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A Discordant Monozygotic Twin Approach to Testing Environmental Influences on Sexual Dysfunction in Women

Andrea Burri · Timothy Spector · Qazi Rahman

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Abstract The present study explored the causal role played by putative environmental factors on variation in female sexual dysfunction (FSD) by investigating FSD discordant monozygotic (MZ) twins, which permits a control over genetic confounders. In a population-based sample of female twins aged 25–69 years ($M = 55$ years), MZ twins discordant for recent and lifelong FSD were selected. Sample sizes varied depending on the specific sexual problem ($N = 33$–90 pairs). The Female Sexual Function Index (FSFI) score was used to discriminate cases from controls. Once genetic factors were controlled for, relationship satisfaction emerged as the strongest independent predictor for recent and lifelong FSD, being associated with FSFI dimensions measuring desire, arousal, and lubrication problems. The association with orgasm problems was especially strong (OR 7.1, 95 % CI: 1.9–25.3) as was the association with sexual dissatisfaction (OR 5.1, 95 % CI: 2.1–12.1). Furthermore, obsessive–compulsive symptomatology was weakly associated with desire problems (OR 1.5, 95 % CI: 1.4–1.8) and anxiety-sensitivity with orgasm problems (OR 1.1, 95 % CI: 0.9–1.3). Negligible effects were found for personality factors and small effects for self-reported abusive experiences. These data indicate, for the first time, that in women at identical genetic risk, relationship factors play a key role in the development of sexual problems. These findings require replication in prospective designs which can provide additional powerful tests of the direction of causality between interpersonal factors and later sexual dysfunction.

Keywords Female sexual dysfunction · Twins · Genetics · DSM-5

A. Burri (✉) · T. Spector
Department of Twin Research and Genetic Epidemiology, King's College, St. Thomas Hospital, Westminster Bridge Road, SE1 7EH London, UK
e-mail: andrea.burri@kcl.ac.uk

A. Burri
Institute of Psychology, University of Zurich, Zurich, Switzerland

Q. Rahman
Biological and Experimental Psychology Group, School of Biological and Chemical Sciences, Queen Mary University of London, London, UK

Q. Rahman
Department of Psychology, Institute of Psychiatry, King's College, London, UK

Introduction

Female sexual dysfunction (FSD) is a common and progressive problem across female populations (Burri, Cherkas, & Spector, 2009; Derogatis & Burnett, 2008). According to the current nosological systems, FSD is categorized into problems of desire, arousal, orgasm, and pain (American Psychiatric Association, 1994; World Health Organization, 1992). Despite recent research efforts, the etiology underlying FSD is still unclear, but a combination of psychosocial, physiological, and genetic factors have been proposed (Argiolas & Melis, 2003; Clayton, 2007; Motofei & Rowland, 2005).

Risk factors that ostensibly come under the "psychosocial" category, and that have been linked to women's sexual functioning, range from psychiatric symptomatology to interpersonal or relationship variables (e.g., Bradford & Meston, 2006; Burri & Spector, 2011; Dunn, Croft, & Hackett, 1999; Harris, Cherkas, Kato, Heiman, & Spector, 2008; Reynaert, Zdanowicz, Janne, & Jacques, 2010; Schnarch, 1997; Sprecher, 2002). The association between psychiatric problems, such as anxiety and depression, and FSD symptoms has been documented in both large scale epidemiological and community samples. Researchers

have suggested that either a latent risk factor underlies the link between anxiety and mood disorders and FSD or that mental health problems affect other proximate factors which impair sexual functioning (such as excessive rumination or focusing of attention towards body image or the quality of sexual performance) (Dunn et al., 1999; Frohlich & Meston, 2002; Hayes et al., 2008). Relationship factors also appear to be an important correlate of FSD symptoms. Women with sexual problems who report less satisfaction in their current relationship are approximately twice as likely to report symptoms of sexual distress compared to women not reporting any sexual difficulties, although this association is partly mediated by partner compatibility (Witting et al., 2009). The latter example show that it is as yet unclear whether these known correlations between psychosocial factors and FSD symptomatology constitute a clear mechanism in the disorder or are confounded by other mediating factors (e.g., genetics). This lack of knowledge about etiology can hamper progress in both psychiatric nosology (as demonstrated by the range of diagnostic classifications for FSD (e.g., see Basson et al., 2000, 2004) and the range of treatment strategies with variable success rates. Further clarification regarding etiological pathways (biological and psychosocial) will enhance treatment options for women as well as making them more cost-effective.

Many of the psychosocial candidates have been reported to be heritable (using data from twin studies). Psychiatric problems, such as depression (Hettema, Neale, & Kendler, 2001) or anxiety (Sullivan, Neale, & Kendler, 2000), show moderate to high heritabilities of around 40 %. Considering the clear heritability found for most of the aforementioned factors associated with FSD, a genetic susceptibility for FSD is likely (Jang, Wesley, & Vernon, 1996; Vernon, Petrides, Bratko, & Schermer, 2008). Recent twin studies have indeed shown that genetic factors play a significant role in the development of FSD, with reported heritability estimates of up to 51 % (Dawood et al., 2005; Dunn, Cherkas, & Spector, 2005; Witting et al., 2009). Despite this evidence for a genetic component, the specific genetic loci responsible for FSD have yet to be properly explored (reviewed in Burri et al., 2009). Moreover, it is also unclear whether genetic factors responsible for overall FSD symptoms scores covary with genetic factors for known psychosocial correlates (such as anxiety, depression, and relationship satisfaction). One aim of the present study was to utilize a powerful method for disentangling genetic and non-genetic confounds on the association between FSD and psychosocial factors.

