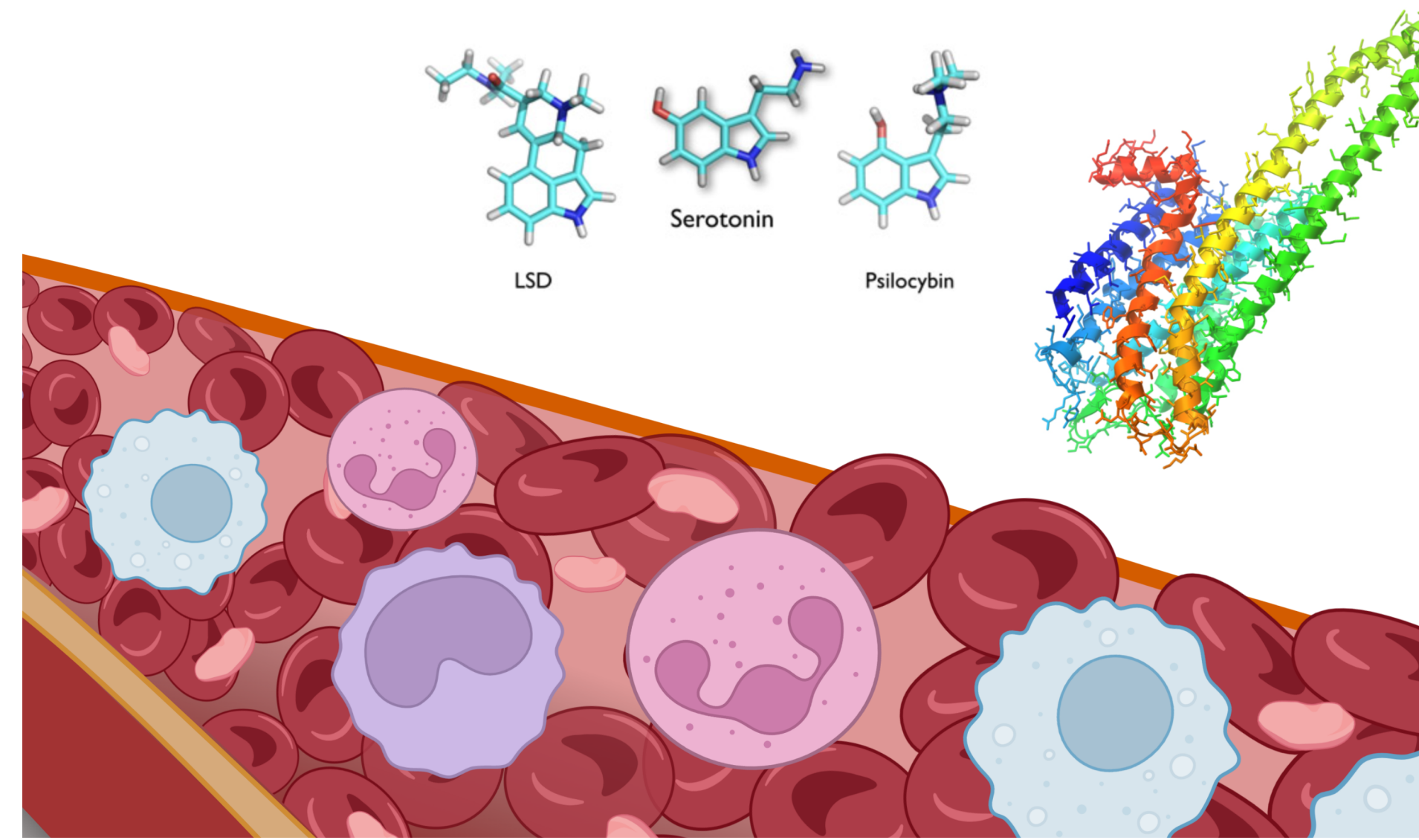


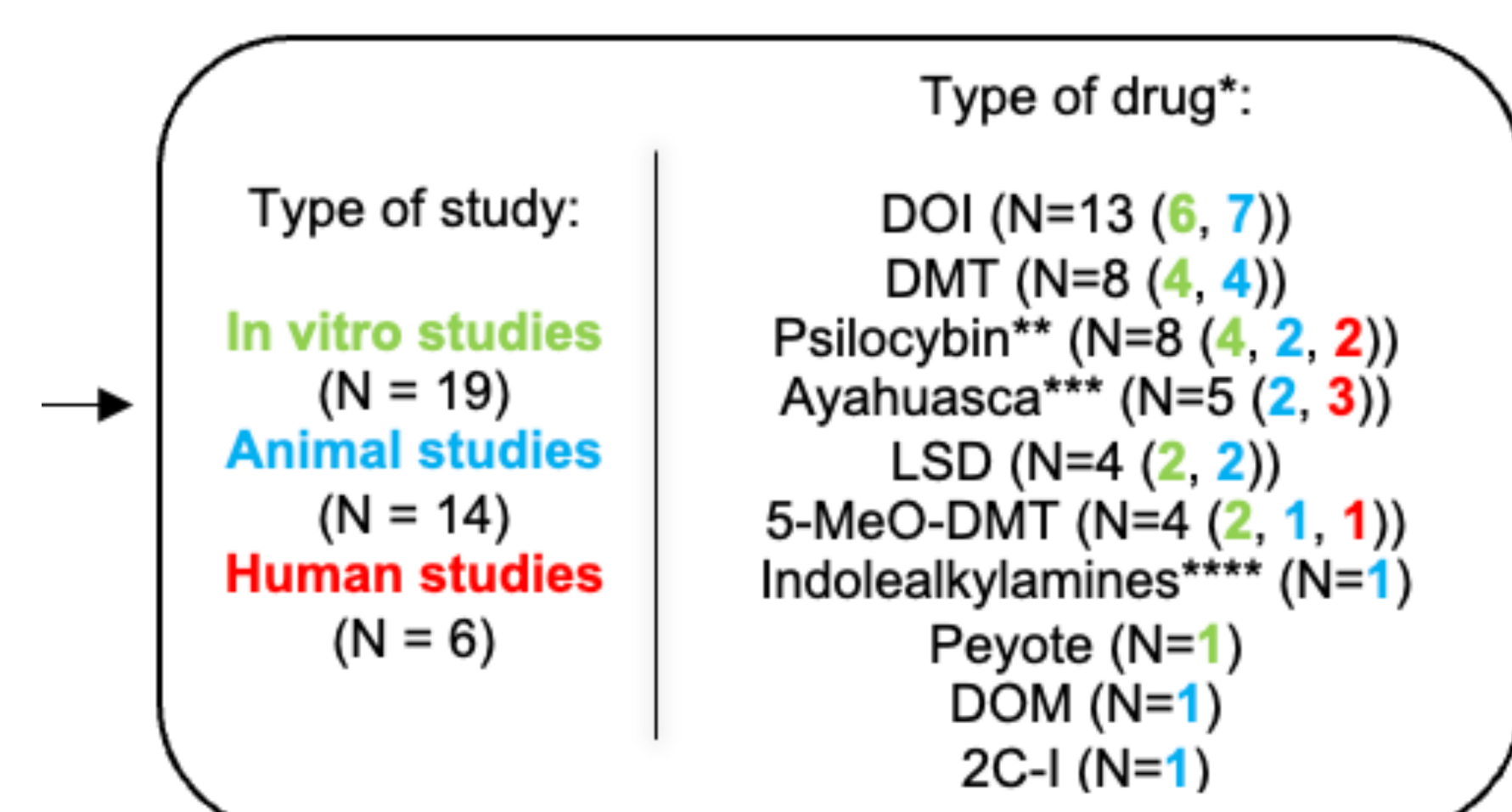
INTRODUCTION



The serotonergic psychedelics work primarily on the serotonin 5-HT_{2A} receptor and have shown potential for helping patients with anxiety, depression, and addiction with effects showing possible lasting improvement over weeks and months. The 5-HT_{2A}R is widely expressed, including in various immune cells, and the regulation of inflammation via serotonin plays a crucial role in immune homeostasis. Recent studies of the psychedelic drug and selective 5-HT₂ receptor agonist (R)-2,4-dimethoxy-4-iodoamphetamine [(R)-2,4-DOI] have shown anti-inflammatory activity in both non-human *in vivo* and *in vitro* studies (Nichols, 2020; Inserra et al., 2020). Immunomodulatory effects have been suggested as a possible method of action, but a thorough, comprehensive systematic review and meta-analysis is lacking.

METHODS

We systematically searched PubMed, EMBASE, PsychINFO, LILACS and ClinicalTrials.gov. All studies investigating the direct or indirect measure of changes in the immune system before and after exposure to serotonergic psychedelics, defined as hallucinogenic drugs with their primary effect on the 5-HT_{2A} receptor, were included. Using random-effects meta-analyses to estimate standardized mean differences (SMD) for effect sizes.



