UNIVERSITY OF AMSTERDAM

UvA-DARE (Digital Academic Repository)

Non-replication of the association between 5HTTLPR and response to psychological therapy for child anxiety disorders

Lester, K.J.; Roberts, S.; Keers, R.; Coleman, J.R.I.; Breen, G.; Wong, C.C.Y.; Xu, X.; Arendt, K.; Blatter-Meunier, J.; Bögels, S.M.; Cooper, P.; Creswell, C.; Heiervang, E.R.; Herren, C.; Hogendoorn, S.M.; Hudson, J.L.; Krause, K.; Lyneham, H.J.; McKinnon, A.; Morris, T.; Nauta, M.H.; Rapee, R.M.; Rey, Y.; Schneider, S.; Schneider, S.C.; Silverman, W.K.; Smith, P.; Thastum, M.; Thirlwall, K.; Waite, P.; Wergeland, G.J.; Eley, T.C.

DOI
10.1192/bjp.bp.114.154997

Publication date
2016

Document Version
Final published version

Published in
British Journal of Psychiatry

License
Article 25fa Dutch Copyright Act (https://www.openaccess.nl/en/policies/open-access-in-dutch-copyright-law-taverne-amendment)

Link to publication

Citation for published version (APA):
Lester, K. J., Roberts, S., Keers, R., Coleman, J. R. I., Breen, G., Wong, C. C. Y., Xu, X., Arendt, K., Blatter-Meunier, J., Bögels, S. M., Cooper, P., Creswell, C., Heiervang, E. R., Herren, C., Hogendoorn, S. M., Hudson, J. L., Krause, K., Lyneham, H. J., McKinnon, A., ... Eley, T. C. (2016). Non-replication of the association between 5HTTLPR and response to psychological therapy for child anxiety disorders. *British Journal of Psychiatry*, *208*(2), 182-188. https://doi.org/10.1192/bjp.bp.114.154997

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

Download date:12 Nov 2026

BJPsych | The British Journal of Psychiatry (2016)
208, 182–188. doi: 10.1192/bjp.bp.114.154997

Non-replication of the association between 5HTTLPR and response to psychological therapy for child anxiety disorders

Kathryn J. Lester,* Susanna Roberts,* Robert Keers, Jonathan R. I. Coleman, Gerome Breen, Chloe C. Y. Wong, Xiaohui Xu, Kristian Arendt, Judith Blatter-Meunier, Susan Bögels, Peter Cooper, Cathy Creswell, Einar R. Heiervang, Chantal Herren, Sanne M. Hogendoorn, Jennifer L. Hudson, Karen Krause, Heidi J. Lyneham, Anna McKinnon, Talia Morris, Maaike H. Nauta, Ronald M. Rapee, Yasmin Rey, Silvia Schneider, Sophie C. Schneider, Wendy K. Silverman, Patrick Smith, Mikael Thastum, Kerstin Thirlwall, Polly Waite, Gro Janne Wergeland and Thalia C. Eley

Background
We previously reported an association between 5HTTLPR genotype and outcome following cognitive–behavioural therapy (CBT) in child anxiety (Cohort 1). Children homozygous for the low-expression short-allele showed more positive outcomes. Other similar studies have produced mixed results, with most reporting no association between genotype and CBT outcome.

Aims
To replicate the association between 5HTTLPR and CBT outcome in child anxiety from the Genes for Treatment study (GxT Cohort 2, $n = 829$).

Method
Logistic and linear mixed effects models were used to examine the relationship between 5HTTLPR and CBT outcomes. Mega-analyses using both cohorts were performed.

Results
There was no significant effect of 5HTTLPR on CBT outcomes in Cohort 2. Mega-analyses identified a significant association between 5HTTLPR and remission from all anxiety disorders at follow-up (odds ratio 0.45, $P = 0.014$), but not primary anxiety disorder outcomes.

Conclusions
The association between 5HTTLPR genotype and CBT outcome did not replicate. Short-allele homozygotes showed more positive treatment outcomes, but with small, non-significant effects. Future studies would benefit from utilising whole genome approaches and large, homogenous samples.

Declaration of interest
R.M.R., J.L.H. and H.J.L. are authors of the Cool Kids programme, but receive no direct payments. C.C. was joint author of a book used in treatment within the Overcoming trial and P.W. was joint editor for a book on the treatment of obsessive–compulsive disorder and they receive royalties from sales of the books. W.K.S. is an author of the Anxiety Disorders Interview Schedule for Children from which she receives royalties.

Copyright and usage
© The Royal College of Psychiatrists 2016. This is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) licence.

Anxiety disorders represent a significant global health burden due to their debilitating nature and high lifetime prevalence.[1] They frequently occur early and show high continuity into adulthood.[2] Cognitive–behavioural therapy (CBT) is the most established treatment option for childhood anxiety, with around 59% of children remitting following treatment.[3] The short, low-expression allele of the functional serotonin transporter promoter polymorphism, 5HTTLPR, has been associated with heightened anxiety and related traits[4] compared with the long allele, although findings are somewhat mixed.[5,6] Gene–environment interaction studies provide evidence that short allele carriers have the poorest outcomes in high stress environments,[7] but also show the largest benefit in response to low stress or enriching environments.[8–11] These findings suggest that 5HTTLPR may represent a 'differential susceptibility' marker, which acts 'for better and for worse'.[12] Some individuals who are more susceptible to the negative effects of poor environments might also be more sensitive to the positive effects of an enriching experience,[13] and therefore may respond better to the supportive influence provided by psychological therapies. The field of 'therapygenetics' – genetic predictors of outcome following purely psychological therapies – is relatively new.[14] In a previous study, we found that 5HTTLPR genotype was significantly associated with CBT outcome.[15] SS homozygotes showed a significantly greater reduction in symptom severity than long allele carriers, and were 20% (18.8%) more likely to be free of their primary (all) anxiety disorder diagnoses by follow-up. A handful of other studies have investigated 5HTTLPR and outcomes following a range of psychological therapies, although results have not been consistent.[15–23] Two studies also found the SS genotype to be associated with more positive outcomes; following a problem-solving intervention with antidepressants in older adults with post-stroke depression,[16] and exposure-based therapy in adults with panic disorder with agoraphobia.[17] However, a third study examining CBT in post-traumatic stress disorder found poorer outcomes in SS carriers.[18] Additional studies in both adults and children found no effect of 5HTTLPR outcome following psychological interventions. Of note, these studies are all of small sample size, and are generally underpowered to detect what is likely to be a small effect of 5HTTLPR genotype. Furthermore, participants in many of the studies were also on concurrent antidepressant or anxiolytic medications. These factors highlight the need for replication in a large sample to further examine the association between 5HTTLPR genotype and outcome following a purely psychological therapy.

*Joint first authors.

Based on our previous research, the aim of this study was to test whether 5HTTLPR genotype was associated with outcome following CBT in a large replication sample of 829 children with anxiety disorders. This sample size far exceeded that required to detect an effect of similar magnitude to that of our previously reported findings, with greater than 95% power at a significance level of $\alpha < 0.01$. We hypothesised that children with the SS genotype would (a) show greater rates of remission at follow-up and (b) show a greater reduction in symptom severity at follow-up than those with the SL or LL genotype. To further increase power to detect an association between 5HTTLPR genotype and outcome and to estimate an upper bound for the magnitude of the effect, mega-analyses were performed on a combined data-set comprising both our discovery ($n = 496$) and replication samples ($n = 829$). Again, we hypothesised that SS genotype carriers would show a more positive outcome following treatment relative to SL or LL genotype carriers.

Method

Study overview

All participants come from the Genes for Treatment (GxT) study, an international multisite collaboration designed to identify clinical, demographic and genetic predictors of outcome following CBT for child anxiety.[24]

Participants and treatment

Participants aged between 5 and 18 years (mean age: 10 years) met DSM-IV criteria for primary diagnosis of an anxiety disorder. Exclusion criteria included significant physical/intellectual impairment, psychoses and concurrent treatment. All participants completed a full course of CBT either as part of a trial or as treatment as usual at one of 11 sites; Sydney, Australia ($n = 293$); Reading, UK ($n = 199$); Aarhus, Denmark ($n = 112$); Bergen, Norway ($n = 35$); Bochum, Germany ($n = 50$); Florida, USA ($n = 36$); Basel, Switzerland ($n = 46$); Groningen, The Netherlands ($n = 35$); Oxford, UK ($n = 11$); Cambridge, UK ($n = 9$) and Amsterdam, The Netherlands ($n = 3$). All treatments were manualised and treatment protocols across sites were comparable for core elements of CBT, including teaching of coping skills, cognitive restructuring and exposure. Treatment modalities fell into three broad groups – individual CBT (39.8%), group-based CBT (46.1%) and parent-supported guided self-help (14.1%). Further sample characteristics and site-specific trial details can be found in the online data supplement to this article.