Consensus among researchers is that FSD symptoms are influenced by multiple factors (Basson et al., 2000, 2004; Burri et al., 2009). This heterogeneity may be due to both common and unique etiologic mechanisms. If this were correct, then some etiologic mechanisms may be common to all women reporting FSD symptoms (e.g., common genetic factors) whereas other mechanisms may be unique to each symptom dimensions. Alternatively, unique etiological mechanisms may produce different symptom clusters of FSD, explaining the phenotypic variation in FSD often observed in both clinical and research contexts. Stronger tests of these possible etiological pathways are now needed and in particular those which separate genetic from non-genetic (or environmental) factors. As mentioned previously, studies documenting psychosocial determinants of FSD are unable to separate cause and effect or rule out genetic contributions given the strong heritable nature of some of these determinants. Even strong associations between an environmental factor and FSD do not allow causal inference because such associations can be the result of confounding or "third" variables or be a case of reversed causation. One way of addressing the problem of "causality" would be to conduct experimental studies which offer controlled testing of causal processes (e.g., the evaluation of time priority and consistency in a causal relationship), but for obvious ethical and practical reasons such research on FSD remains problematic. While the issue of true or reversed causation can be resolved in part through longitudinal studies, such research designs are rare.

One approach to separating, albeit imperfectly, cause and effect relationships as well as controlling for critical "third" variables, is offered by twin research. While researchers have acknowledged the advantages of using twins in quantifying the genetic contribution (heritability) in behavioral traits and common diseases, their utility in exploring the environmental basis of individual differences in behavior has been less widely recognized. One approach, called the discordant monozygotic (MZ)-twin method, has proved useful in separating environmental influences upon a trait from any genetic confounds as well as providing clues to direction of causality. Here, researchers are able to test whether environmental factors (such as psychosocial factors described above in relation to FSD) are responsible for the presence of the trait in one twin compared to his or her co-twin who does not show the trait. As these factors are often assumed to be part of the "non-shared environmental (or NSE)" component of variation often found in classical twin studies, this technique provides some indications as to which NSE factors are actually important (Dick, Rose, Viken, & Kaprio, 2000; Jinks & Fulker, 1970; Kaprio, Buschsbaum, & Gottesman, 1999; Pike, Reiss, Hetherington, & Plomin, 1996). This approach overcomes many of the traditional limitations associated with conventional epidemiology because trait-discordant MZ twins are completely matched for genetics, age, sex, cohort effects, maternal influences, common environmental factors (those shared by siblings), and are closely matched for other environmental factors (such as early upbringing and lifestyle) (Dick et al., 2000; Jinks & Fulker, 1970; Kaprio et al., 1999). Moreover, as twin type always precedes twin similarity on a phenotype, any differences in phenotype outcomes cannot be causally explained by genetic factors. Therefore, it affords a powerful test of detecting disease-related etiological differences compared to studies of unrelated disease cases and controls with different life histories.

The use of this design has already led to the isolation of non-genetic environmental factors in conditions such as heart disease and obesity; the identification of the role of socioeconomic and exercise variables independent of genetics on age-related diseases, as well as identifying new behavioral markers which may be useful areas for studying the effects of interventions in schizophrenia and other psychological disorders (Pietiläinen et al., 2004; Vitaro, Brendgen, & Arseneault, 2009; Williams et al., 2008). While the power of the discordant-twin design in making inferences about probable causality stems largely from the within-MZ pair analysis, comparisons between discordant MZ and DZ pairs allow researchers to fully evaluate the genetic confounding, as well as to increase the sample size in order to boost statistical power.

To our knowledge, no study of psychosocial factors in MZ twins discordant for FSD has been published. We, therefore, aimed to investigate whether the rates of FSD symptoms in discordant twin pairs were higher in MZ and DZ twins who were exposed to psychosocial risk factors suggested by previous research to be important compared to their unexposed co-twins.

Method

Participants

Twins were identified from the TwinsUK register (Spector & Williams, 2006). The study was approved by the St Thomas' Hospital research Ethics Committee and all twins provided informed consent. The register comprises MZ and dizygotic (DZ) twin volunteers who have been recruited since 1992, using other twin registers and successive national media campaigns. Zygosity of twins was assigned using a standard questionnaire, which is accurate in 95 % of cases (Cederlof, Fridberg, Jonsson, & Kaij, 1961). In addition, approximately half of the participants (51 %) had their zygosity assigned with certainty by multiplex DNA fingerprinting using variable tandem repeats on venous blood samples taken on attendance at the Department of Twin Research and Genetic Epidemiology. This well-studied population of MZ and DZ twins is sent regular questionnaires for self-completion concerning wide-ranging lifestyle and behavioral factors, as well as health issues. The cohort has been compared for a number of diseases, traits, and environmental factors to an age-matched UK population and a singleton population cohort from North-East London and was found to be no different in terms of disease prevalence and lifestyle characteristics (Andrews et al., 2001). The cohort has further been shown to be representative of the general population for a wide range of lifestyle and sexual behavioral factors (Burri & Spector, 2011; Dunn et al., 2005; Harris et al., 2008).

Measures

Sexual Functioning

Questionnaires relating to FSD were sent to a subsample of 3,154 women in 2008 (29.7 % of twins from the entire Twins UK registry; aged 18–82 years, $M = 55$). The subsample consisted of female twins who had previously participated in studies related to sexual behavior and had stated their willingness to participate in future similar studies.

To determine the presence of persistent FSD (i.e., ever since sexually active) we used the 19-item Female Sexual Function Index-Lifelong (FSFI-LL), a modified but validated version of the FSFI (Burri, Cherkas, & Spector, 2010; Rosen et al., 2000). The FSFI-LL assesses 6 dimensions of women's average sexual functioning, including desire (2 items), arousal (4 items), lubrication (4 items), orgasm (3 items), satisfaction (3 items), and pain (3 items). Response options for both questionnaires to each question are on a Likert-type scale ranging from 1 to 5 for Items 1 and 2 and from 0 to 5 with the supplementary option "no sexual activity" for all other items (3–19). Domain scores were derived by adding the point values for each item in the domain, and by multiplying the sum by the domain factor weight (Burri et al., 2010; Rosen et al., 2000). Low scores on the FSFI-LL indicate more problems with sexual function. The original FSFI has received extensive psychometric evaluation in clinical and nonclinical samples (Meston, 2003; Wiegel, Meston, & Rosen, 2005). It has shown a high degree of internal consistency (Cronbach's α values of 0.82 and higher) and high test–retest reliability for each domain ($r = .79-.86$) (Rosen et al., 2000). In a validation study in the twin sample used in this study, the FSFI-LL has shown excellent psychometric properties, including test–retest reliability, internal consistency, external and discriminant validity and has demonstrated excellent comparability to the standard FSFI in terms of factor structure and psychometric properties (Burri et al., 2010).

