of negative emotional experiences. This result provides cognitive evidence to explain why women suffer from longer terms of depression, are more susceptible to relapse, and can more easily suffer from major depressive disorder in the future.

1. Introduction

The causes of depression are very complex, affected by many factors including the biological, social, and psychological factors. Considering the differences of biological construction, social roles, and psychological structure between men and women, women are more likely to experience mood disturbances during times of hormonal flux. The etiologic model of depression with onset in the menopause transition proposed by Gordon et al. [1] is very helpful for understanding the female depressive mood. This model shows that in the context of the menopause transition, characterized by fluctuations in ALLO that are consequent to estradiol and progesterone fluctuations, an inability of the GABAA receptor to demonstrate the plasticity necessary to maintain GABA-ergic homeostatic control might exacerbate the response of the HPA axis to stress. Combined with an increased vulnerability to major depressive disorder due to personality or genetic factors and/or stressful life events proximate to the menopause transition, the endocrine profile of the menopause transition sets the stage for depressive symptoms. As a result, the possibility of women suffering from an emotional illness is far greater than that of men [2]. Studies have demonstrated that, compared to men, women with depression have a higher point prevalence of depression, an earlier onset of depression [3], and a higher risk of severe depressive disorder in the future [4, 5]. In addition, females have longer lasting depression and are more likely to experience relapse [6]. There have been many studies on the biological factors that influence gender differences in patients with depression. For example, no significant difference in the risk of depression has been found between postmenopausal women and men [7, 8], indicating that the secretion levels of androgen and estrogen affect a person's psychoactive state.

During stages of hormonal fluctuations and instability, such as adolescence and postpartum, women have relatively strong mood fluctuations and are prone to experiencing anxiety and depression [9–11]. In the context of the menopause transition, neurosteroids (including estradiol, progesterone, and GABA-ergic) fluctuation/dysregulation might increase the response of the HPA axis to stress. Combined with an increased pressure due to personality of the female or genetic factors and/or stressful life events, these physiological and social factors interacting with each other might lead to the occurrence of depression [1]. Clinical studies on males show that the hormone testosterone provides protective benefits against anxiety and depression. A decline in male testosterone levels is accompanied by a significantly higher incidence rate of anxiety and depression [12, 13]. Studies have shown that androgen, depleting drugs used to treat male prostate cancer, will lead to decreased male testosterone, which may result in increased risk of anxiety or depression [14]. For males with gonadal function decline, testosterone-replacement therapy is used, which greatly improves the patients' mood, reduces their anxiety, and alleviates their symptoms of depression [13, 15]. Similarly, among older men and women, low testosterone levels and an increased incidence rate of major depressive disorder are significantly associated [16, 17]. Although the male hormone testosterone level is significantly higher than that of the female (the content of testosterone in males is ten times that in females), in fact, women are more sensitive to testosterone [18]. The antianxiety and antidepression effects of testosterone have been supported by some evidence. For example, female patients with major depressive disorder or anxiety show low levels of salivary testosterone [19]. The use of low doses of testosterone in female patients with severe refractory depression has significantly alleviated their levels of depression [20].

All of the above-mentioned research examined affective disorders from the biological characteristics of sex hormone differences between males and females. In fact, biological characteristics influence cognitive psychology through social activities, interpersonal relationships, and so forth, thus forming stable psychological structures and cognitive styles of the different genders. Numerous studies show that gender differences in cognitive ability are considered to be an indisputable fact. Women have universal advantages in the tasks of speech production [21] and face memorization compared to men [22]. Men display a better ability than women in performing visuospatial tasks [23–25], which has mainly been demonstrated through the large difference in mental rotation ability and the small difference in visual-spatial perception ability [26]. Studies suggest that because of the inhibition effects of estrogen on the right brain, the ability for women to perform visuospatial tasks decreases [27]. Such gender differences in cognitive function may be related to the distribution of different hormone receptors in the brain. According to research, testosterone receptors are found in the hypothalamus and hippocampus [28, 29], whereas estrogen receptors are found in wider brain areas, such as the cerebral cortex, amygdala, hippocampus, and thalamus [30], suggesting that estrogen has greater effects on women's cognitive ability.

However, evidence of the association between gender differences and cognition is far from clear, particularly regarding cognitive differences between genders in patients with depression. Intuitively speaking, female patients with depression are more vulnerable to emotional control and influence compared to males, but evidence is lacking in this area, particularly evidence in the aspect of cognition. With a focus on female and male patients with first untreated depression and depression of a lesser extent, this study investigates differences in emotional working memory and emotional experiences between the two genders, thus providing more experimental evidence for a cognitive function comparison between male and female patients.

2. Methods

All subjects provided signed informed consent and this study was approved by the Ethics Committee at Beijing Anding Hospital, Capital Medical University, China.

2.1. Subjects. Twenty-three patients with depression participated in this experiment, including 12 females and 11 males. The patients arrived at the Outpatient Department of the Beijing Anding Hospital of Capital Medical University for their first visit. The patients with depression were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV). The grouping criteria of these patients were as follows: (1) aged 18–60 years, right-handed, and fit the DSM-IV diagnostic criteria for depression; (2) diagnosed as patients with obvious, mild, and moderate depression; able to continue normal life, work, and study; (3) HAMD < 24; the level of depression was decided using the Hamilton Depression Rating Scale (HAMD-17); (4) did not receive any treatment; did not take any antidepressant drugs; (5) no color blindness or other eye diseases; had normal vision or corrected vision and were able to complete the eye movement test.

2.2. Experiment Materials. The experiment used 60 pictures each of positive, neutral, and negative images. All of the images were from the International Affective Picture System (IAPS). The average merriness of the positive pictures was 7.31 ± 0.44, and the average arousal was 5.54 ± 0.44. The average merriness of the negative pictures was 2.79 ± 0.51, and the average arousal was 5.97 ± 0.44. The average merriness of the neutral pictures was 5.18 ± 0.17, and the average arousal was 3.23 ± 0.22. After picture processing via Picture Manager software, the size, grayscale, and resolution of all of the pictures were the same.

2.3. Experimental Paradigm and Procedures. There were three types of experimental tasks: pictures of positive emotions, pictures of negative emotions, and pictures of neutral emotions. To simultaneously examine mood and emotional working memory, each type of task consisted of four pictures of the same type (i.e., each positive picture task was composed of four positive pictures, each negative picture task was composed of four negative pictures, and each neutral picture task was composed of four neutral pictures). The four pictures

of each task corresponded with four different positions (upper left, upper right, lower left, and lower right). The target stimulus picture type was the same as the prompt task type; the target stimuli were presented at the center of the screen. During the experiment, a Tobii T120 Eye Tracker was used to simultaneously acquire and record the subjects' eye movement data, such as pupil diameter, while they were viewing the stimuli tasks.

The experimental procedure was as follows. First, a "+" sign appeared in the center of the screen for duration of 500 ms to remind the participants that the stimuli tasks would immediately appear. Then, the stimuli appeared for 10,000 ms to allow the subjects to remember all of the images in the clue. After the disappearance of the clue, there was a 5,000 ms memory retention time. Afterwards, a target image appeared in the center of the screen; the subjects stated whether the target image had appeared in the previous stimuli task. If their response was "yes," they left-clicked; if their response was "no," they right-clicked. An "∗" showed up upon the completion of judgment to indicate a break; the break time was 2,000 ms in between trials.

2.4. Statistical Analysis. A comparative analysis of the differences in age and years of education between the men and women was conducted using an independent sample t-test. In this study, the main factors were analyzed with the multivariate and multiple comparison correction method of generalized linear models. A pairwise comparative analysis of the same type of emotion between different gender groups was performed using an independent sample t-test. A pairwise comparative analysis of the same gender between groups of different emotional types was performed using a paired sample t-test. The statistical analyses of all of the data were conducted with SPSS 20.0 (SPSS, Inc., Chicago, IL) statistical analysis software.

3. Experimental Results and Analysis

3.1. Demographic Analysis. Eleven male patients and 12 female patients with depression participated in this experiment. Data from the demographic analysis are shown in Table 1. The difference in age distribution between male and female patients was not significant [$t(21) = 0.126$, $p = 0.901$] and the difference in the distribution of years of education between male and female patients was not significant [$t(21) = 0.015$, $p = 0.989$], but the difference in average HAMD scores (17 items) between male and female patients was significant [$t(21) = 2.59$, $p = 0.01 < 0.05$].

3.2. Comparison of the Accuracy of Working Memory between Male and Female Patients. The results of the average accuracy of working memory in the two genders are shown in Figure 1. We used the accuracy as the dependent variable and the gender factors and emotional factors as the independent variables. We then conducted 2 (gender: female, male) × 2 (emotion: positive, negative) two-way ANOVA. The results showed that gender main effects were not significant [$F(1, 21) = 1.410$, $p = 0.255$, $\eta^2 = 0.092$], whereas the emotional main effects were significant [$F(1, 21) = 9.022$, $p = 0.008 < 0.01$, $\eta^2 = 0.361$]; however, there was no interactive effect between gender and emotion [$F(1, 21) = 1.584$, $p = 0.229$, $\eta^2 = 0.102$]. The results explain that the accuracy of the emotional working memory did not differ between male and female patients.

Table 1: Demographic data analysis.

	Male (mean ± SD)	Female (mean ± SD)	p value
Age (years)	34.63 ± 10.72	34.00 ± 10.19	0.90
Educational level (years)	13.63 ± 3.42	13.60 ± 3.78	0.99
HAMD (17 items)	19.63 ± 5.83	20.58 ± 6.14	0.01

SD: standard deviation; HAMD: Hamilton Depression Rating Scale.

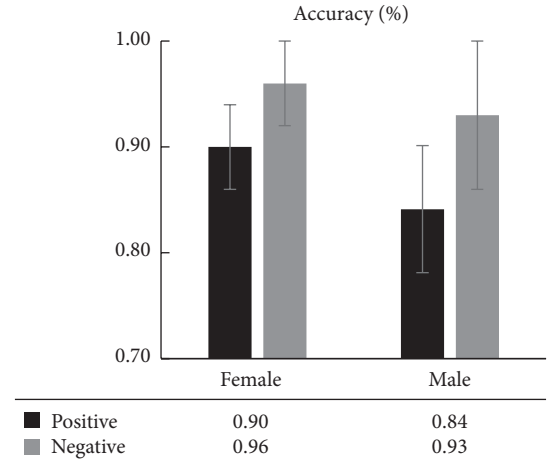

Figure 1: Comparison of the accuracy of the emotional working memory between men and women with depression.

Additionally, we conducted a pairwise t-test on emotional factors. The results revealed that the accuracy of the women's negative emotional memory was significantly greater than that of their positive emotional memory [$F(1, 11) = 2.399$, $p = 0.035 < 0.05$, d(effect size) = 0.899]; similar results were shown for men [$F(1, 10) = 3.000$, $p = 0.020 < 0.05$, $d = 0.966$]. This indicates that both men and women with depression have memory effects of mood congruence; in other words, patients with depression remember more negative information that is consistent with their mood and less positive information [31, 32].

3.3. Comparison of the Reaction Time of Working Memory between Male and Female Patients. The results of the average reaction time of the working memory of men and women are shown in Figure 2. Using reaction time as the dependent variable and gender and emotion factors as the independent variables, we conducted 2 (gender: female, male) × 2 (emotion: positive and negative) two-way ANOVA. The results showed that the gender main effects were not significant [$F(1, 21) = 1.478$, $p = 0.244$, $\eta^2 = 0.096$], the emotional main effects were not significant [$F(1, 21) = 1.228$, $p = 0.287$, $\eta^2 = 0.081$], and the interactive effects between gender

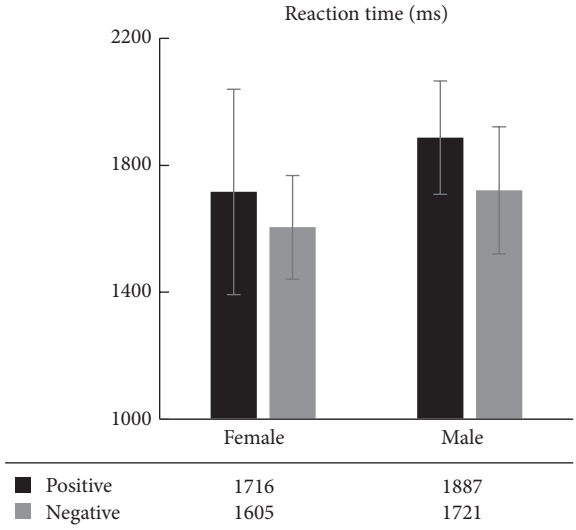

Figure 2: Comparison of the reaction time of emotional working memory between male and female patients with depression.

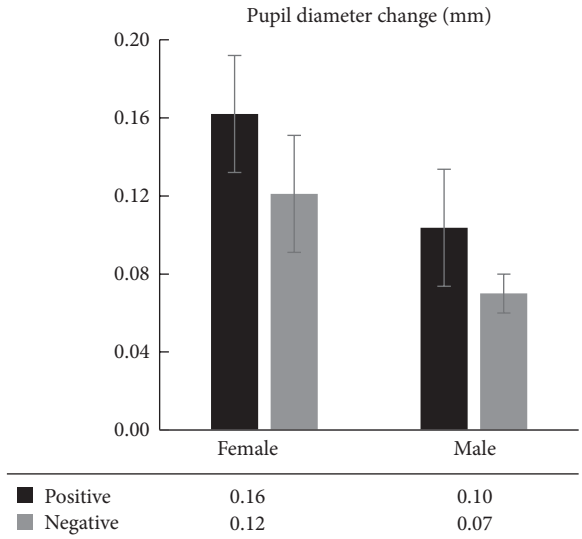

Figure 3: Comparison of pupil diameter changes between male and female patients with depression.

and emotion were not significant [$F(1, 21) = 6.339$, $p = 0.025 < 0.05$, $\eta^2 = 0.312$]. The results indicated that no gender differences were demonstrated in the reaction time of emotional working memory between male and female patients.

Through the study on emotional working memory, we discovered that (1) both male and female patients with depression have memory effects of mood congruence, which is consistent with previous findings about the presence of the memory of mood congruence in patients with depression; and (2) although female patients had a stronger emotional working memory than male patients, no significant gender differences were produced.

3.4. Comparison of Changes in Pupil Diameter between Male and Female Patients. Using pupil diameter during a neutral emotion as the baseline, pupil diameter changes during individuals' positive and negative emotions were calculated. The results of the classified statistical analysis of the pupil diameter changes of different genders during different emotions are shown in Figure 3. Using pupil diameter changes as the dependent variable and gender and emotional factors as the independent variables, we conducted 2 (gender: female, male) × 2 (mood: positive, negative) two-way ANOVA. The results showed that the gender main effects were significant [$F(1, 21) = 4.911$, $p = 0.044 < 0.05$, $\eta^2 = 0.260$], whereas the emotional main effects were not significant [$F(1, 21) = 2.216$, $p = 0.159$, $\eta^2 = 0.137$] and the interactive effects between gender and emotion were not significant [$F(1, 21) = 0.472$, $p = 0.503$, $\eta^2 = 0.033$].

The two-way ANOVA on pupil diameter changes showed that gender differences existed in pupil diameter changes. Therefore, further analysis was required regarding the significance of the difference in pupil diameter changes between men and women during different emotions. The results of the pairwise independent sample t-test showed that women had bigger pupil diameter changes than men during positive emotions, but the difference was not significant [$t(21) = 1.409$, $p = 0.178$, $d = 0.709$]. However, women had bigger pupil diameter changes than men during negative emotions, and the difference was significant [$t(21) = 0.146$, $p = 0.048 < 0.05$, $d = 1.080$]. The results suggest that gender differences exist in pupil diameter changes; this is represented in the discovery that women have significantly greater pupil diameter changes than men during negative emotions.

4. Discussion

This study examines the differences in the emotional working memory and emotional experiences between male and female patients with depression. To rule out the effects of age and years of education on the results, we matched the age and years of education of the men and women so that there was no significant difference in these two factors between genders.

Previous research results have shown the presence of cognitive differences between men and women [33], particularly the phenomenon of hemispheric asymmetry during word processing between men and women: the left brain in men plays the major role, whereas both the left and right brains of women work simultaneously, which is exhibited through women's obvious advantages over men in speech generation [34]. In addition, women have better episodic memory and face recognition abilities than men [35]. Studies have shown that the working memory of patients with depression is impaired, which is manifested in the significant decrease in the accuracy of the working memory and the significantly prolonged reaction time of the working memory compared to the control group [36–39]. In this study, for both the accuracy (Figure 1) and the reaction time (Figure 2), there was no significant difference between the male and female patients. However, the accuracy in women was larger than that of men, and the reaction time in women was shorter

than that of men. Although this difference was not statistically significant, it shows a trend: compared to men, women have more detailed emotional picture coding and a deeper level of emotional information processing; therefore, these emotional images had a greater effect on the cognition of women.

Studies on mood congruence suggest that information that is consistent with emotional stimuli is easier to remember [40] and that people in a negative emotional state are more inclined to remember negative information [41]. Therefore, compared to a healthy control group, patients with depression remember more negative stimuli data because these are consistent with their emotional state; likewise, they remember less positive stimuli data because these are inconsistent with their emotional state [42]. For both men and women in this study, the working memory for negative emotions was significantly stronger than that for positive emotions, and both genders showed memory effects of mood congruence. The study results illustrate that the memory effects of mood congruency are an important reason why patients with depression maintain their depression status.