Measures

Anxiety disorder diagnoses

Anxiety disorders were assessed at three time points; before and after treatment, and at follow-up (3, 6 or 12 months after conclusion of treatment). Diagnoses were made with the Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV-C/P)[25] at all sites except for Bochum and Basel, where the German equivalent (Kinder-DIPs) was used.[26] Clinical severity ratings (CSRs) were usually based on composite parent and child reports, and were assigned on a scale of 0–8 (see Hudson *et al*[24] for further details). A diagnosis was made when the child met diagnostic criteria and received a CSR of 4 or more. Primary diagnoses included generalised anxiety disorder (GAD; 34.9%), separation anxiety disorder (SAD; 25.1%), social anxiety disorder (20.8%), specific phobias (11.9%), panic disorder (3.3%), obsessive–compulsive disorder (OCD; 2.1%), post-traumatic stress disorder (PTSD; 1.3%), selective mutism (0.2%, in the cases with primary selective mutism, a diagnosis of severe social phobia was also given; the selective mutism was considered by the clinician to be primary, the most interfering), and anxiety disorders not otherwise specified (ADNOS; 0.5%).

Ethnicity

Ethnicity was determined by parent-report regarding the ancestry of the child's grandparents. Those with four grandparents of reported White European ancestry were included in the 'White European subset' ($n = 560$, see online data supplement).

Sample collection and genotyping

DNA samples were collected using either buccal swabs or Oragene saliva kits (DNA Genotek, Ottawa, Canada) and extracted using established procedures.[27,28] 5HTTLPR was genotyped using polymerase chain reaction amplification and agarose gel electrophoresis according to published protocols.[15] A selection of samples ($n = 40$) were genotyped in duplicate, with consistent results for each attempt. The genotypic distribution of the sample conformed to Hardy–Weinberg proportions (LL: 25.9%, SL: 51.4%, SS: 22.7%; $\chi^2_1 = 0.69$, $P = 0.444$).

Ethical approval

All trials and collection of samples were approved by site-specific human ethics and biosafety committees. Parents provided informed consent, children assent. The storage and analysis of DNA was approved by the King's College London Psychiatry, Nursing and Midwifery Research Ethics Sub-Committee.

Sample size and power analyses

Participants used in this paper are referred to as Cohort 2, which consisted of 829 participants with clinical data available both at baseline and at least one outcome time-point (post-treatment, a follow-up time-point or both). However, of these, 792 had outcome data at post-treatment; 606 at follow-up.

Power calculations[29] suggested a sample size of 285 would be required for 95% power to detect an effect of similar magnitude to our previously reported findings (Cohort 1, odds ratio (OR) = 0.4), at a significance level of $\alpha = 0.01$ using a recessive allelic model. Our sample of > 600 has $> 90\%$ power to detect a smaller effect size (OR = 0.6) at a significance level of $\alpha = 0.01$, and 80% power to detect an even smaller effect size of OR = 0.7 at $\alpha = 0.05$.

Data analysis

Definition of outcome variables

Treatment outcome was defined in a number of ways. Participants were first classed as remitters or non-remitters based on the presence or absence of their primary anxiety disorder diagnosis (primary anxiety remission). Treatment remission was measured both at post-treatment, and at follow-up (collapsed to include all follow-up time-points; 3, 6 or 12 months). Remission was also categorised as the absence of all anxiety disorder diagnoses at post-treatment and at follow-up (all anxiety response). Finally, treatment response was defined as the change in primary anxiety disorder severity from pre- to post-treatment, and from pre-treatment to follow-up.

Mixed effects models

To investigate the effect of 5HTTLPR genotype on remission, logistic mixed effects models were used including treatment trial as a higher order random effect. For consistency with the statistical analyses used in our previous study, 5HTTLPR genotype was defined by a recessive model, where SS was coded as 1 and SL/LL were coded as 0. Gender, age and baseline severity

were included as covariates in all analyses (age and baseline severity centred at the mean). Analyses were conducted for primary anxiety diagnosis remission and all anxiety disorder diagnoses remission separately at post-treatment and at follow-up. Models focusing on the follow-up time-point included the linear and quadratic effects of time as covariates.

Linear mixed effects models were used to investigate the effect of 5HTTLPR genotype on response (change in primary anxiety disorder severity). Again, trial was included as a higher order random effect, and gender, age and baseline severity were included as covariates. Time was included as a covariate for the model testing change from pre- to post-treatment; and both linear and quadratic effects of time were included as covariates in the model for follow-up.

Mega-analyses

Finally, logistic and linear mixed models were run using participants from both Cohort 1[15] and Cohort 2 combined. A total of 584 samples were genotyped in Cohort 1, from children (aged 6–13) who received CBT for an anxiety disorder. In this sample, 496 had sufficient outcome data to be included in at least one analysis. The sample size of 359 reported in Eley *et al*[8] refers to the White European participants included in the main analysis of response to therapy at follow-up. Further participants were included in analyses of response to therapy at post-treatment, with a total of 496 included in at least one analysis. Participants included in Cohort 1 were recruited at two sites: Sydney, Australia and Reading, UK. Participants who were genotyped in Cohort 1 but whose clinical data were not available at the time of submission were included in Cohort 2. Combining both cohorts increased the sample size, and so the power to detect an association between 5HTTLPR genotype and outcome. Cohort was included as a covariate in these analyses.

Multiple testing corrections

For analyses of remission and response in the mega-analysis, we applied a Bonferroni multiple testing correction to account for the three outcome measures (primary anxiety remission, all anxiety remission and treatment response), giving a corrected significance level of $P = 0.016$. However, the outcome measures used in this study are highly related and nested within each other, and all analyses presented test the same core hypotheses; thus, the correction is likely conservative.

All analyses were performed in STATA version 11.[30]

Results

Remission rates

Remission rates are given in Table 1 and were marginally higher than in previous studies,[3] with 61.1% of children remitting from their primary anxiety disorder after treatment, and 71.8% by follow-up. There were no significant differences between remitters and non-remitters for age and gender (age: primary $t(604) = -0.16$, $P = 0.874$; all anxiety $t(570) = -0.76$, $P = 0.449$; gender: primary $\chi^2_1 = 0.42$, $P = 0.515$; all anxiety $\chi^2_1 = 0.47$, $P = 0.492$). Outcome data by genotype are also given in Table 1 for the additive model, and Fig. 1 shows outcomes for the recessive model. Individuals with the SS genotype were 1.7% more likely than those with SL/LL genotype to remit from their primary anxiety diagnosis and 6.5% more likely to remit from all anxiety diagnoses at follow-up. However, differences between the groups were not statistically significant.

Logistic mixed effects models – predicting remission

No significant effect of genotype on treatment outcome was detected for either primary or all anxiety diagnoses at post-treatment (Table 2; primary: OR = 0.92, $P = 0.551$; all anxiety: OR = 1.09, $P = 0.607$); or at follow-up (Table 2; primary: OR = 0.83, $P = 0.318$; all anxiety: OR = 0.66, $P = 0.293$). The odds ratio of less than 1 indicates that, as found previously, participants with the SS genotype were more likely to remit than SL/LL children. A similar pattern of effects was seen when analyses were restricted to the White European subset (see Table DS1 in the online data supplement).

Change in symptom severity

Mean primary anxiety disorder severity at pre-treatment was 6.20 (s.d. = 1.05). At post-treatment, mean severity was 2.82 (s.d. = 2.12), corresponding with a change from pre-treatment of 3.39 (s.d. = 2.14; Table 1). Mean severity at follow-up was 2.15 (s.d. = 2.17) with a mean change from pre-treatment of 4.04 (s.d. = 2.21). There were no significant effects of age or gender on change in symptom severity in Cohort 2 (age: $\beta = -0.01$, $P = 0.55$; gender: $\beta = 0.04$, $P = 0.53$). Change in severity by genotype is shown in Table 1 and Fig. 1(b). Participants with SS genotype showed a marginally greater reduction in symptom severity by post-treatment (0.10) and by follow-up (0.18) than SL/LL genotype carriers but differences between the groups were not significant.

