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ORIGINAL PAPER

A Reassessment of the Possible Effects of the Serotonin Transporter Gene Linked Polymorphism *5-HTTLPR* on Premature Ejaculation

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Abstract A population-based sample of 1673 (valid phenotypic and genotypic data were available from 1412 individuals) Finnish male twins and siblings of twins aged 18–45 years provided questionnaire data regarding ejaculatory function as well as saliva samples for genotype analyses. Genotypic analyses were conducted controlling for between-subjects dependence. No significant association was found between the *5-HTTLPR* polymorphism and a composite variable measuring premature ejaculation or between this polymorphism and a self-report measure of ejaculation latency time. Previously conducted studies have found contradicting results regarding the possible role of *5-HTTLPR* in premature ejaculation. Methodological inconsistencies have been pointed out in these studies, which have all been conducted on rather small samples. While differences in terms of measurement of ejaculatory function could partly explain why positive findings from some earlier studies could not be replicated, the present study, given the large sample size and multifactorial measures used, indicated that the *5-HTTLPR* polymorphism has a limited, if any, impact on ejaculatory function.

Keywords Premature ejaculation · Serotonin transporter gene · *5-HTTLPR* · Ejaculatory function · Population-based study · Polymorphism

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Introduction

Genetic effects on ejaculatory function have been hypothesized for well over 60 years (Schapiro, 1943) and subsequent studies have identified a familial component in the etiology of premature ejaculation (PE) (Waldinger, Rietschel, Nöthen, Hengeveld, & Olivier, 1998). However, conclusive empirical evidence for the involvement of genes in PE etiology could not be established until recently, when a group of twin studies found evidence for a moderately-sized (around 30 %) heritable component (e.g., Jern et al., 2007, 2009a). Subsequently, six studies have attempted to investigate the genetic etiology of PE on the molecular level and, of these, four (including the first molecular genetic study of PE conducted by Janssen et al., 2009) have investigated the *5-HTTLPR* polymorphism located in the promoter region of the serotonin transporter gene (see below). In addition to these, two studies with conflicting results have also been conducted investigating a repeat polymorphism (*DAT1*) in the dopamine transporter gene (Safarinejad, 2011; Santtila et al., 2010), and a number of single nucleotide polymorphisms in the serotonin 2C receptor gene (Luo et al., 2010), respectively. There are well-founded theoretical reasons for the apparent focus on serotonergic genes in this field of study: research conducted on animals have suggested that serotonergic neurotransmission may play a crucial role in PE etiology (Waldinger & Olivier, 2005), and this notion is also supported by indirect evidence from studies on humans. For example, it is well known that selective serotonin reuptake inhibitors (SSRIs) will delay ejaculation (Waldinger, Berendsen, Blok, Olivier, & Holstege, 1998); recently, the SSRI dapoxetine was launched in a number of European countries as the first drug labeled for PE treatment (e.g., Pryor et al., 2006).

5-HTTLPR, a functional repeat polymorphism in the serotonin transporter gene *SLC6A4* located on chromosome 17, is one of the most intensely studied polymorphisms in the human genome, with one study noting that it has been investigated in more than 300 scientific papers in the last 10 years (Wendland, Martin, Kruse, Lesch,

& Murphy, 2006). The effects of this polymorphism have been studied in a wide array of phenotypes, including neuropsychiatric disorders (Goldberg et al., 2009) and behavioral and personality traits (Saiz et al., 2010), and its pharmacogenetic properties have also been investigated (Gressier et al., 2009). While this polymorphism has several allelic variations, it is usually considered to be a biallelic locus with a "long" (L) and a "short" (S) allele (Nakamura, Ueno, Sano, & Tanabe, 2000). Thus, three genotype combinations are possible: the long/long (L/L) and short/short (S/S) allele homozygotes, and the long/short (L/S) allele heterozygote.

In PE research, *5-HTTLPR* has been the subject of four studies, with equivocal results. Janssen et al. (2009) reported no significant difference in allele frequencies between patients with lifelong PE ($n = 89$) and healthy controls ($n = 92$), but noted that, within the group of lifelong PE patients, L/L genotype carriers had significantly shorter stop-watch timed intra-vaginal ejaculation latency times (IELTs). Ozbek et al. (2009), on the other hand, found a significant difference of the allele frequencies between lifelong PE patients ($n = 70$) and controls ($n = 70$) in a study of Turkish men; however, in contrast to Janssen et al. (2009), they found the S allele to be significantly more prevalent in the PE patient group (suggesting the S and not the L allele to be associated with increased risk of PE). A third study investigating 82 Iranian PE patients and 82 healthy controls echoed the findings of Ozbek et al. (2009), suggesting that the S/S genotype was significantly more prevalent among PE patients (Safarinejad, 2009). It should be noted, however, that the latter two studies have been criticized because genotype frequencies in both studies deviated significantly from what would be expected under Hardy–Weinberg Equilibrium (HWE) (Waldinger, Janssen, & Schweitzer, 2009a, 2009b). In addition to these studies, one study has investigated a possible pharmacogenetic influence of *5-HTTLPR* in SSRI (sertraline) treatment of PE and found that L allele carriers with lifelong PE responded significantly better compared to S allele carriers (Safarinejad, 2010). In summary, although several studies suggest that *5-HTTLPR* influences ejaculatory function, the literature addressing this issue is far from unanimous.