Moreover, there are several potential reasons why we did not find any significant differences in terms of the emotional working memory of male and female patients: (1) the male and female patients in the study groups were from the outpatient department; they had depression of a lesser extent and were still able to work, live, and learn; (2) tasks of emotional working memory are relatively simple; and (3) the male and female groups were not large enough, which may have also affected the statistical validity.

Previous studies have shown that the brain's processing of external emotional information will lead to changes in pupil diameter. The pupil diameter dilated or constricted reflects people's emotional changes and emotional experiences [43–45]. This study used eye movement equipment to measure pupil diameter size when male and female patients with depression were viewing pictures of different emotions. Using pupil diameter for a neutral image as the baseline, we calculated the changes in pupil diameter when men and women were viewing pictures of positive and negative emotions.

The research results about pupil diameter changes showed that the main effects of gender were significant and women's emotional effects were significantly greater than those of men (Figure 3), indicating that women's emotional experiences for external emotional stimuli were far greater than those of men [46]. We further compared men's and women's pupil diameter changes when they were in different emotional tasks. We found that although the pupil diameter changes of the female group during positive emotions were greater than those of the male group, the difference was not significant, whereas the pupil diameter changes of the female group during negative emotions were significantly greater than those of the male group, indicating that women are more concerned about negative events than men. Depressed patients in emotional tasks have attentional bias [47] and processing bias [48] for negative information. Our results suggest that the negative emotional experiences of female patients with depression are significantly stronger than those of male patients, which increases the severity of depression in female patients. This is consistent with the result showing that the HAMD score of the female patients was larger than that of the male patients. The excessive negative emotional experiences of female patients with depression are possibly based on a physiological foundation: there is a greater synthesis of the emotion-related frontal cortex and 5-HT in certain subregions in the limbic system in women than in men [49]. One important feature of gender differences is different sex hormones: women primarily have estrogen and men primarily have androgen. Studies have shown that the high risk of female depression is related to the imbalance of female hormone such as ovarian hormone and progesterone, and the increase of estrogen has a direct relationship with negative emotions [3]. This occurs because, during negative stress, estrogen affects the balance of the hypothalamus-pituitary-HPA axis, leading to the female HPA axis imbalance and increased concentrations of the adrenal cortical hormone [50]. Meanwhile, excessive activity of the HPA axis easily arouses anxiety disorder and major depressive disorder [51–53]. However, there are studies suggesting that the gender difference is mainly due to the higher pressure to women during adolescence, premenstrual and perimenopausal periods, leading to the rise of depressive emotion [54, 55]. Recently, a perimenopausal depression model, proposed by Gordon et al. [1], has shown that the female depressive mood is caused by many factors, such as physiological factors (including estrogen fluctuations, GABA disorder, and HPA axis imbalance), female personality, and genetic vulnerability factors, as well as the psychological pressure; these physiological and social factors interacting with each other might lead to the occurrence of depression.

In addition, women's excessive emotional experiences to negative emotional stimuli can also come from the long-term accumulation of environmental pressure. There are gender differences in men's and women's abilities to respond to working conditions and the living environment and interpersonal skills. Hankin et al. [56] found that adolescent girls reported significantly more interpersonal and peer stressors than boys. Bouma et al. [57] found that girls were more likely to develop depressive symptoms in response to stress than were boys. These studies suggest that adolescent girls experience more objective and subjective psychological stressors than boys; particularly, interpersonal stress has been shown to partially mediate the increased prevalence of depression in girls after puberty [56, 58]. There are also gender differences in pressure venting. Women feel and accumulate more pressure to make themselves more susceptive to negative cognitive schemata, particularly in the face of negative events. Chronic stress increases anxiety and depression-like behavior [59–61]. Long-term stress can induce functional changes in the brain regions that involve anxiety and/or depression, including the parahippocampal gyrus, the amygdala, and the prefrontal cortex [30, 62]. Excessive pressure can cause anxiety-related symptoms [63] and the appearance and maintenance of severe depression [64]. Cognitive vulnerability transactional stress theory tends to support that depressive gender difference is due to sex cognitive vulnerability and stress [65]. The negative emotion caused by negative life events is often expanded by the female cognitive vulnerability. Meanwhile, facing the stress of negative events, men usually have more hostile and angry reaction, while women tend

to meditate alone [66]. Meditation is not a proper way to deal with the pressure, because this way is more likely self-attribution, leading to depression [65]. Female cognitive vulnerability is increased by many factors such as female personality and genetic and estrogen factors. From adolescence especially, female hormone imbalance may result in the disorder of GABA and imbalance of HPA axis, combined with women's cognitive vulnerability, and improper ways to higher psychological pressure caused by the stress events, thus, further deepen negative cognitive process which may produce depressive mood disorder [1]. The present study has explained from the perspective of emotional cognition why females suffer from a longer term of depression and are more susceptive to relapse [6] and why women have a higher risk of severe depression episodes in the future [4, 5].

5. Conclusion

Our study results demonstrate no significant gender differences in emotional working memory among patients with depression of a lesser extent. However, both male and female patients have experienced memory effects of mood congruency, which was represented by the significantly higher accuracy of the negative emotion working memory than of the positive emotion working memory. In addition, gender differences were revealed in emotional experience as a response to external emotional stimuli. The level of emotional experience was higher in women than in men; in particular, women's negative emotional experiences were significantly stronger than those of men. The increased negative emotional experiences in women were likely an important reason why females suffer from longer term depression, are more susceptive to relapse, and have a higher risk of severe depression episodes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Gender Differences in Childhood Lyme Neuroborreliosis

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Background. Many neurological diseases show differences between genders. We studied gender differences in childhood Lyme neuroborreliosis (LNB) in an endemic area of Lyme borreliosis in Norway. *Methods*. In a population based study, all children (<14 years of age) with symptoms suspicious of LNB, including all children with acute facial nerve palsy, were evaluated for LNB by medical history, clinical examination, blood tests, and lumbar puncture. LNB was diagnosed according to international criteria. *Results*. 142 children were diagnosed with LNB during 2001–2009. Facial nerve palsy was more common in girls (86%) than in boys (62%) ($p < 0.001$), but headache and/or neck stiffness as the only symptom was more common in boys (30%) than in girls (10%) ($p = 0.003$). The girls were younger than boys and had a shorter duration of symptoms, but boys had a higher level of pleocytosis than girls. In a multivariate analysis, both gender and having headache and neck stiffness were associated with a higher level of pleocytosis. *Conclusion*. Girls and boys have different clinical presentations of LNB, and boys have a higher level of inflammation than girls independent of the clinical presentation.

1. Introduction

Lyme borreliosis (LB) is caused by the infection of the spirochete *Borrelia burgdorferi* sensu lato (BB) transmitted to humans during bites of BB infected *Ixodes* ticks. BB has strong invading properties into different human tissues and LB is a multisystem disorder with three clinical time related stages including dermatological, neurological, and rheumatological symptoms [1].

The three main human-pathogen BB genotypes identified in European *Ixodes* ticks, *B. afzelii*, *B. garinii*, and *B. burgdorferi* sensu stricto, are found to have specific tissue preferences in humans. *B. afzelii* is mainly dermatotropic, *B. garinii* is mainly neurotropic, and *B. burgdorferi* sensu stricto is mainly arthrogenic. In US, *B. burgdorferi* sensu stricto is the only genotype identified. However, all organ manifestations may develop in LB infected patients with any of the different BB human-pathogen genotypes [2].

LB is the most frequent tick borne infection in Europe and the northern hemisphere. Erythema migrans (EM), the local and first stage of LB, is the most prevalent LB manifestation [1, 3]. Lyme neuroborreliosis (LNB) develops when the BB spirochete disseminates from the tick bite area and invades and affects the nerve system and is the most frequent second stage manifestation of LB in Europe [1, 4]. The incidence of LNB is higher in children than in adults [3], and, in a European region endemic for LB, LNB was the most common reason for childhood infectious meningitis [5].

In USA, a male predominance has been reported in adult LB [6]. This male predominance has been even more accentuated in children. In an early epidemiological study from the east coast of USA, LB was named the disease of "little boys" [7]. In Europe, with a more variety of BB genotypes, a slightly female predominance has been reported in LB in general and in EM in particular [8, 9]. However, in a recent comprehensive study of Slovenian adults focusing on different organ manifestations, a male predominance was found in Lyme arthritis and LNB [9].

There are few strict population based studies reporting on LNB and gender in children. However, in a comprehensive German study from 1993, the prevalence of LNB in children was twice as high in boys than in girls [10].

South Rogaland, Norway, is an endemic area of LB suitable for epidemiological studies of LNB in children. In population based single centre studies, we have previously reported epidemiological and clinical findings in children with LNB [11, 12], facial nerve palsy (FNP) [13], and Lyme meningitis [5]. The aim of this present study was to study the impact of gender on clinical and laboratory characteristics of LNB in children.

2. Material and Methods

2.1. Study Area. The coastal area of Rogaland County of the southwest part of Norway is an endemic area of LB, and the incidence of LNB in children is earlier reported among the highest in Europe [11]. The population of South Rogaland, Norway, includes approximately 62 000 children less than 14 years of age, and the Paediatric Department at Stavanger University Hospital receives all hospital admissions for acute childhood disease in this area (with an upper age limit of 14 years).

2.2. Patients and Testing Procedures. Prior to the study period, all general practitioners and otorhinolaryngologists in the region received a letter recommending that all children under 14 years of age with acute facial nerve palsy (FNP) should be referred immediately to the Paediatric Department. All children aged 3 months to 14 years during the study period 2001–2009 with symptoms suspicious of LNB, including all children with FNP were evaluated systematically, including medical history, clinical examination, blood tests, and lumbar puncture. In addition, medical records from all children admitted to the hospital during the study period with cerebrospinal fluid (CSF) pleocytosis were identified from the hospital records and studied retrospectively. Data regarding gender, age at diagnosis, year and month of admission, number of days from onset of symptoms to admission, clinical symptoms, and results of blood and CSF tests were registered. Clinical symptoms were considered as not present if not mentioned in the medical record. The study was population based, and only children living in South Rogaland were included.

During the whole study period, in all children with symptoms suspicious of LNB, serum and CSF were analysed for BB IgM antibodies using the Enzygnost Lyme Borreliosis ELISA test (Dade Behring, Siemens, Germany). BB IgG antibodies were measured by the Enzygnost Borrelia IgG test from 2001 to July 2006 and thereafter by Enzygnost LymeLink IgG (Dade Behring, Siemens, Germany). We used the Lyme neuroborreliosis Dako test for detection of intrathecal antibody production defined as antibody index (AI) (Dako, Glostrup, Denmark). Additional microbiological tests were performed when clinically indicated.

White blood cell (WBC) count in CSF was analysed by Adiva 120 (Bayer) or Fuchs Rosenthal chamber ($<30 \times 10^6$/L) from 2001 to July 2007 and thereafter by XE-5000 (Sysmex). CSF proteins were analysed by Modular (Roche).

The registry data used in this study were anonymous, and therefore a separate ethical license for the study was not obtained. The study was approved by the Privacy Protection Supervisor of the Hospital.

2.3. Definitions. Pleocytosis was defined as CSF WBC count $>7 \times 10^6$/L, according to Clinical and Laboratory Standards Institute guidelines [14].

LNB was diagnosed in children with neurological symptoms suggestive of LNB with the presence of CSF pleocytosis and BB antibodies and/or EM. Confirmed LNB was defined when intrathecal BB antibody production was proven. Probable LNB was defined if BB antibody in serum and/or EM were found in addition to typical symptoms. Definitions were in accordance with the updated European recommendations [15].

FNP was defined as an acute palsy involving the facial muscles in both upper and lower parts of the face, either unilateral or bilateral. Children were diagnosed with headache and/or neck stiffness as the only symptom if they had no other signs of neurological involvement, anorexia or fever.

2.4. Statistics. Differences in numbers between groups were analysed by the Chi-square test. Comparisons of continuous data between groups were done by the nonparametric Mann-Whitney *U*-test, and the results are presented as median and quartiles. Variance was tested by Levene's test for equality of variances. The influence of gender and covariates on clinical and laboratory outcomes were analysed by linear regression analyses. Each explanatory variable was first analyzed in simple regression models and in a fully adjusted model. All variables were further included in a backward stepwise multiple regression analyses. The final model included variables significant at the 5% level and interaction was tested for. All analyses were 2 tailed, and data were analysed using the IBM-SPSS statistical package (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY; IBM Corp.).

3. Results

As published earlier, in total, 142 children aged 3 months to 14 years were diagnosed with LNB and included in the study, giving an annual incidence of 26/100 000 [5]. Complete numbers of microbiological tests performed in the children are presented in Table 1. All tests except for BB antibodies were negative.

There was no difference in the total rate between genders, neither for all children nor for children with confirmed or probable LNB (Table 2). However, FNP was more common in girls than in boys with LNB. The total rate of children with headache and neck stiffness did not differ between genders, but headache and/or neck stiffness as the only symptom was more common in boys than in girls (Table 2). Having a history of EM did not differ between genders.

The girls diagnosed with LNB were younger than the boys, but the distribution of age did not differ between genders (Table 2). The girls had a shorter duration of symptoms before admission than boys. The CSF cellular pattern was available in 139/142 children, and 137/139 had predominantly mononuclear cells. All children with LNB were diagnosed

Table 1: Numbers of positive and negative microbiological tests in 142 children with Lyme neuroborreliosis.

	Number	CSF bacterial culture*	BB antibodies	BB antibody index	HSV1 CSF-PCR	Enterovirus CSF-PCR	VZV CSF-PCR	*M. pneumoniae* CSF-PCR	*M. pneumoniae* CF test	EBV-antibody	CMV antibody
LNB	**142**	**0/142**	**139/3**	**91/44**	**0/34**	**0/26**	**0/14**	**0/22**	**0/54**	**0/37**	**0/39**
Confirmed NB	91	0/91	91/0	91/0	0/21	0/16	0/10	0/16	0/38	0/27	0/30
Probable NB	51	0/51	48/3	0/44	0/13	0/10	0/4	0/6	0/16	0/10	0/9

*Positive/negative tests. LNB: Lyme neuroborreliosis, CSF: cerebrospinal fluid, BB: *Borrelia burgdorferi*, HSV1: herpes simplex virus type 1, PCR: polymerase chain reaction, VZV: varicella zoster virus, *M. pneumoniae*: *Mycoplasma pneumoniae*, EBV: Epstein-Barr virus, CMV: cytomegalovirus, and CF: complement fixation.

Table 2: Differences in numbers and clinical and laboratorial characteristics between boys and girls in 142 children hospitalized with Lyme neuroborreliosis (LNB) at Stavanger University Hospital during 2001–2009.

	All children ($n = 142$)	Boys ($n = 73$)	Girls ($n = 69$)	Boys versus girls (p value)
All children with LNB (%)		73 (51)	69 (49)	0.89
Confirmed LNB, *n* (%)	91 (64)	46 (63)	45 (65)	0.86
Probable LNB, *n* (%)	51 (36)	27 (37)	24 (35)	0.78
Acute facial palsy, *n* (%)	104 (73)	45 (62)	59 (86)	**0.001**
Headache and neck stiffness; *n* (%)	33 (23)	21 (28)	12 (17)	0.11
Headache and/or neck stiffness as the only symptom *n* (%)	29 (20)	22 (30)	7 (10)	**0.003**
History of erythema migrans, *n* (%)	33 (23)	15 (21)	18 (26)	0.44
Age (years), median (IQR)	6 (5–8)	7 (5–9)	6 (4–7)	**0.005**
Age, variance				0.2
Month of occurrence, variance				0.84
Days of symptoms on admission, median (IQR)	5 (2–14)	7 (3–16)	4 (1–10)	**0.008**
CSF WBC count $\times 10^6$/L, median (IQR)	166 (90–340)	202 (101–430)	131 (77–280)	**0.004**
CSF protein, mg/L, median (IQR)	520 (340–755)	560 (385–795)	480 (330–700)	0.083
CSF glucose, mmol/L, median (IQR)	3.0 (2.8–3.4)	3.0 (2.8–3.3)	3.1 (2.8–3.4)	0.57
Pos BB Ab* *n*; BB index/s-BB IgM/s-BB IgG	91/113/85	46/58/42	45/55/43	0.86/0.86/0.77

*BB: *Borrelia burgdorferi*. 2 girls and 1 boy had ECM but negative BB Ab tests and therefore were diagnosed as probable LNB.

from April to December and there was no difference in the monthly distribution between genders.

The median levels of CSF WBC were higher in boys than in girls, whereas the levels of CSF protein and CSF glucose did not differ between genders. Further, the proportion of children with positive BB antibodies in serum or CSF or with a positive BB index did not differ between genders (Table 2).

By univariate linear regression analyses, gender, having facial palsy, or having headache and/or neck stiffness as the only symptom was associated with the level of WBC in CSF, whereas duration of symptoms and age were not associated with the level of WBC (Table 3). In the multivariate analysis, both gender and having headache and neck stiffness remained associated with the level of CSF WBC in the final model (Table 3).

In a multivariate analysis with duration of symptoms before admittance as outcome, FNP was associated with the duration of symptoms ($B = -14.5$ (-18.9, -10), $p < 0.001$), whereas gender and headache and neck stiffness were not associated with the duration of symptoms (data not shown), meaning that gender did not have an independent effect on the duration of symptoms before admittance.

4. Discussion

In this single centre population based study which is among the largest studies of childhood LNB in Europe, we found genders differences in childhood LNB not reported earlier. There was no difference in the total incidence between genders, but there were significant differences in the clinical presentation of LNB between girls and boys. A striking finding was that girls more often had FNP than boys, whereas boys more often had headache and/or neck stiffness as the only symptom. Boys had a higher level of inflammation in CSF, and gender and headache and neck stiffness were associated with the level of CSF WBC in a multivariate regression analyses. Girls were younger and had a shorter duration of symptoms before admission, but only FNP was associated with the duration of symptoms before admission in the multivariate regression analyses.