RESULTS

Immune outcomes in humans

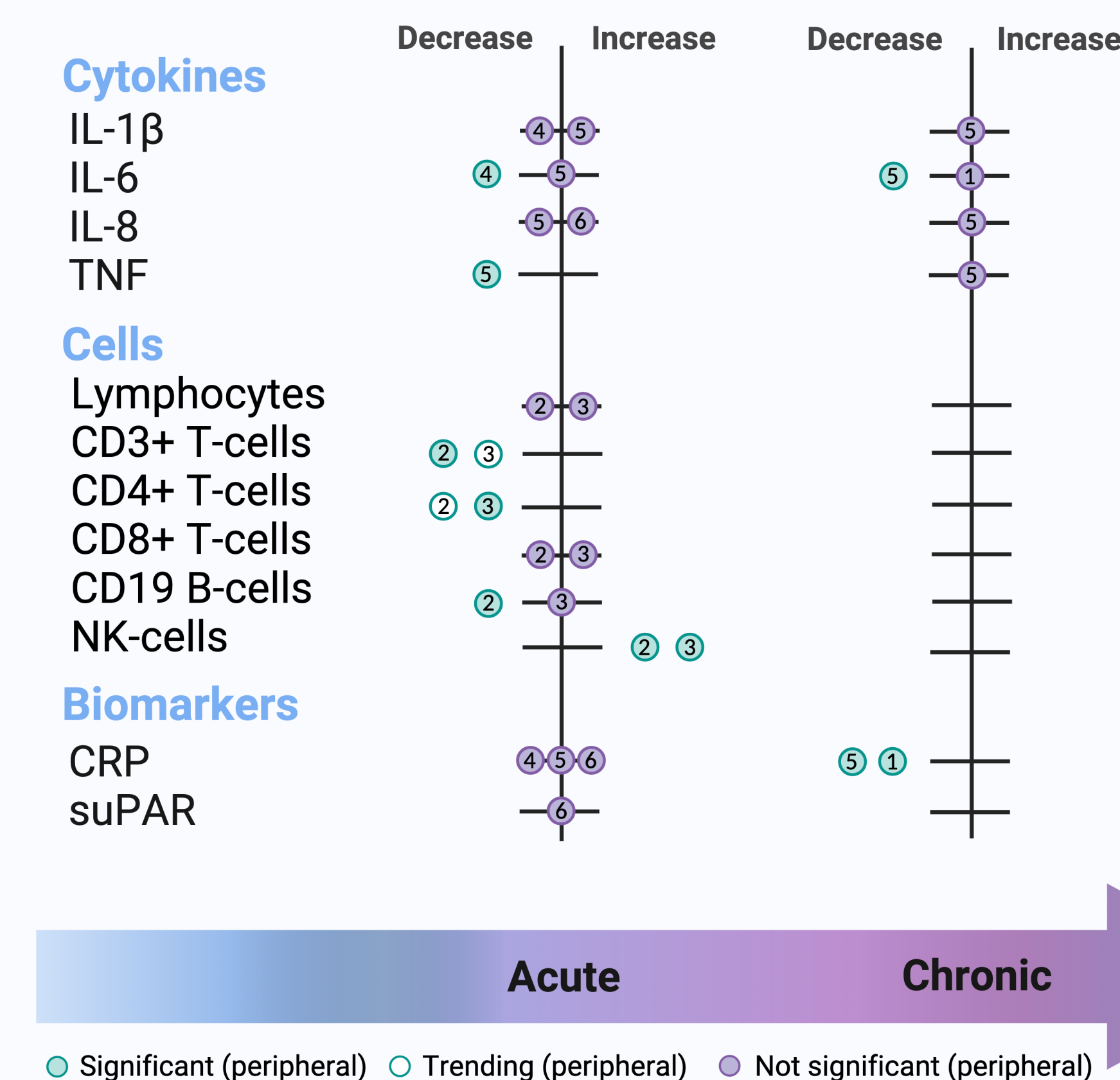