Linear mixed effects models – predicting response

No significant effect of genotype on change in primary diagnosis symptom severity was detected, either during the course of treatment (Table 2; pre-treatment to post-treatment: $\beta = -0.04$, $P = 0.294$) or at follow-up (pre-treatment to follow-up: $\beta = -0.04$, $P = 0.318$). This was also true of the White European subset (online Table DS1). The overall standardised beta coefficient of −0.04 indicates that SS children had a 0.04 s.d. greater reduction in severity scores than SL/LL children.

Table 1 Treatment outcome (response and remission) in Cohort 2 by 5HTTLPR genotype

Treatment outcome	Time point	Cohort 2	SS genotype	SL genotype	LL genotype
Primary anxiety disorder remission[a]	Post-treatment	61.1	63.7	59.2	62.6
	Follow-up	71.8	73.1	72.3	69.5
All anxiety diagnoses remission[a]	Post-treatment	42.0	40.7	42.0	43.2
	Follow-up	55.7	60.8	55.0	52.4
Primary anxiety disorder response[b]	Post-treatment	3.39 (2.14)	3.47 (2.13)	3.29 (2.14)	3.52 (2.16)
	Follow-up	4.04 (2.21)	4.18 (2.16)	3.98 (2.21)	4.04 (2.24)

Comparisons between genotype groups are not statistically significant for any treatment outcome in Cohort 2.
a. Values for remission are the percentage free of primary and all anxiety disorder diagnoses at post-treatment and at follow-up.
b. Values for primary anxiety disorder response are the mean change in severity from the initial assessment at pre-treatment to the time point specified (s.d. in brackets).

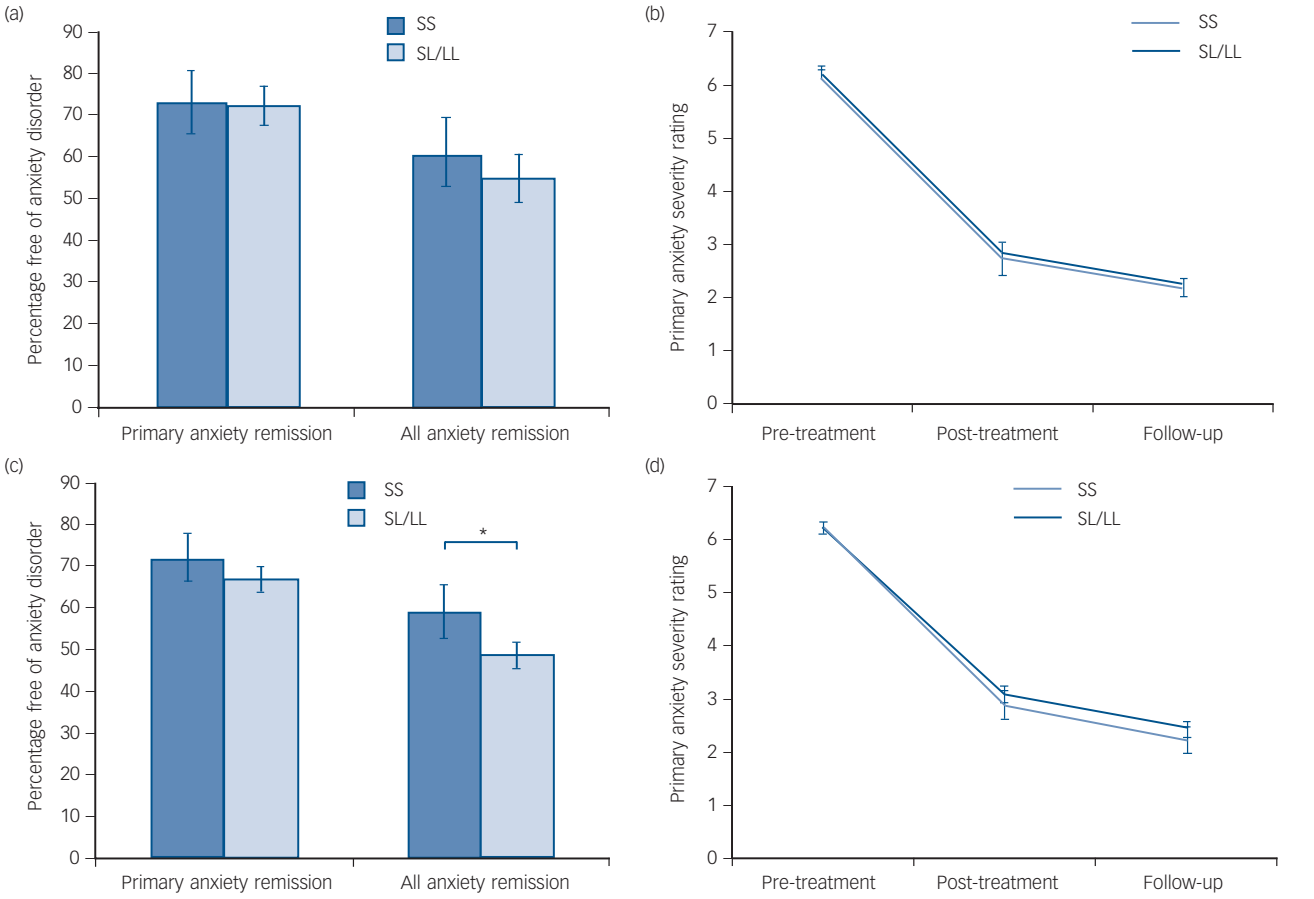

Fig. 1 Remission rates and response to cognitive–behavioural therapy (CBT).

Figure 1(a) shows the proportion of children free of their primary anxiety disorder and all anxiety diagnoses at follow-up, split by 5HTTLPR genotype in Cohort 2. Figure 1(b) shows the change in primary anxiety symptom severity rating across the course of treatment by 5HTTLPR genotype in Cohort 2. Genotype was not significantly associated with any outcome measure ($P>0.05$ for all analyses). Figure 1(c) shows the proportion of children free of their primary anxiety disorder and all anxiety diagnoses at follow-up, split by 5HTTLPR genotype in the combined sample. Figure 1(d) shows the change in primary anxiety symptom severity rating across the course of treatment by 5HTTLPR genotype in the combined sample. Genotype was not significantly associated with primary anxiety remission or response ($P>0.05$ for all analyses), but those homozygous for the short allele showed a significantly greater remission for all anxiety disorders in the combined sample, even when clinical covariates were taken into account (*OR = 0.45, $P=0.014$).

Mega-analyses

Before combining Cohorts 1 and 2 for analyses, the two cohorts were compared for key variables. There were no significant differences in gender distribution ($\chi^2_1=2.39$, $P=0.122$), treatment modality ($\chi^2_2=4.07$, $P=0.131$) or recessive genotype ($\chi^2_1=1.98$, $P=0.159$). Due to the recruitment from additional studies in Cohort 2, a larger age range was included and Cohort 2 was significantly older ($t(1271)=5.15$, $P=0.0001$). Cohort 2 also showed significantly higher rates of remission at post-treatment (primary: $\chi^2_1=7.72$, $P=0.005$; all anxiety: $\chi^2_1=7.35$, $P=0.007$) and at follow-up (primary: $\chi^2_1=7.24$, $P=0.007$; all anxiety: $\chi^2_1=13.60$, $P=0.000$).

In the entire sample (Cohorts 1 and 2 combined), SS participants were 6.6% more likely to remit from their primary anxiety disorder, and 11.4% more likely to remit from all anxiety disorder diagnoses than SL/LL carriers (Fig. 1(c)). Additionally, SS carriers showed a greater reduction in symptom severity from pre-treatment to follow-up than SL/LL carriers (Fig. 1(d); SS: change = 4.01, s.d. = 2.05; SL/LL: change = 3.79, s.d. = 2.19).