Table 3: Linear regression model with cerebrospinal fluid white blood count as dependent variable in 142 children hospitalized with Lyme neuroborreliosis at Stavanger University Hospital during 2001–2009.

Risk factor	Unadjusted model			Adjusted model			Final model		
	B	95% CI	*p* value	*B*	95% CI	*p* value	*B*	95% CI	*p* value
Boys	98.1	(34.7, 162)	0.003	73.7	(8.9, 139)	0.021	84.8	(22.7, 147)	0.008
Facial palsy	−117	(−188, −45.5)	0.002	−83.1	(−167, 1.2)	0.053			
Headache and neck stiffness	131	(56.3, 205)	<0.001	99.8	(23.3, 176)	0.011	117	(43.8, 191)	0.002
Age (months)	5.2	(−7.1, 17.4)	0.404	−1.2	(−13.1, 10.8)	0.847			
Duration (days)	1.4	(−1.1, 3.9)	0.27	−1.1	(−3.8, 1.6)	0.412			

There was no interaction between gender and headache and neck stiffness.

The epidemiological results and conclusions in our study depend on a correct diagnosis of LNB. We based the diagnosis on the most updated European case definitions [15]. According to these case definitions, demonstration of CSF pleocytosis is mandatory for the diagnosis of LNB.

In contrast to our results, several other studies report LNB to be more common in boys than in girls [3, 10, 16, 17]. A male predominance in LNB was recently reported in a comprehensive study in adult patients from Slovenia, where 61% of patients with LNB were male [9]. In a Swedish study of patients of all ages, 62% were male; however, the proportion among children was not specified [18].

Compared to other studies, we found a higher proportion of girls with LNB and they had FNP more commonly. The female predominance of FNP in children with LNB in the present study has not been reported previously to our knowledge. The opposite was reported in a small prospective German study, with 11 of 16 consecutive children with FNP and LNB being boys [19].

We have previously reported the highest incidence of FNP in children in Europe [5]. Children in the study area with FNP were admitted to the Paediatric Department without delay, and a lumbar puncture was performed. To our knowledge, no other studies have used this diagnostic approach [17]. The need for a lumbar puncture for the diagnosis of LNB in children with FNP is still under debate [20, 21]. However, depending on serological blood tests only, high numbers of false negative tests are likely [11, 22]. With our diagnostic routine, we consider the number of children diagnosed with LNB to be close to the true incidence.

In general, LNB is more common in children than in adults, and the frequency of FNP is more common in children than in adult patients with LNB in Europe [3, 23]. Furthermore, Berglund et al. observed that children more often had tick bites in the head and neck region compared to adults, possibly explaining these findings [3]. This may relate to the tick behaviour, questing on average 50 cm above the ground [24]. When playing, children may expose their head and neck to grass and bushes in a different way than adults, and a tick bite in this region may have a higher tendency to result in FNP. Possibly, due to longer hair, girls may be more exposed to BB by catching up questing ticks and thereafter cover the ticks more effectively than in boys with short hair. This may contribute to a higher proportion of girls presenting with FNP due to LNB, but this needs to be further studied. If LNB with FNP is more common in girls as our results suggest, our aggressive approach to children with FNP may have included more girls with LBN compared to other studies, thereby equalizing the male predominance in children with LNB found in other studies.

Headache and/or neck stiffness as the only symptom with absence of other neurological signs has also been shown by others to be a common presentation of childhood LNB [17], which may represent symptoms of meningeal inflammation. This is the first study to show a male predominance in this clinical subgroup of childhood LNB, but the reason for this is not known. Different genospecies of BB may give different clinical presentations of LNB, and all of the human pathogenetic BB gene-species have been detected in questing ticks from a nearby area to the study area [25]. Strle and his group have reported a male predominance in *B. garinii* skin infections [9]. Furthermore, different gene-species of BB are reported to give different clinical presentations of LNB as demonstrated in a study of adult patients with LNB [2]. In that study, *B. garinii* was more common in CSF in patients with typical early LNB with painful meningoradiculoneuritis (Bannwarth syndrome), whereas *B. afzelii* was more common in patients with less specific manifestations of LNB. A speculation could be that the difference in clinical presentation between girls and boys in our study could to some extent be due to different gender disposition for infection with different BB genospecies. However, it has not yet been studied if different genospecies of BB have any gender preferences in children with LNB.

We also found a higher level of CSF inflammation in boys, independent of the clinical presentation. BB produces no toxins and the manifestations of LB and LNB are probably mainly a result of the immune response of the host [26, 27]. In general, the immune system may show differences between genders on a DNA sequence level and on a secondary epigenetic genome regulation level [28]. Furthermore, specific immune responses differ between genders with age, as a result of changing levels of sex steroid hormones through the dynamic interaction with the immune system [29]. Possibly, this could partly explain the observed sex-specific infection rates in humans, even in LNB. In postmenopausal women, a T-helper lymphocyte type 2 (Th2) pattern was associated with a higher tendency for reinfection with borreliosis, compared to men [30]. Also, the CSF cytokine pattern beyond the acute stage of LNB is associated with a Th2 response [31]. Atopy

is considered to be a Th2-driven immunopathy, and during childhood atopic disease is more common in boys. We could speculate if this may be related to a more generalised and stronger immune response in boys with LNB, but this has to be further studied.

Further, headache and/or neck stiffness as the only clinical presentation was also independently related to the level of CSF inflammation, suggesting a pathophysiological link. It has been speculated that the dissemination of BB in LNB may differ between meningoradiculitis and more diffuse meningitis [4]. Both Bannwarth's syndrome and FNP may be the result of a local invasion of the spirochete in the nerve root, whereas general meningitis may be the result of haematogenous spread [4, 32]. This may result in differences both in clinical presentation and in laboratory results, as shown in our study. How this is related to gender needs further studies.

The retrospective design of the study may to some extent weaken the quality of the clinical characteristics recorded in the medical records. Data about clinical symptoms are based on parents' and physicians' observations, and some of these variables may be less reliable in younger children. However, we focused on objective variables as FNP, and laboratory results are independent of the retrospective design. It is in our opinion a strength of the study that uniform and extensive procedures to identify and diagnose children with LNB were introduced in the region before the study period and were performed consistently during this period.

5. Conclusion

In this single centre population based study of children with LNB, we found that FNP was a more common presentation in girls, whereas headache and/or neck stiffness as the only symptom was more common in boys. Boys had a higher level of CSF inflammation, independent of the clinical presentation. The interplay between the properties of ticks and BB genospecies and children causing Lyme borreliosis is complex. The observed differences between genders may be of importance for the understanding of the pathophysiology in LNB.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Differences according to Sex in Sociosexuality and Infidelity after Traumatic Brain Injury

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Objective. To explore differences according to sex in sociosexuality and infidelity in individuals with TBI and in healthy controls. *Participants*. Forty-two individuals with mild, moderate, and severe TBI having completed a postacute TBI rehabilitation program, at least six months after injury, and 47 healthy controls. *Main Measures*. Sociosexual Orientation Inventory-Revised (SOI-R) and Attitudes toward Infidelity Scale. *Results*. Overall, men score significantly higher than women in sociosexuality. However, there was a nonsignificant trend towards a reduction of sociosexuality levels in men with TBI. Infidelity levels were comparable in healthy controls and individuals with TBI. In individuals with TBI, less acceptance of infidelity was significantly associated with an unrestricted sociosexual orientation, but not in healthy controls. *Conclusions*. As documented in previous cross-cultural studies, men have higher levels of sociosexuality than women. However, men with TBI showed a tendency towards the reduction of sociosexuality. The possibility of a latent explanatory variable is suggested (e.g., post-TBI neuroendocrinological changes). TBI does not seem to have an impact on infidelity, but individuals with TBI who express less acceptance of infidelity also report a more promiscuous mating strategy regarding their behavior, attitudes, and desire. Theoretical implications are discussed in terms of evolutionary theories of human sexuality and neuropsychology.

1. Introduction

Nonmonogamy is part of the evolutionary trends preserved in humans [1]. In fact, infidelity constitutes probably one of the most complex problems faced by mental health professionals, especially couple therapists, marriage and family therapists, and psychotherapists [2, 3]. Based on evolutionary theories, there are sex differences regarding reactions to infidelity. For instance, men seem to be more distressed by sexual infidelity (e.g., sexual relationship or sexually oriented physical contact with another person), while women may be more distressed by emotional infidelity (e.g., diversion of the partner's emotional commitment toward another person) [4]. Interestingly, human brains show different activation patterns in response to different types of infidelity; men and women process sexual and emotional infidelity using different neuropsychological networks [5].

Nonetheless, the experience of infidelity is linked to the individuals' proneness to be unfaithful. This is the research area of sociosexuality, also known as sociosexual orientation (SO). Kinsey was the first to introduce the term in his pioneer studies describing individual differences in people's willingness to engage in uncommitted sexual relationships [6, 7]. Sociosexuality levels range from an unrestricted SO to a restricted SO. Individuals with an unrestricted SO tend to a more promiscuous mating strategy, are quicker to have sex, and may experience lower levels of romantic relationship closeness or commitment. Conversely, individuals with

a restricted SO tend to a more monogamous mating approach, invest more time in courtship, and develop strong emotional connections in long-term relationships [8].

Undoubtedly, the most striking cross-cultural evidence of the existence of SO comes from the international sexuality description project [9]. This groundbreaking analysis of sociosexuality in 48 nations demonstrated that, compared to women, men have higher levels of sociosexuality across cultures and that sex differences in sociosexuality are culturally universal. Furthermore, even though sex differences in sociosexuality are attenuated in cultures with more gender equality in terms of political, economic, and relational freedom, the findings of this study did not suggest that men and women tend to become equally promiscuous in attitudes and behaviors. Research has demonstrated the existence of a sociosexuality-testosterone association in both men and women and revealed that the nature of these associations varies by gender and relationship status (e.g., partnered men who reported an unrestricted sociosexuality had testosterone levels that were comparable to those of single men) [10]. However, research in the area of sociosexuality has included not only differences according to sex [11] but also many other variables, such as racial differences [12], infidelity [13], attachment style [4], self-image [14], physical attractiveness and sexual aggression perpetration [15], and personality styles [16], among others.

Overall, the aforementioned studies highlight the importance of sociosexuality, from both an evolutionary and an environmental/sociocultural perspective to explain the reasons behind the fact that, on average, men are more willing than women to engage in casual sex. Two different interpretations have been suggested. In his seminal theory of parental investment and sexual selection, Trivers (1973) defined parental investment as the resources that a parent spends on his offspring in order to increase the chances of surviving and reproducing, at the cost of this parent's ability to invest in other offspring [17–19]. Together, these studies outline that, from an evolutionary perspective, men have more to gain and less to lose by having sex outside a committed relationship. In contrast, women have to invest time and energy devoted to pregnancy and childbearing. This interpretation contrasts with an environmental/sociocultural perspective, suggesting the possibility that differences in sociosexuality can be associated, in part, with the variations in the regional prevalence of infectious diseases. People in regions with a history of a high prevalence of infectious diseases report lower levels of sociosexuality [20].

Given the evolutionary, neuropsychological, and environmental/sociocultural rationales put forward in the research literature on sociosexuality, its presentation in acquired medical conditions where changes in brain functions are induced warrants investigation. Traumatic brain injury (TBI), which is among the most common neurological conditions [21], is a form of brain injury which is receiving increasing attention in the area of research on sexuality, given its biopsychosocial consequences [22–27].

Also, TBI impacts people's sexuality, with 50 to 60% of persons reporting some level of disruption after injury [28–30], and sexual function is compromised as a result of the post-TBI changes involving the neurological aspects of sexuality [27]. Sexual difficulties after TBI have thus been associated with medical and physical issues (e.g., neuroendocrine and hormonal disorders [31, 32], neuropsychological and psychological effects (e.g., depression [33]), and relationship changes (e.g., intimacy [34])) [25].

To our knowledge, previous studies on sexuality and TBI have not addressed attitudes towards infidelity and sociosexuality in individuals with TBI. The current study thus aimed to explore differences according to sex in sociosexuality and attitudes towards infidelity in individuals with TBI and in healthy controls. In the current study, infidelity is defined as a person being unfaithful while in a committed monogamous relationship. Since this is a novel and exploratory study, no specific hypotheses related to TBI participants are advanced, but it is postulated that there are statistically significant differences according to sex in sociosexuality for healthy controls, with men having higher levels of SO compared to women.

2. Methods

2.1. Participants. The sample consisted of 42 individuals with TBI and 47 healthy controls. Individuals with TBI were recruited from a TBI outpatient rehabilitation center in Montreal, which offers social and vocational rehabilitation services to individuals with moderate or severe TBI, as well as to individuals with mild or complex mild TBI showing atypical recovery to which the brain injury appears to contribute predominantly. Individuals with TBI were recruited based on the following inclusion criteria: (1) individuals who have sustained, according to the TBI guidelines put forward by the Québec Ministry of Health [35], a mild (Glasgow coma scale (GCS) scores 13–15), moderate (GCS scores 9–12), or severe (GCS scores 3–8) TBI, (2) individuals who are six or more months post-injury, (3) individuals who are 18 years or older, and (4) individuals who report to be able to read, write, and speak either French or English. Exclusion criteria, as verified in medical records, included (1) history of learning or language disability, including aphasia or communication disorders and (2) self-report of preinjury psychiatric, sexual, or neurological disorders other than TBI. A detailed description of the sociodemographic characteristics of the sample is provided in Table 1.

In terms of clinical characteristics, as indicated in Table 2, the majority corresponds to mild TBIs (66.8%). The cause of the injury was predominantly associated with a motor vehicle accident (42.9%) followed by work and sports-related accidents (14.3%). Half of them had a history of loss of consciousness (50%) and 47.6% had also a history of posttraumatic amnesia documented in the medical chart. Individuals with TBI were on average 3.3 years after the injury (SD = 4.3). Positive findings on CT scan or MRI suggesting a brain injury were documented in 59.5%. Glasgow coma scale at admission was on average 12.5 (SD = 3.6), with a loss of consciousness of a mean of 5.8 hours (SD = 28.8) and posttraumatic amnesia duration of 80.8 hours (SD = 203.8) as indicated in medical records.

Table 1: Sociodemographic characteristics of the TBI and healthy control samples ($N = 89$).

	TBI	Healthy controls	TBI	Healthy controls
	Frequency (%)		Mean (SD)	
Gender				
Male	19 (45.2%)	24 (51.1%)		
Female	23 (54.8%)	23 (48.9%)		
Race and ethnicity				
White	38 (90.5%)	45 (95.7%)		
Hispanic	4 (9.5%)	2 (4.3%)		
Work status				
Full time	16 (38.1%)	26 (55.3%)		
Part time	7 (16.7%)	7 (14.9%)		
Unemployed	19 (45.2%)	13 (27.7%)		
Missing	0 (0%)	1 (2.1%)		
Relationship status				
Single	26 (61.9%)	21 (44.7%)		
Married	4 (9.5%)	5 (10.6%)		
Separated	0 (0%)	4 (8.5%)		
Divorced	2 (4.8%)	2 (4.3%)		
Common-law	10 (23.8%)	14 (29.8%)		
Widow/widower	0 (0%)	1 (2.1%)		
Age (years)			37.9 (9.7)	37.6 (10.7)
Education (years)			12.8 (3.3)	13 (3.0)
Annual income (CAD)			39 007.5 (19 239.6)	31 975.6 (18 909.9)

Note. CAD, Canadian dollars.

Healthy controls were recruited from the community following these inclusion criteria: (1) being 18 years or older and (2) reporting to be able to read, write, and speak either French or English. Exclusion criteria included (1) self-reported history of learning or language disability and (2) self-report of diagnosed psychiatric, sexual, or neurological disorders. Their sociodemographic characteristics are presented in Table 1.

2.2. Procedure. The current study was approved by the Research Ethics Board (REB) of the Center for Interdisciplinary Research in Rehabilitation of Greater Montreal (CRIR). Data collection was undertaken between April 2013 and August 2014.

From the rehabilitation center's database, a total of 345 individuals with TBI were eligible for participation. Following telephone contact by a person independent of the research project (e.g., archives technician) who proposed participation in the study, 13 of them refused to participate and 224 could not be reached. Individuals with TBI who accepted to participate were mailed two envelopes: (a) a consent form (which included a thorough explanation of the study) and (b) a package containing the questionnaires. Each of the envelopes contained a stamped and addressed envelope so that the participant could return each document independently. Questionnaires and consent forms were sent to 108 individuals with TBI and 42 of them successfully completed and returned both (41 in French and 1 in English).

In the context of a larger sexuality study, healthy controls were recruited from the general community through newspaper advertisements, as well as notices in community centers, universities, and libraries. A total of 242 people from the community expressed their interest to participate in the sexuality study. Following a phone call by the research team to verify inclusion/exclusion criteria, questionnaires and consent forms were sent to 191 healthy controls. Twenty-eight of them did not return both the questionnaires and consent forms while 163 returned them. For the purposes of this study, 47 healthy controls (41 in French and 6 in English) were matched to TBI participants from the database of the aforementioned large sexuality study, based on sociodemographic variables (e.g., age, gender, years of education, annual income, work, and relationship status). Questionnaire data were subsequently analyzed.

Voicemail and email accounts were created in order to receive and answer any questions for individuals with TBI or healthy controls. All participants received a financial compensation of CAN$15 (fifteen Canadian dollars) for their participation after returning their questionnaires and consent forms.