Failure to replicate findings from association studies is not limited to PE research. It is a rather common obstacle in molecular genetic research in general (Sillanpää & Auranen, 2004), and thus replication of any findings from association studies in independent samples should be viewed as crucial. Replication failure may be the result of several factors, most notably inadequate sample sizes and variability of phenotype definitions between studies (Greene, Penrod, Williams, & Moore, 2009), both of which are prominent features of PE studies in general. For example, none of the studies investigating effects of *5-HTTLPR* on PE have had sample sizes exceeding 200 individuals with cases and controls combined. Furthermore, there is an ongoing debate regarding definitions and diagnostic criteria of PE, and variation between PE measures between studies are common (Althof et al., 2010).

The aim of the present study was to investigate the effects of *5-HTTLPR* on ejaculatory function in a large, population-based sample. Given the equivocal findings from the three studies that have previously investigated the possible effects of this polymorphism on PE, we postulated no a priori hypothesis regarding the outcome.

Method

Participants

The present study involved 1673 male twins and non-twin brothers of twins (M age = 26.89 years, $SD = 4.71$, range = 18–45) who had provided saliva samples for DNA analyses. Of these, genotyping failed for 38 individuals (2.3 %) and another 223 individuals (13.3 %) had more than 50 % missing (i.e., more than 3 out of 7 items) phenotypic (i.e., ejaculatory functioning) data. Thus, the final sample for statistical analyses involving genotype data consisted of 1412 men. A total of 65 participants had missing phenotypic data (none of these had missing values on more than 3 out of 7 items); for these, missing values were replaced with item-specific means. The participants were a subset from the second data collection of the Genetics of Sex and Aggression sample, which is a population-based sample of young adult Finnish twins and their siblings (for a more detailed description of the sample see Santtila et al., 2010). The study, including its voluntary nature, was thoroughly explained to potential participants in a cover letter and confidentiality was guaranteed. No invasive procedures were carried out (DNA was collected using saliva samples; see below). The research plan was approved by the Ethics Committee of the Åbo Akademi University.

Measures

A composite score of seven different self-reported indicators was used to measure PE. This multifactorial instrument measures different aspects of ejaculatory function on a 5-point Likert scale and has been used in several prior studies (e.g., Jern et al., 2007, 2009a, 2009b). Factor analyses previously conducted on these indicator variables (Jern et al., 2009a) have shown good factorability (Kaiser–Meyer–Olkin measure of sampling adequacy = .62, Bartlett's test of sphericity $\chi^2[6] = 413.07$, $p < .001$), with all items loading clearly on one factor. As the sample size of the present study was somewhat smaller than that of, for example, Jern et al. (2009a), we re-calculated the factor loadings using a principal components analysis. Factor loadings in the present sample ranged from .43 to .80. Results from confirmatory factor analyses have indicated good reliability (Jern et al., 2009a). These indicator variables (factor loadings for each variable are presented in brackets) were: ejaculation latency time (.67), number of penile thrusts (.46), frequency of occurrence of anteportal ejaculation (.43), feeling of control (.61), subjective experience of PE (.80), worrying about PE (.72), and having tried to slow down intercourse in order to prevent ejaculation (.47).

A composite score measuring PE was subsequently computed by summing the raw variables. Since a composite score can be expected to have superior reliability to any individual indicator

variable, we firstly tested effects of all the polymorphism against the composite score. Thereafter, since previous studies have primarily focused on ejaculation latency time as a proxy measure of PE, we investigated effects of the *5-HTTLPR* polymorphism on the item measuring ejaculation latency time (ELT). The ordinal ELT variable "On average, during intercourse, how much time elapses between when you first enter your partner (vaginally or anally) with your penis and when you first ejaculate?" had five categories: (1) less than 1 min (33 men, 2.3 %; (2) between 1 and 5 min (327 men, 22.6 %); (3) between 5 and 10 min (552 men, 38.2 %); (4) more than 10 min (494 men, 34.2 %); and (5) I usually do not ejaculate (21 men, 1.5 %). A total of 17 men (1.2 %) had missing values on this particular variable and had the item-specific M = 3.10 inserted as specified above.

