EXAGGERATED HYPERALGESIA AND BLUNTED CONDITIONED PAIN MODULATION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

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Background and aims: There is an extensive mutual co-morbidity of chronic pain and major depression (MDD). Most MDD patients experience pain, and 30-60% of pain patients exhibit significant depressive symptoms. Despite clinical evidence, neural mechanisms mediating the co-morbidity of pain and depression are not characterized and enhanced pain sensitivity not convincingly proven.
In this project we compared acute and remitted MDD patients with healthy subjects (HC) to study the expression of experimentally-induced LTP-like pain plasticity (pain-LTP) and descending pain control.

Methods: We assessed experimentally induced hyperalgesia in 38 MDD patients and 51 HC by two human surrogate models, namely repeated heat stimulation (60 x 48°C for 6s, each - RHS) and electrical high-frequency stimulation - 5 x 1 s trains @ 100 s^{-1} and 10x detection threshold (Digitimer™ DS7) delivered through a 10-pin circular electrode array - HFS). Pain was estimated by 0-100 numerical rating scales before and after induction of hyperalgesia. Hyperalgesia was tested by short heat ramps, single electrical stimuli at 10x detection threshold, calibrated punctate mechanical stimuli (*The Pinprick*™, MRC-Systems) and light touch stimuli (cotton wool, cotton stick, brush) in the primary and secondary pain areas. Conditioned pain modulation (CPM) was assessed by a change of pressure pain thresholds elicited by 3 min cold pressor task.

Results: In the RHP model MDD patients exhibited significantly increased hyperalgesia to punctate mechanical and light touch stimuli in the primary and secondary hyperalgesia areas (all p<0.05; ***Fig.1***). Patients and healthy controls exhibited significant heat hyperalgesia of similar magnitude. In the pain-LTP model the magnitude of punctate hyperalgesia and pain to light touch was significantly enhanced (p<0.05, ***Fig.2***) and the magnitude of punctate hyperalgesia correlated significantly with the magnitude of depression and of trait anxiety.

Repeated heat stimulation hyperalgesia model (RHS)

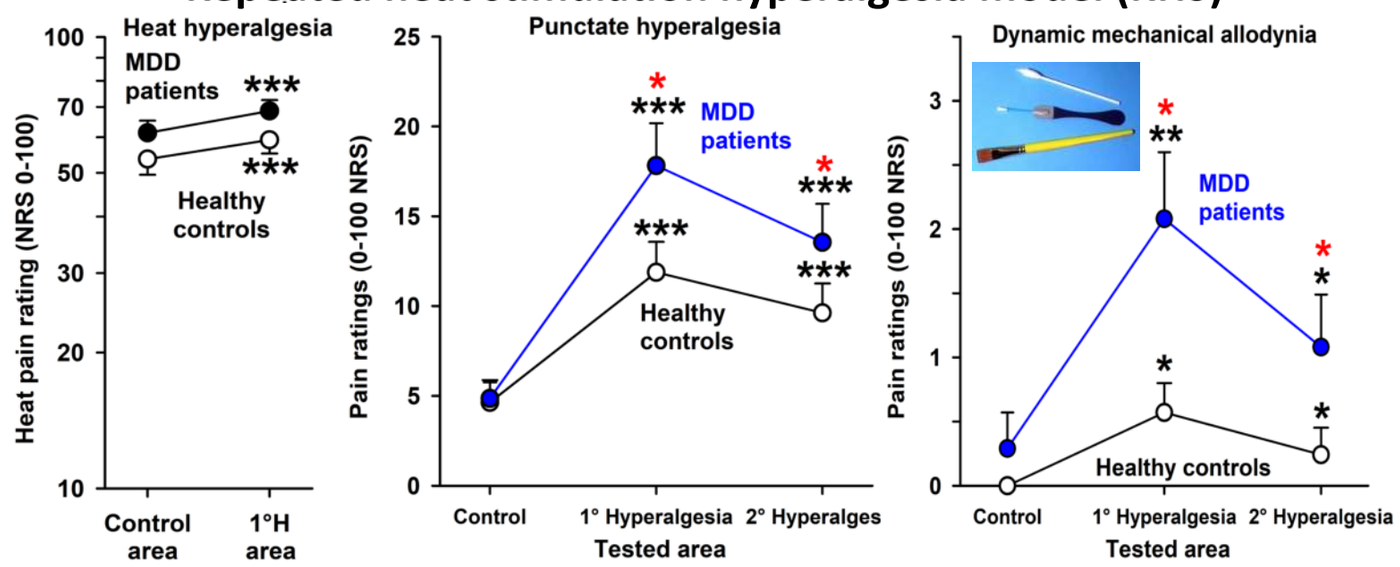

Fig. 1: Hyperalgesia to heat, punctate stimuli and light touch stimuli in the primary (1°H) and secondary (2°H) hyperalgesia areas following conditioning by repeated 48°C heat stimuli in patients with MDD (filled symbols) and matched healthy controls (HC).