2.3. Instruments

2.3.1. Medical History and Demographic Information. Participants completed an in-house short medical and sociodemographic questionnaire that included questions related

Table 2: Clinical characteristics of the sample of individuals with TBI ($N = 42$).

	Frequency (%)	Mean (SD)
Cause of the injury		
Motor vehicle accident	18 (42.9%)	
Violence	2 (4.8%)	
Falls	4 (9.5%)	
Sports-related	6 (14.3%)	
Work accident	6 (14.3%)	
Other	3 (7.1%)	
Missing	3 (7.1%)	
LOC		
Yes	21 (50%)	
No	18 (42.9%)	
Missing	3 (7.1%)	
PTA		
Yes	20 (47.6%)	
No	19 (45.3%)	
Missing	3 (7.1%)	
Positive CAT or MRI		
Yes	25 (59.5%)	
No	10 (23.8%)	
Missing	7 (16.7%)	
Severity of the injury		
Mild TBI	28 (66.8%)	
Moderate TBI	3 (7.1%)	
Severe TBI	8 (19%)	
Missing	3 (7.1%)	
GCS		12.5 (3.6)
Years after injury		3.3 (4.3)
Length of LOC (hours)		5.8 (28.8)
Length of PTA (hours)		80.8 (203.8)

Note. LOC, loss of consciousness; PTA, posttraumatic amnesia; CAT, computed axial tomography; MRI, magnetic resonance imaging; and GCS, Glasgow coma scale.

to participant's age (e.g., number of years), race/ethnicity (e.g., white, Hispanic), gender (e.g., male, female), years of education (e.g., number of years), relationship status (e.g., single, married), annual income (in Canadian dollars), work status (e.g., full time, unemployed), frequency of alcohol (e.g., never to everyday), and recreational drug use (e.g., yes, no). For TBI participants, data regarding preinjury and injury related variables (e.g., severity of injury, number of years after injury, length of loss of consciousness in hours, length of posttraumatic amnesia in hours, and presence/absence of neuroradiological abnormalities) were extracted from medical records.

Each of the participants was administered the following questionnaires.

Sociosexual Orientation Inventory-Revised (SOI-R). The SOI-R is a 9-item self-report questionnaire, each with a 9-point response scale, developed to measure individual differences in willingness to engage in casual, uncommitted sexual relationships [8]. In particular, the SOI-R assesses individual's past behavior in terms of number of casual and changing sex partners, the explicit attitude towards uncommitted sex, and sexual desire for people with whom no romantic relationship exists [36]. Scores for behavior, attitude, and desire facets as well as a total score are obtained [37]. Higher scores on the SOI-R correspond to individuals who have an unrestricted sociosexual orientation (or have a more promiscuous mating strategy) whereas lower scores correspond to restricted sociosexual orientation (or individuals who follow a more monogamous mating strategy). The SOI-R proposes adequate reliability and validity both within and across the diverse range of human cultures [9] and has been used widely in a variety of research and clinical samples [37–44]. For items 1 to 3, values of 1 to 9 should be assigned to the responses. Thus, all nine items have values from 1 to 9 (9-point scale). Item 6 should be reverse-keyed. Items 1 to 3 are aggregated (summed or averaged) to form the behavior facet, items 4 to 6 form the attitude facet, and items 7 to 9 form the desire facet. Finally, all nine items can be aggregated to form a full-scale score that represents the global SO. In the current study, the internal consistency of SOI-R (Cronbach's $\alpha = 0.89$), as well as all of the three facets of the SOI-R, was very good (behavior Cronbach's $\alpha = 0.91$, attitude Cronbach's $\alpha = 0.84$, and desire Cronbach's $\alpha = 0.88$).

Attitudes toward Infidelity Scale. This is a 12-item self-report questionnaire to measure the acceptance of infidelity. In the context of this scale, infidelity is defined as a person being unfaithful in a committed monogamous relationship. Each item is rated on a 7-point Likert scale with 1 reflecting the least acceptance of infidelity and 7 the greatest acceptance of infidelity. The lower the total score (12 is the lowest possible score), the less the person's acceptance of infidelity, whereas the higher the total score (84 is the highest possible score), the greater the respondent's acceptance of infidelity [45]. A score of 48 places the person at the midpoint between being very disapproving of infidelity and very accepting of infidelity. Before adding the numbers, score items 2, 5, 6, 7, 8, and 12 must be reversed (e.g., 1 = 7, 2 = 6, 3 = 5, 4 = 4, 5 = 3, 6 = 2, and 7 = 1). After making these changes, the numbers must be added to obtain the full-scale score [46]. A translation/back-translation procedure was implemented in order to obtain the French version that was used in the present study and its internal consistency was good (Cronbach's $\alpha = 0.79$).

2.4. Statistical Analyses. Demographic characteristics of individuals with TBI were compared to those of healthy controls using t-tests for continuous variables and χ^2 tests for nominal variables, taking into account a significance level $p < 0.05$.

Two-way between-groups analyses of variance (two-way ANOVA) were performed to explore the impact of sex (e.g., male and female) and group (e.g., individuals with TBI and healthy controls) on sociosexuality.

An independent-samples t-test was performed to compare infidelity levels between individuals with TBI and healthy controls. Pearson correlation analyses were used

to examine the relationship between sociosexuality facets (behavior, attitude, and desire), infidelity levels, and injury characteristics (years after injury, GCS score, and hours of posttraumatic amnesia) in individuals with TBI.

Statistical analyses were conducted with IBM SPSS version 21 [47].

3. Results

Comparison of the sociodemographic characteristics of the TBI and healthy control groups, described in Table 1, indicates that there were no significant differences between groups in terms of age, gender, race/ethnicity, work status, relationship status, years of education, and annual income. Also, both groups were comparable in frequency of alcohol consumption, recreational drug use, and the use of one prescribed medication. Comparison of the sociodemographic and clinical characteristics of the TBI group by gender indicates that there were no significant differences between men and women with TBI in terms of age, race/ethnicity, work status, relationship status, years of education, annual income, alcohol consumption, recreational drug use, medication intake, injury severity, time after injury, neuroimaging evidence of brain injury, or loss of consciousness/posttraumatic amnesia duration (all p's > 0.05).

As summarized in Table 3, a two-way between-groups analysis of variance was performed to explore the impact of sex (male-female) and group (individuals with TBI and healthy controls) on sociosexuality, as measured by the SOI-R. The interaction effect between sex and group was not statistically significant, $F(1, 85) = 0.6$, $p > 0.05$. There was a statistically significant main effect for sex, $F(1, 85) = 7.2$, $p < 0.05$; and the effect size was in the range of medium to large effect size (partial eta squared = 0.07) according to the guidelines for the behavioral sciences [48]. The main effect for group, $F(1, 85) = 1.0$, $p > 0.05$, did not reach statistical significance. Compared to females, overall, males had higher levels of sociosexuality. However, there appeared to be a tendency towards a reduction of sociosexuality levels in males with TBI (see Figure 1).

Finally, compared to healthy controls, individuals with TBI did not show statistically significant differences in infidelity, as measured by the total score of the Attitudes toward Infidelity Scale, $t(85) = -0.8$, $p > 0.05$.

3.1. Correlation Matrix. The relationship between infidelity (as measured by the Attitudes toward Infidelity Scale), sociosexuality (as measured by the SOI-R), and TBI characteristics (severity as measured by the score on the GCS scale and by length of posttraumatic amnesia in hours, years after injury) in the group of individuals with TBI was investigated using Pearson product-moment correlation coefficient (see Table 4). There was a large negative correlation between the scores on the infidelity scale and the SOI-R ($r = -0.58$, $p < 0.01$), with low levels of infidelity scores (less permissiveness regarding infidelity) associated with high levels of SO (unrestricted SO). In addition, infidelity scores were moderately associated with behavioral sociosexuality ($r = -0.34$, $p < 0.05$) and sociosexual desire ($r = -0.49$, $p < 0.01$). Also, infidelity scores showed a large correlation with sociosexual attitudes ($r = -0.57$, $p < 0.01$). In contrast, these associations were not significant in the group of healthy controls (all p's > 0.05).

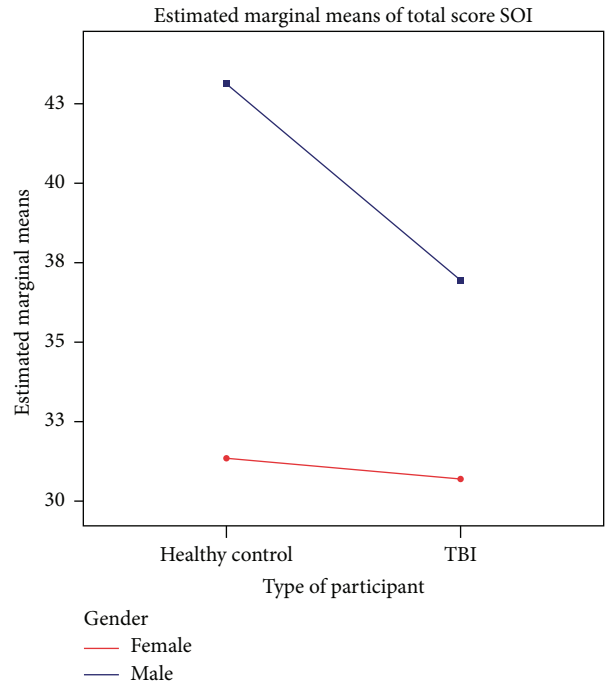

Figure 1: Estimated marginal means for sociosexuality as a function of group and gender. Abbreviation: SOI, total score of the Sociosexual Orientation Inventory.

Finally, neither infidelity scores nor sociosexuality was associated with severity of the injury (GCS score or length of posttraumatic amnesia), or with time since injury (all p's > 0.05).

4. Discussion

The current study aimed to explore differences according to sex in sociosexuality and attitudes towards infidelity in individuals with TBI and healthy controls. The main finding of the current study is that, compared to healthy controls, our TBI sample appeared to show a tendency towards a reduction of differences according to sex in sociosexuality. Interestingly, there was a trend suggesting a decrease in sociosexuality levels in men with TBI. To our knowledge, this study is the first suggesting the possibility of a decline of this cross-cultural and evolutionary distinction following TBI in males. This finding is important since it could suggest that a complex and deeply rooted psychosexual trait, such as sociosexuality, could be modified after a neurological insult such as TBI.

The tendency towards the reduction of differences according to sex in sociosexuality levels following TBI does not seem to be explained by sociodemographic or clinical variables. Then, it is possible that a latent variable could account for this trend. From the standpoint of neuropsychology, a possible explanation for this might be

Table 3: Means, standard deviations, and analysis of variance (ANOVA) results for sociosexuality and infidelity as a function of group and sex.

Measure	TBI		Healthy controls		ANOVA F		
	M	SD	M	SD	Group (G)	Sex (S)	G × S
SOI-R					1.0	7.2*	0.6
Female	30.7	14.8	31.3	12.9			
Male	36.9	19.2	43.1	16.0			
SOI-BEH					0.3	2.5	3.5
Female	8.2	5.0	6.6	3.0			
Male	7.8	7.3	11.0	7.6			
SOI-ATT					2.0	3.3	0.1
Female	14.1	7.8	15.7	7.2			
Male	16.4	7.9	19.2	6.2			
SOI-DES					0.1	10.3*	0.0
Female	8.3	4.9	9.0	5.5			
Male	12.7	7.9	12.9	5.9			
ATIS					0.7	0.6	0.0
Female	62.7	12.9	60.5	15.4			
Male	60.7	14.8	58.0	10.9			

Note. * $p < 0.05$.
SOI-R, total score of the Sociosexual Orientation Inventory-Revised; SOI-BEH, sociosexual behavior; SOI-ATT, sociosexual attitudes; SOI-DES, sociosexual desire; and ATIS, Attitudes toward Infidelity Scale.

Table 4: Correlation matrix between infidelity, sociosexuality, and brain injury characteristics.

		1	2	3	4	5	6	7
1	ATIS	—						
2	SOI-R	−0.58**	—					
3	SOI-BEH	−0.34*	0.77**	—				
4	SOI-ATT	−0.57**	0.84**	0.45**	—			
5	SOI-DES	−0.49**	0.84**	0.52**	0.57**	—		
6	GCS	0.12	−0.30	−0.22	−0.30	−0.21	—	
7	Years after TBI	0.17	−0.18	−0.15	−0.27	0.01	0.05	—
8	PTA (hours)	−0.01	0.18	0.31	0.12	0.02	−0.58**	−0.05

Note. * $p < 0.05$; ** $p < 0.01$.
ATIS, scores of the attitudes toward infidelity scale; SOI-R, total score of the Sociosexual Orientation Inventory-Revised; SOI-BEH, sociosexual behavior; SOI-ATT, sociosexual attitudes; SOI-DES, sociosexual desire; GCS, Glasgow coma scale; and PTA, posttraumatic amnesia.

the existence of post-TBI neuroendocrine changes. Previous research indicating the existence of a link between testosterone and sociosexuality could represent a basis for such modifications [10]; the effects of neuroendocrine post-TBI dysfunction on testosterone levels and its precursors could modify sociosexuality levels. In fact, posttraumatic hypopituitarism is an underdiagnosed complication of TBI [49] and reports indicating that TBI is a common cause of pituitary dysfunction are compelling [50–98]. The main gonadal male hormone is testosterone, which is essential for the development of secondary sexual characteristics and behavioral patterns [99]. In addition, evidence from animal models of sexuality following TBI indicates that TBI-induced hypopituitarism in male rats causes decreased testosterone production and changes in sexual behavior [100]. However, this interpretation must be considered with caution since we did not measure testosterone levels in our study participants. Hence, further research in individuals with TBIs of different severities needs to be conducted to determine if this is an actual contributing cause.

As expected and consistent with previous reports, our results showed that there are statistically significant differences according to sex in sociosexuality. The results of the current study support our hypothesis and add new evidence to the fact that, compared to women, men have higher levels of sociosexuality across cultures [9]. These findings corroborate a great deal of the previous work in the field of sociosexuality [8, 11, 14, 15, 37, 101–104]. The results are also in the same direction of Canadian reports of sexual attitudes and behaviors. Specifically, the results of a Canadian study revealed that, compared to women, men had more frequent sexual thoughts, were more likely to report having engaged in oral sex, had a lower age at first intercourse, had more sexual partners, and were more willing to have casual sex [105].

Theories from evolutionary and comparative psychology bring elements to try to understand the fact that, on average,

men are more willing than women to engage in casual sex, as can be explained by the theory of parental investment and sexual selection. The literature in the area of evolutionary psychology suggests that, compared to males, viviparity and the development of the placenta placed an important burden of time and energy in females [106]. This differential investment would be responsible for hypothalamic distinctions in the course of evolution, with differential hormonal effects during the development of the brain. It is therefore likely that post-TBI neuroendocrine dysfunction could change the expression of these evolutionary characteristics. However, this interpretation needs to be considered with caution not only because we did not measure hormonal changes, but also because human sexual behavior does not rely only on hormones. Human sexuality is multifactorial and based on psychological traits, behaviors, and cultural specificities, among others. Studies incorporating a more environmental/sociocultural perspective in this area are thus warranted considering the complexity and inherent multidisciplinary nature of sexuality.

Our third main finding is that infidelity levels, with infidelity defined as a person being unfaithful in a committed monogamous relationship, were comparable in healthy controls and individuals with TBI. Also, there were no differences according to sex. Taken together, these results are the first to reveal the nature of attitudes toward infidelity following TBI. It can thus be suggested that attitudes towards infidelity following TBI are not different from those of healthy controls. Therefore, a possible explanation is that, after a TBI, people's attitudes toward infidelity do not change.

In contrast to earlier findings showing that an unrestricted sociosexual orientation is associated with a greater willingness to engage in infidelity [13], the results of the current study could not find evidence of this link. A possible explanation of this might be that we used a general infidelity scale, while Mattingly et al.'s study included ambiguous, deceptive, and explicit infidelity [13]. This lack of uniformity in instruments to measure infidelity is one of the challenges regarding research in this area and may be responsible for incongruent findings [2].

Surprisingly, infidelity scores were negatively associated with sociosexual behavior, sociosexual attitudes, and sociosexual desire in individuals with TBI but not in healthy controls. This finding was unexpected and suggests that individuals with TBI reporting low levels in infidelity scores (e.g., disapproving of infidelity) also show high levels of SO (unrestricted SO). This finding indicates that individuals with TBI who express less acceptance of infidelity also report a more promiscuous mating strategy in terms of behavior (e.g., number of sexual partners in the last year), attitudes (e.g., imagining themselves enjoying casual sex with different partners), and desire (e.g., reporting a high frequency of spontaneous sexual fantasies with someone they have just met).

There are several possible explanations for these results. Firstly, individuals with TBI may have problems with emotional regulation that contribute to difficulties to control their own behavior [107]. As a consequence, thinking that being unfaithful in a committed monogamous relationship is not acceptable does not necessarily translate into regulating their own behaviors, attitudes, and desires regarding their willingness to engage in uncommitted sex. In fact, difficulties with behavioral regulation and social cognition are also common symptoms following TBI [108]. Another possible explanation is related to difficulties involving lack of awareness or anosognosia [109]. Anosognosia can affect emotional recognition and the interpretation of social signals [110]. This could explain the existence of this discrepancy where individuals with TBI can have difficulties in integrating what they do with what they think and what they feel. Another possible explanation to address this result can be related to hypersexuality. However, in a multicenter study, the estimated prevalence of inappropriate sexual behaviors following TBI was 8.9% and particularly evidenced in a minority of younger individuals with more severe injuries [111]. Such an explanation seems to be less probable as the sample of this study included a majority of milder injuries.