When using linear and logistic mixed effect models, the effect of genotype on primary anxiety disorder response and remission did not reach statistical significance (Table 3; change in CSR: $\beta=-0.06$, $P=0.070$; remission: OR = 0.55, $P=0.095$). However, there was a significant effect of genotype on all anxiety diagnoses remission (Table 3; OR = 0.45, $P=0.014$), which remained nominally significant when multiple testing corrections were made. In the White European subset, a similar pattern of results was detected, although these did not reach statistical significance (see online Table DS2).

Discussion

We attempted to replicate our previously reported association between 5HTTLPR genotype and outcome following CBT. Our replication sample comprised 829 children with a primary anxiety diagnosis. We found no significant association between genotype and remission of primary or all anxiety diagnoses at post-treatment or follow-up time-points. Furthermore, change in primary anxiety disorder symptom severity (response) across the course of treatment did not differ as a function of 5HTTLPR genotype. Mega-analyses combining data from this and our previous report[15] revealed a significant association between 5HTTLPR genotype and remission of all anxiety disorders at follow-up. Children carrying the SS genotype were more likely to be free of all anxiety disorder diagnoses than children with the SL/LL genotype. This effect remained significant after multiple testing corrections.

In our previous paper, 20% (18.8%) more children with the SS compared with SL/LL genotypes were free of their primary (all) anxiety disorders at follow-up.[15] The odds ratios were 0.39

Table 2 Mixed effect models; categorical remission and change in symptom severity at post-treatment and follow-up for primary anxiety diagnosis; remission from all anxiety disorder diagnoses at post-treatment and follow-up

	Remission						Response – change in CSR		
	Primary anxiety disorder ($n=792$)			All anxiety diagnoses ($n=747$)			Primary anxiety disorder ($n=788$)		
Time point	OR	95% CI	*P*	OR	95% CI	*P*	β	95% CI	*P*
Post-treatment									
Genotype	0.92	0.71 to 1.20	0.551	1.09	0.79 to 1.48	0.607	−0.04	−0.11 to 0.03	0.294
Time							−1.36	−1.41 to 1.30	0.000
Baseline severity	1.15	1.03 to 1.29	0.013	1.22	1.07 to 1.39	0.003	0.29	0.26 to 0.32	0.000
Age	1.02	0.97 to 1.08	0.367	1.00	0.94 to 1.07	0.936	0.01	−0.00 to 0.03	0.083
Gender	1.07	0.86 to 1.33	0.539	1.25	0.97 to 1.62	0.088	0.03	−0.03 to 0.09	0.279
	Primary anxiety disorder ($n=606$)			All anxiety diagnoses ($n=573$)			Primary anxiety disorder ($n=581$)		
Time point	OR	95% CI	*P*	OR	95% CI	*P*	β	95% CI	*P*
Follow-up									
Genotype	0.83	0.35 to 1.99	0.679	0.66	0.31 to 1.43	0.293	−0.04	−0.13 to 0.04	0.318
Time	0.00	0.00 to 0.01	0.000	0.00	0.00 to 0.02	0.000	−1.03	−1.09 to 0.97	0.000
Time^2	2.72	1.76 to 4.19	0.000	2.27	1.64 to 3.13	0.000	0.15	0.13 to 0.16	0.000
Baseline severity	2.05	1.31 to 3.21	0.002	1.99	1.36 to 2.93	0.000	0.27	0.23 to 0.30	0.000
Age	0.96	0.80 to 1.14	0.631	1.02	0.88 to 1.20	0.750	0.00	−0.02 to 0.02	0.957
Gender	0.79	0.39 to 1.62	0.523	1.20	0.64 to 2.23	0.569	0.03	−0.04 to 0.10	0.461

CSR, clinical severity rating.
5HTTLPR genotype is defined using a recessive model, where SS = 1 and LL/LS = 0. Age and baseline severity are centered at the mean.

Table 3 Mega-analyses; results combining Cohorts 1 and 2. Outcome measures; primary anxiety disorder remission at follow-up, change in primary anxiety CSR from pre-treatment to follow-up, all anxiety disorder diagnoses remission at follow-up

	Remission						Response – change in CSR		
	Primary anxiety disorder ($n=1044$)			All anxiety diagnoses ($n=1011$)			Primary anxiety disorder ($n=1019$)		
Predictor variable at follow-up	OR	95% CI	*P*	OR	95% CI	*P*	β	95% CI	*P*
Genotype	0.55	0.27 to 1.11	0.095	0.45	0.25 to 0.88	**0.014**	−0.06	−0.13 to 0.01	0.070
Time	0.00	0.00 to 0.01	0.000	0.00	0.00 to 0.01	0.000	−0.91	−0.95 to 0.86	0.000
Time^2	2.55	1.94 to 3.36	0.000	2.17	1.73 to 2.72	0.000	0.13	0.11 to 0.14	0.000
Baseline severity	2.05	1.44 to 2.91	0.000	2.30	1.63 to 3.23	0.000	0.27	0.24 to 0.29	0.000
Age	0.95	0.83 to 1.10	0.497	0.99	0.87 to 1.12	0.833	−0.01	−0.02 to 0.01	0.360
Gender	1.21	0.70 to 2.09	0.502	1.33	0.81 to 2.20	0.257	0.05	−0.00 to 0.10	0.070
Cohort	0.65	0.33 to 1.27	0.206	0.55	0.30 to 1.02	0.056	−0.05	−0.12 to 0.01	0.100

CSR, clinical severity rating.
5HTTLPR genotype is defined using a recessive model, where SS = 1 and LL/LS = 0. Age and baseline severity are centred at the mean. Statistically significant results for genotype are highlighted.

(0.44) for primary (all) anxiety remission. In this study, the effects observed were in the same direction but were markedly smaller and non-significant. This overestimation of effect size within discovery samples is often, at least in part, responsible for the failure of subsequent studies to replicate genetic effects. This is because replication studies are usually underpowered. This study far exceeded the required *N* of 285 needed to detect an effect of OR = 0.39 (as observed in our previous study) with 80% power and $\alpha = 0.01$. With a sample size of at least 600 in each analysis, this study was sufficiently powered to detect an OR = 0.39 with greater than 99% power and $\alpha = 0.001$. However, if the true effect of 5HTTLPR in predicting CBT response is closer to the 0.66 observed in the present study, then this would require a sample of $N > 900$ to detect this effect at $\alpha = 0.01$ with 80% power (taking into account the higher remission rate in the Cohort 2).

Mega-analyses are one means of increasing statistical power. To this end, we examined the overall effect of 5HTTLPR genotype on CBT outcome using all data available from this and our previous paper. This allowed us to increase the available sample size to $n = 1044$. The effect of genotype on change in primary anxiety disorder symptom severity was suggestive of an improved response for SS genotype carriers but did not reach conventional levels of significance. We found weak evidence of an association between 5HTTLPR genotype and remission of all anxiety diagnoses at follow-up, which was consistent with our previous findings.[15] SS genotype carriers were half as likely as SL/LL carriers to retain any anxiety disorder diagnosis at follow-up (OR = 0.45). The odds ratio for primary anxiety disorder remission was in the same direction (OR = 0.55) but did not attain statistical significance. These findings suggest that the 5HTTLPR genotype accounts for only a very small amount of the variance in outcome following CBT. Importantly, the 95% confidence intervals around the OR of 0.45 (for all anxiety disorder remission) suggest that the true effect size lies somewhere between 0.25 and 0.88 and thus effectively provides an upper bound for estimating the effect of 5HTTLPR on remission following CBT. However, given the tendency of early candidate gene discoveries to overestimate the true effect, it remains highly plausible that the true effect may in fact be nearer the lower bound estimate of 0.88 (a higher value represents a smaller effect size with respect to these analyses; see results section for further details). Future research attempting to investigate outcome following psychological treatments as a function of 5HTTLPR genotype should use this information when making decisions regarding appropriate sample size.

