

# Effect of electroconvulsive therapy on 5-HT<sub>1A</sub> receptor binding in major depressive disorder



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## INTRODUCTION:

Electroconvulsive therapy (ECT) is a highly effective treatment option when employed against treatment-refractory depression. In recent years, ECT has been increasingly used, due to its ameliorated practicability and safety level. To date, despite its approved effectiveness, the neurobiological mechanisms underlying ECT remain unclear, the findings related to this topic being quite inconsistent. However, a number of preclinical studies point toward a significant involvement of the serotonergic system, particularly the main inhibitory 5-HT<sub>1A</sub> receptor, in the mode of action of ECT [1, 2]. Since alterations of the 5-HT<sub>1A</sub> receptor are consistently reported in major depressive disorder [3], **this study aims to investigate the effects of ECT on the 5-HT<sub>1A</sub> receptor in the human brain in vivo using positron emission tomography (PET).**

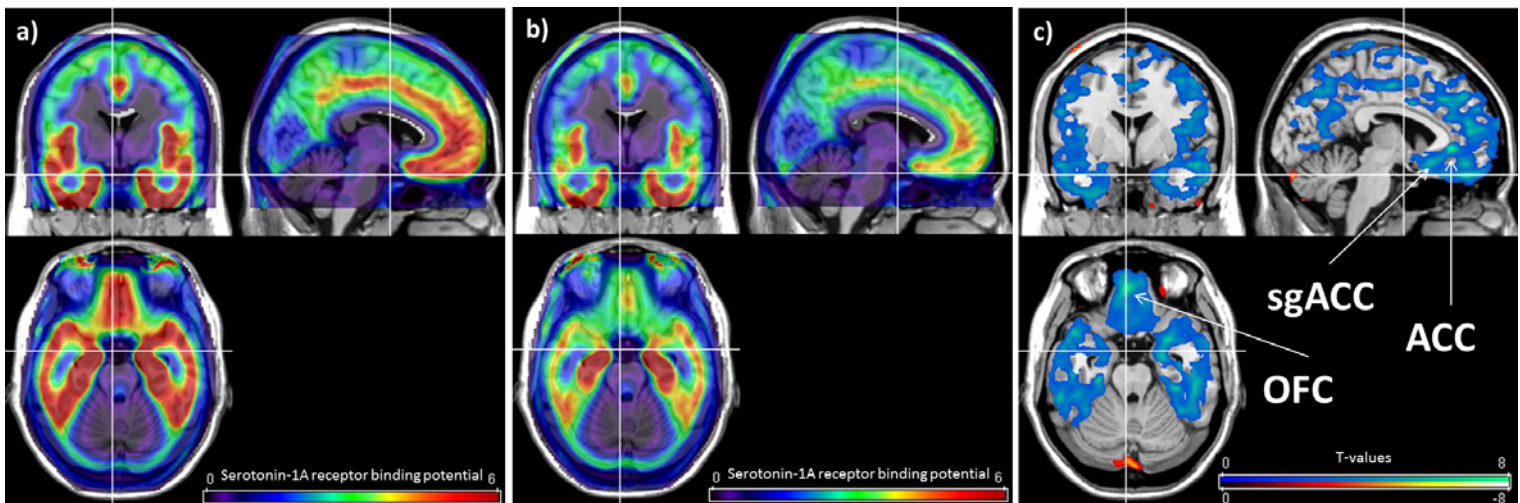
**Figure.** Voxel-wise 5-HT<sub>1A</sub> receptor distribution on a triplanar view, superimposed on the single-subject MNI standard structural magnetic resonance image. Figure a) and b) display the 5-HT<sub>1A</sub> BP<sub>ND</sub> before and after ECT respectively, showing a clear treatment-induced reduction of 5-HT<sub>1A</sub> BP<sub>ND</sub> in the whole brain. Figure c) reveals the mean difference of 5-HT<sub>1A</sub> BP<sub>ND</sub> before/after ECT using a repeated-measures ANOVA (t-statistics>2.4, p<0.05, FDR-corrected) using sex and anticonvulsive medication as covariates. In fact, blue spots represent one interconnected cluster (632cm<sup>3</sup>, p<0.05, FDR-corrected) indicating a global decrease of 5-HT<sub>1A</sub> BP<sub>ND</sub> after ECT with peak values in the anterior cingulate cortex (ACC), the subgenual part of the ACC (sgACC) and the orbitofrontal cortex (OFC).

## METHODS:

10 subjects (8 female, 2 male, mean age ± SD= 49.8 ± 7.9 years) with severe unipolar depression, determined by a structural clinical interview and the 17-item Hamilton Rating Scale for Depression (HAM-D<sub>17</sub> score ≥ 23), participated in this longitudinal PET study.