Pain-LTP hyperalgesia model (HFS)

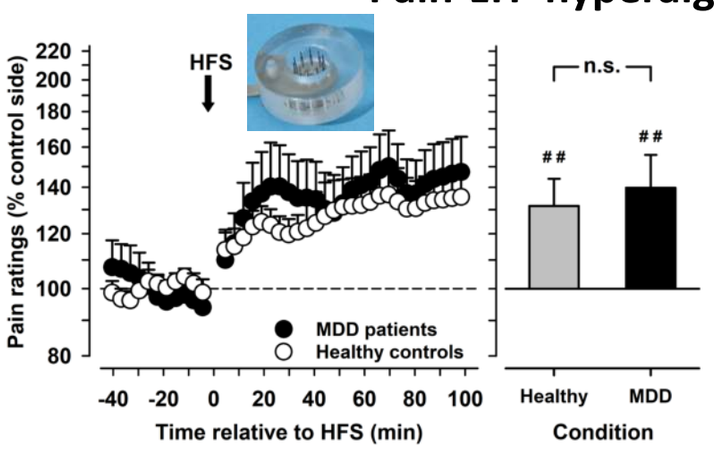

Fig. 2A: Hyperalgesia to electrical test stimuli at the site of HFS

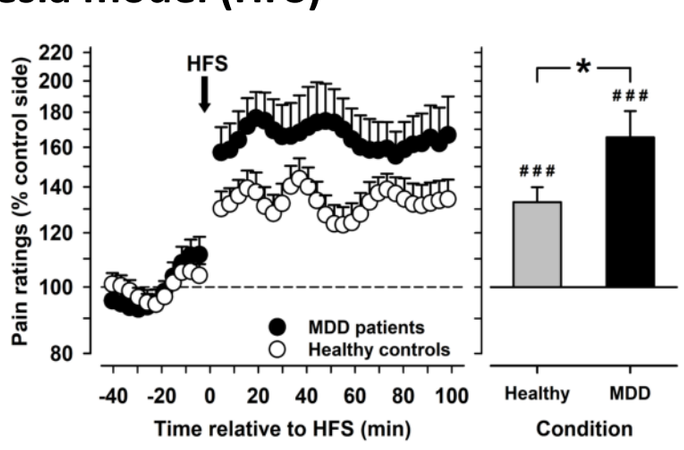

Fig. 2B: Secondary hyperalgesia to pinprick stimuli after HFS

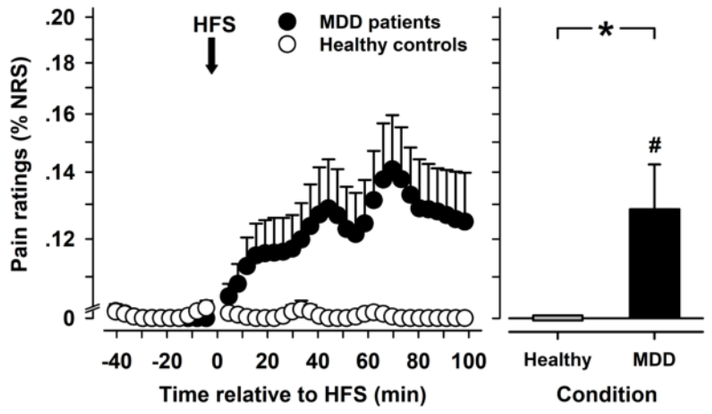

Fig. 2C: Dynamic mechanical allodynia to stroking light touch stimuli following HFS

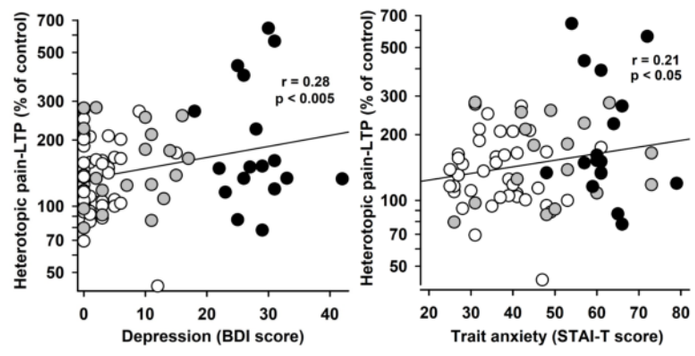

Fig. 3: Heterotopic pain-LTP correlated significantly with depression and trait anxiety

# p<0.05, ## p < 0.01, ### p < 0.001 vs. control site

* p < 0.05 MDD vs. HC

Healthy subjects exhibited a significant CPM effect (p<0.001), while it was overall absent in MDD patients (MDD vs. HC, p<0.05, ***Fig.4***). Medication by monoamine reuptake inhibitors (in half of the MDD patients cohort, n=5 SSRI, n=14 SNRI) revealed that in these patients the magnitude of hyperalgesia was significantly mitigated in all components of pain-LTP (***Fig.5A-C)*** and lowered by approximately 0.7 SD in the aggregated normalized overall pain plasticity (p< 0.005, ***Fig.5D***). Their reduced hyperalgesia paralleled partial restitution of CPM (***Fig.5E***).