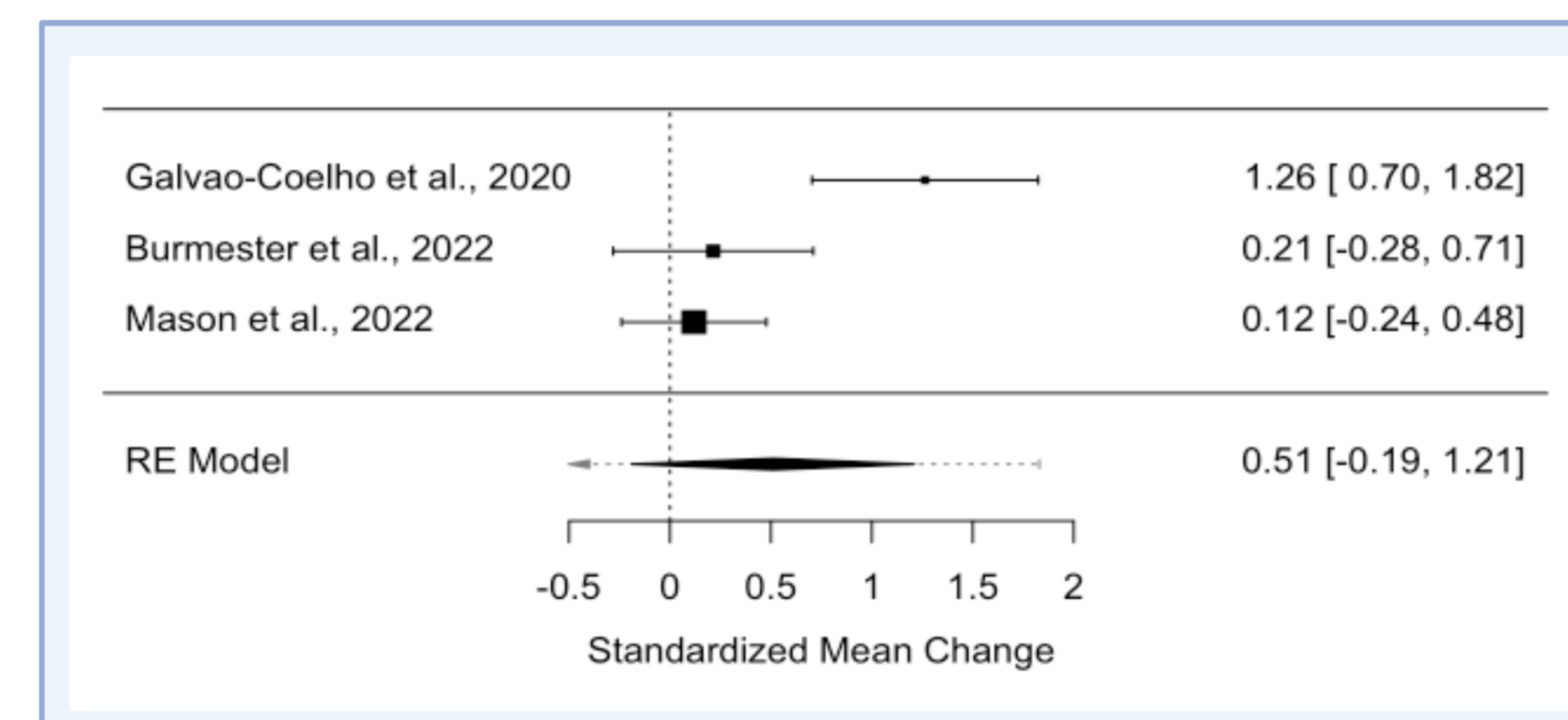