Limitations and Future Directions. The current study investigated the relationship between sociosexuality and attitudes towards infidelity following TBI. However, the results should be interpreted with caution in the face of several limitations. First, contrary to the epidemiological data of TBI in Canada, the sample included predominantly women with TBI whilst, regardless of age group, the overall rate of TBI is higher in men than women [112]. However, most of research conducted in sexuality and TBI has an underrepresentation of women [113]; so this could also be interpreted as one of the strengths of our study which included more than 45% of males. Furthermore, in the current study, 67% of TBI individuals had a mild TBI. Hence, caution is warranted in generalizing our results to moderate to severe TBI. In consequence, research on sociosexuality and infidelity needs to be conducted in larger samples, in particular with moderate to severe TBI.

Secondly, participants completed self-report measures to describe their sexual behavior. As sex is typically a highly private activity, people can conceal their true sexual behavior in an interview because sometimes they feel intensely embarrassed and threatened and may experience fear of reprisals when asked to reveal their sexual life [114]. However, to increase the validity of self-reported sexual behavior and avoid self-presentation bias, the questionnaires were completed anonymously. The study was conducted in a province that is highly open with respect to sexuality. For example, the results of a study revealed that people living in Quebec were more likely than participants from all other regions of Canada to report an interest in engaging in casual sex [105]. In this respect, our results cannot be extrapolated to other countries with different cultural backgrounds, especially those with more conservative attitudes towards sexuality. Future research should therefore concentrate on the investigation of cultural differences in sociosexuality and attitudes towards infidelity, by carefully controlling for methodological difficulties, such as presentation bias, among others [115].

As a third limitation, the current study was correlational/cross-sectional; so it was not possible to infer directional relationships between sociosexuality and attitudes towards

infidelity in this group of individuals with TBI. Consequently, we cannot make inferences about causation and our interpretations should be treated as exploratory hypotheses. Prospective and longitudinal studies with larger samples will allow further more solid study of attitudes towards infidelity. The reasons are twofold: attitudes can change over time and also the relationships between attitudes with other psychological variables can also change with time. More broadly, additional research is required to understand this dynamics. This information would be useful when addressing psychosexual issues in individuals with TBI.

Finally, our study included exclusively a small sample of adults and, as such, results cannot be generalized to teenagers or older adults with TBI. In fact, most research has focused on adult TBI brain-behavior correlates with minimal involvement of adolescents [116]. In consequence, research needs to examine adolescents with TBI regarding sociosexuality and attitudes toward infidelity. Also, it would be interesting to compare experiences of sexually diverse people regarding infidelity and sociosexuality, such as lesbian, gay, bisexual, transgender, and intersex individuals with TBI [117].

As a closing remark, little attention has been given to within-sex individual differences in the type of infidelity found to be more distressing. This was not part of our study objectives. However, it is recommended to explore the hypothesis that greater sexual permissiveness (e.g., higher scores on sociosexuality) is associated with greater distress to sexual infidelity [4]. Sexual and emotional types of infidelity need to be addressed following TBI.

Despite all these limitations, the present study makes a unique contribution to the field of sexuality following TBI. Our study provides additional evidence with respect to sociosexuality after TBI and suggests a possible link between evolutionary psychology and neuropsychological effects of TBI. A better understanding of the interplay between biological, psychological, and sociocultural processes is needed to do justice to the complexity of this subject matter [118], in particular as it is expressed or modified following TBI.

5. Conclusions

This paper reports the fact that men with TBI show a trend towards the reduction of sociosexuality levels, suggesting the possible modification of a complex and deeply rooted psychosexual trait after a TBI. In addition, our results confirm that there are statistically significant differences according to sex in sociosexuality, supporting previous evidence that, compared to women, men have higher levels of sociosexuality across cultures. Finally, our findings indicate that although infidelity was comparable in healthy controls and individuals with TBI, individuals with TBI who express less acceptance of infidelity also report a more promiscuous mating strategy in terms of behavior, attitudes, and desire. This work contributes to existing knowledge in the field of sexuality and psychosexual changes following TBI. Taken together, the main theoretical implications correspond to the development of a link between evolutionary psychology and neuropsychology.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Sex Differences in Neuropsychiatric Symptoms of Alzheimer's Disease: The Modifying Effect of Apolipoprotein E $\varepsilon 4$ Status

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Sex differences in neuropsychiatric symptoms of Alzheimer's disease (AD) have been demonstrated in previous studies, and apolipoprotein E (ApoE) $\varepsilon 4$ status influences psychiatric manifestations of AD. However, whether ApoE $\varepsilon 4$ status modifies the sex differences in neuropsychiatric symptoms of AD is still unclear. In this study, sex differences in neuropsychiatric abnormalities were stratified and analyzed by ApoE $\varepsilon 4$ status in mild AD and moderate to severe AD separately. The Clinical Dementia Rating (CDR) scale and the Neuropsychiatric Inventory (NPI) were used to assess dementia severity and neuropsychiatric symptoms. No sex differences were found in mild AD. In moderate to severe AD, among $\varepsilon 4$ positive individuals, disinhibition was significantly more prevalent (8.0% in men versus 43.2% in women, $p = 0.003$) and severer ($p = 0.003$) in female patients. The frequency (16.0% in men versus 51.4% in women, $p = 0.005$) and score ($p = 0.004$) of irritability were of borderline significance after strict Bonferroni correction. In conclusion, this study supported the modifying effect of ApoE $\varepsilon 4$ status on sex differences in neuropsychiatric symptoms of AD, and this modifying effect was pronounced in moderate to severe stage of AD. The interaction between gender and ApoE $\varepsilon 4$ status should be considered in studies on neuropsychiatric symptoms of AD.

1. Introduction

Although Alzheimer's disease (AD), as the most common dementia and the major cause for senile dementia, is usually characterized by cognitive impairments, neuropsychiatric symptoms affect most of patients with AD [1]. Neuropsychiatric symptoms are significantly associated with decreased quality of patients' life [2], the heavy burden on caregivers [3], rapid cognitive decline, increased risk of institutionalization, and low survival rate of patients with AD [4, 5]. Sex difference is a common phenomenon in AD and manifests in many ways, and some previous studies had suggested sex-specific neuropsychiatric symptoms in AD. It was reported that male patients with AD were more frequently to exhibit apathy and anxiety, while delusion was more common in female patients [6–8]. The sex differences in neuropsychiatric symptoms also influence the decision of treatment, and male patients are more likely to receive antipsychotic medications [9].

Apolipoprotein E (ApoE) $\varepsilon 4$ allele, as a generally acknowledged genetic risk factor for AD, extensively influences the clinical manifestations of AD, as well as neuropsychiatric symptoms. The associations between ApoE genotype and delusion, aggression, anxiety, apathy, and depression symptoms of AD have been reported [10–12]. Interestingly, the influences of ApoE $\varepsilon 4$ allele on AD are more pronounced in females than in males [13]. Our previous study also suggested that ApoE $\varepsilon 4$ status regulated the effects of sex hormones on neuropsychiatric symptoms of AD in female patients but not in males [14]. Thus, we inferred that ApoE $\varepsilon 4$ status influences sex differences in neuropsychiatric symptoms of AD. However, this aspect still lacks systematic studies.

In this study, we investigated the interactions between gender and ApoE $\varepsilon 4$ status in neuropsychiatric symptoms of AD. Sex differences in neuropsychiatric abnormalities of AD were stratified and analyzed by ApoE $\varepsilon 4$ status.

Considering that dementia severity influences sex differences in neuropsychiatric symptoms [9], gender comparisons were conducted in mild AD and moderate to severe AD separately.

2. Materials and Methods

2.1. Subjects. All subjects were selected from consecutive patients diagnosed with AD in the baseline stage of China Cognition and Aging Study (China COAST), which is a national study on the mild cognitive impairment (MCI) and dementia based on hospital population [14, 15]. The diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), criteria. Patients diagnosed with AD met the criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) for probable AD. Interrater reliability for cognitive tests and diagnosis was required to exceed 0.90 with videotaped interviews in China COAST. Written informed consent was obtained from all participants or their relatives. This study was approved by the Institutional Review Board of Xuan Wu Hospital.

2.2. Assessments. All the participants in the present study underwent the following cognitive and neuropsychiatric assessments. The Mini-Mental State Examination (MMSE) [16] and the Clinical Dementia Rating (CDR) scale [17] were used to assess global cognitive ability and dementia severity. We used the Neuropsychiatric Inventory (NPI) to determine neuropsychiatric symptoms [18]. The scoring of NPI was based on the information from the caregivers. The NPI includes the following symptoms: delusions, hallucinations, agitation/aggression, apathy, anxiety, depression, euphoria, disinhibition, irritability, aberrant motor behavior, sleep behavior disturbances, and appetite abnormalities. If a patient did not have any of these symptoms in the last month, the NPI score was 0. If the answer was "yes," then the frequency and severity were asked. The score of each symptom was calculated as the product of the frequency and severity (maximum score = 12).

The ApoE genotypes were determined using the restriction enzyme digestion approach previously described [19]. Subjects were classified as ApoE $\varepsilon 4$ positive if they carried at least one copy of the $\varepsilon 4$ allele.

2.3. Statistical Analysis. To summarize demographic data of our patients, we used χ^2 tests or Fisher's exact tests if needed for dichotomous variables and independent sample t-tests for continuous data. We analyzed gender differences among patients with different dementia severities separately with similar analytic strategies. Patients were classified into mild dementia (CDR = 1) and moderate to severe dementia (CDR = 2 or 3) according to the CDR scores. Mann-Whitney U tests were used to compare sex differences in the total NPI score and each NPI item score. Sex differences in the prevalence of each NPI subscale (present, a score of 1 or higher; not present, a score of 0) were examined using χ^2 tests or Fisher's exact tests. Logistic regression analyses were performed to control for age and educational duration. The individual symptoms were dependent variable, and sex, ApoE $\varepsilon 4$ status, and the interaction term (ApoE $\varepsilon 4$ status × sex) were added to regression models as independent variables. A p value < 0.05 was regarded as statistically significant. For multiple comparisons, the α level was set at 0.004 (0.05/12) in accordance with the Bonferroni adjustment.

3. Results

3.1. Patients' Characteristics. A total of 315 patients were included in our study, including 158 mild AD patients (CDR = 1) and 157 moderate to severe AD patients (113 with the CDR = 2 and 46 with the CDR = 3). The characteristics of our subjects are presented in Table 1. Male patients had a significantly higher educational level than female patients. None of all subjects had the ApoE genotype of $\varepsilon 2/\varepsilon 2$. In mild AD, male patients had significantly higher frequencies of $\varepsilon 3/\varepsilon 3$ genotype than female patients, while females had higher $\varepsilon 3/\varepsilon 4$ frequencies than males. In moderate to severe AD, there was no sex difference in ApoE genotype frequencies.

3.2. Sex Differences in the Scores and Frequencies of Neuropsychiatric Symptoms. Table 2 shows the gender comparisons of the prevalence and scores of individual NPI symptoms. In mild AD, 74.3% of men and 70.2% of women reported at least one neuropsychiatric symptom. There were no sex differences in either scores or frequencies of neuropsychiatric symptoms in mild AD, even after stratified analysis by ApoE $\varepsilon 4$ status. In moderate to severe AD, 81.5% male patients and 90.2% female patients had neuropsychiatric symptoms. In all the moderate to severe AD patients, sex differences were not found. However, in $\varepsilon 4$ positive group, disinhibition was significantly more prevalent in female patients (8.0% in men versus 43.2% in women, $p = 0.003$), and the score of disinhibition ($p = 0.003$) was also significantly higher in females. The prevalence (16.0% in men versus 51.4% in women, $p = 0.005$) and score ($p = 0.004$) of irritability were of borderline significance after strict Bonferroni correction.

After controlling for age and educational duration, the logistic regression analyses demonstrated that the ApoE $\varepsilon 4$ status × sex interaction was associated with disinhibition and irritability in moderate to severe AD. Compared to other patients in moderate to severe stage, those female patients carrying $\varepsilon 4$ allele were 7.7 times (95% CI 1.09–54.5, $p = 0.040$) and 8.3 times (95% CI 1.64–42.1, $p = 0.010$) more likely to have disinhibition and irritability, respectively.

4. Discussion

In this study, we systematically investigated the sex differences in neuropsychiatric symptoms in mild AD and moderate to severe AD, and we analyzed the modifying effect of ApoE $\varepsilon 4$ status. Our results demonstrated that, before stratified analysis by ApoE $\varepsilon 4$ status, there were no sex differences in neuropsychiatric symptoms. However, in $\varepsilon 4$ positive individuals, female patients had significantly higher frequency and score of disinhibition than male patients in

Table 1: Characteristics of subjects and ApoE genotype frequencies.

	Mild AD			Moderate to severe AD		
	Male ($n = 74$)	Female ($n = 84$)	p value	Male ($n = 65$)	Female ($n = 92$)	p value
Age	71.0 (9.1)	70.9 (10.0)	0.967	69.0 (10.1)	66.7 (10.6)	0.156
Education (yr)	9.2 (4.6)	6.4 (5.4)	**0.001**	8.0 (4.6)	4.8 (4.4)	**<0.001**
MMSE	17.9 (5.6)	17.1 (4.9)	0.294	12.8 (6.0)	12.0 (5.1)	0.803
ApoE genotype*						
$\varepsilon4$ negative	56 (75.7)	46 (54.8)	**0.006**	40 (61.5)	55 (59.8)	0.825
$\varepsilon2/\varepsilon3$	7 (9.5)	9 (10.7)	0.794	6 (9.2)	5 (9.1)	0.365
$\varepsilon3/\varepsilon3$	49 (66.2)	37 (44.0)	**0.005**	34 (52.3)	50 (54.3)	0.801
$\varepsilon4$ positive	18 (24.3)	38 (45.2)	**0.006**	25 (38.5)	37 (40.2)	0.825
$\varepsilon2/\varepsilon4$	0	1 (1)	1.000	1 (1.5)	2 (2.2)	1.000
$\varepsilon3/\varepsilon4$	14 (18.9)	34 (40.5)	**0.003**	19 (29.2)	30 (32.6)	0.653
$\varepsilon4/\varepsilon4$	4 (5.4)	3 (3.6)	0.707	5 (7.7)	5 (5.4)	0.742

*Values are presented as numbers (percentages).

moderate to severe AD even after strict Bonferroni correction. For irritability, after Bonferroni correction, our study only confirmed a borderline significance, which needs to be further investigated. It was suggested that female patients with at least one copy of the $\varepsilon4$ allele were significantly more likely to have some neuropsychiatric symptoms in moderate to severe AD.

Consistent with previous studies [6, 7], gender differences were not significant in the overall prevalence and severity of NPI symptoms in our study. With respect to individual symptoms, some previous studies suggested there were sex differences in apathy [6], delusions [7], and anxiety [8] in AD. However, before stratified analysis according to ApoE $\varepsilon4$ status, no sex differences were found in this study. The discrepancies of these results were probably attributed to different study subjects and approaches. The demographics of subjects, including ethnicity and age, may influence the onset of neuropsychiatric symptoms [7]. The differences in dementia severities of participants may also cause the inconsistencies between studies [8]. Furthermore, the different instruments used to evaluate neuropsychiatric symptoms, other than NPI [6], may also partially explain the diverse results.

The underlying pathophysiological mechanisms of neuropsychiatric symptoms of AD are still not completely clear. However, increasing evidence has suggested that some pathological or neuroimaging biomarkers of AD were associated with neuropsychiatric disorders. Interestingly, it was also suggested that there was an interaction between sex and ApoE $\varepsilon4$ status on these biomarkers of AD. In pathological and CSF biomarkers, tau phosphorylation had been reported to be accelerated in AD with psychosis [20], and the increase of CSF concentration of amyloid β protein ($A\beta$) was related to the presence of agitation and irritability [21]. Correspondingly, females with ApoE $\varepsilon4$ allele were found to have greater $A\beta$ and neurofibrillary tangle in autopsy cases [22] and higher CSF levels of tau in healthy elderly adults [23]. In terms of neuroimaging biomarkers, it was reported that the atrophy of hippocampal region was associated with agitation and aggression in AD [24], and the amygdala atrophy, which was comparable to hippocampal atrophy, was potentially related to irritability [25]. Meantime, previous studies have showed that the presence of ApoE $\varepsilon4$ allele was associated with smaller hippocampal volumes in women than in men in mild cognitive impairment (MCI) and AD [26]. Psychological symptoms in AD were also associated with white matter hyperintensities (WMH), and the disinhibition symptom was related to lower WMH volume [27]. Interestingly, female ApoE $\varepsilon4$ carriers had significantly reduction of white matter integrity of the tract connecting the hippocampus [28]. In addition, compared to females without ApoE $\varepsilon4$ and male carriers, females with ApoE $\varepsilon4$ allele had significantly reduced default mode connectivity [23], which was associated with neuropsychiatric disorders and reduced in AD patients [29, 30]. All these lines of evidence suggested that ApoE $\varepsilon4$ allele may have important modifying effects on gender-specific manifestations of neuropsychiatric symptoms.

There are some limitations in our study. Our subjects were chosen from neurology outpatients and therefore were not representative of the general population, though our study results might be of value in clinical setting. Furthermore, although the NPI we used is a validated and widely used instrument, it relies on the information from caregivers instead of patients.

