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### ABSTRACT

#### **Reinforcement Learning Predicts Response to SSRIs in Medication-Naïve Patients with Major Depressive Disorder**

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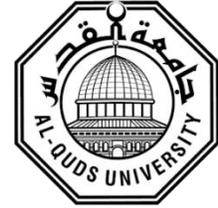
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**Background:** Patients with major depressive disorder (MDD) exhibit hyposensitivity to positive reinforcement and hypersensitivity to negative reinforcement. In patients who respond to treatment, selective serotonin reuptake inhibitor (SSRI) antidepressants arguably modulate MDD symptoms by attenuating learning from negative reinforcement. However, only 30% of patients with MDD respond to antidepressants including SSRI. Cognitive differences between responders and non-responders were heretofore not investigated medication-naïve patients with MDD.

**Objectives:** We investigated cognitive predictors of response to SSRIs in medication-naïve patients with MDD.

**Methods:** Using a probabilistic category-learning task that dissociates learning from positive and negative feedback, we evaluated medication-naïve patients with MDD and healthy subjects. Response to SSRIs was assessed after 4-6 weeks of SSRI administration for MDD. We investigated differences between responders (54%) and non-responders (46%) to SSRIs in processing positive and negative feedback at the medication-naïve state.



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**Results:** Both medication-naïve responders and non-responders exhibited impaired learning from positive reinforcement compared to healthy subjects. Medication-naïve non-responders were significantly more impaired in learning from negative reinforcement than medication-naïve responders and healthy subjects. Machine learning classifiers accomplished 80% accuracy in distinguishing MDD responders and non-responders before starting their SSRI regimen.

**Conclusion:** Our results can have immediate clinical relevance for a priori classification of responders and non-responders to SSRI treatment among MDD patients.

**Research Keywords:** Major depressive disorder, reinforcement learning, selective serotonin reuptake inhibitors (SSRIs), prediction of treatment response, machine learning.