The influence of the serotonin transporter gene 5-HTTLPR polymorphism on suicidal behaviors: a meta-analysis

Giuseppe Fanelli[1], Alessandro Serretti[1]*

[1]Department of Biomedical and NeuroMotor Sciences - University of Bologna, Bologna, Italy
(*correspondence to: alessandro.serretti@unibo.it)

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BACKGROUND and AIM

BACKGROUND: Suicidal Behavior (SB) is the second leading cause of death among youth worldwide and the tenth among all age groups. Inherited genetic differences have a role in suicidality, as shown by family, adoption and twin studies, with heritability ranging from 30 to 55%. The serotonergic system and the ***SLC6A4 5-HTTLPR* gene variant** have been largely investigated for association with SB, with controversial results.

Over the years, six meta-analytic studies have attempted to summarize previous evidence: four of them showed significant associations, though with some variability in the results [2-5]. Lin and Tsai showed lack of association between the *5-HTTLPR* polymorphism and Suicidal Behavior, but a significant effect on Violent Suicide. Likewise, Clayden et al. only found an association with Attempted Suicide and not with the whole Suicidal Behavior.

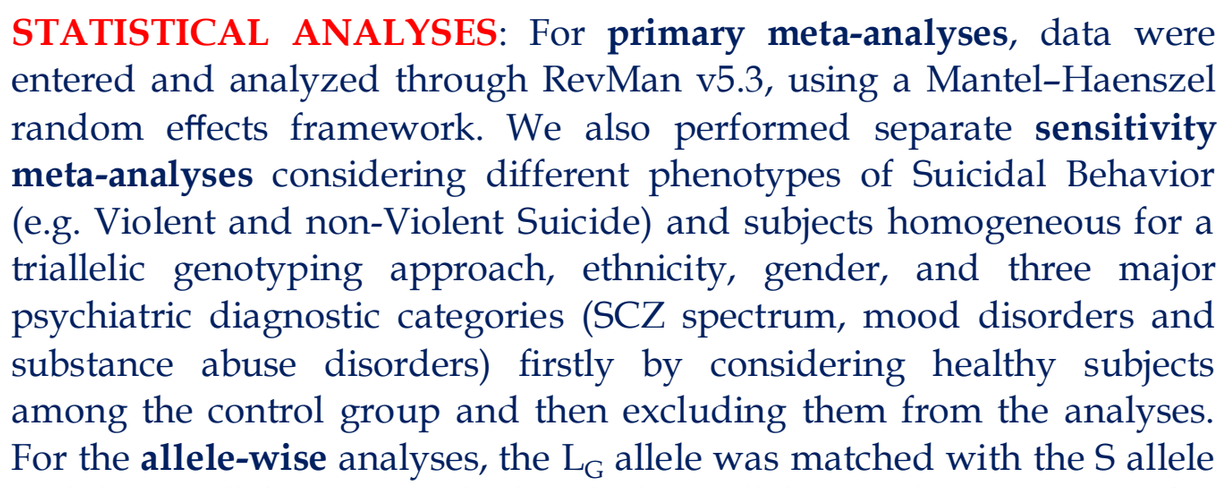
In this work, we sought to determine whether the results of previous meta-analyses were confirmed or modified subsequent to the inclusion of more recent literature data.

METHODS

LITERATURE SEARCH: Medline/PubMed, Web of Science, Scopus and PsycINFO databases were searched for papers published until **July 2018**. The search terms were related to the gene and its polymorphism as well as to the Suicidal Behavior phenotypes. The reference lists of the selected articles were inspected to retrieve additional papers not indexed by the scientific literature databases.