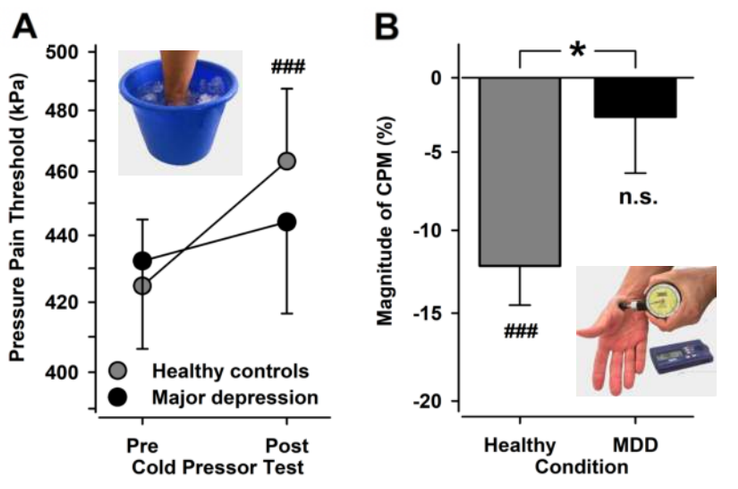

Fig. 4A: Pressure pain thresholds before and after the Cold Pressor Test (CPM)
p<0.0001 pre vs. post CPM
Fig. 4B: Reduction of pain sensitivity in the CPM condition, * p<0.05 MDD vs. HC

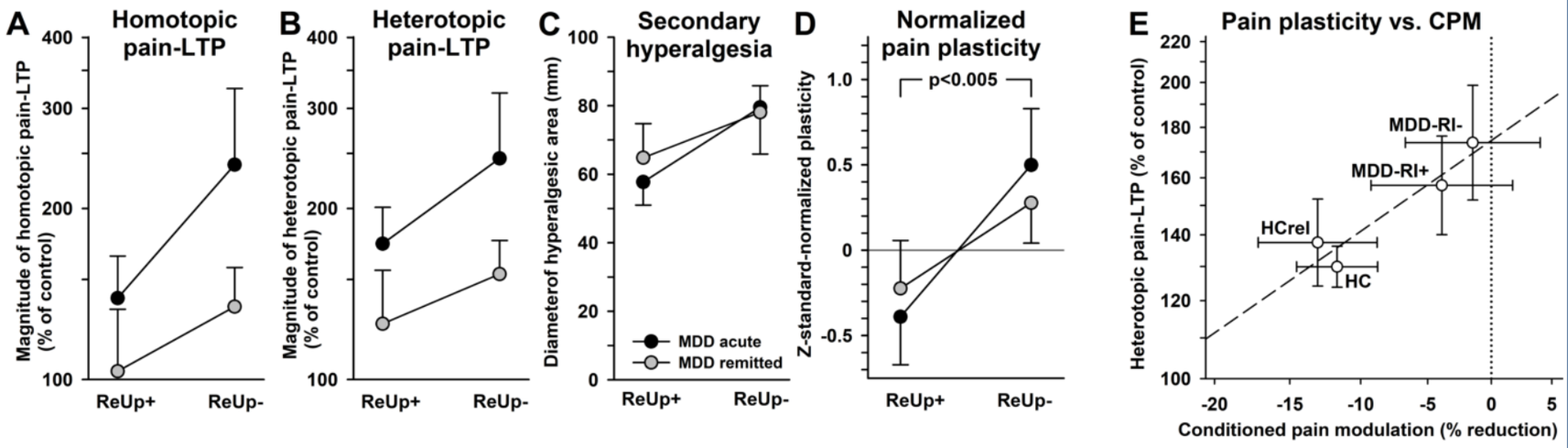

Fig. 5: The impact of medication by monoamine reuptake inhibitors
ReUp+ MDD under medication with monoamine reuptake inhibitors
ReUp- MDD w/o medication with monoamine reuptake inhibitors
Solid black circle: acute MDD; solid grey circle: remitted MDD

HC Healthy controls
HCrel Healthy relatives of MDD patients
MDD-RI+/- MDD patients w or w/o reuptake inhibitors

Conclusion: Enhanced hyperalgesia and allodynia in experimental models highlight a risk of exaggerated pain plasticity in MDD patients related to depression and trait anxiety. This was paralleled by a blunting of the CPM response. Notably, treatment with monoamine reuptake inhibitors – likely their noradrenergic component – was not only an adequate antidepressant treatment but also mitigated pain plasticity suggesting that reduced (noradrenergic) pain control may facilitate the precipitation of a chronic pain phenotype in MDD patients.

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