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Neuroplastic effects of SSRIs evaluated with learning tasks and fMRI

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Introduction

Animal studies using selective serotonin reuptake inhibitors (SSRIs) and learning paradigms demonstrated that serotonin is important for flexibility in executive functions and learning [1,2]. SSRIs might facilitate relearning through neuroplastic processes and thus exert their clinical effects in psychiatric diseases where cognitive functioning is affected [3,4]. However, translation of these mechanisms to humans is missing. In this randomized placebo-controlled trial, we assessed functional brain activation during learning and memory retrieval in healthy volunteers performing associative learning tasks aiming to translate facilitated relearning by SSRIs.

Methods

To this extent, seventy-six healthy participants underwent three MRI scanning sessions: (1) at baseline, (2) after three weeks of daily associative learning and subsequent retrieval (face-matching or Chinese character–noun matching) and (3) after three weeks of relearning under escitalopram (10mg/day) or placebo. Associative learning and retrieval tasks were performed during each fMRI session. Statistical modelling was done using a repeated-measures ANOVA, to test for content-by-treatment-by-time interaction effects and was cluster + Bonferroni corrected $P < 0.025$.

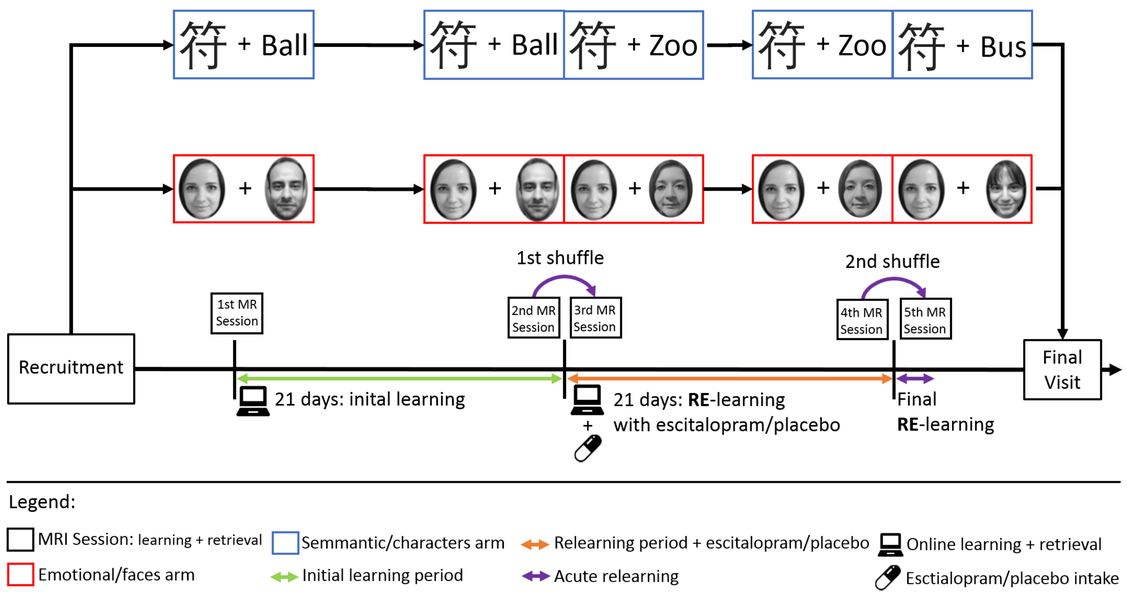

Figure 1 *Illustration of the study design: The study comprised of 3 MR sessions, each session contained a learning and relearning scan. The 2nd and 3rd MR sessions contained 2 MR learning and retrieval scans. Before the 1st MRI appointment, each participant was randomly assigned to one of 2 groups (faces/Chinese characters). Each subject then completed their first onsite learning and retrieval session in the MRI scanner (1st MR Session). Thereafter, they were instructed to learn further associations at home for 21 days and returned for a 2nd MRI appointment during which they underwent another learning and retrieval session (2nd MR Session) before the pairs were shuffled and the relearning phase was initiated in the scanner (3rd MR Session). Another 21 days of relearning at home took place during which participants received double-blind treatment with escitalopram 10mg daily or placebo. Subjects then returned for another session which again included a relearning and retrieval paradigm (4th MR Session). To conclude the last MRI session, pairs were shuffled again, and participants underwent a second relearning paradigm under medication or placebo (5th MR Session).*

Results

During the learning task, a significant substance-by-time interaction was found in the right insula showing a greater deactivation in the SSRI cohort after 21 days of relearning compared to the learning phase (Figure 2).
In the retrieval task, there was a significant content-by-time interaction in the left angular gyrus (AG) with an increased activation in face-matching compared to Chinese-character matching for both learning and relearning phases (Figure 3).