ECT was carried out unilaterally according to international standard operating procedures, whereby 5 subjects received additional bilateral ECT, due to initial insufficient symptom relief (9.4 ± 2.4 ECT sessions). Drugs with a high affinity to 5-HT<sub>1A</sub> receptor were excluded and the current medication remained in steady-state 10 days prior inclusion and during treatment.

Patients underwent 2 PET scans using the highly specific radioligand [*carbonyl*-<sup>11</sup>C]WAY-100635, one before and one after completed ECT session. PET scans were normalized to MNI-space (SPM8). Quantification of 5-HT<sub>1A</sub> receptor binding potential (BP<sub>ND</sub>) was carried out in PMOD 3.3 using the multilinear reference tissue model 2 with the cerebellar grey (excluding vermis) as reference.



## RESULTS:

The paired-samples t-test showed a significant decrease ( $t = 7.77$ ,  $p < 0.001$ ; mean =  $18.01 \pm 7.37$ ) in HAM-D values after ECT compared to baseline scores.

Voxel-wise repeated-measures ANOVA revealed a global decrease of the 5-HT<sub>1A</sub> receptor binding potential (5-HT<sub>1A</sub> BP<sub>ND</sub>) after ECT ( $p < 0.05$ , FDR-corrected) using sex and anticonvulsive therapy as covariates. The overall change of 5-HT<sub>1A</sub> BP<sub>ND</sub> corresponded to one interconnected cluster of 632cm<sup>3</sup> with peak areas in the anterior cingulate cortex (ACC:  $t = -9.18$ ,  $x/y/z = -8/36/-2$ mm MNI space), the orbitofrontal cortex (OFC:  $t = -7.83$ ,  $x/y/z = -6/48/-24$ mm) and the subgenual part of the cingulate cortex (sgACC:  $t = -6.88$ ,  $x/y/z = 0/22/-14$ mm).

As anticipated, no changes were found in the occipital cortex.

## CONCLUSIONS:

To begin with, our results display once again the efficacy of ECT in depression, given the significant reduction of HAM-D scores after ECT, testifying for a successful treatment response.

Furthermore, we determined a significant global decrease of 5-HT<sub>1A</sub> BP<sub>ND</sub> in depressed patients after ECT, which undermines the hypothesis, implying 5-HT<sub>1A</sub> receptor changes might be involved in the effectiveness of ECT. We did not replicate the findings of Saijo et al. [4], equally using PET with [*carbonyl*-<sup>11</sup>C]WAY-100635 and suggesting unchanged 5-HT<sub>1A</sub> BP<sub>ND</sub> in major depression after ECT. These discrepancies may be due to differences in the method applied and the clinical characteristics of the study participants. However, our results play in concert with previous findings, emphasizing the role of the ACC, sgACC and OFC in controlling emotional and cognitive processes and showing altered function and activity as well as grey matter reductions in these regions in depressed patients [5]. **To our knowledge, this is the first study, substantiating the role of serotonergic neurotransmission in the mode of action of ECT in vivo. Our results suggest, that antidepressant treatment using ECT acts - similarly to SSRIs - through a reduction of 5-HT<sub>1A</sub> receptor binding.**

## References:

- [1] Gur E., Dremencov., Garcia F., Van de Kar L.D., Lerer B., Newman M.E., 2002 Functional effects of chronic electroconvulsive shock on serotonergic 5-HT(1A) and 5-HT(1B) receptor activity in rat hippocampus and hypothalamus. *Brain Research* 952(1), 52-60
- [2] Ishihara K., Amano T., Hayakawa H., Yamawaki S., Sama M. 1999 Enhancement of serotonin(1A) receptor function following repeated electroconvulsive shock in young rat hippocampal neurons in vitro. *International Journal of Neuropsychopharmacology* Jun;2(2):101-104.
- [3] Savitz J., Lucki I., Drevets W.C. 2009 5-HAT(1A) receptor function in major depression. *Progress in Neurobiology* May;88(1):17-31. Epub 2009 Feb 7.
- [4] Saijo T., Takano A., Suhara T., Arakawa R., Okumura M., Ichimiya T., Ito H., Okubo J. 2010 Effect of electroconvulsive therapy on 5-HT<sub>1A</sub> receptor binding in patients with depression: a PET study with [<sup>11</sup>C]WAY 10063. *International Journal of Neuropsychopharmacology* 13, 785-791
- [5] Drevets W.C., Savitz J., 2008 The subgenual anterior cingulate cortex in mood disorders. *CNS Spectrum* 13(8), 663-681

## Acknowledgements:

This research was supported by a grant from the Austrian National Bank (OENB P13219) to R. Frey and a NARSAD grant to R. Lanzenberger.