Next, we dichotomized the ELT variable so that men with an ELT of less than 1 min were compared against the men with longer ELTs. Given the uneven group sizes (33 men reported ELTs of 1 min or less, whereas 1379 men reported longer ejaculatory latencies), we also conducted this analysis using a group of 33 of age-matched controls with ELTs exceeding one minute. Finally, we compared the genotype frequencies between the group of men with ELTs of 1 min or less and the group of men who reported ELTs of 11 min or more as well as the group of men who reported that they usually do not ejaculate during penetrative sex (i.e., the other extreme end of the ELT variable. Previous studies have indicated that self-reported and stop-watch measured ELTs are interchangeable (Rosen et al., 2007).

DNA Extraction and Genotyping

Saliva samples were collected using Oragene™ DNA self-collection kits that were posted to the participants and returned by mail. The participants were instructed to follow the manufacturer's instructions on how to collect the samples (DNA Genotek, Inc., Kanata, Ontario, Canada) and to deposit approximately 2 mL of saliva into the collection cup. When an adequate sample was collected, the cap was placed on the cup and closed firmly. The collection cup was designed so that a stabilizing solution from the cap is released when closed. This solution mixes with the saliva and stabilizes the saliva sample for long-term storage at room temperature. The region in *SLC6A4* was amplified by polymerase chain reactions (PCRs) performed on a Perkin Elmer 9700 thermal cycler. The *5-HTTLPR* polymorphism was amplified by using the PCR primers 5′-ATGCCAGCACCTAACCCCTAATGT-3′ and 5′-GGACCGCAAGGTGGGCGGGA-3′, yielding a product of 419 base pairs for the 16-repeat allele (L) and 375 base pairs for the 14-repeat allele (S). The reaction was carried out using 1 U of a HotstarTaq polymerase from Qiagen, in a total volume of 15 μl containing 1.5 mM $MgCl_2$, 0.3 μM PCR primers and 50 ng genomic DNA. After an initial 15 min denaturation step at 95 °C, 35 cycles were performed, including 30 s at 95 °C, 30 s at 66 °C and an elongation step at 72 °C for 1 min. Genotyping was performed on 2 % agarose gels. DNA was visualized using ethidium bromide.

Procedure

For all statistical analyses, PASW 18.0 for Windows was used. Genotype effects were calculated with the Generalized Estimating Equations procedure. This linear model appropriately controls for between-subjects dependence, which was necessary since the sample in the present study consisted of twins and siblings. The polymorphism was inserted as a factor in the model. Given that there may be small but significant effects of age on PE (Jern et al., 2009b), age was included as a covariate in all analyses.

Results

Descriptive Statistics

Of the participants who had provided DNA, 33 men (2.3 %) reported ELTs of less than one minute. In total, 504 men were homozygous for the L allele (i.e., carriers of an L/L genotype), 222 men were homozygous for the S allele, and 686 men were heterozygotic L/S genotype carriers. Genotype distributions did not differ significantly from what would be expected under Hardy–Weinberg equilibrium, $\chi^2 = 0.20$.

Genotype Analyses

Firstly, we examined the effects of *5-HTTLPR* on the composite variable measuring PE. No significant polymorphism effect could be detected, Wald $\chi^2(2) = 3.50$. As can be seen in Table 1, the estimated marginal means of the composite variable between the three genotype groups were similar and not significantly different from one another on any level. Next, we fitted an ordinal logistic model to test polymorphism effects on the categorical variable measuring ELT. Again, no significant effect of the polymorphism was found, Wald $\chi^2(2) = 2.44$. We then tested two binary logistic models on the dichotomized ELT variable. Firstly, participants were divided into two groups depending on whether they had an ELT exceeding 1 min or not. This analysis involved the whole sample (i.e., 33 men with ELTs of less than 1 min were tested against 1379 men with ELTs of more than 1 min). No significant effect of the polymorphism was detected in this case either, Wald $\chi^2(2) < 1$. Secondly, in order to address potential problems of analyzing two groups of very uneven size, we conducted the same analysis using an age-matched control group of similar size ($n = 33$), but found no significant effects in this case either, Wald $\chi^2(2) = 0.122$. Finally, we compared the extreme ends of the ELT variable against each other. That is, the men with ELTs of less than 1 min were compared against the two groups of men with the longest ELTs (i.e., men who reported ELTs of 11 min or more, and men who reported that they usually did not ejaculate during intercourse) in two separate analyses. Neither of these analyses revealed any significant differences in genotype frequencies.

