Stage I

Planning the Review — **Blaya C, Salum GA, Lima MS, Segal SL and Manfro GG**

Research question: Is there an association between the 5-HTTLPR and panic disorder?

Identification of the need for a review: Several studies with incongruent results and lack of power to detect small effects of this polymorphism determine the need for a supportive theoretical construct.

Stage II

Conducting a Review

Identification of research: Studies were identified through PubMed, PsychInfo, Lilacs and ISI. The PubMed search was run using the Mesh terms: ("Serotonin Plasma Membrane Transport Proteins"[MeSH] OR "5-HTTLPR" OR "5-HTT" OR "SLC6A4") AND "Panic Disorder"[MeSH]. In PsychINFO, Lilacs and ISI the following words were used: "Panic" AND ("serotonin transporter" OR "serotonergic transporter" OR "5-HTT" OR "5-HTTLPR" OR "SLC6A4"). Check reference section of publications found through our search was used to identify additional studies that may have been missed. Contact was tried with all authors in order to identify unpublished data

Study quality assessments and study inclusion / exclusion criteria:

Quality assessment criteria

- Panic Disorder diagnosis (DSM or ICD);
- Case-control or family-based studies;
- Hardy-Weinberg Equilibrium (HWE).

Exclusion criteria

- All patients with major psychiatric disorders other than PD;
- Replicated data;
- Insufficient data to perform statistical analysis.

Selection of studies: Studies were selected by two authors (CB and GAS) independently. Discrepancies were resolved by mutual consent and a third opinion (GGM). Exclusion reasons can be seen below the flowchart.

Included Studies	*Excluded Studies*
Deckert et al. (German) [34];	Hajduk [31] ¶;
Deckert et al. (Italian) [34];	Maron et al. [28] *;
Ishiguro et al. [35];	Maron et al. [29] ¶;
Maron et al. [12];	Perez et al. [32] ‡;
Martinez-Barondo et al. [40]	Perna et al. [26] *;
Matsushita et al. [36];	Rotondo et al. [25] ¶¶;
Ohara et al. [37];	Rotondo et al. [33] †;
Olesen et al. [39];	Sand et al. [30] ¶.
Samochowiec et al. [38];	
Hamilton et al. [21];	
Kim et al. [41].	

Data synthesis and data analysis: Only case-control studies were included in the analyses. The fixed-effect OR was used to summarize the results of each single study and the pooled OR. The Q test and I^2 statistic were used to assess heterogeneity between studies. We carried out allelic and genotypic (s dominant) tests stratifying each one for ethnicity, control group quality and agoraphobia comorbidity, in a total of fourteen analyses sets.

Stage III

Reporting and Dissemination

The report

Analyses	*OR (CI95%)*	*p-value (z)*	*Heterogeneity Q test (p-value; I^2)*
Allele analysis (s vs. l)	0.91 (0.80-1.03)	0.14 (1.47)	$X^2_{df=9}$=9.75 (0.37; 7.7%)
Stratified analysis (s vs. l)			
High Quality	0.88 (0.75 to 1.04)	0.13 (1.52)	$X^2_{df=4}$=6.51(0.16; 38.6%)
Caucasian	0.86 (0.74 to 1.01)	0.06 (1.88)	$X^2_{df=5}$=4.72 (0.45; 0%)
Agoraphobia comorbidity	0.94 (0.77 to 1.15)	0.57 (0.57)	$X^2_{df=3}$=5.21 (0.16; 42.1%)

Recommendations for further investigation:

1. Adopt a lifelong perspective of PD;
2. Appropriate analysis of HWE;
3. Larger samples to detect the expected small effect of this polymorphism;
4. An adequate control group with: (a) standardized psychiatric diagnoses (DSM or CIDI, for example) assessing the lifelong absence of psychiatric disorders, (b) controls should be old enough in order to reduce the possibility for the late onset of the disorder;
5. An exploratory analysis of the clinical manifestation, considering the nuances of Panic Disorder (i.e., agoraphobia, phobic avoidance, panic attacks, etc.) and other ways to investigate the heritable portion of PD;
6. Special attention to comorbidities, considering the significant influence of this polymorphism in other psychiatric conditions;
7. The role evaluation of this polymorphism in other situations such as therapeutic responses;
8. Genotypes must be determined blinding to case-control status in order to minimize the risk of a result influenced by an investigator's preconceptions [13];
9. Corrections for multiple comparisons (e.g., Bonferroni correction), in case of multiple diagnostic schemes, models of inheritance or multiple genes tests;
10. Caution on interpretation of results, considering the non-causal pathways, the alpha error and the prior probabilities.

Getting evidence into practice: The role of 5-HTTLPR in PD still needs more adequate investigation.

Based on CDR Report, NHS Centre for Reviews and Dissemination, University of York and Cochrane Handbook

Exclusion reasons: *Without control group; ¶Replicated data; ¶¶ All patients with major Psychiatric comorbidity other than PD; ‡ Hardy-Weinberg departure; † Insufficient data;