## **EPP0183**

## Time Moderates the interplay between 5-HTTLPR and stress on depression risk: gene x environment interaction as dynamic process

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**Introduction:** The role of the interaction between the serotonintransporter-linked promoter region (5HTTLPR) and stressful condition in determining the vulnerability to depression has been widely investigated. Nevertheless, empirical research provides contrasting findings. Recently, the differential susceptibility to environment model proposed a conceptual shift respect to the classical interpretation of 5-HTTLPR: viewing the short (s) and the long (l) allele not as associated to different traits of vulnerability (respectively vulnerable or not), but determining different plasticity levels (respectively, more and less plasticity) and, thus, different susceptibilities to the environment (respectively, high and low susceptibility).

**Objectives:** As 5-HTTLPR is involved in plasticity, the main goal of the present study is to demonstrate that the interaction between the polymorphism and stress emerges when assessing its effects according to temporal factors in a **dynamic process perspective**.

**Methods:** We explored our hypothesis, exploiting a meta analytic approach. We searched PubMed, PsychoINFO, Scopus and EMBASE databases and 1096 studies were identified and screened, resulting in 22 studies to be included in the meta-analyses. We applied the DerSimonian and Laird random-effects model to estimate crude odds ratios for risk of depression according to 5HTTLPR and we assessed heterogeneity using the  $I^2$  and Cochran's Q statistic. We stratified the staties according to (i) stress duration (i.e., chronic vs. acute stress) and (ii) time elapsed between the end of the stressful condition and the assessment of depression (i.e., within one year vs. more than one year).

**Results:** When stratifying for the duration of stress, the effect of the 5-HTTLPR x stress interaction emerged only in the case of chronic stress (OR 1.43, 95%IC 1.16-1.77,  $I^2 = 52\%$ , Q=25.25; Figure 1), with a significant subgroup difference (p=0.004). The stratification according to time interval revealed a significant interaction only for intervals within one year (OR 1.23, 95%IC 1.03-1-46,  $I^2 = 67\%$ , Q=39.35), though no difference between subgroups was found. The critical role of time interval clearly emerged when considering only chronic stress: a significant effect of the 5-HTTLPR and stress interaction was confirmed exclusively within one year (OR 1.53, 95%IC 1.17-2.02,  $I^2 = 45\%$ , Q=10.94; Figure 2) and a significant subgroup difference was found (p=0.01).

## Image:

Study	OR	[95%CI]	Weight
Duration of stress : acute			
Caspi et al 2003a	0.74	[0.55; 0.99]	6.3%
Chipman et al 2007a		[0.86; 1.09]	
Coventry et al 2010a	1.01	[1.00; 1.02]	12.2%
Fandiño-Losada et al 2013b		[0.91; 4.38]	
Gilliespie et al 2005		[0.83; 1.50]	
Juhasz et al 2015a		[1.01; 1.41]	
Kim et al 2017		[1.07; 2.63]	
Power et al 2010a		[0.37; 1.06]	
Surtees et al 2006a		[0.71; 1.17]	
Wilhelm et al 2006a		[0.20; 2.01]	
Random Effect		[0.91; 1.12]	
Heterogeneity: $I^2 = 58\%$ , $\chi_9^2 = 21.3$ ( $p = 0.0$	1)		
Duration of stress : chronic			
Chipman et al 2007d	0.49	[0.16; 1.52]	0.8%
Cutuli et al 2013b		[0.55; 5.62]	0.8%
Eley et al 2004		[0.91; 3.77]	1.9%
Gutierrez et al 2015		[1.22; 3.34]	3.3%
Haberstick et al 2016a		[0.79; 1.24]	
Hankin et al 2015		[1.07; 1.48]	
Kudinova et al 2015		[0.51; 1.46]	
Laucht et al 2009a		[1.22: 3.29]	
Özcürümez et al 2019		[0.59; 6.21]	
Quinn et al 2012		[1.10; 5.26]	
Rocha et al 2015		[1.10; 2.30]	
Roy et al 2011		[0.09;13.74]	
Sales et al 2015		[1.20;11.97]	0.8%
Random Effect		[1.16; 1.77]	
		[1.10, 1.77]	30.0%
Heterogeneity: $I^2 = 52\%$ , $\chi^2_{12} = 25.25$ ( $p = 0$ .	01)		
Random Effect		[1.03; 1.27]	100.0%
Heterogeneity: $I^2 = 66\%$ , $\chi^2_{22} = 65.30$ (p < 0.1	01)		
Test for subgroup differences: $\chi_1^2 = 8.26$ , df		0.01)	