Table 1 Genotype Group Comparisons for a Composite Score Measuring Premature Ejaculation and a Dichotomous Variable Measuring Ejaculation Latency Time

5-HTTLPR genotype	Composite variable measuring PE			Dichotomous variable measuring ejaculation latency time		
	EMM	*SE*	95 % Wald CI	EMM	*SE*	95 % Wald CI
S/S	2.14	0.024	2.09–2.18	0.98	0.009	0.96–1.00
S/L	2.11	0.012	2.09–2.13	0.98	0.006	0.97–0.99
L/L	2.14	0.013	2.12–2.17	0.97	0.007	0.96–0.99

The dichotomous variable measuring ejaculation latency time was constructed so that participants were divided into two groups depending on whether they reported an ejaculation latency of less than one minute or not

PE premature ejaculation, *S* short allele, *L* long allele, *EMM* estimated marginal mean

Discussion

The three previously conducted studies investigating the effects of the *5-HTTLPR* polymorphism on PE have reported conflicting results, in that the two most recent studies (Ozbek et al., 2009; Safarinejad, 2009) found the S/S genotype to be associated with PE, contradicting the results of the first study (Janssen et al., 2009), which found no significant differences in allele frequencies between cases and controls but that the S/S genotype was associated with *longer* IELTs within the group of PE patients. The results of the present study indicated no significant association between the *5-HTTLPR* polymorphism and ELT or any other self-reported indicator of PE in a large population-based cohort.

Our findings do not contradict the results of Janssen et al. (2009), in that they did not report any differences in genotype frequencies between cases and controls, but a genotypic effect on IELT within the group of PE patients only, with the L/L genotype being associated with shorter IELTs. No stop-watch measured IELT data were available for the present study, and it can be argued that a self-report measure, such as the one used in the present study, cannot be compared to the continuous, linear IELT measure used by Janssen et al. (2009). On the other hand, both the present results and those of Janssen et al. (2009) argue against *5-HTTLPR* exerting a significant effect on the proneness for PE in a general population (the latter by failing to detect a difference between patients and controls).

Our results contradict those of Ozbek et al. (2009) and Safarinejad (2009), who both reported a significantly higher occurrence of the S allele among groups of PE patients. These two studies have previously been criticized for potential methodological flaws in that the populations of both studies deviate from what would be expected under HWE (Waldinger et al., 2009a, 2009b). While this criticism is obviously potentially valid, it should, however, be pointed out that deviation from HWE is not necessarily indicative of sampling inadequacy or neglect, since neither allele nor genotype frequencies are free from disturbing influences in nature (Griffiths, Gelbart, Miller, & Lewontin, 2002). For example, non-random mating, migration and natural selection will distort allele (and thus genotype) frequencies in populations (Wigginton, Cutler, & Abecasis, 2005).

Compared to the three previously conducted studies, the present study had an exceptionally large sample size. Therefore, if *5-HTTLPR* had a significant main effect on ejaculatory function, it must be considered likely that this effect would have been detected even when considering the fact that this study was based on retrospective self-report rather than stop-watch assessments. Also, analyses comparing genotypes of men who ejaculated within 1 min to those of men with longer ELTs did not reveal any significant effects of *5-HTTLPR*. In the present study, men with ELTs of less than 1 min occurred with a frequency that is comparable to that of other population-based studies (Waldinger et al., 2005). The lack of difference in genotype frequencies between this group and men with longer ELTs support the conclusion that *5-HTTLPR* does not influence the risk for PE. However, it should be noted that the group of men who would qualify for a clinical diagnosis of lifelong PE according to, for example, the standards suggested by the International Society of Sexual Medicine (Althof et al., 2010), by which an ejaculatory latency of about one minute or less is required, were relatively few in the present study (33 men).

In summary, the results of the four studies (including the present) conducted to investigate effects of *5-HTTLPR* on ejaculatory function do not provide any convincing evidence for a significant main effect of *5-HTTLPR* on PE or (I)ELT, especially when potential flaws and distorting factors in and between the studies are considered. However, given the strong theoretical evidence for serotonergic involvement in ejaculatory function, it is plausible that this particular polymorphism could indirectly effect ejaculatory function through gene-environment or gene–gene interaction. Therefore, we suggest that efforts should be concentrated to identifying interactive effects of this polymorphism involving other factors that have been hypothesized to effect ejaculatory function (e.g., other polymorphisms and environmental factors) in the future. Since evidence from quantitative genetic studies (Jern et al., 2007, 2009a) has revealed that PE is under only moderate (about 30 %) genetic influence, and given that knowledge of environmental/circumstantial factors that may be causal of PE is scarce, efforts to investigate non-genetic contributors to PE etiology would be particularly welcome.

Conclusions

The present study sought to replicate three previously conducted studies investigating the association of the serotonin transporter gene linked polymorphism *5-HTTLPR* and premature ejaculation

that have yielded conflicting results. In the present study, no significant genotype effect was found neither for a composite measure of PE nor self-reported ejaculation latency time in a large, population-based sample. Whereas no support for any of the previously reported findings was detectable in our data, serotonergic genes may nevertheless play a significant role in PE etiology and should be investigated. Differences regarding PE measures between studies pose a problem to between-study comparisons and detection of genotype effects.

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