Demographic, Psychological, and Interpersonal Measures

Potential risk factors were selected based on previous literature and availability and included measures of demographics, anxiety, obsessive–compulsive behavior, personality, history of abuse, emotional intelligence, and relationship satisfaction. Sociodemographic information on all twins, including age, current marital status, social class, and years of education, were obtained from the TwinsUK database. Information on number of pregnancies (including miscarriage) was obtained from an independent questionnaire on general health that had been sent to the twins a few months ahead of this survey. Events of physical, emotional, and sexual abuse were assessed using self-constructed questions with yes/no response options (asking for example "Have you ever been sexually abused?"). Current and lifelong relationship

dissatisfaction was assessed with a single question with response options ranging from "very satisfied" (1) to "not satisfied at all" (6).

Data on obsessive–compulsive behavior were available from the 42-item Obsessive Compulsive Inventory. The measure is primarily used in clinics to aid the diagnosis and determine the severity of obsessive–compulsive disorder (OCD) (Foa, Huppert, Kichic, Hajcak, & Salkovskis, 2002). The OCI has shown excellent internal consistency ($r = .93$) and high test–retest reliability in an OCD sample ($r = .84-.87$) and in non-patient controls ($r = .89$–90) (Foa et al., 2002). Response options range from "never" (0) to "almost always" (4). A total score can be calculated by adding the scores for all items.

Data on anxiety were obtained from the 16-item self-report Anxiety Sensitivity Index (Reiss, Peterson, Gursky, & McNally, 1986). The psychometric properties and predictive validity of this widely used instrument have been well established and a number of studies have provided replicated evidence that the ASI has adequate internal consistency ($\alpha = 0.81$–0.94), a good degree of test retest reliability ($r = .71-.75$), and a high degree of inter-item relatedness (Reiss et al., 1986). The response options for the ASI are on a 5-point Likert-type scale, ranging from "Very little" (0) to "Very much" (4). The sum of all ASI responses yields the total ASI score, which ranges from 0 to 64.

The Big Five personality dimensions and the related construct of emotional intelligence were assessed using the Ten-item Personality Index (TIPI) and the Trait Emotional Intelligence Questionnaire (TEIQue-SF) (Hampson, 2005; Petrides & Furnham, 2006). The TIPI has adequate levels in terms of convergence with widely used multi-item Big-Five measures (e.g., BFI) in self, observer, and peer reports (M of $r = .77$) and good test–retest reliability ($r = .62-.77$) (Hampson, 2005). Response options are on a 7-point Likert scale ranging from "Disagree strongly" (1) to "Agree strongly" (7). Dimension scores were created by summing up the two item values for the different dimensions. Similar to the TIPI, the TEIQue-SF has also shown to have high levels of internal consistency (Cronbach's $\alpha > 0.80$) and good construct validity (Petrides & Furnham, 2006). Items of the TEIQue-SF are responded to on a 7-point Likert scale ranging from "Completely Disagree" (1) to "Completely Agree" (7). A total emotional intelligence score can be derived by adding the point values for each item together.

Statistical Analysis

Phenotypic or outcome variation (P) is a function of (1) additive genetic effects (A), which are shared completely by MZ twins but are only 50 % shared by DZ twins; (2) shared environmental effects (C), which are shared completely by both MZ and DZ twins; and (3) NSE, which are not shared by either MZ or DZ twins. To achieve the fullest possible control over potential confounding, we conducted three steps of analyses: (1) Individual-level associations which reflect potential confounding of exposure and outcome by A, C, and NSE effects; (2) within pair analysis in discordant DZ twins to control for C effects and partially for A effects; (3) within pair analysis in discordant MZ twins to control for both C and A effects. If the proposed etiological factor truly is a probable cause of sexual problems, then we expect exposure to be associated with outcome at all three levels.

Different strategies, albeit related analytically, exist to conduct discordant MZ-analysis (for an overview, see Asbury, Dunn, & Plomin, 2006; Vitaro et al., 2009). In this study, we used the *difference score strategy*, which is based on the correlation between relative differences between members of a MZ twin pair with respect to "risk factors" and relative differences between members of an MZ twin pair with respect to FSD scores. Both the dependent and independent variables are treated separately and the relative within-pair difference scores are calculated by first randomly assigning one of the twins (from each pair) as Twin 1 and the other as Twin 2 and, second, by subtracting the score of one twin from the score of the co-twin (Vitaro et al., 2009). Conditional regression models were fitted to assess the association between difference scores on the environmental factors and on the FSD outcome measure; hence, to test for risk of developing sexual problems in twins as measured by the FSFI (meaning more sexual problems), compared with their less affected co-twin controls. Predictors that were non-significant in the univariate models were dropped from the multivariate regression models.

To include zygosity as a potential moderator of the linkages between within-pair differences on the predictor variables and within-pair differences on the outcome variables, all analyses were extended to FSD-discordant DZ twin pairs. If the same pattern of results applies in both zygosities, and the differences in environmental experiences predict discordance in FSD equally well in MZ and DZ twin pairs, it is possible to conclude that the mechanism whereby the environmental factor affects FSD is not only likely causal, but also likely non-genetic (i.e., entirely environmental). Associations on an individual level were established using a linear regression design and treating the twins as non-related individuals.