Figure 1. Timeline showing the observations of various changes in inflammatory response following treatment with a single dose of any serotonergic psychedelic in human trials. Abbreviations: Acute = outcome measures measured > 24 hours after exposure. Prolonged = outcome measures < 24 hours after exposure. IL = interleukin. CRP = C-Reactive Protein. suPAR = Soluble urokinase plasminogen activator receptor.

Figure 4: Forrest plot (healthy humans, N=68)

3 human studies (N=68) were eligible for meta-analysis. Treatment with a single dose of a psychedelic 5-HT_{2A} drug in healthy adults, was not significantly associated with any change in blood levels of CRP (SMD, 0.51; 95% CI, -0.19-1.21, $P = 85.20\%$, $k = 3$, $N = 68$), from baseline to 48h, 24h and 1.2h post-exposure.



Abbreviations: RE=Random Effects. Results are presented as: SMD (95% CI). Results presented are changes in CRP-levels in blood in healthy human adults receiving one dose of a psychedelic 5-HT_{2A} drug

Non-human in vivo and in vitro studies

Of 14 studies in non-human in vivo subjects, 12 studies favored anti-inflammatory effects of exposure to a serotonergic psychedelic. Of 19 studies in in vitro models, 17 studies favored anti-inflammatory effects of exposure to a serotonergic psychedelic.