5. Conclusions

This study supported the modifying effect of ApoE $\varepsilon4$ status on sex differences in neuropsychiatric symptoms of AD, and this modifying effect was pronounced in moderate to severe stage of AD. The interaction between sex and ApoE $\varepsilon4$ status should be considered in further studies on neuropsychiatric symptoms of AD.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Table 2: The gender comparisons of the frequencies and scores of neuropsychiatric symptoms.

NPI items	Mild AD						Moderate to severe AD					
	All		ε4 negative		ε4 positive		All		ε4 negative		ε4 positive	
	M	F	M	F	M	F	M	F	M	F	M	F
	$n = 74$	$n = 84$	$n = 56$	$n = 46$	$n = 18$	$n = 38$	$n = 65$	$n = 92$	$n = 40$	$n = 55$	$n = 25$	$n = 37$
Delusions	16.2	26.2	12.5	21.7	27.8	31.6	33.8	39.1	37.5	41.8	28.0	35.1
	0.7 ± 2.3	1.3 ± 4.1	0.5 ± 1.9	0.8 ± 1.9	1.3 ± 3.2	1.9 ± 5.8	2.1 ± 3.9	2.0 ± 3.7	2.3 ± 4.0	1.9 ± 3.4	1.8 ± 3.9	2.3 ± 4.3
Hallucinations	10.8	15.5	8.9	8.7	16.7	23.7	24.6	26.1	25.0	21.8	24.0	32.4
	0.3 ± 1.3	0.8 ± 2.6	0.2 ± 1.1	0.4 ± 1.5	0.6 ± 1.9	1.3 ± 3.4	1.3 ± 3.3	1.5 ± 3.3	1.4 ± 3.2	1.2 ± 3.0	1.2 ± 3.3	2.0 ± 3.9
Agitation/aggression	20.3	20.2	17.8	17.4	27.8	23.7	32.3	35.9	37.5	30.9	24.0	43.2
	0.7 ± 2.0	1.1 ± 2.8	0.7 ± 2.1	0.9 ± 2.5	0.8 ± 1.6	1.2 ± 3.2	1.5 ± 3.2	1.8 ± 3.4	1.5 ± 3.1	1.3 ± 3.1	1.4 ± 3.5	2.5 ± 3.9
Depression	28.4	32.1	26.8	34.8	33.3	28.9	40.0	46.7	42.5	45.4	36.0	48.6
	1.1 ± 2.4	1.7 ± 3.7	1.1 ± 2.6	1.5 ± 2.8	1.0 ± 1.7	1.9 ± 4.6	1.3 ± 2.6	1.9 ± 3.0	1.4 ± 2.9	1.9 ± 2.8	1.3 ± 3.0	2.0 ± 3.2
Anxiety	18.9	19.0	19.6	19.6	16.7	18.4	35.4	45.7	32.5	43.6	40.0	48.6
	0.7 ± 2.1	0.9 ± 2.6	0.8 ± 2.4	1.1 ± 2.8	0.4 ± 1.0	0.8 ± 2.4	1.8 ± 3.6	2.5 ± 3.7	0.7 ± 2.2	1.8 ± 3.0	2.4 ± 4.4	3.5 ± 4.7
Euphoria	6.7	3.6	7.1	4.3	5.6	2.6	10.7	5.4	17.5	7.3	0	2.7
	0.3 ± 1.2	0.1 ± 0.7	0.3 ± 1.3	0.2 ± 0.8	0.2 ± 0.9	0.1 ± 0.6	0.4 ± 1.7	0.3 ± 1.5	2.8 ± 4.0	0.4 ± 1.5	—	0.2 ± 1.3
Apathy	36.5	27.4	35.7	32.6	38.9	21.1	52.3	52.2	50.0	52.7	56.0	51.4
	1.7 ± 3.1	1.3 ± 2.9	1.7 ± 3.1	1.8 ± 3.5	1.8 ± 3.3	0.7 ± 1.5	3.3 ± 4.4	3.0 ± 4.2	1.0 ± 2.7	2.8 ± 4.1	4.0 ± 5.0	3.3 ± 4.3
Disinhibition	5.4	10.7	5.3	13.0	5.6	7.9	12.3	27.2	15.0	16.4	**8.0****	**43.2****
	0.1 ± 0.5	0.5 ± 2.0	0.1 ± 0.6	0.7 ± 2.6	0.1 ± 0.2	0.2 ± 0.9	0.7 ± 2.2	1.2 ± 2.6	1.0 ± 2.7	0.6 ± 1.9	**0.3 ± 1.2**††	**2.1 ± 3.3**††
Irritability	14.7	16.7	16.1	8.7	11.1	26.3	20.0	30.4	22.5	16.4	**16.0***	**51.4***
	0.9 ± 2.6	0.6 ± 1.8	0.9 ± 2.7	0.2 ± 1.0	0.9 ± 2.6	0.9 ± 2.4	1.3 ± 3.3	1.7 ± 3.4	1.6 ± 3.7	0.9 ± 2.8	**0.8 ± 2.5**†	**3.0 ± 3.9**†
Aberrant motor behavior	13.5	16.7	12.5	21.7	16.7	10.5	24.6	38.0	35.0	34.5	28.0	43.2
	0.6 ± 2.0	1.0 ± 2.8	0.6 ± 2.1	1.4 ± 3.2	0.6 ± 1.6	0.4 ± 2.0	1.7 ± 3.7	2.3 ± 4.0	1.6 ± 3.7	2.0 ± 4.1	2.0 ± 3.8	2.7 ± 4.3
Sleep behavior disturbances	16.2	13.1	14.3	10.9	22.2	15.8	30.8	28.3	35.0	23.6	24.0	35.1
	0.7 ± 1.9	0.9 ± 2.7	0.6 ± 1.7	0.7 ± 2.6	1.1 ± 2.6	1.1 ± 2.9	2.1 ± 4.0	1.6 ± 3.5	2.8 ± 4.8	1.2 ± 3.0	0.9 ± 2.1	2.3 ± 4.2
Appetite abnormalities	8.1	11.9	8.9	13.0	5.6	10.5	16.9	15.2	17.5	12.7	16.0	18.9
	0.3 ± 1.3	0.5 ± 1.8	0.3 ± 1.3	0.6 ± 2.0	0.3 ± 1.4	0.4 ± 1.5	1.3 ± 3.4	0.8 ± 2.4	1.4 ± 3.5	0.5 ± 2.0	1.2 ± 3.4	1.2 ± 2.9
Total	74.3	70.2	69.6	71.7	88.9	68.4	81.5	90.2	82.5	90.9	80.0	89.2
	8.1 ± 10.3	10.6 ± 16.7	7.8 ± 9.7	10.3 ± 13.0	9.1 ± 12.4	11.0 ± 20.3	18.6 ± 24.6	20.7 ± 21.4	19.7 ± 27.0	17.2 ± 18.9	16.8 ± 20.5	25.9 ± 24.0

Data are expressed as percentages of patients with individual symptoms and means of scores ± SDs.
Please note that the means with standard deviations of scores are represented the same as previous literatures, though the data are not normally distributed.
*Gender differences in the prevalence of NPI symptoms, χ^2 tests, $p < 0.05$, and $^{**}p < 0.004$.
†Gender differences in NPI scores, Mann-Whitney U test, $p < 0.05$, and $^{\dagger\dagger}p < 0.004$.

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Review Article

Relationship between Postmenopausal Estrogen Deficiency and Aneurysmal Subarachnoid Hemorrhage

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Aneurysmal subarachnoid hemorrhage (SAH) is one of the most severe forms of stroke, which results from the rupture of a cerebral aneurysm. SAH is the only type of stroke with a female predominance, suggesting that reproductive factors may play a significant role in the etiology. Estrogen has important effects on vascular physiology and pathophysiology of cerebral aneurysm and SAH and, thus, potential therapeutic implications. There have been growing bodies of epidemiological and experimental studies which support the hypothesis of a significant relationship between estrogen deficiency and cerebral aneurysm formation with subsequent SAH. This hypothesis is the focus of this review as well as possible pathology-based therapeutics with regard to aspects of molecular pathophysiology, especially related to women's health.

1. Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating stroke subtype, which frequently occurs as the result of a ruptured cerebral aneurysm. Mortality rates for ruptured cerebral aneurysms continue to average near 50%, with 10% of patients dying before ever reaching the hospital and approximately 20% sustaining severe disability [1]. Unlike most other types of cerebrovascular disease, SAH occurs more frequently in women than in men [2]. Mortality rates of female SAH patients have been reported to be higher than those for men [3]. Women are also more likely to have multiple aneurysms than men [4]. Women had a significantly higher risk for *de novo* aneurysm formation than men in a long-term follow-up study, and being female was a significant independent risk factor for aneurysm growth [5]. Additionally, it has been shown that faster aneurysm growth increases the likelihood of rupture. Aneurysm size was also associated with a tendency to rupture. There are few reports that have specifically examined the differences in aneurysmal size between the sexes. Although Li et al. reported that the mean diameter of unruptured cerebral aneurysms (UCAs) was larger in women than in men [6], no difference was found in another report [7], and the sizes of ruptured cerebral aneurysms were not statistically significantly different between the sexes [8].

The gender-related predominance is important because many of the risk factors for cerebral aneurysm, including hypertension, cigarette smoking, and alcohol use, are generally more common in men. A systematic review suggested that the gender distribution of SAH varies with age. At younger ages, the incidence is higher in men, whereas, after the age of 55, the incidence is higher in women [9]. Furthermore, earlier age at menopause is associated with a greater risk of cerebral aneurysm [10]. The loss of estrogen earlier in a woman's life may contribute to the pathogenesis of cerebral aneurysm formation. Because the incidence of SAH is higher after menopause than before [11], it has been suggested that the sex hormones, especially estrogen, might be protective against the condition [12]. Herein is a review focused on the hypothesis of the relationship between aneurysmal SAH and estrogen deficiency along with a discussion of the therapeutic implications.

2. Review

2.1. Sex-Specific Hormonal Factors and SAH. Premenopausal women, especially those without a history of smoking or hypertension, are at a reduced risk for subarachnoid hemorrhage (SAH) compared with age-matched postmenopausal

women [13]. A study of Japanese women with their first occurrence of aneurysmal SAH found that an earlier age at menarche (adjusted odds ratio, 3.24) and nulliparity (adjusted odds ratio, 4.23) were associated with an increased risk of SAH. These effects appeared to be additive, and women with both early menarche and nulliparity had a correspondingly increased risk (adjusted odds ratio, 6.37) of SAH [14]. Therefore, a sex-specific hormonal factor may play a role in the pathogenesis of aneurysm formation and rupture. The collagen wasting commonly observed in bone and skin in the postmenopausal period due to decreased estrogen levels could possibly be responsible for the formation of aneurysms in the proximal segments of the cerebral arteries, as it occurs in various connective tissue diseases [15–17]. Between the ages of 50 and 59, menopause typically occurs, and estrogen levels begin to decrease. Hemodynamics, in conjunction with progressive collagen loss in the vascular wall, appears crucial for the development of an aneurysm. In a population-based, case-control study, several hormonal factors in women were reported to alter the risk for SAH. Factors leading to a state of relative estrogen deficiency, such as menopause and the immediate perimenstrual phase of the menstrual cycle, were associated with an increased risk [18]. Conversely, hormone replacement therapy (HRT) was associated with a reduced risk for SAH [13]. As estrogen deficiency alone would not explain the higher incidence in women compared with that in men, the change in estrogen levels may be more important than the absolute levels. Men would be at less risk because they do not experience as much of a dramatic estrogen withdrawal as women. Estrogen levels markedly change during the menstrual cycle, and relative estrogen deficiency occurs in the immediate perimenstrual phase of the menstrual cycle [13]. This periodic hormonal change may promote aneurysm formation [19].

Many studies on UCAs with location-based evaluation have shown similar results suggesting that UCAs in the internal carotid artery (ICA) were most common [7, 20, 21]. Harada et al. examined the prevalence of UCAs in healthy asymptomatic Japanese adults and found that there were significant differences in the locations of UCAs by gender ($P < 0.001$). ICA involvement was more frequent in women, whereas the anterior cerebral artery (ACA) and middle cerebral artery (MCA) were more common in men [7]. Even in cases of ruptured aneurysms, the rate of occurrence in the ICA was reported to be higher in women than in men [22–25]. As the aneurysms of the ACA and MCA are more commonly found in men, it can be speculated that hemodynamic factors are more important in the formation of aneurysms in men. On the other hand, an intrinsic weakness of the vessel wall due to hormonal factors may play a major role in promoting the formation of cerebral aneurysm in female patients [24].

Chen et al. reported that exposure to exogenous estrogen agents in women is associated with a lower frequency of cerebral aneurysms [26]. The physiologic drops in estrogen and/or low endogenous levels of estrogen that occur during the menstrual cycle, and particularly at menopause, may not only play an important role in cerebral aneurysm formation but may also serve as potential therapeutic targets.

2.2. Cerebral Aneurysm Formation and Estrogen. Aneurysms are abnormal dilatations of vessels in the vascular system, and they exist in two major forms: saccular and fusiform. As for cerebral aneurysm, the saccular type dominates. The saccular aneurysm is a thin-walled, sphere-like expansion from the branching region of a major cerebral artery. Meanwhile, fusiform aneurysms have different etiologies (arteriosclerosis, intramural dissection, etc.) and are classified into different entities [27, 28]. Unlike saccular aneurysms, which present more often with SAH, fusiform aneurysms present more often with ischemic stroke or mass effect [29]. Thus, saccular aneurysms are the focus of this paper.

Like all arteries, cerebral arteries consist of three layers: intima (adjacent to the lumen), media, and adventitia. The internal elastic lamina separates the intima from the media and is essentially a fenestrated sheet of elastin. The media is composed of smooth muscle cells and collagen fibers. The adventitia consists of collagen fibers, elastin, fibroblasts, and the vasa vasorum. The adventitia is thought to limit acute overdistension in all vascular vessels at higher levels of pressure [30]. Collagen fibers are mainly produced by fibroblasts. Fibroblasts also produce, organize, and remove the extracellular matrix. The repair and maintenance of connective tissue are performed predominantly by fibroblasts. The loss of media in the location of aneurysms is taken to be responsible for the initiation of aneurysm growth. The aneurysm is regarded as a development of the adventitia, which is composed of a layer of collagen fibers. The collagen fibers are the only load-bearing constituent in the aneurysm wall; their production and degradation depend on the stretch of the wall and are responsible for aneurysm growth [31].

Hemodynamics also play an important role in the development of aneurysms. There are three hemodynamic forces to consider. They include shear stress, dynamic blood pressure, and static blood pressure. The shear stresses are considerably higher at the apex of arterial bifurcations. This explains why cerebral aneurysm is commonly found at arterial bifurcations where excessive hemodynamic stresses are exerted on arterial walls [32].

Handa et al. reported three important factors in the formation of cerebral aneurysms in experimental animals: altered hemodynamic stress in the circle of Willis, hypertension, and increased vessel fragility. Estrogen could potentially affect all of these factors and thus influence the risk for cerebral aneurysm formation and rupture [33]. Estrogen has been found to improve lipid profiles [34, 35] and thus may reduce the risk for arteriosclerosis, which has been considered a risk factor for aneurysm formation because of altered hemodynamics. In addition, low-dose estrogens are associated with a reduced blood pressure, as is HRT [36].

It is thought that the arteries, including the internal carotid artery (ICA), could undergo postmenopausal connective tissue changes. The media layer has the highest connective tissue component, including collagen types I and III. It has been shown that menopause has similar effects on the connective tissue changes of the carotid artery media [37]. HRT has a morphological effect on the carotid arteries, encouraging thickening of the layers with the highest

connective tissue component (media and adventitia) in postmenopausal women [38].

Wall thickness of a cerebral aneurysm is important for the integrity of the aneurysm wall and aneurysmal growth and rupture, which is poorly documented. Kadasi et al. reported an interesting observation about wall thickness of UCAs using intraoperative microscopy. They reported that the proportion of superthin translucent tissue at the aneurysm dome was significantly greater ($P = 0.038$) in women compared with men, suggestive of the susceptibility for rupture [39]. Estrogen might play an important role in vascular and aneurysmal integrity through the control of collagen content and wall thickness.

Taken together, it is considered that estrogen makes a significant contribution to the etiology of cerebral aneurysm formation and growth.

2.3. Estrogen Signaling in Cerebral Arteries and Aneurysm. Endogenous natural estrogens include estrone (E1), estradiol (E2), and estriol (E3).

In women, E2 is the main form of circulating estrogen. The ovaries are the main source of circulating E2 in premenopausal women [40]. Most E1 and E3 are formed in the liver from E2 or in peripheral tissues from androstenedione. The sources and plasma levels of estrogens change with age. In postmenopausal women, circulating androstenedione, testosterone, and E1 are the major precursors of estrogen production in peripheral tissues. E2 metabolism varies with the phase of the menstrual cycle, menopausal status, ethnic background, and gene polymorphism [41]. Changes in E2 metabolism with aging may alter its effects on the vasculature.

Estrogens bind estrogen receptors (ERs) with high affinity and specificity. There are two established genes encoding ER: ER-alpha and ER-beta. These receptors are members of the nuclear receptor superfamily and function as ligand-activated transcription factors to produce so-called genomic effects. Endothelial and vascular smooth muscle cells are replete with both ER-alpha and ER-beta receptors [42, 43]. Sex- and age-related differences in ER expression have been shown [44]. Levels of ER-alpha and ER-beta appear to be differentially regulated by estrogen itself. However, regulation of estrogen receptors may be dependent upon the tissue and duration of estrogen treatment [45].