All dimensions of the FSFI-LL, as well as anxiety sensitivity, obsessive–compulsive behavior, personality, emotional intelligence, relationship satisfaction, and number of pregnancies were handled as continuous measures. Previous history of abuse and having children were handled as dichotomous measures. All discordant MZ-twin analyses were conducted using STATA, Version 10.0. Because of the skewness of the distributions, all FSD-related phenotypes and psychological measures except desire, arousal, and extraversion were either log-, square or square-root transformed.

Results

Of the 3,154 women, 1,589 individuals returned the questionnaire (response rate, 50 %). For reason of standardization, 19 (1.3 %) women reporting being homosexual were omitted. Seventy-two (4.8 %) females with more than five of the 19 items in the FSFI-LL missing were further dropped from the sample. To maximize the number of twin pairs available for analyses, in cases where subjects had answered more than five of the 19 items in the FSFI-LL, missing values ($n = 72$) were imputed with item-specific means of the non-missing values, separately calculated for four different age groups: 18–30, 31–45, 46–55, and 56–85 years. After applying exclusion criteria and imputation, information on sexual functioning was available for a total of 1,489 women, comprising 244 full MZ pairs, 189 full DZ pairs, and 623 women whose co-twins did not participate (41.8 %). The comparability of the MZ and DZ twins in terms of sexual functioning (FSFI-LL scores) has been ascertained in a previous study conducted by our group (Burri et al., 2010)

Individual-Level Associations

Our individual-level regression analyses conducted on 866 twin individuals (twin individuals, whose co-twin did not participate were dropped from the study) supported the results obtained in an earlier study conducted by our group on a larger sample ($n = 1489$) (Burri & Spector, 2011). Similar to this previous study, we found relationship dissatisfaction to be significantly associated with elevated risk of reporting sexual problems on all domains, except sexual pain (Table 1). We further found associations between anxiety sensitivity, previous experience of abuse, and several personality traits with sexual problems. However, the effects of personality, such as extraversion and openness to new experience, were silenced when including the variables in multivariate models, taking into account potential inter-correlations between the variables.

Conditional Regression Analyses in Discordant MZ Twins

Because results may reflect potential confounding of exposure and outcome by not controlling for A, C, and NSE effects, we extended the analyses to discordant MZ twins, which allows us to completely control for both C and A effects. Table 2 displays the β coefficients (95 % CI) of the intra-pair differences in the potential risk factors for MZ twins discordant for FSD. When taking into account the possible inter-correlations between the variables, relationship dissatisfaction remained the strongest, independent predictor of sexual problems, with the strongest association found between relationship satisfaction and any type of sexual problem ($\beta = 2.32$, 95 % CI: 1.36–3.29; $p < .001$). Overall, effect sizes tended to be slightly smaller ($\beta = 0.20$–2.32) compared to individual-level results ($\beta = 0.26$–2.82). Most of the individual-level associations found between experience of abuse and FSD (such as associations between sexual abuse and orgasm problems or emotional abuse and low desire) could not be detected in discordant MZ twins. However, there were particularly strong associations between previous experience of sexual abuse and physical abuse, respectively, with overall FSD-symptoms ($\beta = -6.56$, 95 % CI: −11.00–2.12, $p < .001$ and $\beta = -6.26$, 95 % CI: −9.08 to 1.46, $p < .001$, respectively). No effects of emotional abuse on any FSFI domains could be detected. Furthermore, in contrast to the individual-level analysis, there were no significant associations between anxiety sensitivity and any of the sexuality-related measures (Table 2). Similarly, no significant relationship between the personality traits extraversion, agreeableness, and openness to new experience and sexual problems could be detected in the conditional regression analyses conducted on discordant MZ twins only.

Conditional Regression Analyses in Discordant DZ Twins

If the above reported risk factors were truly causes of FSD, we would expect them to be associated with FSD within DZ twin pairs discordant for exposure as well. Therefore, to fully assess the associations between potential risk factors and FSD and the relative degree of causality, we further investigated the associations within DZ twin pairs discordant for FSD to completely control for C effects and partially for A effects. Again, relationship dissatisfaction remained the strongest independent predictor for FSD (β ranging from .22 to 2.82 with the strongest effect on overall FSD, $\beta = 2.82$, 95 % CI: 2.30–3.33, $p < .001$; Table 3). Similar to the results for discordant MZ twins, having experienced sexual or physical abuse increased the odds of suffering from FSD, although effect sizes in DZ twins were significantly lower compared to MZ twins ($\beta = -0.65$, 95 % CI: −1.65 to 1.95, $p < .05$ and $\beta = -0.46$, 95 % CI: 2.23–2.16, $p < .05$, respectively). In terms of psychological/personality factors, no significant associations with any of the FSFI domains could be detected.

Discussion

Our results showed that, once genetic factors have been controlled, self-reported relationship dissatisfaction had the most significant effect on lifelong FSD, replicating the association found in less conclusive study designs (Burri & Spector, 2011; Schnarch, 1997; Sprecher, 2002). Significant associations between relationship dissatisfaction and sexual problems could be observed, not only at the individual-level, but also within DZ and MZ twin pairs discordant for FSD. Our findings were in line with recent research on FSD, emphasizing the impact of interpersonal factors, such as relationship satisfaction, level of intimacy, unresolved conflicts, and communication on the development