Immune outcomes for in vivo animal studies

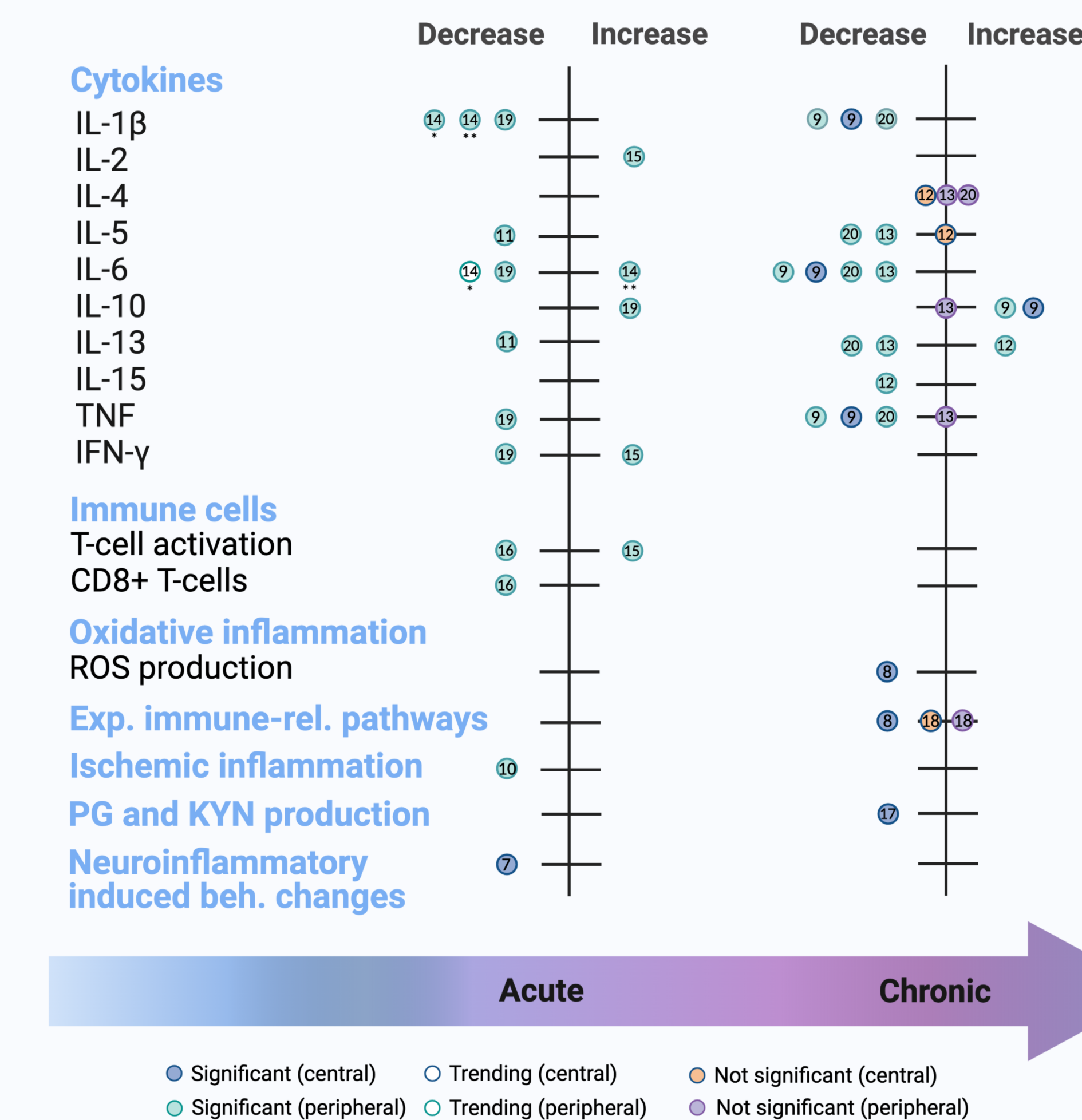


Figure 2. Timeline showing the observations of various changes in inflammatory response following treatment with a single dose of any serotonergic psychedelic in non-human animal trials. Abbreviations: Acute = outcome measures measured > 24 hours after exposure. Prolonged = outcome measures < 24 hours after exposure. IL = interleukin. IFN- γ = Interferon- γ . ROS = Reactive oxygen species. Exp. = expression of. Immune-rel. = Immunorelated. PG = prostaglandin. KYN = kynurenine. Beh. = behavioural. *in the aortic arch. **in the small intestines.