The current paper adds to the expanding therapygenetics literature investigating the 5HTTLPR polymorphism.[14] Although

this marker is a plausible candidate for involvement in outcome following psychological therapy, 8 out of 11 studies have failed to find a significant association between the 5HTTLPR and treatment response, with the present study being by far the most highly powered. The remaining studies observed mixed effects: two studies[16,22] found a significant association between the SS genotype and a more positive treatment response, which is consistent with the mega-analyses reported herein. However, a third small study[18] reported the opposite with the SS genotype associated with fewer treatment gains. The weak and contradictory findings seen thus far may reflect varying disorder and treatment response phenotypes, the role of medication in some studies and small, underpowered sample sizes.[14]

The use of a semi-structured diagnostic instrument to characterise treatment outcome and agreement across study sites on the definition of response are significant strengths of this study. This study is also the largest to date to investigate genetic predictors of outcome following psychological therapy. However, there are some limitations. First, the sample is very heterogeneous, including a range of anxiety diagnoses and several different CBT modalities. One possibility is that the 5HTTLPR may have greater predictive power when the sample and treatment is more homogeneous.[31] Second, the current study takes a candidate gene approach. In all areas of psychiatric genetics, candidate gene studies typically report very small effect sizes, often fail to replicate and are sensitive to publication bias.[32] To be able to nominate candidate genes for investigation also requires a clear understanding of the pathophysiology of the phenotype under investigation and the putative mechanisms through which psychological therapies may act. We know that psychological treatment response is a complex trait, thus it is very unlikely that a single genetic polymorphism such as the 5HTTLPR will explain a sufficiently large amount of variance in outcome to be clinically meaningful in its own right. Although there remains a place for adequately powered studies of plausible candidate genes within the therapygenetics field, this challenge means it will become increasingly important to move towards a whole-genome array-based 'therapygenomics' approach. Whole-genome studies are hypothesis free and thus have the potential to identify completely novel and unexpected variants associated with psychological treatment response. Perhaps, most importantly, there is the ability to move beyond single variants and to identify groups of markers and important biological pathways and systems, which collectively capture a (clinically) significant proportion of the variance in outcome. However, it is important to note that some genetic variants (including the 5HTTLPR) cannot be adequately inferred from array data and will continue to need to be genotyped directly. Given the importance of clinical and demographic predictors,[24] optimal prediction of CBT response is likely to come from analytic approaches, which aggregate genetic information with clinical and demographic variables.[33]

In summary, this study failed to replicate our previously reported association between 5HTTLPR genotype and outcome following CBT for child anxiety disorders. Consistent with our previous findings SS genotype carriers had a more positive treatment response compared with SL/LL genotype carriers. However, these effects were very small and mostly non-significant. The increased sample size afforded by a mega-analytic approach revealed a significant association between SS genotype and remission of all anxiety disorders, which survived multiple testing corrections. Importantly, this work provides an upper and lower bound for estimating the effect size of association between 5HTTLPR and CBT outcomes, which are informative for other researchers working in this area. Going forward, the therapygenetics field needs to embrace whole genome approaches and to look to recruit large, homogenous samples in which to explore genetic predictors of outcome following psychological therapies.

Kathryn J. Lester, DPhil, School of Psychology, University of Sussex, and King's College London, MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Susanna Roberts**, MSc, King's College London, MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Robert Keers**, PhD, King's College London, MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Jonathan R. I. Coleman**, MSc, King's College London, MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Gerome Breen**, PhD, King's College London, MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK and National Institute for Health Research Biomedical Research Centre, South London and Maudsley National Health Service Trust, UK; **Chloe C. Y. Wong**, PhD, King's College London, MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Xiaohui Xu**, MD, King's College London, MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Kristian Arendt**, MSc, Department of Clinical Psychology and Experimental Psychopathology, University of Groningen, The Netherlands; **Judith Blatter-Meunier**, PhD, Department of Psychology, University of Basel, Basel, Switzerland; **Susan Bögels**, PhD, Research Institute Child Development and Education, University of Amsterdam, The Netherlands; **Peter Cooper**, DPhil, School of Psychology and Clinical Language Sciences, University of Reading, UK and Department of Psychology, Stellenbosch University, South Africa; **Cathy Creswell**, DClinPsy, PhD, School of Psychology and Clinical Language Sciences, University of Reading, UK; **Einar R. Heiervang**, MD PhD, Institute of Clinical Medicine, University of Oslo, Oslo, Norway; **Chantal Herren**, PhD, Department of Forensic Psychiatry, University of Basel Psychiatric Clinics, Basel, Switzerland; **Sanne M. Hogendoorn**, PhD, Department of Child and Adolescent Psychiatry/De Bascule, Academic Medical Centre, Amsterdam, The Netherlands; **Jennifer L. Hudson**, PhD, Department of Psychology, Centre for Emotional Health, Macquarie University, Sydney, Australia; **Karen Krause**, DiplPsych, Department of Psychology, Ruhr-Universität Bochum, Bochum, Germany; **Heidi J. Lyneham**, PhD, Department of Psychology, Centre for Emotional Health, Macquarie University, Sydney, Australia; **Anna McKinnon**, PhD, Brain and Mind Research Institute, University of Sydney, Sydney, Australia, and The MRC Cognition and Brain Sciences Unit, Cambridge, UK; **Talia Morris**, BPsych(Hons), Department of Psychology, Centre for Emotional Health, Macquarie University, Sydney, Australia; **Maaike H. Nauta**, PhD, Department of Clinical Psychology and Experimental Psychopathology, University of Groningen, The Netherlands; **Ronald M. Rapee**, PhD, Department of Psychology, Centre for Emotional Health, Macquarie University, Sydney, Australia; **Yasmin Rey**, PhD, Child Anxiety and Phobia Program, Department of Psychology, Florida International University, Miami, USA; **Silvia Schneider**, PhD, Department of Psychology, Ruhr-Universität Bochum, Bochum, Germany; **Sophie C. Schneider**, BPsych(Hons), Department of Psychology, Centre for Emotional Health, Macquarie University, Sydney, Australia; **Wendy K. Silverman**, PhD, Yale University School of Medicine, Child Study Center, New Haven, Connecticut, USA; **Patrick Smith**, PhD, King's College London, Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, London, UK; **Mikael Thastum**, PhD, Department of Psychology and Behavioural Sciences, Aarhus University, Aarhus, Denmark; **Kerstin Thirlwall**, DClinPsy, School of Psychology and Clinical Language Sciences, University of Reading, UK; **Polly Waite**, DClinPsy, School of Psychology and Clinical Language Sciences, University of Reading, UK; **Gro Janne Wergeland** MD, Department of Child and Adolescent Psychiatry, Haukeland University Hospital, Bergen, Norway; **Thalia C. Eley**, PhD, King's College London, MRC Social, Genetic and Developmental Psychiatry (SGDP) Centre, Institute of Psychiatry, Psychology and Neuroscience, London, UK

Correspondence: Thalia C. Eley, SGDP Centre, Institute of Psychiatry, King's College, Box PO80, London SE5 8AF, UK. Email: thalia.eley@kcl.ac.uk

First received: 28 Jul 2014, final revision 8 Dec 2014, accepted 11 Dec 2014

Funding

Combined study supported by UK Medical Research Council grant G0901874/1 to Eley. Lester supported by UK Medical Research Council grant (MR/J011762/1) and Jacobs Foundation Young Scholar grant. Keers supported by UK Medical Research Council Population Health fellowship (MR/K021281/1). Individual trials support by Australian Research Council grant DP0878609 to Hudson, Rapee, and Eley; Australian NHMRC grants to Rapee, Hudson, Lyneham, Mihalopolous (1027556), Lyneham, Hudson and Rapee (488505) and Hudson and Rapee (382008); TrygFonden grant (7-10-1391) to Thastum & Esben Hougaard; Edith ogGodtfred Kirk Christiansens Fond grant (21-5675) to Thastum; Swiss National Science Foundation grant (105314-116517) to Schneider, Western Norway Regional Health Authority grants to Odd Havik (911253) and Heiervang (911366); UK Medical Research Council Clinical Fellowship (G0802821) to Richard Meiser-Stedman; NIMH R01 (MH079943) to Silverman; UK NIHR grants to Creswell (PB-PG-0110-21190) and Cooper (PB-PG-0107-12042); UK Medical Research Council Grants to Cooper and Creswell (09-800-17), Thirlwall, Cooper and Creswell (G0802326), Waite, Creswell and Cooper (G1002011), and Creswell (G0601874). Grant 09/800/17 was managed by NIHR on behalf of the MRC-NIHR partnership. UK NIHR grants to Creswell, Cooper, Emma McIntosh & Lucy Willetts (PB-PG-0110-21190) and Cooper, Creswell, Lucy Willetts & Paul Sheffied (PB-PG-0107-12042); This study presents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Acknowledgements

We thank Irma Knuistingh Neven, Marianne Bjerregaard Madsen, Lisbeth Jørgensen, Carmen Adornetto, Kristine Fonnes Griffin, Elisa Kulewski, Jonas Großekathöfer, Nora Dirks, Evelyn Kmelnitski, Sabrina Heuser, Adrian Boyle, Clare Dixon, Harma Moorlag, Nienke Boersma, Sue Cruddace, Marie Weber, Zoe Hughes, Kiri Clarke, Francoise Hentges, Liz White, Nynke Wagenaar, Luci Motoca, Yesenia Rodriguez, Klaudia Perreira, Erin Hedemann, Cristina Del Busto, Gillian O'Neill, Lucy Lindley, Rachel Banham, Nora Delvendahl, HjaltiJonsson, Kristen Lavallee, Tina In-Albon, Odd E. Havik, Krister Fjermestad, Katrin Hötzel, Richard Meiser-Stedman, Tim Dalgleish, and Carla Marin for their contributions.