STATISTICAL ANALYSES: For **primary meta-analyses**, data were entered and analyzed through RevMan v5.3, using a Mantel–Haenszel random effects framework. We also performed separate **sensitivity meta-analyses** considering different phenotypes of Suicidal Behavior (e.g. Violent and non-Violent Suicide) and subjects homogeneous for a triallelic genotyping approach, ethnicity, gender, and three major psychiatric diagnostic categories (SCZ spectrum, mood disorders and substance abuse disorders) firstly by considering healthy subjects among the control group and then excluding them from the analyses. For the **allele-wise** analyses, the L_G allele was matched with the S allele and the L_A allele was matched with the L allele. For the **genotype-wise** analyses, we tested the comparison of the S' carrier genotypes (SS, SL) (low expression) versus the LL genotype (high expression), assuming that the S allele had a dominant effect on the L allele, as previously reported in the literature. For studies examining the *5-HTTLPR* as a triallelic polymorphism, we included the SS, SL, SL_G, SL_A, L_GL_A, L_GL_G in the S' carrier genotypes group and the L_AL_A was combined with the LL genotype.

***Figure 1**. Study flow*



RESULTS

1) ***45 pertinent case-control studies** were identified (15,341 subjects).*
2) No association was found between the low-expressing alleles or genotypes ($S+L_G$ alleles or S' carrier genotypes) and SB in the **general primary analyses**, which include all the studies we previously selected (*allele-wise analysis: OR=0.97, C.I. 0.88-1.06, p=.45; genotype-wise analysis: OR=1, C.I. 0.87-1.14, p=.99 [images not shown]*.
3) The **sensitivity analyses** did not show any significant effect of the *5-HTTLPR* polymorphism either when we considered only studies which used a triallelic genotyping approach or homogeneous data for ethnicity, gender, SCZ spectrum and mood disorder diagnoses. An effect of the low-expressing alleles ($S+L_G$ alleles) on SB was found in a subpopulation of substance abusers, although this result was not confirmed after the exclusion of healthy subjects from the control group.
4) *The low-expressing alleles or genotypes ($S+L_G$ alleles or S' carrier genotypes) were associated with an increase in the risk of Violent Suicide, mainly in the **Violent Suicide Attempt** subgroup (allele-wise analysis: OR=1.44, C.I. 1.17-1.78, p=.0007 [Fig. 2]; genotype-wise analysis: OR=2.49, C.I. 1.45-4.29, p=.001 [image not shown]).*

DISCUSSION and CONCLUSION

- Some clinical, personality and sociodemographic features may allow to distinguish suicide attempters from completers [6];
- The effect of the low-expressing alleles and genotypes is more evident where the **psychopathological dimension**, underlying the SB, is more substantial and robust, as it happens for **Suicide Attempters**. Conversely, negative socio-economic aspects or physical health problems might play a predominant causal role in the Completed Suicide subgroup.

→ ***Our findings contribute to clarify the contrasting previous evidence by suggesting an association of the 5-HTTLPR and* Violent SB**. Environmental factors and epigenetic mechanisms may act to further increase the level of complexity.

LIMITATIONS: diversity in the genotyping methods; controversial definitions of SB; partial or not shown data for some studies.

