1-30-2014

Overcoming Fear: The Effect of Anxiolytic Medication Administration on Interval Timing Distracters

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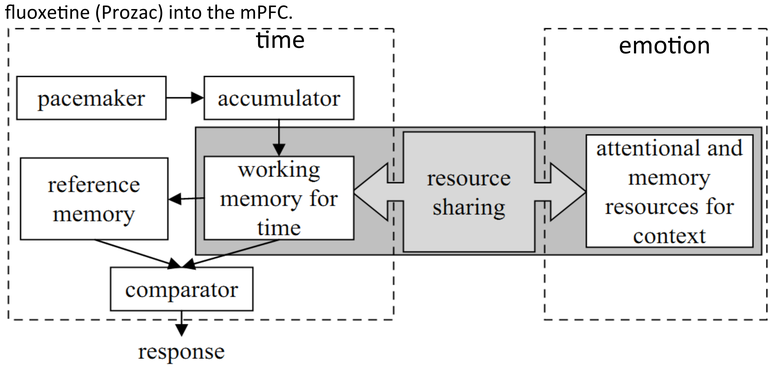
Introduction

Time and emotion are linked together, and as such emotions can influence timing abilities. Interval timing, or the ability to measure time in the second and millisecond range is important in the everyday survival of an organism, and also involved in goal achievement activities. Interval timing relies upon the frontal-striatal circuits located within the anterior portion of the brain [1]. The speed of an internal clock depends on the dopaminergic modulation of this circuit [2], but the role of serotonin in modulating this circuit is unknown. The processing of temporal information by the usage of the internal clock that can be "stopped" and "reset" by the presentation of novel events, especially events with strong emotional ties. This disruption is especially detrimental to persons suffering from anxiety disorders such as post traumatic stress disorder (PTSD) [5]. We explored the role of serotonin in the sharing of resources associated with timing and emotional events in rats by evaluating the effect of emotional distracters (distracters previously paired with foot shock, a negatively paired stimulus) [6,7], and by microinfusion administration [7] of selective serotonin reuptake inhibitor (SSRI) fluoxetine (Prozac) into the mPFC.



Relative time-sharing hypothesis. Attentional and/or memory resources are shared between timing and other processes. Reproduced from [4].

Methods

Interval Timing: Sprague Dawley rats (300-350g) were trained to lever press for a 40s duration, signaled by a visual signal, in the Peak-Interval (PI) procedure. During testing, the interval timing behavior was tested in "peak" trials. Interval timing behavior was trained and assessed in a "timing context" (timing chambers).

Fear Conditioning: Rats in the FEAR group were presented with an auditory stimulus paired with footshock in a "fear" context (fear chambers). CTRL rats were exposed to the noise, but no footshock was given.

Test sessions: During test sessions, 5minutes after rats were locally infused as described above, rats were placed in the "timing chambers" and presented with "peak" (PI) trials randomly intermixed with "noise" trials, which were similar to PI trials, except for the emotionally-charged noise which was presented unexpectedly during the trial.

Neuropharmacology: Bilateral cannula guides were implanted into the medial prefrontal cortex (mPFC). During test sessions, rats were locally infused with either saline (SAL) or SSRI fluoxetine (FLX) 6ug/0.5uL/side.

Histology: Rats were transcardially perfused with formalin, their brains removed and sectioned for histological analyses. Only rats with correct cannula placement into the mPFC were used in analyses. CTRL, n = 8, FEAR, n = 13.