Table 1 Results from individual-level regression analyses

	Desire *b* (95 % CI)	Arousal *b* (95 % CI)	Lubrication *b* (95 % CI)	Orgasm *b* (95 % CI)	Satisfaction *b* (95 % CI)	Pain *b* (95 % CI)	Total *b* (95 % CI)
Sexual abuse	−.02 (−.19 to .15)	−.22 (−.33 to .07)	−.11 (−.19 to .09)	**−.39 (−.84 to .31)***	**−.45 (−.91 to .59)***	−.10 (−.19 to .20)	**−1.31 (−2.53 to .54)****
				−.26 (−.54 to .29)*	−.04 (−.12 to .14)		**−2.83 (−3.36 to 1.29)****
Physical abuse	−.1 (−.21 to .17)	−.07 (−.15 to .29)	−.03 (−.17 to .24)	−.16 (−.09 to .43)	**−.47 (−.81 to .26)***	−.15 (−.32 to .13)	**−.67 (−1.12 to 1.06)***
					−.02 (−.12 to .14)		**−.16 (−1.49 to 1.43)***
Emotional abuse	**−.16 (−.33 to .00)***	−.05 (−.11 to .23)	−.02 (−.18 to .13)	−.14 (−.26 to .15)	**−.59 (−.77 to .32)****	.05 (−.06 to .18)	**.88 (−.15 to 1.92)***
	−.28 (−.46 to .12)*				−.05 (−.11 to .12)		**.23 (−1.00 to .93)***
Education	.01 (−.00 to .03)	.04 (.02−.06)	.03 (.02−.05)	.01 (−.01 to .04)	.01 (−.019 to .04)	.01 (−.01 to .03)	.14 (.04 to .23)*
							.15 (.04 to .27)*
Number of pregnancies	.01 (−.08 to .10)	.00 (−.09 to .09)	−.03 (−.12 to .04)	−.01 (−.10 to .08)	.03 (−.00 to .13)	.00 (−.05 to .07)	−.00 (−.39 to .39)
Relationship satisfaction	**.26 (.03 to .40)****	**.46 (.13 to .59)****	**.30 (.04 to .44)***	**.57 (.19 to .79)****	**1.04 (.85 to 1.21)****	.17 (.03 to .24)	**2.82 (1.34 to 3.96)****
	.28 (.04 to .41)**	**.45 (.19 to .58)****	**.29 (.05 to .43)***	**.54 (.16 to .77)****	**1.02 (.81 to 1.23)****		**2.83 (1.37 to 3.87)****
Emotional intelligence	.00 (−.00 to .01)	.00 (−.01 to .00)	.00 (.00 to .01)	.00 (.0 to .01)	.00 (−.00 to .01)	.04 (.00 to .07)	.02 (.00 to .04)
Obsessive compulsive	.002 (−.00 to .00)	.00 (−.00 to .00)	.00 (−.01 to .00)	.00 (−.012 to .00)	−.01 (−.02 to .00)	.00 (−.01 to .00)	−.03 (−.07 to .00)
Anxiety sensitivity	.00 (−.0 to .00)	−.05 (−.13 to .00)	**−.11 (−.02 to .00)***	−.07 (−.17 to .02)	**−.11 (−.21 to .00)****	−.11 (−.22 to .00)	**−.15 (−.18 to .02)***
			−.10 (−.01 to .18)*		.00 (−.01 to .00)		**−.11 (−.4 to .01)***
Extraversion	−.04 (−.09 to .00)	−.05 (−.09 to .00)	−.07 (−.11 to .02)	−.07 (−.13 to .01)	−.02 (−.08 to .03)	−.05 (−.09 to .01)	**.32 (.04 to .79)****
							.13 (−.31 to .53)*
Agreeableness	−.04 (−.11 to .01)	.00 (−.06 to .06)	−.02 (−.08 to .03)	−.05 (−.126 to .02)	**−.10 (−.19 to .02)***	−.01 (−.08 to .03)	−.24 (−.55 to .06)
					−.03 (−.05 to .00)		
Emotional stability	−.04 (−.09 to .00)	**−.09 (.15 to .04)***	**−.08 (−.13 to .03)***	**−.10 (−.16 to .04)***	**−.14 (−.21 to .08)***	−.09 (−.13 to .04)	**−.57 (−.81 to .32)***
		−.04 (−.08 to .00)	−.02 (−.08 to .02)	−.01 (−.07 to .04)	−.01 (−.03 to .01)		−.07 (−.27 to .12)
Conscientiousness	−.04 (−.12 to .02)	−.04 (−.10 to .03)	**.10 (−.18 to .21)***	−.10 (−.19 to .00)	−.05 (−.15 to .04)	−.01 (−.08 to .04)	**.36 (−.78 to .64)***
			.06 (−.13 to .12)	−.07 (−.15 to .00)			**.28 (−.89 to .43)***
Openness	**−.11 (−.16 to .05)***	**−.08 (−.14 to .02)***	−.07 (−.13 to .01)	**.11 (−.08 to .34)***	−.02 (−.1 to .04)	−.03 (−.08 to .01)	**−.43 (−.71 to .16)***
	−.09 (−.14 to .04)*	−.07 (−.12 to .02)		.09 (−.51 to .31)			**−.24 (−.47 to .02)***

Results from individual-level regression analyses on a total sample of 866 women, comprising 244 full MZ pairs and 189 full DZ pairs. Variables relating to sexual, physical, emotional abuse were handled as dichotomous measures, all other variables as continuous measures. Results from multivariate analyses for the variables included in the models are presented below the results from the univariate analyses. Significant results are highlighted in bold

* $p < .05$

** $p < .001$

Table 2 Results from univariate regression analyses in a subsample of MZ twin pairs discordant for sexual problems