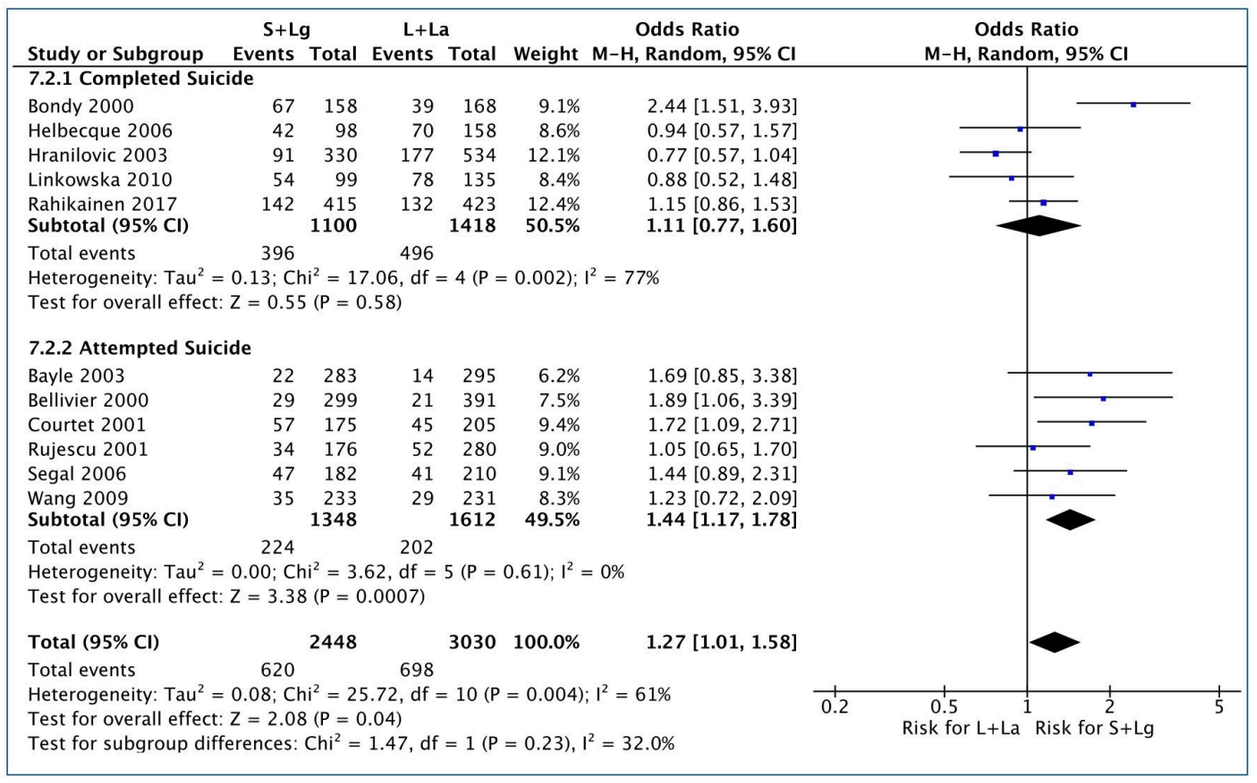


***Figure 2.** Forest plot for the effect of the 5-HTTLPR polymorphism on Violent Suicidal Behavior, pooling $S+L_G$ alleles versus $L+L_A$ alleles (allele-wise analysis). Subjects with a history of Violent Suicide are compared with non-suicidal patients and healthy controls.*

REFERENCES

[1]. Antypa, N., A. Serretti, and D. Rujescu, Serotonergic genes and suicide: a systematic review. Eur Neuropsychopharmacol, 2013. 23(10): p. 1125-42.
[2]. Anguelova, M., C. Benkelfat, and G. Turecki, A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: II. Suicidal behavior. Mol Psychiatry, 2003. 8(7): p. 646-53.
[3]. Li, D. and L. He, Meta-analysis supports association between serotonin transporter (5-HTT) and suicidal behavior. Mol Psychiatry, 2007. 12(1): p. 47-54.
[4]. Schild, A.H., et al., Genetic association studies between SNPs and suicidal behavior: a meta-analytical field synopsis. Prog Neuropsychopharmacol Biol Psychiatry, 2013. 46: p. 36-42.
[5]. de Medeiros Alves, V., et al., Genetic Polymorphisms Might Predict Suicide Attempts in Mental Disorder Patients: A Systematic Review And Meta-Analysis. CNS & Neurological Disorders - Drug Targets- CNS & Neurological Disorders), 2015. 14(7): p. 820-827.
[6]. Parra Uribe, I., Blasco-Fontecilla, H., Garcia-Pares, G., Giro Batalla, M., Llorens Capdevila, M., Cebria Meca, A., de Leon-Martinez, V., Perez-Sola, V., Palao Vidal, D.J., 2013. Attempted and completed suicide: not what we expected? J Affect Disord 150, 840-846.

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NO CONFLICT OF INTEREST