Immune outcomes for in vitro studies

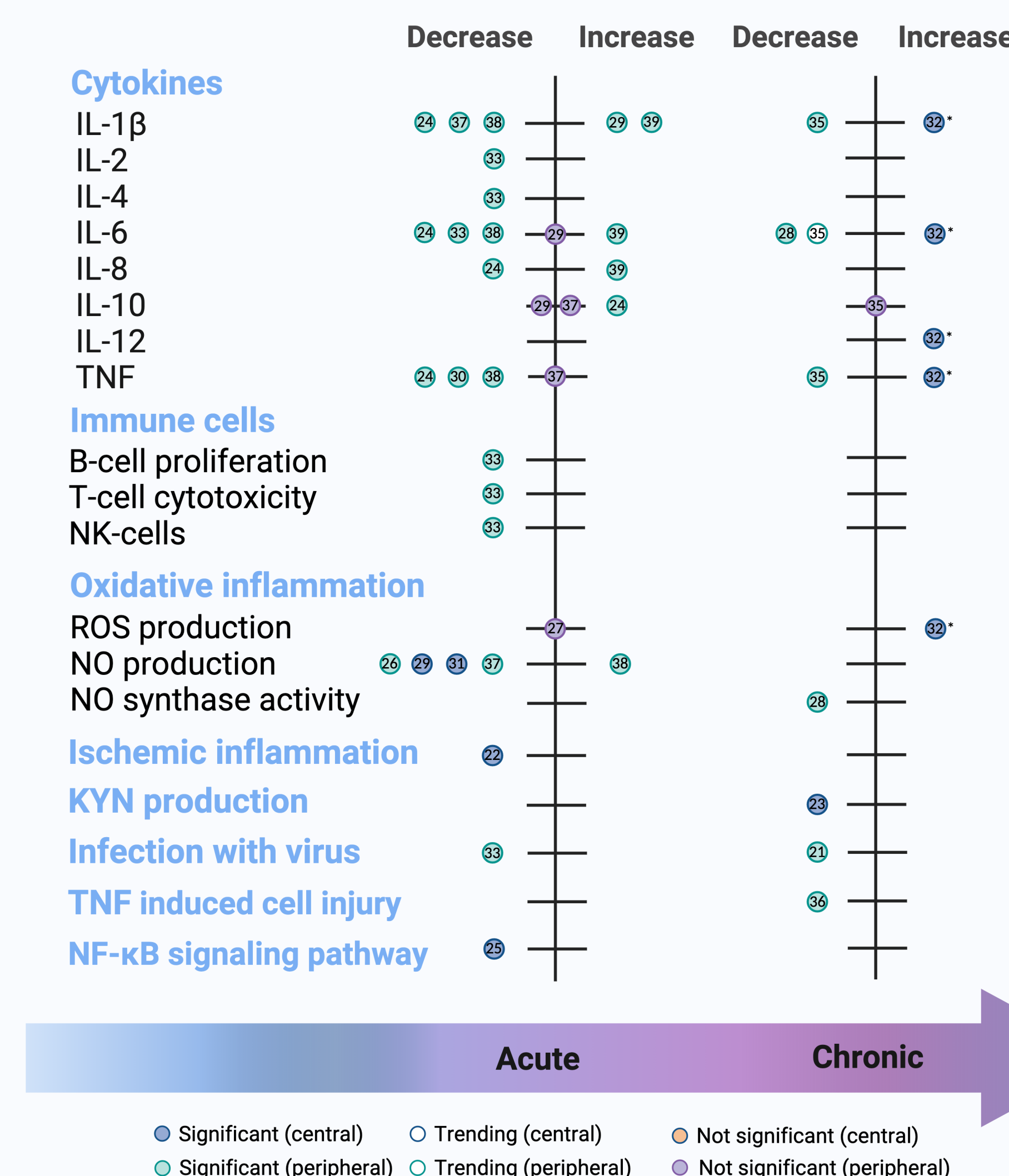


Figure 3. Timeline showing the observations of various changes in inflammatory response following treatment with a single dose of any serotonergic psychedelic in in vitro trials. Abbreviations: Acute = outcome measures measured > 24 hours after exposure. Prolonged = outcome measures < 24 hours after exposure. IL = interleukin. ROS = reactive oxygen species. NO = nitric oxide. KYN = kynurenine.

CONCLUSION

The current evidence suggests that serotonergic psychedelics have immunomodulatory effects in pre-clinical studies. However, results from human studies have been mixed and limited, as most studies have only included healthy participants with low baseline inflammation and with small sample sizes. Further studies are needed to understand the full implications of serotonergic psychedelics as therapeutic immunomodulatory drugs, including participants with increased baseline inflammation, larger sample sizes, and multiple dosing regimens and measurement times. The question remains whether these immunomodulatory effects are translatable to human subjects and to other diseases characterized by heightened inflammation.

Future perspectives for clinical trials

Currently there is limited evidence in human trials

There is evidence of immunomodulator effects in preclinical research - but mainly in models of increased baseline inflammation

Human trials have almost exclusively investigated populations of low level baseline inflammation and with small sample sizes

Research in larger populations, in populations of increased baseline inflammation, with multiple sample times and placebo-control is warranted for further research

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The study protocol is registered at PROSPERO (CRD42022360820)