	Condition	OCD (N=95)		HC (N=45)		F	p
		Mean	SD	Mean	SD		
Reaction time (msec)	NS/CP	1635.2	558.8	1315.5	497.6	9.0	.003
	NS/NP	1766.1	655.3	1545.5	577.9	5.9	.017
	PS/CP	1317.4	433.6	1126.5	314.1	10.5	.002
	PS/NP	1336.4	504.5	1305.4	461.4	0.5	.474
Emotional intensity	NS/CP	3.2	1.1	3.4	1.1	1.6	.210
	NS/NP	2.3	1.0	2.7	0.9	5.1	.026
	PS/CP	3.6	0.5	3.8	0.3	3.5	.065
	PS/NP	1.7	0.7	1.9	0.7	3.7	.055

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The effect of selective serotonin reuptake inhibitors on fear learning: a systematic review and meta-analysis

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Selective serotonin reuptake inhibitors (SSRIs) are the first choice of treatment for anxiety-like disorders such as panic disorder, generalized anxiety disorder and post-traumatic stress disorder. Fear learning plays an important role in the etiopathology of these disorders. However, it is unclear if and which fear learning processes are affected by SSRIs. This systematic review investigated the effect of six clinically effective SSRIs on the fear learning processes acquisition, expression and extinction. Since SSRIs have been shown to effectively treat anxiety-like disorders, the results of this systematic review could provide insight into which fear learning processes are important to include in future research regarding the development and treatment of anxiety-like disorders.
A systematic search in the Medline and Embase databases yielded 128 articles that met the inclusion criteria. Of these articles 120 were eligible for the meta-analysis. Data regarding the study subjects, intervention, experimental design and size and direction of the effects were extracted. Meta-analysis was conducted in R, the R-package metafor [1] was used to estimate the overall effect size, using a random-effects model. Five categorical predefined moderators were coded to account for between-studies heterogeneity (type of SSRI, duration of treatment, disease induction, species, type of test). The effect of these moderators was analysed with a Bayesian penalized meta-regression (BRMA) which is a new method. This analysis was carried out with the pema R-package [2].
The meta-analysis showed that SSRIs significantly reduced contextual fear expression and facilitated extinction learning to cue. Bayesian penalized meta-regression further suggested that chronic treatment with SSRIs is associated with stronger anxiolytics effects on cued fear expression than acute treatment. Other variables, including type of SSRI, species, disease induction and type of test, did not seem to moderate the effect of SSRIs
This systematic review suggests that the clinical efficacy of SSRIs may be specifically related to their effects on fear expression and extinction, rather than fear acquisition. It could be that the effects of SSRIs on these fear processes are due to general inhibition of fear-related emotions. Therefore, it would be interesting to investigate how SSRIs affect other forms of anxiety, such as unconditioned fear responses. In addition, studies aimed at explaining the sources of the high levels of heterogeneity observed in our meta-analyses could help to optimise the experimental set-up to further investigate the mechanisms underlying fear learning. In order to gain more insight in how the effects of SSRIs on these processes contribute to the anxiolytic effects seen in the clinic, it would be valuable to conduct studies that use experimental designs that allow us to selectively evaluate the effects of SSRIs on fear extinction. This experimental data is interesting to obtain since various exposure therapies in patients are based on promoting extinction. Furthermore, we want to encourage fellow researchers to consider using BRMA when working with a dataset with small sample sizes containing high levels of multicollinearity to avoid overestimation of effects.

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Which clinical factors delay a proper treatment in panic disorder? A cross-sectional multicentric study

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Introduction: A long period between the onset and the first adequate pharmacological treatment, defined as Duration of Untreated Illness (DUI), is associated with worse clinical outcome, higher rates of comorbidities and scarce response to treatments in both psychotic [1] and affective disorders [2]. Also anxiety disorders, if not promptly treated, may lead to several complications [3]. Nevertheless, DUI has been poorly investigated in panic disorder (PD).
Aim: To investigate clinical and socio-demographic factors associated with a long DUI and, consequently, with a delay in a proper treatment, in PD.
Methods: Data were collected from patients' medical records of two mental health services in Milan and in Monza (Italy). Socio-demographic (gender, occupational and marital status) and clinical (psychiatric and medical comorbidities, substance abuse, family history of psychiatric disorders, suicide attempts, hospitalizations, obstetric complications, main pharmacological treatment, poly-therapy, reason for discontinuation, lifetime psychotherapy) variables were collected. Descriptive analyses on the entire sample were performed. Linear regression analyses were run to analyse the relation between DUI and quantitative variables, while analyses of variance (ANOVAs) have been performed to compare the length of DUI among groups identified by qualitative variables.
Summary of Results: The total sample included 157 subjects, 64 (40.8%) males and 93 (59.2%) females. Mean DUI was 27.33 (±50.56) years. The presence of a substance use disorder before PD onset showed a trend to be associated with a longer DUI ($F=2.19$; $p=0.06$). Moreover, patients with heroin misuse before PD onset had a longer DUI than those presenting an alcohol use disorder ($p=0.03$) or without a substance use disorder ($p=0.04$). In addition, a longer DUI was associated with poly-substance misuse before PD onset ($F=5.63$; $p=0.02$), lifetime psychotherapy ($F=6.86$; $p=0.01$), a longer duration of illness ($t=3.93$; $p<0.01$), and a shorter treatment duration ($t=7.41$; $p<0.01$).
Conclusions: Taken as a whole, our results showed that PD patients, although experiencing troublesome anxiety symptoms, wait a lot of time before receiving an appropriate treatment (e.g. Selective Serotonin Reuptake Inhibitors), consistently with previous findings [4]. Alcohol and (poly-) substance abuse before the PD onset may represent an attempt to self-medicate sub-threshold anxiety symptoms [5], thus leading to a significant delay in treatment seeking for subjects suffering from PD. As expected, patients who underwent a lifetime psychotherapy showed a delay in starting an appropriate pharmacological treatment. Finally, our results showed that a longer DUI was associated to a longer duration of illness and with a more frequent suspension of treatment, thus supporting the hypothesis that prolonging the time between the clinical PD onset and a proper pharmacological treatment may facilitate a chronic course of the disorder with scarce compliance and likely poor treatment response [4]. Further