	Desire *b* (95 % CI)	Arousal *b* (95 % CI)	Lubrication *b* (95 % CI)	Orgasm *b* (95 % CI)	Satisfaction *b* (95 % CI)	Pain *b* (95 % CI)	Total *b* (95 % CI)
Sexual abuse	−.38 (−.89 to .10)	**−.51 (−1.06 to .03)***	−.35 (−.87 to .16)	**−.55 (−1.25 to .14)***	**−.70 (−1.33 to .08)***	−.04 (−.53 to .46)	**−2.55 (−4.75 to .35)****
		−.29 (−.79 to .21)		−.27 (−.97 to .41)	−.04 (−.47 to .39)		**−6.56 (−11.00 to 2.12)****
Physical abuse	−.10 (−.31 to .32)	−.15 (−.31 to .21)	−.05 (−.39 to .28)	−.38 (−.58 to .37)	−.09 (−.51 to .49)	−.03 (−.31 to .38)	**−.72 (−1.28 to 1.53)***
							−6.26 (−9.08 to 1.46)**
Emotional abuse	−.06 (−.39 to .26)	−.01 (−.34 to .32)	−.10 (−.28 to .18)	−.20 (−.41 to .09)	−.12 (−.24 to .01)	.16 (−.13 to .45)	.51 (−.93 to 1.97)
Education	.01(−.06 to .08)	.03 (−.02 to .09)	−.03 (−.08 to .01)	.00 (−.06 to .05)	.05 (−.02 to .12)	.00 (−.09 to .07)	.05 (−.17 to .28)
Number of pregnancies	−.04 (−.20 to .12)	.08 (−.057 to .22)	−.10 (−.26 to .04)	−.12 (−.29 to .05)	−.07 (−.28 to .12)	**−.19 (−.31 to .06)***	**−.45 (−1.13 to .23)***
							−.00 (−.67 to .66)
Relationship satisfaction	**.20 (.10–.29)****	**.39 (.28–.50)****	**.23 (.13–.34)****	**.46 (.35–.58)****	**.99 (.94–1.05)****	.02 (−.06 to .12)	**2.32 (1.88–2.76)****
	.20 (.06–.31)**	**.39 (.27–.51)****	**.29 (.15–.42)****	**.45 (.33–.58)**	**.95 (.87–1.03)****		**2.32 (1.36–3.29)****
Emotional intelligence	.00 (−.00 to .01)	.00 (−.01 to .00)	.00 (.00–.01)	.00 (.0–.01)	.00 (−.00 to .01)	.04 (.00–.07)	.02 (.00–.04)
Obsessive compulsive	.01 (−.02 to .02)	.00 (−.01 to .02)	−.01 (−.02 to .01)	.01 (−.02 to .03)	−.01 (−.02 to .00)	.00 (−.02 to .01)	.00 (−.08 to .07)
Anxiety sensitivity	.00 (−.02 to .02)	.00 (−.02 to .00)	.00 (−.02 to .01)	.00 (−.02 to .02)	−.01 (−.03 to .00)	.01 (−.00 to .02)	.00 (−.07 to .05)
Extraversion	.01 (−.08 to .11)	.03 (−.11 to .16)	.07 (−.05 to .19)	−.02 (−.17 to .11)	−.02 (−.17 to .12)	.00 (−.09 to .09)	.07 (−.48 to .624)
Agreeableness	.03 (−.11 to .16)	.05 (−.11 to .21)	.01 (−.13 to .14)	.00 (−.17 to .16)	−.10 (−.29 to .07)	−.07 (−.18 to .04)	−.09 (−.77 to .58)
Emotional stability	.04 (−.07 to .16)	−.08 (−.21 to .04)	−.01(−.10 to .07)	−.09 (−.24 to .04)	**−.13 (−.28 to .02)***	.03 (−.06 to .13)	**−.24 (−.71 to .22)***
					−.07 (−.1480753 to .01)		−.46 (−.61 to .83)
Conscientiousness	**.19 (.01–.37)***	.00 (−.21 to .21)	**.13 (−.07 to .32)***	−.05 (−.26 to .15)	−.08 (−.37 to .19)	.02 (−.12 to .16)	.19 (−.77 to 1.14)
	.19 (.03–.38)		.15 (−.01 to .32)				
Openness	.00 (−.13 to .12)	−.02 (−.16 to .12)	.05 (−.06 to .17)	.03 (−.10 to .17)	−.06 (−.24 to .10)	−.05 (−.15 to .04)	−.04 (−.58 to .48)

Results from univariate regression analyses in a subsample of MZ twin pairs discordant for sexual problems. Within pair differences in the various subdomains of the FSFI are regressed against within-pair differences in potential environmental risk factors for FSD. Variables relating to sexual, physical, emotional abuse were handled as dichotomous measures, all other variables as continuous measures. Results from multivariate analyses for the variables included in the models are presented below the results from the univariate analyses. Significant results are highlighted in bold

* $p < .05$

** $p < .001$

Table 3 Results from univariate regression analyses in a subsample of DZ twin pairs discordant for sexual problems