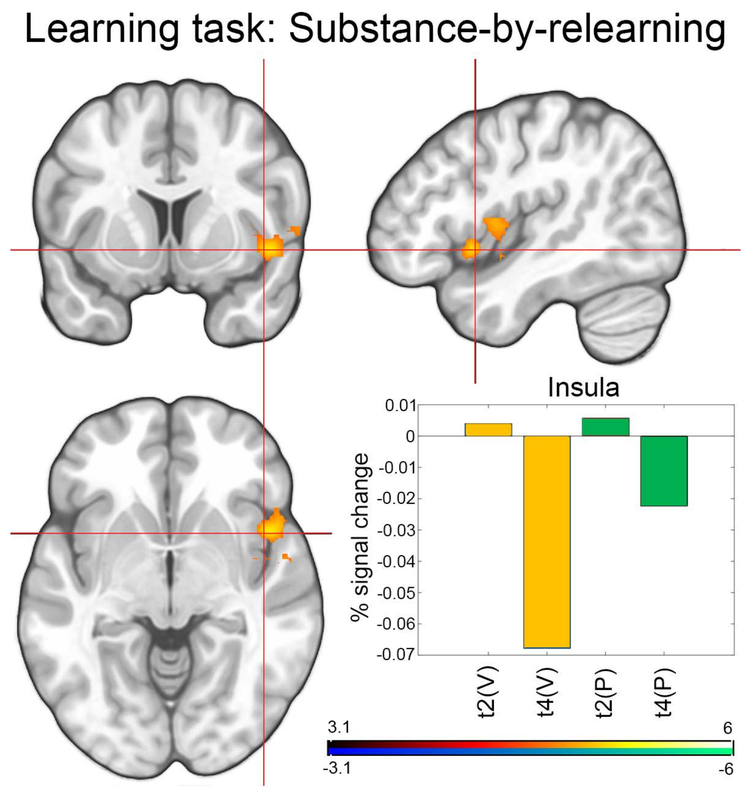

Figure 2: *Substance-by-time interaction effect on the learning task. After 21 days of relearning under a daily dose of 10mg escitalopram, the verum group (orange bars) showed a significantly greater deactivation of the right insula in comparison to placebo (green bars). For each cohort, the median parameter estimates for the contrast (stimuli > control) are plotted (percent signal change as calculated in (Luo and Nichols 2003). Abbreviations: P, Placebo; V, Verum; t, time; t2, learning phase scan; t4, relearning phase scan.*

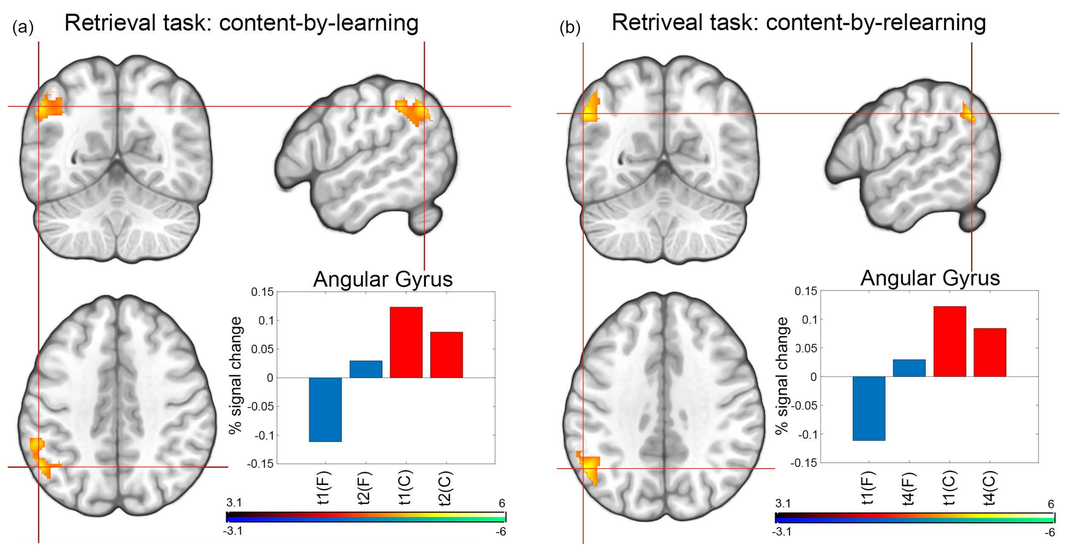

Figure 3: *Content-by-time retrieval interaction effects were discovered for both the learning and relearning phases when contrasting correctly retrieved pairs > control pairs in the left AG. After 21 days of learning (a) and again 21 days of relearning (b) the face matching group (blue bars) showed an increase in task activation over time while the character group (red bars) showed a decrease in task activation over time. For each group, the parameter median estimates for the contrast (correctly learned - control) are plotted. Abbreviations: C, characters; F, Faces, t, time; t1, baseline; t2, learning phase; t4, relearning phase.*

Conclusion

Our finding that 5-HT neurotransmission modulates insula activation demonstrates successful translation of relearning as a mechanism of SSRIs in human. Furthermore, we show that the left AG is an active component of correct memory retrieval, which coincides with previous literature. We extend the function of this region by demonstrating its activation is not only stimulus dependent but also time constrained.

References

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Acknowledgments

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