References

1 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry* 2005; **62**: 593–602.

2 Bittner A, Egger HL, Erkanli A, Jane Costello E, Foley DL, Angold A. What do childhood anxiety disorders predict? *J Child Psychol Psychiatry* 2007; **48**: 1174–83.

3 James AC, James G, Cowdrey F, Soler A, Choke A. Cognitive behavioural therapy for anxiety disorders in children and adolescents. *Cochrane Database Syst Rev* 2013; **6**: CD004690.

4 Lesch K-P, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996; **274**: 1527–31.

5 Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *Am J Med Genet B Neuropsychiatr Genet* 2004; **127B**: 85–9.

6 Munafò MR, Freimer NB, Ng W, Ophoff R, Veijola J, Miettunen J, et al. 5-HTTLPR genotype and anxiety-related personality traits: a meta-analysis and new data. *Am J Med Genet B Neuropsychiatr Genet* 2009; **150B**: 271–81.

7 Karg K, Burmeister M, Shedden K, Sen S. The serotonin transporter promoter variant (5-httlpr), stress, and depression meta-analysis revisited: evidence of genetic moderation. *Arch Gen Psychiatry* 2011; **68**: 444–54.

8 Eley TC, Sugden K, Corsico A, Gregory AM, Sham P, McGuffin P, et al. Gene-environment interaction analysis of serotonin system markers with adolescent depression. *Mol Psychiatry* 2004; **9**: 908–15.

9 Taylor SE, Way BM, Welch WT, Hilmert CJ, Lehman BJ, Eisenberger NI. Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biol Psychiatry* 2006; **60**: 671–6.

10 Wilhelm K, Mitchell PB, Niven H, Finch A, Wedgwood L, Scimone A, et al. Life events, first depression onset and the serotonin transporter gene. *Br J Psychiatry* 2006; **188**: 210–5.

11 Stein MB, Campbell-Sills L, Gelernter J. Genetic variation in 5HTTLPR is associated with emotional resilience. *Am J Med Genet B Neuropsychiatr Genet* 2009; **150B**: 900–6.

12 Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes. *Mol Psychiatry* 2009; **14**: 746–54.

13 Hankin B, Nederhof E, Oppenheimer C, Jenness J, Young J, Abela J, et al. Differential susceptibility in youth: evidence that 5-HTTLPR x positive parenting is associated with positive affect ''for better and worse''. *Transl Psychiatry* 2011; **1**: e44.

14 Lester KJ, Eley TC. Therapygenetics: using genetic markers to predict response to psychological treatment for mood and anxiety disorders. *Biol Mood Anxiety Disord* 2013; **3**: 1–16.

15 Eley TC, Hudson JL, Creswell C, Tropeano M, Lester KJ, Cooper P, et al. Therapygenetics: the 5HTTLPR and response to psychological therapy. *Mol Psychiatry* 2012; **17**: 236–7.

16 Kohen R, Cain KC, Buzaitis A, Johnson V, Becker KJ, Teri L, et al. Response to psychosocial treatment in poststroke depression is associated with serotonin transporter polymorphisms. *Stroke* 2011; **42**: 2068–70.

17 Bockting CL, Mocking RJ, Lok A, Koeter MW, Schene AH. Therapygenetics: the 5HTTLPR as a biomarker for response to psychological therapy? *Mol Psychiatry* 2012; **18**: 744–5.

18 Bryant R, Felmingham K, Falconer E, Benito L, Dobson-Stone C, Pierce K, et al. Preliminary evidence of the short allele of the serotonin transporter gene predicting poor response to cognitive behavior therapy in posttraumatic stress disorder. *Biol Psychiatry* 2010; **67**: 1217–9.

19 Andersson E, Rück C, Lavebratt C, Hedman E, Schalling M, Lindefors N, et al. Genetic polymorphisms in monoamine systems and outcome of cognitive behavior therapy for social anxiety disorder. *PLoS ONE* 2013; **8**: e79015.

20 Furmark T, Carlbring P, Hammer S, Wahlgren I, Ekselius L, Eriksson E, et al. Effects of serotonin transporter and tryptophan hydroxylase-2 gene variation on the response to cognitive-behavior therapy in individuals with social anxiety disorder. *Biol Psychiatry* 2010; **67** (9 suppl): 1S–271S.

21 Hedman E, Andersson E, Ljótsson B, Andersson G, Schalling M, Lindefors N, et al. Clinical and genetic outcome determinants of Internet-and group-based cognitive behavior therapy for social anxiety disorder. *Acta Psychiatr Scand* 2012; **126**: 126–36.

22 Knuts I, Esquivel G, Kenis G, Overbeek T, Leibold N, Goossens L, et al. Therapygenetics: 5-HTTLPR genotype predicts the response to exposure therapy for agoraphobia. *Eur Neuropsychopharmacol* 2014; **24**: 1222–8.

23 Lonsdorf T, Ruck C, Bergstrom J, Andersson G, Ohman A, Lindefors N, et al. The COMTval158met polymorphism is associated with symptom relief during exposure-based cognitive-behavioral treatment in panic disorder. *BMC Psychiatry* 2010; **10**: 99.

24 Hudson JL, Keers R, Roberts S, Coleman JR, Breen G, Arendt K, et al. Clinical predictors of response to cognitive-behavioral therapy in pediatric anxiety disorders: the Genes for Treatment (GxT) study. *J Am Acad Child Adolesc Psychiatry* 2015; **54**: 454–63.

25 Silverman WK, Albano AM. *The Anxiety Disorders Interview Schedule for Children-IV (Child and Parent Versions)*.Oxford University Press, 1996.

26 Schneider S, Unnewehr S, Margraf J. *Kinder-DIPS für DSM-IV-TR. Diagnostisches Interview bei psychischen Störungen im Kindes-und Jugendalter [Child-DIPS for DSM-IV-TR. Diagnostic Interview for Psychiatric Disordes in Childhood and Adolescence]*. Springer, 2009.

27 Freeman B, Smith N, Curtis C, Huckett L, Mill J, Craig IW. DNA from buccal swabs recruited by mail: evaluation of storage effects on long-term stability and suitability for multiplex polymerase chain reaction genotyping. *Behav Genet* 2003; **33**: 67–72.

28 DNA Genotek. *Laboratory Protocol for Manual Purification of DNA from 0.5mL of Sample*. DNS Genotek, 2015.

29 Purcell S, Cherny SS, Sham PC. Genetic power calculator: design of linkage and association genetic mapping studies of complex traits. *Bioinformatics* 2003; **19**: 149–50.

30 StataCorp. Stata Statistical Software: release 11. Stata Corp LP, 2009.

31 Beevers CG, McGeary JE. Therapygenetics: moving towards personalized psychotherapy treatment. *Trends Cogn Sci*. 2011; **16**: 11–2.

32 Duncan LE, Keller MC. A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *Am J Psychiatry* 2011; **168**: 1041–9.

33 Hudson JL, Lester KJ, Lewis CM, Tropeano M, Creswell C, Collier DA, et al. Predicting outcomes following cognitive behaviour therapy in child anxiety disorders: the influence of genetic, demographic and clinical information. *J Child Psychol Psychiatry*. 2013; **54**: 1086–94.

EXTRA CONTENT ONLINE OPEN ACCESS CC BY

[doi: 10.1192/bjp.bp.114.154997]

Online supplement

Sample characteristics and site specific trial details

Unless otherwise specified, clinical trials included all primary anxiety disorder diagnoses. All sites made secondary anxiety disorder diagnoses where appropriate.

