Meta-analysis in translational research is not a straightforward road. A case-study on IL-6 and depression.

Begoña Treceño, Javier Ballesteros.

Area de Psicología y Psiquiatría, Departamento de Neurociencias, Facultad de Medicina. Universidad del País Vasco. UPV/EHU. (Barrio Sarriena s/n, Leioa, Bizkaia)

Background

Recent meta-analyses have suggested that proinflammatory cytokines, such as interleukin-6 (IL-6) are associated with major depression. We wanted to ascertain if the prior accumulated evidence with animal experiments could lead to and support these findings.

Objectives

To perform a rapid review on the association of IL-6 and depression models in animal research, using stress based depression models, differentiating between chronic and acute stress.

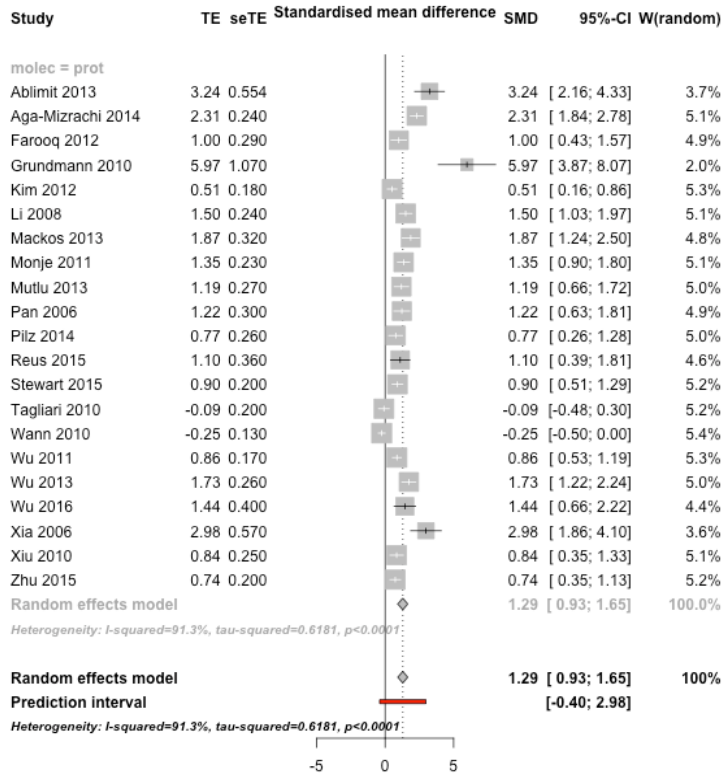
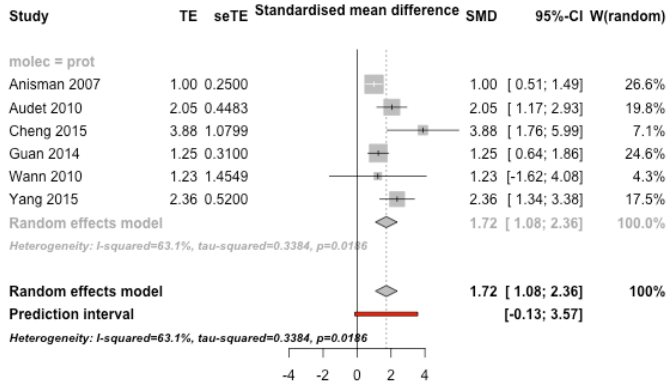


Figure 1: Plasma IL-6 differences in chronic stress induced animal models.



AREA	mRNA		PROTEIN		ALL OUTCOMES		
	ACUTE		ACUTE		ACUTE		
	SMD	95%-CI	SMD	95%-CI	SMD	95%-CI	I^2
Plasma			1.72	[1.0817; 2.3626]	1.72	[1.0817; 2.3626]	63.10%
Hippocampus	0.70	[0.2500; 1.1508]			0.70	[0.2500; 1.1508]	
Hypothalamus	0.26	[-0.3084; 0.8284]	0.99	[-0.3461; 2.3343]	0.37	[-0.1514; 0.8952]	0%
PFCx	0.41	[0.2303; 0.5971]			0.41	[0.2303; 0.5971]	0%
	CHRONIC		CHRONIC		CHRONIC		
	SMD	95%-CI	SMD	95%-CI	SMD	95%-CI	I^2
Plasma			1.29	[0.9251; 1.6523]	1.29	[0.9251; 1.6523]	91.30%
Hippocampus	0.51	[-0.1842; 1.2000]	1.53	[0.9787; 2.0809]	1.17	[0.6125; 1.7369]	95%
Hypothalamus	0.84	[0.0602; 1.6268]	1.20	[0.4160; 1.9840]	0.92	[0.2402; 1.5966]	86.70%
PFCx	0.34	[-0.1506; 0.8395]	0.29	[-2.1656; 2.7450]	0.37	[-0.2288; 0.9771]	95.10%

Figure 2 (up): Plasma IL-6 differences in acute sress induced animal models.
Figure 3 (down): Results of meta-analysis in all areas.

Methods

A PubMed and OVID search was run with appropriate terms. Effect sizes (standardized mean differences, SMD) were estimated directly from the data and/or statistics reported in the included studies. We used a random effects model to pool the effect estimates and estimate prediction intervals and also a sensitivity analysis was performed.

Results

Thirty-nine trials on the alterations of IL-6 levels in chronic stress based depression models were included. Random effects model resulted in SMD=1.29; I^2=91.3% in plasma (Fig. 1) and 0,37<SMD<1.16; 86.7%<I^2<95% in different parts of the brain (Fig. 3).Sensitivity analysis showed no trial exerted a significant influence on the pooled estimate (data not shown). Eleven trials on the alterations of IL-6 levels in acute stress based depression models were included. Overall, IL-6 increased in depression. Random effects model showed SMD=1.72; I^2=63.1% in plasma (Fig. 2) and 0.37<SMD<0.70; I^2=0% in different parts of the brain (Fig.3). Sensitivity analysis showed no trial exerted a significant influence on the pooled estimate (data not shown).

Conclusions

Although it seems to be an overall increase of IL-6, high heterogeneity was found between the models, the different areas studied and between trials. Similar problems could be presented in other areas of translational research, and must be deal with appropriately before jumping directly from the bench to the human.