	Desire *b* (95 % CI)	Arousal *b* (95 % CI)	Lubrication *b* (95 % CI)	Orgasm *b* (95 % CI)	Satisfaction *b* (95 % CI)	Pain *b* (95 % CI)	Total *b* (95 % CI)
Sexual abuse	.00 (−.51 to .50)	−.30 (−.86 to .25	−.23 (−.77 to .29)	−.05 (−.75 to .63)	−.80 (−1.52 to .08)*	−.27 (−.63−.08)	**−1.67 (−4.21 to .85)***
							−.65 (−1.65 to 1.95)*
Physical abuse	−.01 (−.44 to .40)	−.38 (−.91 to .13)	**−.42 (.90 to .04)***	−.38 (−1.05 to .28)	−.48 (−1.21 to .23)	−.18 (−.26 to .63)	**−1.51 (−3.82 to .78)***
			−.71 (−1.52 to .09)				**−.46 (−2.23 to 2.16)***
Emotional abuse	−.09 (−.49 to .30)	**−.43 (−.87 to .00)***	−.11 (−.53 to .30)	−.08 (−.68 to .51)	−.58 (−1.17 to .00)	.05 (−.31 to .41)	1.26 (−1.25 to 2.72)
		−.36 (−.90 to .17)					
Education	.00 (−.03 to .04)	.07 (.04 to .11)	.03 (−.00 to .08)	.06 (−.01 to .12)	.02 (−.08 to .13)	.01 (−.03 to .05)	.22 (−.04 to .48)
Number of pregnancies	−.15 (−.38 to .06)	**−.20 (−.37 to .04)***	**−.24 (−.45 to .02)***	−.22 (−.48 to .02)	−.08 (−.32 to .15)	.00 (−.13 to .15)	−.91 (to 1.84 to .01)
		−.14 (−.26 to .01)*	**−.20 (−.41 to .00)***				
Relationship satisfaction	**.22 (−.02 to .33)****	**.47 (.29–.56)****	**.34 (.15–.52)****	**.56 (.31–.71)****	**1.03 (.91–1.16)****	.14 (.06–.23)	**2.88 (2.28–3.28)****
		.48 (.27–.59)**	**.28 (.19–.39)***				**2.82 (2.30–3.33)****
Emotional intelligence	.00 (−.00 to .01)	.00 (−.01 to .00)	.00 (.00–.01)	.00 (.0–.01)	.00 (−.00 to .01)	.04 (.00–.07)	.02 (.00–.04)
Obsessive compulsive	.00 (−.01 to .02)	−.00 (−.02 to .00)	.00 (−.01 to .02)	−.00 (−.02 to .01)	−.00 (−.03 to .02)	−.00 (−.02 to .01)	−.00 (−.08 to .07)
Anxiety sensitivity	.00 (−.01 to .01)	−.00 (−.02 to .01)	−.02 (−.03 to .01)	.00 (−.02 to .01)	.00 (−.03 to .00)	−.01 (−.02 to .00)	−.04 (−.11 to .01)
Extraversion	−.07 (−.15 to .00)	**−.10 (−.19 to .00)***	−.09 (−.20 to .00)	−.10 (−.24 to .028)	−.10 (−.23 to .014)	−.10 (−.17 to .03)	−.59 (−1.05 to .13)
		−.01 (−.13 to .11)					
Agreeableness	−.02 (−.1415109 to .08)	−.02 (−.1705013 to .09)	−.09 (−.2384773 to .05)	−.12 (−.3137038 to .07)	−.08 (−.2733272 to .11)	−.07 (−.1799868 to .03)	−.42 (−1.086556 to .22)
Emotional stability	−.05 (−.14 to .04)	**−.13 (−.24 to .02)***	−.05 (−.16 to .05)	−.07 (−.22 to .06)	−.08 (−.22 to .05)	−.06 (−.15 to .01)	**−.46 (−.96 to .02)***
		−.09 (−.21 to .01)					−.32 (−.67 to .01)
Conscientiousness	−.05 (−.18 to .06)	.00 (−.14 to .16)	−.12 (−.29 to .04)	.08 (−.12 to .28)	−.02 (−.25 to .20)	−.05 (−.17 to .06)	−.16 (−.89 to .56)
Openness	−.02 (−.15 to .09)	.02 (−.11 to .16)	.03 (−.09 to .16)	.03 (−.15 to .21)	.07 (−.11 to .26)	−.07 (−.18 to .03)	.07 (−.56 to .70)

Results from univariate regression analyses in a subsample of DZ twin pairs discordant for sexual problems. Within pair differences in the various subdomains of the FSFI are regressed against within-pair differences in potential environmental risk factors for FSD. Variables relating to sexual, physical, emotional abuse were handled as dichotomous measures, all other variables as continuous measures. Results from multivariate analyses for the variables included in the models are presented below the results from the univariate analyses. Significant results are highlighted in bold

* $p < .05$

** $p < .001$

and maintenance of sexual problems (Apt, Hurlbert, Pierce, & White, 1996; Burri & Spector, 2011; Hurlbert, Apt, & Rabehl, 1993; Schnarch, 1997). A study exploring risk factors of FSD in a random sample of Australian women ($n = 356$, aged 20–70 years) found relationship factors to be more strongly associated with low desire than age or menopause (Hayes et al., 2008). Similarly, a study conducted by our group using the full twin sample ($n = 1489$) found relationship dissatisfaction to be the most common independent, clinical predictor of recent and lifelong FSD (OR 1.20–4.49) (Burri & Spector, 2011).

Given our strong design and its maximized internal validity, our findings not only support, but also extend, previous literature by suggesting relationship dissatisfaction to be a potential causative factor in the development of FSD symptoms. These findings, if replicated, could suggest that clinicians and researchers consider relationship satisfaction as a criterion in the classification of FSD as well as separating women out by relationship status in order to isolate further putative environmental contributions to symptoms. The fact that relationship dissatisfaction did not contribute to variation in experienced sexual pain and that we were not able to find any determinant for this phenotype at all (apart from number of pregnancies, however, not at all different levels of analyses) endorses the assumption shared by many sex researchers that pain should not be classified as a sexual dysfunction as it is phenomenologically very different from the other sexual dysfunctions (Binik, 2010; Binik et al., 2002).

While we were able to confirm a slight, yet significant contribution of anxiety sensitivity to the pathogenesis of lubrication problems and overall FSD at an individual level, this association could not be observed in FSD-discordant DZ or MZ twins. Similarly, none of the identified personality traits associated with sexual problems in the full sample could be replicated in the subsamples of DZ or MZ twins discordant for FSD. The failure to observe an association within discordant MZ and DZ twin pairs implies that the observed association of psychological and personality factors with FSD is attributable to genetic or shared environmental effects rather than true causality. Thus, the results gained from the individual-level associations are likely to reflect potential confounding due to the presence of gene–environment correlation. It has been suggested that associations in singleton studies may be inflated, as they do not control for the possible effect of genes on the environmental variables (i.e., gene–environment correlations) and on the outcome variables (Plomin, DeFries, & Loehlin, 1977). However, in relation to the discordant MZ approach, it should be noted that even extra-familial experiences may be, at least in part, under genetic influence and might be susceptible to the risk of genetic overmatching (Plomin et al., 1977). Given that anxiety sensitivity and personality show heritabilities of up to 50 % (Jang et al., 1996), this might explain why they were not significantly contributory to FSD in our co-twin control analyses.