Sydney, Australia (n = 293**).** Participants aged 6-18 were recruited from the Centre for Emotional Health, Macquarie University, Sydney. All participants completed the Cool Kids program (1), with 10-12 family sessions involving the parents (the majority of which were conducted in groups; 8% of the sample's DNA were collected retrospectively). Variations on this treatment program include a subgroup from previous randomised trials who received group, individual or phone-based CBT sessions (2, 3); participants from a guided self-help trial with phone support for children in rural Australia (4); a group from a trial with additional parental anxiety management (5); and those recruited from an ongoing randomised trial of progressive allocation to treatment (Stepped Care).

Reading and Oxford (n = 199**), UK** Participants aged 5-18 were recruited jointly from Reading and Oxford from eight trials at the Berkshire Child Anxiety Clinic (University of Reading) and the Oxfordshire Primary Child and Adolescent Mental Health Service. Participants received treatment in three main themes; one focussing on children with anxious mothers; a set of trials using a parent-guided self-help CBT program; and an online CBT program for adolescents.

The Mother and Child (MaCh) project (6). Children whose mother also had a current anxiety disorder completed an 8 session manual-based CBT treatment based on the Cool Kids program (7). The mothers of these children also received extra sessions focussing on their own anxiety and on mother-child interactions.

Overcoming. Children were treated with a parent-guided self-help CBT program, comprised of the same primary components as the Cool Kids program (7, 8). This consisted of 2-4 in-person sessions and 2-4 telephone sessions. A sub-set of this group with a primary anxiety disorder diagnosis of Social Phobia also received targeted Cognitive Bias Modification Training (CBM-I, (9)). Additionally, participants with highly anxious parents (screened using DASS or by meeting ADIS criteria) were randomised to groups in a trial including additional sessions for the parents which focussed on strategies for tolerating children's negative emotions. In Oxford, treatment was based on the same basic program, and delivered by primary health workers as part of a feasibility trial (10).

BRAVE. The final treatment group completed a therapist-supported online CBT program for adolescents (BRAVE), consisting of 10 sessions, half with 5 additional parent sessions and half without parent sessions.

Aarhus, Denmark (n = 112**).** Participants aged 7-17 years were recruited from the Department of Psychology and Behavioural Sciences, Aarhus University, and all anxiety disorder diagnoses were included. Participants received CBT using the Cool Kids manual (including the adolescent version where appropriate (7, 11)). Participants came from two groups; one aged 7-17, from a trial including treatment and waitlist conditions; and another

group aged 7-12 from a trial comparing efficacy of traditional group-based treatment with Cool Kids versus a guided self-help version with clinician support (bibliotherapy). In both trials only participants that received in-person CBT were included.

Bergen, Norway (n = 35**).** Participants aged 5-13 were recruited from the child part of the "Assessment and Treatment – Anxiety in Children and Adults" study, Haukeland University Hospital, Bergen. Patients referred to outpatient mental health clinics in Western Norway, with a primary diagnosis of separation anxiety, social phobia, or generalized anxiety, received group or individual treatment with the FRIENDS program (4^{th} edition (12, 13)) in a randomised control trial comparing active treatment with a waitlist condition (14).

Bochum, Germany (n = 50**).** Participants aged 5-18 were recruited from the Research and Treatment Centre for Mental Health, Ruhr-Universität Bochum. Participants received either exposure-based CBT (8-25 sessions, with sessions occurring at least every 2 weeks), the Coping Cat program (15), or a family-based version of CBT specifically designed to target separation anxiety disorder (TAFF (16, 17)). Diagnoses were provided separately for parent- and child-report. The primary diagnosis was selected as being the most severe from either reporter. If the most severe disorder reported by each was of equal severity but was a different diagnosis, the parent-reported diagnosis was selected.

Basel, Switzerland (n = 46**).** Participants aged 5-13 (all with a primary diagnosis of Separation Anxiety Disorder) were recruited from the Faculty of Psychology, University of Basel. All participants took part in a randomised control trial comparing a family-based version of CBT specifically designed to target separation anxiety disorder (TAFF(16, 17)) with Coping Cat (15). All participants received 16 sessions over 12 weeks.

Florida, USA (n = 36**).** Participants aged 7 to 16 (including all primary anxiety disorder diagnoses except PTSD) were recruited from the Child Anxiety and Phobia Program, Florida International University, Miami. All participants received 12 to 14 hour-long sessions of individual manualised CBT. Additionally, two conditions included parental involvement focussing on different parent skills (Relationship Skills Training or Reinforcement Skills Training).

Groningen, the Netherlands (n = 35**).** Participants aged 8 to 17 were recruited from the Department of Child and Adolescent Psychiatry, University of Groningen. All participants were treated within a randomised control trial of Coping Cat (Dutch version (18) including 12 individual child sessions and 2 parent sessions.

Cambridge, UK (n = 9**).** Participants aged 8-17 were recruited from the MRC Cognition and Brain Sciences Unit, Cambridge, UK. Participants were taking part in the ASPECTS trial, which recruited individuals exposed to a recent (i.e. in the previous six months) traumatic stressor (i.e. any event that involve the threat of death, severe injury, or threat to bodily integrity, or witnessing such an event). Those that developed PTSD were randomised to a 10-week waitlist or individual PTSD-specific CBT (19), which consisted of up to 10 sessions over a 10 week period. Only participants that received treatment were included

Amsterdam, the Netherlands (n = 3**).** Participants aged 10-14 were recruited from the Academic Treatment Centre for Parent and Child, University of Amsterdam UvA Minds and received either 12 weeks of CBT in individual sessions or 8 weeks of CBT in group sessions, according to the Dutch protocol Discussing + Doing = Daring (20). Diagnoses were provided

separately for parent- and child-report with the primary diagnosis selected from these data by the trial manager.

Table DS1: White Subset Cohort 2 results; categorical remission and change in symptom severity at post-treatment and follow-up for primary anxiety diagnosis, and remission from all anxiety disorder diagnoses at post and follow-up.

Cohort 2 – White Subset		Remission						Response – Change in CSR		
		Primary Anxiety Disorder (n = 550)			All Anxiety Diagnoses (n = 516)			Primary Anxiety Disorder (n = 529)		
Time-point	Predictor Variable	**OR**	**β**	**β**	**OR**	**95% CI**	**P**	**β**	**95% CI**	**P**
Post-Treatment	Genotype	0.92	-0.06	-0.06	1.16	0.80-1.68	0.421	-0.06	-0.15-0.02	0.124
	Time							-1.37	-1.44--1.30	0.000
	Baseline severity	1.12	0.27	0.27	1.22	0.96-1.31	0.136	0.27	0.24-0.31	0.000
	Age	1.04	0.02	0.02	0.99	0.92-1.07	0.806	0.02	0.00-0.03	0.040
	Sex	1.13	0.04	0.04	1.41	1.03-1.92	0.030	0.04	-0.03-0.11	0.294
		Primary Anxiety Disorder (n = 442)			All Anxiety Diagnoses (n = 411)			Primary Anxiety Disorder (n = 421)		
Time-point	Predictor Variable	**OR**	**β**	**β**	**OR**	**95% CI**	**P**	**β**	**95% CI**	**P**
Follow-up	Genotype	1.11	-0.01	-0.01	0.94	0.43-2.04	0.875	-0.01	-0.12-0.09	0.781
	Time	0.00	-1.09	-1.09	0.00	0.00-0.05	0.000	-1.09	-1.16--1.01	0.000
	$Time^2$	2.61	0.16	0.16	2.19	1.53-3.12	0.000	0.16	0.14-0.18	0.000
	Baseline severity	1.84	0.24	0.24	1.82	1.22-2.70	0.003	0.24	0.20-0.28	0.000
	Age	0.91	-0.01	-0.01	1.01	0.86-1.19	0.889	-0.01	-0.03-0.02	0.621
	Sex	0.87	0.05	0.05	1.37	0.71-2.65	0.348	0.05	-0.03-0.13	0.240

Note. 5HTTLPR genotype is defined using a recessive model, where SS=1 and LL/LS=0. Age and baseline severity are centred at the mean

Table DS2: White Subset Mega-analyses; results combined Cohorts 1 & 2. Outcome measures; primary anxiety disorder remission at follow-up, change in primary anxiety CSR from pre-treatment to follow-up, all anxiety disorder diagnoses remission at follow-up

