

Modafinil enhances cognitive, but not emotional conflict processing via enhancing inferior frontal cortex activation and communication with the dorsomedial prefrontal cortex

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Introduction

One of the essential functions of executive processes is the inhibitory control of interferences by conflicting task-irrelevant distracters. Previous neuroimaging studies further demonstrated separable neural substrates of cognitive and emotional conflict processing, with cognitive conflict engaging lateral prefrontal systems (particularly the inferior frontal cortex, IFG) while emotional conflict stronger engages medial prefrontal systems¹. The putative neuroenhancer modafinil (MOD) modulates neurotransmitters in prefrontal regions² which may improve inhibitory functions in healthy subjects and patient populations. However, it is unknown whether MOD shows distinct effects on cognitive versus emotional conflict processing. To this end the present pre-registered pharmaco-fMRI experiment aimed at determining effects of modafinil on cognitive and emotional conflict processing and the underlying neural mechanisms.

Methods

A randomized double-blind, placebo-controlled, between-subject design was employed with 72 healthy male participants (age, 21.51 ± 2.58 years) being randomly assigned to single-dose p.o. administration of either 200mg MOD ($n = 35$) or placebo (PLC; $n = 37$). Two hours after treatment conflict processing was assessed via a validated affective Stroop paradigm incorporating emotional (fear/happy) and cognitive (male/female) conflict resolution¹. During the paradigm participants were instructed to ignore word distracters written over facial stimuli (congruent/incongruent) and to identify the emotional expression (emotional conflict) or gender (cognitive conflict) of the facial stimuli. Behavioral performance and simultaneous acquired fMRI data served as primary outcomes to evaluate the effects of MOD. Unspecific effects of MOD were controlled by assessing a range of potential confounders (e.g. mood, cardiovascular activity).

Behavioral Results

Examining MOD effects on behavioral performance demonstrated a significant congruence (congruent/incongruent) \times treatment (MOD/PLC) interaction effect during cognitive ($F_{(1, 70)} = 4.12, p < 0.05$, partial $\eta^2 = 0.056$), but not emotional ($F_{(1, 70)} = 0.17, p = 0.678$) conflict processing. Post-hoc analysis revealed that MOD specifically enhanced accuracy on cognitive conflict (Fig. 1a; $t_{70} = 2.20, p < 0.05, d = 0.519$).

fMRI Results

fMRI data analyses revealed a significant treatment \times congruence \times task (emotional/cognitive) interaction effect located in the left IFG (Fig. 1b; peak MNI coordinates: $[-57, 18, 9], k = 25, F_{(1, 70)} = 16.64, p_{SVC-FWE} < 0.05$). Post-hoc analyses showed that compared with PLC, MOD increased IFG activation during cognitive conflict ($t_{70} = 3.00, p < 0.01, d = 0.707$), whereas no effects for emotional conflict were observed (Fig. 1c).

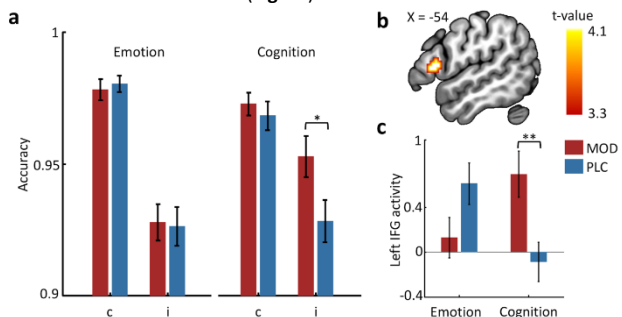


Fig. 1 (a) MOD selectively enhanced behavioral performance towards cognitive incongruent distractors, (b) which was observed in increased IFG activation and (c) specifically in cognitive but not emotional conflict domain.

Examining distinct conflict processes within separate groups revealed increased right amygdala activation following MOD treatment during cognitive relative to emotional conflict (Fig. 2a; peak MNI coordinates: $[33, -3, -18], k = 116, t_{34} = 4.42, p_{FWE-cluster} < 0.05$). The neuroenhancing effect of MOD was observed during cognitive but not emotional conflict (Fig. 2b; $t_{70} = 2.03, p < 0.05, d = 0.479$). In MOD group, behavioral performance was positively correlated with right amygdala activity in cognitive (Fig. 2c; $\rho = 0.44, p < 0.01$) but not emotional conflict processing ($\rho = -0.29, p = 0.078$), whereas no association was observed in PLC group.

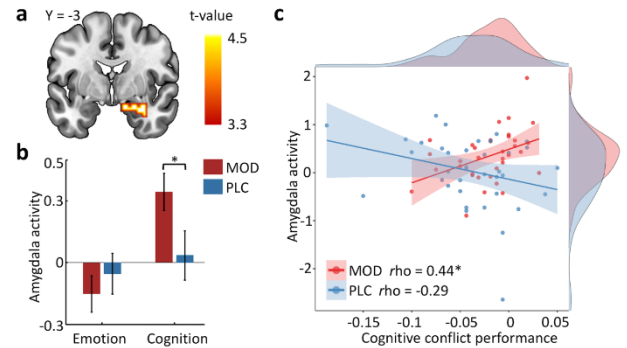


Fig. 2 (a) MOD enhanced brain reactivity in the right amygdala, (b) which was only observed in cognitive conflict processing and (c) positively associated with behavioral performance.

Functional connectivity analysis indicated that MOD enhanced the right IFG coupling strength with the bilateral dorsomedial PFC (dmPFC, peak MNI coordinates: $[6, 51, 24], k = 92, t_{70} = 4.10, p_{SVC-FWE} < 0.05$) specifically during cognitive conflict (Fig. 3), but not during emotional conflict.

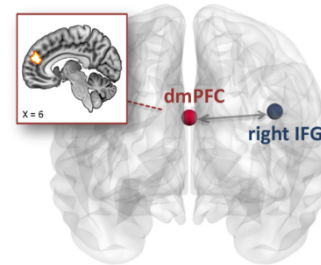


Fig. 3 Functional connectivity on cognitive conflict. Two sample t-tests revealed that MOD increased the right IFG coupling strength with the dmPFC in cognitive conflict.

Conclusion

Overall, MOD selectively enhanced cognitive but not emotional conflict processing, with stronger engagement of the left IFG and communication between the right IFG and dmPFC, which suggest specific neuroenhancing effects of MOD on cognitive deficits.

References

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