A novel seven-transmembrane, G protein-coupled receptor, originally identified as an orphan receptor termed GPR30, has been identified [45]. This receptor was later named the G protein-coupled estrogen receptor (GPER). GPER is structurally unrelated to ER-alpha or ER-beta, binds E2 with high affinity, and mediates some of its nongenomic effects [46]. Although GPER is widely distributed in the brain and vasculature [45], its functional role needs further investigation [40].

ER-beta is a predominant form of ER in human cerebral aneurysms and cerebral arteries [47, 48]. Tada et al. reported that estrogen prevented cerebral aneurysmal growth and rupture in ovariectomized female mice, consistent with epidemiological studies [47, 48]. The protective effect of ER-beta activation for aneurysm growth and rupture is dependent on the production of nitric oxide (NO). Cardioprotective effects of estrogen can also be mediated by ER-beta in an NO-dependent manner [49].

2.4. Preventive and Therapeutic Potential of Hormone Replacement Therapy (HRT) in Unruptured Cerebral Aneurysms (UCAs)

2.4.1. HRT and Its Problems. Estrogen regulates a number of inflammatory cascades and contributes to vascular wall integrity. The dysregulation of these mechanisms has been linked to aneurysm formation, growth, and rupture, with the strong suggestion that administration of estrogen replacement therapy could prevent this pathology. However, the negative results for beneficial effects of E2 therapy (HRT) have been reported in several randomized controlled trials (RCTs) for menopausal symptoms. The failure of HRT in RCTs is suspected to be related to age-related changes in ER number, distribution, and downstream signaling mechanisms, as well as structural changes in vasculature [40]. If estrogen is protective from menopausal symptoms but cannot reverse preexisting vascular disease, then perhaps HRT has not been administered early enough in menopause in these studies to be effective [50]. Age may be an important factor in estrogenic effects on inflammatory responses, with a loss of estrogenic efficacy in elderly women. The vascular action of estrogenic treatments suggests that timing matters [51]. Recent animal and human studies now support the "critical period" hypothesis for E2 therapy whereby E2 therapy must begin soon after the loss of endogenous E2 production to have a significant effect [52]. When administered earlier in the disease progression, estrogen may be advantageous by decreasing the likelihood of the development of cerebral aneurysm and subsequent rupture leading to SAH.

Besides HRT's beneficial effects, there is clear evidence that oral estrogens increase the risk of venous thromboembolism (VTE) among postmenopausal women [53]. The Estrogen and Thromboembolism Risk (ESTHER) study confirmed that oral estrogens increased VTE risk, whereas transdermal estrogens had little or no impact on the development of thrombosis [54]. There is increasing evidence that the timing of HRT initiation may play a crucial role in determining chronic heart disease risk among estrogen users [55]. Coronary risk tended to be lowered compared to placebo when HRT was initiated during the first 10 years after the onset of menopause. This risk, however, tended to increase when HRT was started 10 years after menopause and was further intensified after 20 years [55]. Another significant drawback is that long-term HRT may increase the risk of breast cancer and meningioma in women [56].

At present, there are many obstacles that need to be overcome prior to the actual application of conventional HRT to the prevention/treatment of cerebral aneurysm.

2.4.2. Selective Estrogen Receptor Modulators (SERMs). Subtype-specific ER agonists coupled with specific targeting or drug-delivery techniques could be useful in modulating vascular ER activity in a specific blood vessel without affecting other vessels in the systemic circulation. A number

of selective estrogen receptor modulators (SERMs) have been developed [57]. SERMs could be selective in targeting vascular ERs while having few undesirable effects, such as VTE, cardiovascular disease, and breast cancer. It is conceivable that one could design SERMs that would retain most of the desired effects of E2 to targeted tissues and organs but that would be devoid of the undesirable effects of E2. SERMs confer vasoprotective effects by reducing the release of reactive oxygen species. In prior reports, the studied SERM attenuated the development of experimental aneurysms *in vivo* [58]. As superior protective effects on the development and rupture of cerebral aneurysms of selective ER-beta agonists have been reported compared to estrogen [47, 48], production of new-generation SERMs with a favorable tissue specificity profile may be promising in preventing the growth and rupture of cerebral aneurysms in postmenopausal women.

2.4.3. Phytoestrogens. Phytoestrogens are estrogenic compounds of plant origin classified into different groups with structural similarities to E2 that allow them to mimic the effects of E2. Among them, isoflavones such as genistein are the most studied and are most potent phytoestrogens and are found mainly in soy bean-derived foods [59]. The effects of phytoestrogens are partly mediated via estrogen receptors: ER-alpha, ER-beta, and possibly GPER. The interaction of phytoestrogens with ERs is thought to induce both genomic and nongenomic effects in many tissues, including the vasculature. Genistein has a high affinity for ER-beta, almost identical to that of E2, while its affinity for ER-alpha is only 6% of that of E2 [59]. As clinical trials have shown negative results for vascular benefit and an increased risk of cardiovascular disease with conventional HRT [60], phytoestrogens are being considered as an alternative to conventional HRT [59].

Extracellular matrix (ECM) is a major component of the blood vessel architecture and plays an important role in the control of vascular wall integrity and vascular remodeling. Phytoestrogens affect various components of the ECM, including collagen and elastin [59]. One experimental study showed that phytoestrogens inhibit aneurysm formation in mice [61]. Further studies are needed to investigate the potential beneficial effects of phytoestrogens in preventing cerebral aneurysm formation and growth.

2.5. Future Perspectives for Prevention and Treatment of Unruptured Cerebral Aneurysm (UCA) in Women. Current medical management options in patients with UCAs are limited, consisting largely of smoking cessation, blood pressure control, radiological surveillance, and neurosurgical or endovascular interventions. There is no pharmacological treatment available to decrease the risk of aneurysm growth and rupture. The current management of UCAs is controversial. There is an urgent need to understand the etiology of cerebral aneurysm and to establish reliable criteria by which surgeons can predict the risk of rupture and thus need for surgical intervention. There is growing interest in the pathogenesis of cerebral aneurysm focused on the development of drug therapies to decrease the incidence of aneurysm growth and rupture. Pathology-based therapies for patients harboring UCAs, especially in postmenopausal woman, are expected.

As previously mentioned, the pathology, etiology, and essential effector of cerebral aneurysm formation and progression are different in men and women and may also differ by age (i.e., those less than 40 years of age, those in their 40s–60s, and those older than 70). Based on these differences, it is possible that specific pharmacological treatment approaches may improve outcomes and the development of tailor-made medicines might be expected.

Although there are a number of factors that can potentially limit the translational potential of previously reported experimental findings, new-generation HRT may have a beneficial role in the prevention of aneurysm growth and rupture if initiated properly, that is, at the timing of perimenopause in women diagnosed with having small UCAs. Although the beneficial effect of this therapy in older women is less plausible because of preexisting cerebrovascular and cardiovascular risk factors, the continuation of this therapy through the menopausal period may have some benefit in older woman to some extent and should be elucidated in the future. Alternatives to traditional HRT, such as the use of highly selective ER-beta agonists and/or phytoestrogens, as well as the appropriate route of administration, dosage, timing, and choice of repetitive or periodic administration simulating the menstrual cycle (instead of chronic administration) could provide better approaches to increasing the benefits of HRT for prevention of aneurysmal growth and subsequent rupture causing SAH in postmenopausal women.

As sex differences remain an important issue in the development of cerebral aneurysm and SAH, further clinical studies are needed. An understanding of the relationship between estrogen and cerebral aneurysm/SAH pathophysiology may have significant implications for women's health.

3. Conclusion

There is growing interest in the pathogenesis of cerebral aneurysm focused on the development of drug therapies to decrease the incidence of aneurysm growth and rupture. Estrogen deficiency in postmenopausal women has a significant impact on the pathophysiology of cerebral aneurysm and SAH. Pathology-based therapies for patients harboring UCAs, especially in postmenopausal woman, seem to be a reasonable starting point for a disease with otherwise few treatment options and should be developed in the future.

Conflict of Interests

The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this paper.

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Research Article

A Disproportionate Burden of Care: Gender Differences in Mental Health, Health-Related Quality of Life, and Social Support in Mexican Multiple Sclerosis Caregivers

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Background. Multiple sclerosis (MS) rates in Latin America are increasing, and caregivers there experience reduced mental and physical health. Based on rigid gender roles in Latin America, women more often assume caregiving duties, yet the differential impact on women of these duties is unknown. *Methods*. This study examined gender differences in mental health (Patient Health Questionnaire-9, Satisfaction with Life Scale, Rosenberg Self-Esteem Scale, State-Trait Anxiety Inventory, and Zarit Burden Inventory), health-related quality of life (HRQOL; Short Form-36), and social support (Interpersonal Support Evaluation List-12) in 81 (66.7% women) Mexican MS caregivers. *Results*. As compared to men caregivers, women had lower mental health ($p = 0.006$), HRQOL ($p < 0.001$), and social support ($p < 0.001$). This was partially explained by women caregivers providing care for nearly twice as many hours/week as men (79.28 versus 48.48, $p = 0.018$) and for nearly three times as many months (66.31 versus 24.30, $p = 0.002$). *Conclusions*. Because gender roles in Latin America influence women to assume more substantial caregiving duties, MS caregiver interventions in Latin America—particularly for women caregivers—should address the influence of gender-role conformity on care and psychosocial functioning.

1. Introduction

Multiple sclerosis (MS) is a chronic, progressive, disabling disease which affects an estimated 2.3 million people worldwide [1]. In Latin America in particular, the focus of the current study, the number of individuals diagnosed with MS has been increasing over the past two decades [2, 3]. MS is characterized by autoimmune damage to the myelin sheaths around nerve cells [4]. MS manifests via deficits in the domains of physical (pain and impairments in visual, motor, vestibular, and somatosensory systems), cognitive (attention, processing speed, learning, memory, and executive functions), and emotional (depression and anxiety) functioning [5–8].

Due to the wide-ranging difficulties associated with MS, individuals often require care and support from informal caregivers, usually family members [9]. Caregivers often provide significant assistance with personal, medical, homemaking, mobility, and leisure tasks [10–14]. Providing care for an individual with MS has been associated with reduced caregiver mental health, physical health, and quality of life, as well as social and financial difficulties [9, 15–18]. Compared with

caregivers of individuals with other neurological conditions, the issues faced by MS caregivers unfortunately have received relatively little research attention [19].

However, some studies have begun to examine gender differences in the provision and effects of MS caregiving, with inconsistent results. For instance, men spousal MS caregivers report having fewer total resources and lower perceived social support than women caregivers [20]. Additionally, Buchanan and colleagues [21] found that men caregivers had 71.1% greater odds of reporting higher burden than women caregivers. The same group's earlier findings [22] indicated that greater burden in men caregivers was associated with more hours of care per week, as well as with greater restriction of caregivers' ability to perform daily activities.

On the other hand, Knight et al. [23] reported that women spousal MS caregivers had higher levels of burden than husbands. Patti and colleagues [9] similarly found that women caregivers had higher psychological morbidity than men caregivers and that women gender was one of the chief predictors of lower quality of life in caregivers. Higher burden scores were interpreted to be related to higher levels of physical distress and exhaustion/tiredness experienced by women caregivers, while lower morbidity in men caregivers was attributed to less perceived psychological stress or better coping skills.

In Latin America, MS caregiver adjustment may be based on unique traditions, cultural norms, and societal beliefs. For instance, individuals in Latin America are generally collectivist and have strong familial ties and a sense of obligation to support immediate and extended family members who are sick [24]. Latino caregivers may be particularly vulnerable to "role engulfment" (i.e., basing one's identity on the assumed role of a primary caregiver) and consequently experience greater psychological morbidity and burden than caregivers from other cultural groups [25].

In addition to strong family values, cultural norms in Latin America also influence rigid gender-role expectations [26]. For example, *machismo*, an ethos of masculine behaviors expected of men in Latin America, is a good predictor of Latino men's health-related behaviors [27]. It might contribute to poor coping mechanisms (e.g., not reporting medical problems or asking for help) and lead to men being less knowledgeable about health-related issues as men see themselves as less vulnerable to disease than women [28]. Women in Latin America also face rigid gender roles by which they are expected to take care of the family, cook and clean, care for children, be submissive to and take orders from husbands, and restrict leisure activities and socialization outside home, which may predispose women to experiencing higher mental health problems [29–31].

To our knowledge, very few studies have been conducted examining MS caregiver experiences in Latin America and none examining gender differences in caregiver psychosocial functioning despite the unique cultural norms and beliefs in this region. Therefore, the purpose of the current study is to examine gender differences in mental health, health-related quality of life, and social support in a group of MS caregivers from Guadalajara, Mexico. It is hypothesized that women MS caregivers will experience lower scores on measures of these outcomes than men.

Table 1: Caregiver participant demographics.

Variable	Men ($n = 27$)	Women ($n = 54$)	p value
Age, years, mean (SD)	37.63 (15.65)	46.24 (14.46)	.016
Marital status %			NS
Single	33.3	31.5	
Partnered	66.6	68.5	
Relationship to patient %			.000
Spouse	55.6	14.8	
Parent	11.1	63.0	
Sibling	18.5	9.3	
Child	3.7	7.4	
Partner	11.1	0	
Professional caregiver	0	1.9	
Other	0	3.8	
Education, years, mean (SD)	13.41 (3.78)	10.91 (4.52)	.016
Working outside the home %	92.6	44.4	.000
Weekly time caregiving, hours, mean (SD)	48.48 (41.05)	79.28 (59.74)	.018
Total time caregiving, months, mean (SD)	24.30 (23.04)	66.31 (66.68)	.002

SD: standard deviation; NS: not significant.

2. Materials and Methods

2.1. Participants. A purposive sample of 81 caregivers was recruited from the Mexican Foundation for Multiple Sclerosis and the Department of Neurosciences at the University of Guadalajara, Mexico, to participate in this cross-sectional study. Caregivers had to have provided care for a minimum of six months and be the primary caregiver of a person with MS. Exclusion criteria consisted of having a history of serious neurological, psychiatric, or learning disability. See Table 1 for participant demographics broken down by participant gender.

2.2. Measures

2.2.1. Demographic Information. Demographic items assessed participants' gender, age, romantic partnership status, years of education, employment status, hours per week and total months spent caring for the MS patient, and caregiver relationship to the patient (parent, sister/brother, son/daughter, uncle, aunt, partner/spouse, or other relatives). All scales used in this study were previously published and validated Spanish versions that had already undergone extensive validation and were the most common indices of mental health and HRQOL administered in studies of caregivers of individuals with neurological conditions in Latin America and especially Mexico.

2.2.2. Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a 9-item self-administered screening measure of depressive symptoms used in clinical and epidemiological studies [32].

2.2.3. Satisfaction with Life Scale (SWLS). The SWLS is a 5-item self-report measure of global life satisfaction [33]. The Spanish version of the SWLS has well-established psychometric properties [34, 35].

2.2.4. Rosenberg Self-Esteem Scale (RSES). The RSES is a 10-item measure of perceived self-worth [36, 37]. The RSES has well-established psychometric properties [38], including 53 countries, with many in Latin America [37].

2.2.5. State-Trait Anxiety Inventory (STAI). The STAI is a 40-item self-report measure of anxiety with two subscales [39]. Intensity of anxiety as an emotional state is measured by the S-Anxiety subscale. Anxiety as a personality trait and not just temporary responses to a situation is measured with the T-Anxiety scale [40].

2.2.6. Zarit Burden Interview (ZBI). The ZBI [41] is a 22-item self-report questionnaire that evaluates a caregiver's health condition, psychological well-being, financial situation, and social life in the context of the caregiver-patient relationship. The Spanish version of the ZBI has good internal reliability [42, 43].

2.2.7. Interpersonal Support Evaluation List-Short Version (ISEL-12). The ISEL-12 is a 12-item self-report instrument that assesses perceived social support according to participants' ratings of the availability of various types of social support [44] across three subscales: belonging, appraisal, and tangible.

2.2.8. Short Form Health Status Survey (SF-36). The SF-36 was used to assess health-related quality of life (HRQOL) across eight domains [physical functioning, role-physical (role limitations due to physical health problems), bodily pain, vitality, social functioning, role-emotional (role limitations due to emotional distress), mental health, and general health]. The Spanish version of the SF-36 has high reliability and validity [45].

2.3. Procedure. The Institutional Review Board (IRB) at the Mexican Foundation of Multiple Sclerosis reviewed and approved the study protocol prior to recruitment. Prospective participants for the study were recruited by the Mexican Foundation for Multiple Sclerosis and the Department of Neuroscience at the University of Guadalajara, Mexico. All participants reviewed and signed a consent form prior to the beginning of the study. Demographic, mental health, social support, and HRQOL information from caregivers were collected during a 40-minute face-to-face interview by a psychologist under the supervision of a member of the university teaching staff. No participant incentives were provided.

2.4. Statistical Analyses. Two multivariate analyses of variance (MANOVAs) compared women and men caregivers' mental health and social support (MANOVA 1) and HRQOL (MANOVA 2) with preset significance level of $p < 0.05$. In the first MANOVA, participant gender (women versus men) was the independent variable, and participants' total scores on each of the measures of satisfaction with life, depression, burden, self-esteem, anxiety, and social support were the dependent variables. In the second MANOVA, the independent variable was the same, but the dependent variables were participants' scores on the eight indices of HRQOL. Post hoc univariate analyses of variance (ANOVAs) were run to identify the locations of significant differences between women and men in each of the MANOVAs when the omnibus MANOVAs were statistically significant. Demographic characteristics (age, marital status, relationship to patient, education, working outside the home, and weekly and total time caregiving) of women and men participants were compared using t-tests for continuous variables and χ^2 tests for nominal variables. Two MANCOVAs were then run in the same manner as the first two MANOVAs but including as covariates any demographic variables that differed between women and men. MANOVAs and MANCOVAs were run first instead of proceeding immediately to ANOVAs and ANCOVAs in order to control for the potentially substantial family-wise error involved in the latter approach. As a result, ANOVAs and ANCOVAs were run only if the initial MANOVAs and MANCOVAs were statistically significant with a stringent cutoff of $\alpha = 0.05$.