White Subset Mega-analyses		Remission						Response – Change in CSR		
		Primary Anxiety Disorder (n = 722)			All Anxiety Diagnoses (n = 701)			Primary Anxiety Disorder (n = 691)		
		OR	**95% CI**	**P**	**OR**	**95% CI**	**P**	**β**	**95% CI**	**P**
Follow-up	Genotype	0.58	0.25-1.32	0.52	0.52	0.25-1.07	0.074	-0.06	-0.14-0.02	0.140
	Time	0.00	0.00-0.01	0.00	0.00	0.00-0.02	0.000	-0.97	-1.03--0.92	0.000
	$Time^2$	2.65	1.89-3.74	2.18	2.18	1.66-2.86	0.000	0.14	0.13-0.15	0.000
	Baseline severity	2.21	1.43-3.41	2.29	2.29	1.53-3.42	0.000	0.26	0.22-0.29	0.000
	Age	0.87	0.73-1.03	1.00	1.00	0.86-1.15	0.973	-0.01	-0.03-0.01	0.295
	Sex	1.28	0.67-2.44	1.66	1.66	0.93-2.97	0.085	0.08	0.02-0.15	0.010
	Cohort	0.66	0.30-1.47	0.49	0.49	0.24-0.99	0.047	-0.06	-0.14-0.02	0.116

Note. 5HTTLPR genotype is defined using a recessive model, where SS=1 and LL/LS=0. Age and baseline severity are centred at the mean

References

1. Rapee R, Lyneham H, Schniering C, Wuthrich V, Abbott M, Hudson J, et al. *The Cool Kids® Child and Adolescent Anxiety Program*. Centre for Emotional Health, Macquarie University, 2006.
2. Hudson JL, Rapee RM, Deveney C, Schniering CA, Lyneham HJ, Bovopoulos N. Cognitive-Behavioral Treatment Versus an Active Control for Children and Adolescents With Anxiety Disorders: A Randomized Trial. *J Am Acad Child Adolesc Psychiatry*. 2009; **48**(5): 533-44.
3. Rapee RM, Abbott MJ, Lyneham HJ. Bibliotherapy for children with anxiety disorders using written materials for parents: A randomized controlled trial. *J Consult Clin Psychol*. 2006; **74**(3): 436-44.
4. Lyneham HJ, Rapee RM. Evaluation of therapist-supported parent-implemented CBT for anxiety disorders in rural children. *Behav Res Ther*. 2006; **44**(9): 1287-300.
5. Hudson JL, Newall C, Rapee RM, Lyneham HJ, Schniering CC, Wuthrich VM, et al. The Impact of Brief Parental Anxiety Management on Child Anxiety Treatment Outcomes: A Controlled Trial. *J Clin Child Adolesc Psychol*. 2013: 1-11.
6. Creswell C, Cruddace S, Gerry S, E. M, J. M, Murray L, et al. Treatment of childhood anxiety disorder in the context of maternal anxiety disorder: A randomised controlled trial. In: Health Technology Assessment 2007.
7. Lyneham HJ, Abbott MJ, Wignall A, Rapee RM. *The Cool Kids Anxiety Treatment Programme*. MUARU, Macquarie Unversity, 2003.
8. Thirlwall K, Cooper PJ, Karalus J, Voysey M, Willetts L, Creswell C. Treatment of child anxiety disorders via guided parent-delivered cognitive-behavioural therapy: randomised controlled trial. *Br J Psychiatry*. 2013; **203**(6): 436-44.
9. Vassilopoulos SP, Banerjee R, Prantzalou C. Experimental modification of interpretation bias in socially anxious children: Changes in interpretation, anticipated interpersonal anxiety, and social anxiety symptoms. *Behav Res Ther*. 2009; **47**(12): 1085-9.
10. Creswell C, Hentges F, Parkinson M, Sheffield P, Willetts L, Cooper P. Feasibility of guided cognitive behaviour therapy (CBT) self-help for childhood anxiety disorders in primary care. *Ment Health Fam Med*. 2010; **7**(1): 49-57.
11. Rapee RM, Lyneham HJ, Schniering CA, Wuthrich VM, Abbott MJ, Hudson JL, et al. *Cool Kids "Chilled" Adolescent Anxiety Program*. MUARU, Macquarie University, 2006.
12. Barrett PM, Farrell LJ, Ollendick TH, Dadds M. Long-Term Outcomes of an Australian Universal Prevention Trial of Anxiety and Depression Symptoms in Children and Youth: An Evaluation of the Friends Program. *J Clin Child Adolesc Psychol*. 2006; **35**(3): 403-11.
13. Barrett PM. *FRIENDS for Life program - Group leader's workbook for children*. Australian Academic Press, 2004.
14. Wergeland GJH, Fjermestad KW, Marin CE, Haugland BS-M, Bjaastad JF, Oeding K, et al. An effectiveness study of individual vs. group cognitive behavioral therapy for anxiety disorders in youth. *Behav Res Ther*. 2014; **57**(0): 1-12.
15. Kendall PC. Treating anxiety disorders in children: Results of a randomized clinical trial. *J Consult Clin Psychol*. 1994; **62**(1): 100-10.
16. Schneider S, Blatter-Meunier J, Herren C, In-Albon T, Adornetto C, Meyer A, et al. The efficacy of a family-based cognitive-behavioral treatment for separation anxiety disorder in children aged 8–13: A randomized comparison with a general anxiety program. *J Consult Clin Psychol*. 2013; **81**(5): 932-40.
17. Schneider S, Lavallee K. Separation Anxiety Disorder. In: The Wiley-Blackwell Handbook of The Treatment of Childhood and Adolescent Anxiety (eds E C.A., O T.): 301-34. Wiley-Blackwell, 2013.
18. Nauta MH, Scholing A. *Cognitieve gedragstherapie bij kinderen en jongeren met angststoornissen: een protocol van 12 sessies. Handleiding voor de therapeut.* Rijksuniversiteit Groningen (Klinische en Ontwikkelingspsychologie), 1998.
19. Smith P, Yule W, Perrin S, Tranah T, Dalgleish TIM, Clark DM. Cognitive-Behavioral Therapy for PTSD in Children and Adolescents: A Preliminary Randomized Controlled Trial. *J Am Acad Child Adolesc Psychiatry*. 2007; **46**(8): 1051-61.
20. Bögels S. *Behandeling van angststoornissen bij kinderen en adolescenten met het cognitief-gedragstherapeutische protocol Denken + Doen = Durven.* Houten: Bohn Stafleu van Loghem, 2008.

Non-replication of the association between 5HTTLPR and response to psychological therapy for child anxiety disorders

Kathryn J. Lester, Susanna Roberts, Robert Keers, Jonathan R. I. Coleman, Gerome Breen, Chloe C. Y. Wong, Xiaohui Xu, Kristian Arendt, Judith Blatter-Meunier, Susan Bögels, Peter Cooper, Cathy Creswell, Einar R. Heiervang, Chantal Herren, Sanne M. Hogendoorn, Jennifer L. Hudson, Karen Krause, Heidi J. Lyneham, Anna McKinnon, Talia Morris, Maaike H. Nauta, Ronald M. Rapee, Yasmin Rey, Silvia Schneider, Sophie C. Schneider, Wendy K. Silverman, Patrick Smith, Mikael Thastum, Kerstin Thirlwall, Polly Waite, Gro Janne Wergeland and Thalia C. Eley

BJP 2016, 208:182-188.
Access the most recent version at DOI: 10.1192/bjp.bp.114.154997

Supplementary Material Supplementary material can be found at: http://bjp.rcpsych.org/content/suppl/2015/08/10/bjp.bp.114.154997.DC1.html

References This article cites 28 articles, 4 of which you can access for free at: http://bjp.rcpsych.org/content/208/2/182#BIBL

Reprints/ permissions To obtain reprints or permission to reproduce material from this paper, please write to **permissions@rcpsych.ac.uk**

You can respond to this article at **/letters/submit/bjprcpsych;208/2/182**

Downloaded from http://bjp.rcpsych.org/ on April 8, 2016
Published by The Royal College of Psychiatrists

To subscribe to *The British Journal of Psychiatry* go to:
http://bjp.rcpsych.org/site/subscriptions/