## Image 2:

Study	OR	[95%	6CI]	Weight												
Time Interval : > 1 year								1				1		1		Li.
Chipman et al 2007b	0.97	[0.88;	1.08]	13.7%				-		i i i i i i i i i i i i i i i i i i i	i i i i i i i i i i i i i i i i i i i	i i i i i i i i i i i i i i i i i i i	i i i i i i i i i i i i i i i i i i i	<b></b>	i i i i i i i i i i i i i i i i i i i	i i i i i i i i i i i i i i i i i i i
Fandiño-Losada et al 2013a	0.82	[0.43;	1.56]	3.8%												
Gutierrez et al 2015	2.02	[1.22;	3.34]	5.3%								- <u>-</u>	- <u></u>		- <u></u>	
Haberstick et al 2016a	0.99	[0.79;	1.24]	10.9%						*	*		*	*	*	*
Juhasz et al 2015b		[0.87;						害	光	美	美	美	美	美	美	美
Kudinova et al 2015				5.0%			_		- 2							
Özçürümez et al 2019				1.4%			-									
Quinn et al 2012		[1.10;														
Roy et al 2011		[0.09;														
Surtees et al 2006c				11.3%				1		て	モ	て	1	て	モ	气
Random Effect		[0.91;	1.17]	66.9%				Ť	. ■	Ť	Ť	T	Ť	Ť	Ť	T.
Heterogeneity: $I^2 = 42\%$ , $\chi_9^2 = 15.46$ ( $p = 0.08$ )	)															
Time Interval : ≤ 1 year																
Chipman et al 2007d	0.49	[0.16;	1.52]	1.5%		_										
Cutuli et al 2013b	1.76	[0.55;	5.62]	1.4%			-									
Eley et al 2004	1.85	[0.91;	3.77]	3.3%				H	×				- <del>- x</del>			
Hankin et al 2015	1.26	[1.07;	1.48]	12.4%				8	<del>20</del>							
Laucht et al 2009a	2.00	[1.22;	3.29]	5.4%												
Rocha et al 2015	1.59	[1.10;	2.30]					-			- <del></del>	+				- <del>1</del>
Sales et al 2015		[1.20;														
Random Effect		[1.17;	2.02]	33.1%					•	-	-	•	-	-	-	-
Heterogeneity: $I^2 = 45\%$ , $\chi_6^2 = 10.94$ ( $\rho = 0.09$ )	)															
Random Effect	1.20	[1.04;	1.39]	100.0%					· · · · ·	· · · · · · · · · · · · · · · · · · ·	· · · · ·	· · · · · · · · · · · · · · · · · · ·		· · · · · · · · · · · · · · · · · · ·	·	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: $l^2 = 63\%$ , $\chi^2_{16} = 43.03$ (p < 0.01)	)															
Test for subgroup differences: $\chi_1^2 = 6.59$ , df = 1	(p = 0	.01)				0.1	0.1 0.5	0.1 0.5 1	0.1 0.5 1 2	0.1 0.5 1 2	0.1 0.5 1 2	0.1 0.5 1 2 1	0.1 0.5 1 2 10	0.1 0.5 1 2 10	0.1 0.5 1 2 10	0.1 0.5 1 2 10
· · · · · · · · · · · · · · · · · · ·							Odd	Odds F	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio

**Conclusions:** Our results show that the 5-HTTLPR x stress interaction is a dynamic process, producing different effects at different time-points, and indirectly confirm that s-allele carriers are both at higher risk and more capable to recover from depression. Overall, these findings expand the current view of the interplay between 5-HTTLPR and stress adding the temporal dimension, resulting in a three-way interaction: **gene x environment x time**.

Disclosure of Interest: None Declared

Odds Ratio