3. Results

3.1. MANOVA 1. The first MANOVA revealed a statistically significant effect for participant gender, Pillai's Trace = 0.259, $F(9, 69) = 2.681$, $p = 0.01$, and $\eta^2 = 0.259$. As a result, nine post hoc univariate analyses of variance (ANOVAs) were run to identify the location of the significant differences between women and men on the mental health and social support variables. In each of these ANOVAs, the independent variable was participant gender, and the dependent variables were each of the mental health and social support variables used in the omnibus MANOVA. The results of these ANOVAs appear in Table 2.

Across every index except satisfaction with life, women reported substantially worse functioning on the mental health and social support variables than men. The effect sizes [45] of two of the social support differences were large and one medium; one of the five mental health differences was a small effect, two were medium, and three were large effect sizes. As a result, this study's hypothesis that women caregivers would have poorer mental health and social support than men found extremely strong support.

3.2. MANOVA 2. The second MANOVA revealed a statistically significant effect for participant gender, Pillai's Trace = 0.316, $F(8, 72) = 4.17$, $p < 0.001$, and $\eta^2 = 0.316$. As a result, eight follow-up univariate analyses of variance (ANOVAs) were run to identify the location of the significant differences

Table 2: Mental health, social support, and health related quality of life scores for women and men.

Variables	Women	Men	F-statistic	p value	Cohen's d
Satisfaction with life	22.70 (6.27)	24.89 (6.39)	2.158	.146	.35
Depression	7.35 (5.48)	3.07 (3.85)	13.752	.000	.90
Burden	25.09 (16.61)	16.56 (7.78)	6.388	.014	.66
Social support: appraisal	10.83 (2.58)	13.30 (3.04)	14.593	.000	.88
Social support: belonging	11.50 (2.85)	13.40 (2.36)	9.013	.004	.73
Social support: tangible	10.81 (2.68)	13.15 (2.63)	13.836	.000	.88
Self-esteem	29.56 (5.52)	33.70 (4.61)	11.292	.001	.81
Anxiety: state	24.96 (12.17)	18.07 (9.77)	6.537	.012	.62
Anxiety: trait	27.63 (10.73)	18.31 (7.96)	15.469	.000	.99
Physical functioning	77.50 (24.57)	99.33 (10.65)	10.20	.002	.84
Role-physical	74.53 (35.85)	81.48 (25.56)	.81	.372	.22
Role-emotional	64.20 (41.39)	81.48 (32.47)	3.59	.062	.46
Vitality	51.48 (17.50)	71.11 (17.28)	22.83	.000	1.29
Emotional well-being	56.44 (19.34)	73.63 (17.72)	15.00	.000	.93
Social functioning	70.37 (21.21)	86.11 (14.84)	11.91	.001	.86
Pain	69.40 (21.98)	89.91 (15.14)	18.95	.000	1.09
General health	52.87 (19.54)	72.59 (15.65)	20.80	.000	1.11

Note. Cohen's d effect size: .20 = small, .50 = medium, and .80 = large. p values are two-tailed. Standard deviations are in parentheses.

between woman and men on health-related quality of life. In each of these ANOVAs, the independent variable was participant gender, and the dependent variables were each of the HRQOL scores in the omnibus MANOVA. The results of these ANOVAs appear in Table 2.

Across every index except role-physical and role-emotional, women reported substantially lower HRQOL than men. The effect sizes [45] of the six statistically significant effects were all large. As a result, this study's hypothesis that women caregivers would have lower HRQOL than men had strong support.

3.3. Gender Differences in Demographics. The t-tests and χ^2 tests examining gender differences in participant demographics found differences in age, relationship to the individual with MS, education, work status outside the home, and hours per week and total months spent caregiving. See Table 1 for these means and standard deviations. Because of the significant gender differences in demographics, these variables were included as covariates in multivariate analyses of covariance (MANCOVAs) 3 and 4, except for relationship status to the individual with MS because categorical data with multiple categories cannot be included meaningfully in a MANCOVA.

3.4. MANCOVA 3. A third MANCOVA was run in the same manner as the first MANOVA for the mental health and social support variables with the addition of the following covariates: age, years of school, employment status, hours per week providing care, and months as a caregiver. The third MANCOVA revealed a statistically significant effect for participant gender, Pillai's Trace = 0.222, $F(9, 64) = 2.06$, $p = 0.050$, and $\eta^2 = 0.222$. As a result, nine follow-up univariate analyses of covariance (ANCOVAs) with the five covariates were run to identify the location of the significant differences between woman and men on the mental health and social support variables. In each of these ANCOVAs, the independent variable was participant gender, and the dependent variables were each of the total mental health and social support scores in the omnibus MANCOVA. The results of these ANCOVAs appear in Table 3.

Five out of the nine ANCOVAs were statistically significant in that women reported higher state and trait anxiety, lower self-esteem, and lower appraisal and tangible social support. The effect sizes [45] of the two social support differences were medium; two out of three mental health differences were medium effects; and the other difference was a large effect. As a result, this study's hypothesis that women would have poorer mental health and social support than men, even while controlling for demographic variables, was supported.

3.5. MANCOVA 4. The fourth MANCOVA did not reveal a statistically significant effect for participant gender, Pillai's Trace = 0.184, $F(8, 67) = 1.89$, $p = 0.075$, and $\eta^2 = 0.184$. Because this MANCOVA was not statistically significant, no follow-up ANCOVAs were run, and the study's hypothesis that women would have lower HRQOL than men, even while controlling for demographic variables, was not supported.

4. Discussion

The purpose of this study was to examine gender differences in mental health, social support, and HRQOL in Mexican MS caregivers. As compared to men caregivers, women caregivers had lower scores across the three sets of variables. When covarying for demographic variables that differed as a function of gender, the gender difference in HRQOL was no

Table 3: Covariate-adjusted mental health and social support scores for women and men.

Variables	Women	Men	F-statistic	p value	Cohen's d
Satisfaction with life	23.03 (6.80)	24.23 (7.15)	.46	.499	.17
Depression	6.76 (5.10)	4.25 (5.36)	3.60	.062	.48
Burden	23.35 (14.95)	19.99 (15.75)	.74	.393	.22
Social support: appraisal	10.95 (2.92)	13.07 (3.07)	7.90	.006	.71
Social support: belonging	11.81 (2.65)	12.78 (2.79)	1.99	.163	.36
Social support: tangible	10.93 (2.79)	12.92 (2.94)	7.53	.008	.69
Self-esteem	29.54 (5.65)	33.74 (5.94)	8.20	.005	.72
Anxiety: state	25.12 (12.21)	17.76 (12.84)	5.39	.023	.59
Anxiety: trait	27.78 (10.65)	18.01 (11.21)	12.22	.001	.89

Note. Cohen's d effect size: .20 = small, .50 = medium, and .80 = large. p values are two-tailed. Standard deviations are in parentheses.

longer significant, but the differences in mental health and social support remained. This was the first study to examine and find gender differences in the psychosocial functioning of MS caregivers in Latin America. This is particularly notable given that MS rates in Latin America are increasing and caregivers there experience reduced mental and physical health, which may be influenced by rigid gender roles with women often assuming more substantial caregiving duties.

4.1. Gender Differences in Mental Health and Social Support. The finding that women reported lower scores on the mental health and social support variables than men (except satisfaction with life) is consistent with previous research in other global regions. In a sample of MS caregivers from New Zealand, Knight et al. [23] found that female spouses had higher burden than husbands and Patti and colleagues [9] similarly found that Italian female caregivers had higher levels of psychological morbidity than male caregivers. However, these findings were also discrepant from those in Good, Bower, and Einsporn's [20] study in which men spousal MS caregivers in the US had lower perceived social support than women caregivers and from Buchanan and colleagues' [21] finding in which men caregivers, also in the US, had higher burden than women caregivers.

Possible reasons for these robust significant differences found here may be related to differences in sample characteristics of Knight et al. [23] and Good et al. [20] and this study's sample and cultural perspectives on disability and caregiving. Both Knight et al. and Good et al. studied only MS spousal caregivers, and caregiver relationships to the MS patient may have a differential influence on mental health outcomes. More women were parents and more men were spouses and partners in the current study. In Mexican families, parents look to their adult children to provide them with care in old age and not the reverse [46]. Although women caregivers reported generally lower mental health than men, perhaps these differences were due also to the high self-sacrifice involved in fulfilling traditional nurturing and caregiving gender roles [29–31], and they did not report lower satisfaction with life, perhaps because fulfilling their gender role to provide care for a family member may have actually provided them with life satisfaction as they fulfilled a culturally prescribed role.

When age, years of school, employment status, hours per week providing care, and months as a caregiver were entered as covariates, the overall model still suggested that gender differences were present. However, in the follow-up ANCOVAs, several previously significant gender differences were no longer significant including depression, burden, and belonging social support. In previous studies, both employment and hours of caregiving have contributed significantly to caregiver burden and depression [19, 21, 22]. However, in this sample significantly more men worked, and women provided significantly more caregiving hours. Thus, controlling for these variables likely reduced their influences on the mental health and social support outcomes and pointed to a possible source of the gender difference on these variables.

Yet, differences still remained for appraisal and tangible social support, self-esteem, and state and trait anxiety. Cultural explanations of disability as either God's will or punishment for some previous actions of the parent have been described in Latin American cultures [47] and may account for the persistence of these results. Either belief could make appraisal and tangible social support for caregivers who are mothers less forthcoming and could place women caregivers of adult children at higher risk for lower mental health than the men caregivers of their spouses in this sample. Furthermore, awareness that these adult children with MS will be unavailable to provide care one day for these women caregivers in their old age could contribute to a lower self-esteem and higher levels of anxiety about their future.

4.2. Gender Differences in HRQOL. The finding that women reported lower HRQOL than men (except role limitations: physical and role limitations: emotional) is also generally consistent with previous research [48]. Studies by Rivera-Navarro and colleagues [49], as well as Patti and colleagues [9] and Giordano and colleagues [50], found that female gender was a major predictor of lower quality of life in MS caregivers and that male spousal caregivers had significantly higher scores than female spousal caregivers on the SF-36. Aymerich et al. [51] reported that while there were no significant differences by gender in physical HRQOL, women scored significantly lower on mental HRQOL than men MS caregivers [52]. Similar gender differences in HRQOL have been reported in caregivers of patients with other

neurological conditions, such as Alzheimer's disease, amyotrophic lateral sclerosis, and stroke [53–55]. These gender differences may reflect how men and women vary in their perceptions of and coping with caregiving stress. It is possible that even though women experience and express greater disturbances in their health-related quality of life, their socially dictated need to continue their caregiving duties (despite the toll this may take on their personal well-being) makes them less likely to report that such disturbances limit their caregiving role. When the covariates were added to the model, the overall model was no longer statistically significant, suggesting that gender differences in these covariates may have accounted for some of the gender differences in HRQOL. However, it is important to note that the model approached statistical significance ($p = 0.075$), so follow-up ANCOVAs, if they had been performed, likely would have revealed some gender differences even after controlling for the covariates.

4.3. Gender Differences in Demographics. The analyses examining gender differences in demographics found that, in comparison to men, women caregivers had fewer years of education, were less likely to work outside the home, spent almost twice as many hours per week providing care (79.28 versus 48.48, $p = 0.018$), and had provided care for nearly three times as many months (66.31 versus 24.30, $p = 0.002$). These findings suggest a profound disproportionate burden of care in Latin America falling on women as opposed to men. This is consistent with the rigid gender roles in Latin America, which are likely influenced by a history of unequal distribution of resources within society. The vast majority of the population and families affected by serious illnesses (except for those in higher echelons) have access only to family care since it carries no monetary cost; this, in turn, may have the effect of reinforcing social specialization via traditional gender roles and assigning principal caregiving tasks to women [56]. Although gender differences in the relationship of caregivers to patients could not be taken into account in the MANCOVAs due to their multiple categorical nature, it is notable that 55.6% of men caregivers were the patient's spouse, while only 14.8% of women caregivers were. Conversely, only 11.1% of men caregivers were parents of the patient, whereas 63.0% of women caregivers were. It is unlikely that these demographic differences accounted for the gender differences in mental health and HRQOL found in this study because there was still adequate representation in the other relationship-to-patient categories, but it does beg for future studies to investigate why men MS caregivers in this region are more likely to be spouses and women MS caregivers are more likely to be parents. A potential reason could be parental caregivers being older on average than spousal caregivers and women simply having greater longevity than men, an epidemiological trend that might mean that there are more older mothers alive in families who are able to take on the caregiving role.

Within traditional Latin American cultures with strong gender-role divisions, women are expected to be dependent, chaste, and submissive, in contrast to the idealized masculine gender role of being independent, virile, and dominant [57]. While Latino cultures are not homogenous, rigid gender roles generally dictate that women play a central role in the organization and maintenance of family life and traditions [58]. From an early age, girls and women are socialized into their expected tasks of providing care for the family, while foregoing and sacrificing personal time, self-care, socialization, and employment opportunities for the well-being of children and husband providers, as well as helping maintain their families' social respectability [29, 59]. These social forces likely influence the significant gender differences in care provision variables observed in this study. In addition, women caregivers in the current sample scored lower on all scales of the SF-36 compared to a normative sample of Mexican women [60]. This suggests that an additional load of providing full-time care to a loved one with MS takes a significant toll on women caregivers' HRQOL, beyond that already experienced by Mexican women in the general population.

4.4. Clinical Implications. The findings from the current study have implications for MS caregiver interventions in Latin America and possibly for caregivers in other global regions or cultural groups with similar values and beliefs. MS caregiver interventions in Latin America—particularly for women caregivers—should address the influence of gender-role conformity on care and psychosocial functioning. While gender is not a variable that can be changed, the pervasive effect of roles expected of women in Latin America in the context of being the principal providers of care for individuals with MS is potentially malleable. For women MS caregivers, quality of life may be reduced because the time spent on caregiving tasks incurs an opportunity cost of giving up engaging in recreational, socialization, or self-care activities.

Mexican women, especially over the age of 40, have been reported to have a higher likelihood of engaging in poor self-care practices (e.g., lack of exercise, poor eating habits, poor sleep, obesity, and overweight), forego preventive medical procedures (e.g., breast self-exams or uterine and cervical cancer exams), only go to the doctor when ill, and lack social security [61], consistent with previously reported traditional expectations of self-sacrifice in the name of caring for one's family [29]. Clinicians can help women MS caregivers become aware of and perhaps renegotiate social roles which place an undue burden of care on them, a process that could improve women caregivers' mental health and HRQOL by reducing their caregiving load. Clinicians could also initiate discussions about the roles that women caregivers assume implicitly and increase caregivers' awareness of the negative physical and mental health consequences of neglected self-care. Clinicians could use the present findings to guide the assessment of caregivers' needs and plan their interventions accordingly. Family-based or systemic approaches may include strategies which lead to delegating care tasks, whenever possible and acceptable, to extended family members and other individuals who constitute the caregiver's social support group.

As was observed in this study's sample, women caregivers had fewer years of education and were less likely to work outside of home. It has been suggested that reducing work

hours to accommodate the caretaking load may predispose caregivers to greater vulnerability later in life by accumulating fewer benefits such as social security and possibly by experiencing more poverty [62]. Creation and extension of social programs to assist family caregivers—especially women—such as respite or financial assistance also could have a positive effect on their mental health and HRQOL. As such services are very limited in Mexico and other Latin American countries [63], more funding and intervention at the policy level may be needed in order to establish the formal networks of support for informal caregivers, whose unpaid labor in Mexico accounts for up to 15% of the GDP [64].

4.5. Limitations and Future Directions. Despite the current study's implications for MS caregiver interventions in Latin America, it has several limitations and, as a result, directions for future research. First, the data are limited because they are cross-sectional and were only collected in one city in Mexico. The findings therefore do not take into account change over time, so trajectories of mental health, social support, and HRQOL cannot be examined. The findings also might not generalize to other countries in Latin America or Latinos in the US. Second, although gender-role conformity was extensively used as an explanation for the findings, no self-report measures of gender-role conformity were collected. This would be a ripe area for future research. Third, all participants volunteered to participate in the study, which does not exclude the possibility that these individuals presented with different levels of mental health, HRQOL, and social support than the majority of Mexican MS family caregivers who did not have access to the health facility from which caregivers were recruited. Fourth, perhaps the most significant limitation is that no measures of patient disability or needs were collected, so the potentially differential impact of disease symptoms on men and women caregivers' psychosocial functioning cannot be examined. A number of clinical variables should be assessed in future similar research including patient functional independence, MS symptoms, disability level, mobility and wheelchair needs, cognitive impairments, and secondary medical conditions. All of these variables can play a major role in caregiving and should be primary subjects of investigation in future research on gender differences in MS caregiver psychosocial functioning.

5. Conclusions

With these limitations in mind, this study represents the first to examine gender differences in mental health, HRQOL, and social support among MS caregivers in Latin America. The findings robustly suggest that, in Mexico, women assume substantially more caregiving duties, and therefore MS caregiver interventions in Latin America—particularly for women caregivers—should address the influence of gender-role conformity on care and psychosocial functioning.

Conflict of Interests

No competing financial interests exist for the authors.

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