Acknowledgements

Supported by NIH grants MH065561 and MH073057

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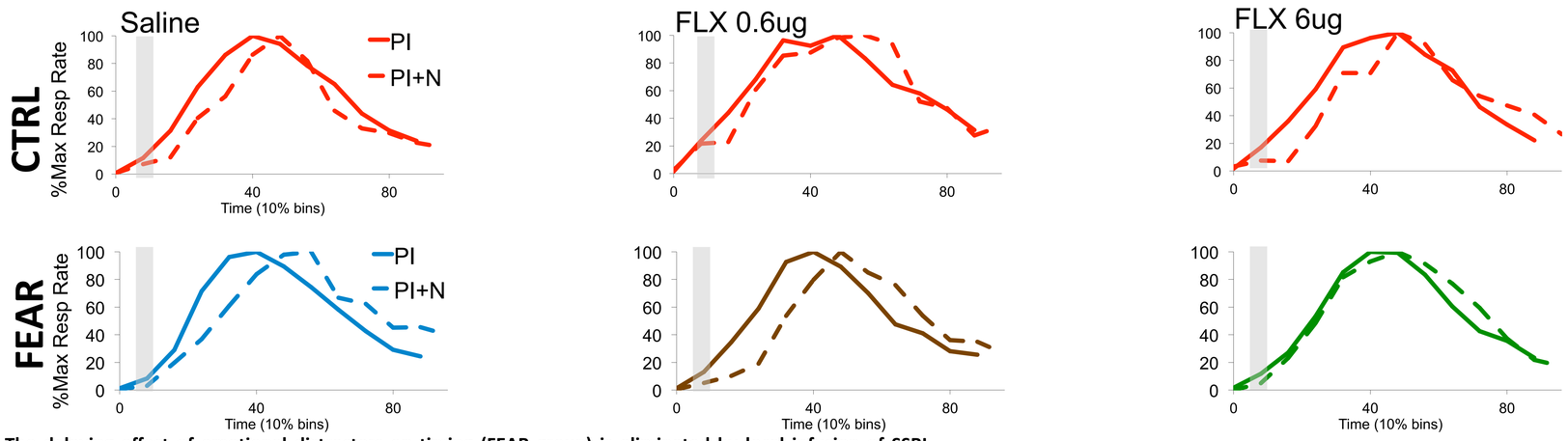
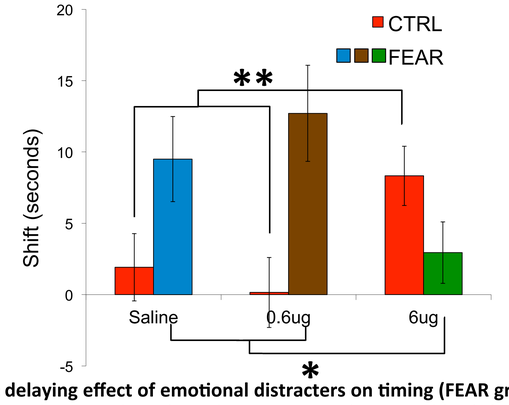
Effect of Emotional Distracter on Timing

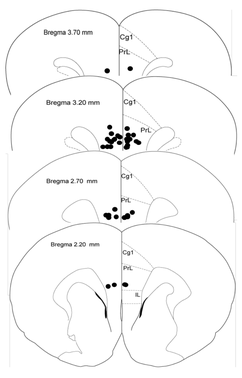


The delaying effect of emotional distracters on timing (FEAR group) is eliminated by local infusion of SSRI fluoxetine in mPFC. Neutral distracters do not affect timing under saline (CTRL group, upper left panel). Emotional distracters delay timing in "noise" trials (FEAR group, bottom left two panels). When infused in mPFC, SSRI fluoxetine eliminates the delaying effect of emotional distracters on timing (FEAR group, right lower panel.)

Shift vs Linear Decay

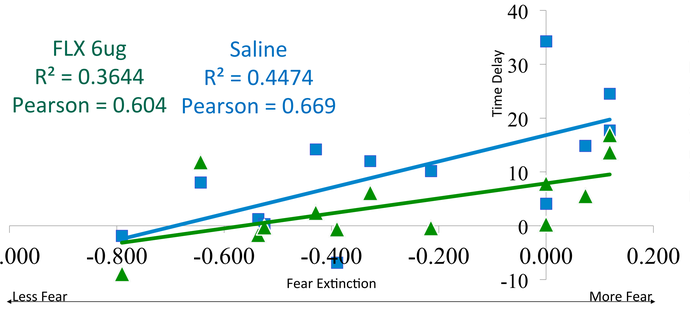


Histology



The delaying effect of emotional distracters on timing (FEAR group) is diminished by the microinfusion of FLX. As shown above, under saline, the FEAR group has a sizable shift, with the CTRL group having a minimal shift, this is reversed under high dose of FLX6ug, showing that fear increased in CTRL due to lack of pairing [8]. * indicates *p<0.05*, ** indicates *p<0.01*.

Time Delay vs Fear Extinction



Time-Delay correlates with Fear Extinction. The delaying effect of distracters (time delay, vertical axis) correlates with the emotional charge (freezing extinction, horizontal axis) both under saline and 6ug FLX.

Conclusions

Interval Timing

- Both CTRL and FLX rats showed accurate timing in the absence of an emotional distracter. As seen, the timing functions peaked near the expected time, indicating that they acquired the interval timing task.
- FLX infusions did not impact timing in the absence of distracters
- Cannula placement did not alter timing behavior
- As shown in previous studies, emotionally paired distractors cause greater delays than novel distractors [6,7].

Effect of fluoxetine on timing to emotional distracters

- Infusion of FLX at 6ug significantly decreased the shift in responding during distracted trials (PI+N) for FEAR rats
- Infusion of FLX at 6ug significantly increased the shift in responding during distracted trials (PI+N) for the CTRL rats.
- Infusions of FLX 0.6ug were not effective in changing the delay in responding seen under the saline condition

Time Delay vs Fear Extinction

- CTRL group did not show a relationship between freezing fear behavior, indicated by Fear Extinction and time shift, as expected. The FEAR showed a statistically significant relationship between freezing behavior and time shift, under both the Saline and FLX 6ug dose.

References

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