In contrast to the commonly reported psychological and personality risk factors, we were partly able to replicate the associations between FSD and a history of abuse (Burri & Spector, 2011; Harris et al., 2008; Laumann, Paik, & Rosen, 1999). While there was a relationship between sexual, physical, and emotional abuse and various types of sexual problems at an individual-level, in FSD-discordant MZ and DZ twin pairs sexual and physical abuse was associated with overall FSD only. No effect of emotional abuse could be detected. Noteworthy in this context were the effect sizes for sexual and physical abuse which were more than twice as large in MZ compared with DZ twins. It is unlikely that this difference in effect size can be attributed to divergent statistical power as the sample sizes of DZ and MZ pairs were similar and there were no significant differences in within-twin pair variability for DZ and MZ twins in the outcome measures. One possible explanation is that heritable influences on personality could become translated as heritable influences on experience of abuse, raising the possibility that the association of sexual abuse with overall FSD reflects genetic selection rather than true causation. Given that MZ twins are genetically identical, this would explain the elevated effect sizes in MZ compared to DZ twins. Indeed, a recent survey on 2,116 twins aged 9–10 years found that genetic influences explained 73 % of children's risk for being a victim (Ball et al., 2008). This could lead to a scenario in which some twins with certain personality characteristics are reluctant to talk about their past abusive experiences (whereas their co-twins might not have been abused), again reflecting some form of a gene–environment correlation mechanism. In this context, linking the differential social experiences to divergent patterns of DNA methylation that may emerge over the life span of MZ twins would be an interesting next step (Bell & Spector, 2011).

Limitations

There were several limitations to the discordant-twins design that need to be considered. Most importantly, the design does not rule out reverse causation even if it addresses issues related to confounding. It is still possible that differences in sexual functioning lead to differences in relationship satisfaction, in which case we would still expect to observe within-pair association. To rule out reverse causation, longitudinal designs would be needed.

While individual-level associations reflect potential confounding of genetic and common/unique environmental effects, associations within DZ twin pairs discordant for FSD control for C and partially for A. MZ twins share 100 % of their genetic background and they grow up sharing a multitude of factors in their environment; therefore, associations within MZ twin pairs discordant for FSD control for both C and A effects but not for confounding due to E (i.e., non-shared; e.g., partner choice). By

focusing on the within-twin pair differences with respect to these unique experiences and traits and by linking them to within-pair differences in sexual functioning, the discordant MZ twin approach allows the establishment of a probable pathway between NSE variables and each twin's sexual function/dysfunction (Asbury et al., 2006; Vitaro et al., 2009).

Although the design provides the basis for a more powerful test of causality in a natural observational setting compared to other epidemiologic studies, the design does not guarantee certain causal inference as MZ twins do not provide a perfect counterfactual pair. In other words, we were not able to control for confounding due to non-shared experiences that make the MZ twin individuals psychologically unique. Although they are matched on genotype and early rearing environment, within-MZ pairs association of exposure with outcome may reflect the effect of the non-shared experiences that led to differences in exposure. Likewise, only exposures on which MZ twins differ can be explored so that shared environmental exposures (e.g., strict upbringing) cannot be explored in MZ twins that have been reared together. Special attention also needs to be brought to the quality of the within-pair data. Specifically, measurement error in the exposure variable is expected to attenuate within-pair associations to a greater degree than individual-level associations because of the compounding of error involved in calculating a difference score (Ashenfelter & Krueger, 1994). Moreover, since MZ twin correlations are typically higher than DZ twin correlations, we expect the within-pair attenuation to be greater for MZ than DZ pairs. Measurement error might be present when, for example, predictor and outcome variables are influenced by recall bias and these inter-individual differences create false results. Similarly, some twins may have deliberately under- or over-reported their sexual problems (Machin, 1996). However, as can be found elsewhere (Burri & Spector, 2011), prevalence rates of sexual problems in our twin sample closely matched the average rates across cross-national population-level studies; therefore, a major bias seems implausible. It may also be informative to explore each twin's perceptions and reactions to the same experience as additional sources of differential-unique experiences. Certain environmental experiences shared between twins in a pair (e.g., abuse) may be perceived by each member of a MZ pair as different at the subjective level (Turkheimer & Waldron, 2000). These potentially different subjective reactions to shared environmental experiences could attenuate findings and create false discordance.

While using both members of an MZ twin pair allowed us to control for both genetic and common environmental contributions, there may be other non-measured variables that differ between two members of a MZ twin pair that act as confounders (Turkheimer & Waldron, 2000). For example, twins can affiliate with different partners whose sexual function differs. These differences in the partner's sexual performance can contribute to the twin's differentiation with respect to their own sexual function as much as differences in relationship satisfaction can. However, it is also plausible that MZ twins are more likely to choose similar partners, due to similar preferences and bonding patterns, which are partly influenced by genes (Eisenberg et al., 2010). This would again represent a case of gene–environment correlation leading to underestimation of associations due to overmatching.

Although the design had a strong internal validity, statistical power may be lower compared to individual-level analyses mostly due to the smaller number of discordant pairs. In order to take full advantage of the discordant-twin design, we would ideally need larger samples to fully evaluate the genetic confounding alternative. However, successful associations of environmental risk factors have been found with samples much lower than ours (Williams et al., 2008). Furthermore, the external validity or generalizability of the findings from research on twins is often questioned, despite research repeatedly proving that twins are unremarkable with respect to many traits, behaviors, and disease (Andrews et al., 2001; Burri & Spector, 2011; Johnson, Krueger, Bouchard, & McGue, 2002).

In summary, we found strong evidence that relationship satisfaction plays a role in the development and maintenance of FSD independent of genetic factors. Further, prospective work is now needed to establish whether relationship variables are causative in the development of female sexual problems. Tentatively, clinicians may wish to consider interventions designed to work on relationship dynamics and other interpersonal factors for some women and their partners. Despite the strong design, most of the variance in FSD remains unexplained. Furthermore, it seems that the effects of previously suggested psychological risk factors (such as anxiety or personality) are mediated by other factors as a result of gene–environment correlation and that these factors are not directly causative of sexual problems.

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