Immediate antidepressant effects on functional brain connectivity

Neurotransmitters are the brain's chemical messengers that allow for communication between neurons. They 'jump' from one neuron to the next causing excitation or inhibition of cell firing. Since healthy brain functioning relies on adequate neural communication, neurotransmitter systems are highly important for multiple brain functions that influence our behaviour. The neurotransmitter serotonin is known to affect our mood and selective serotonin reuptake inhibitors (SSRIs) are the main choice of drug treatment in depression and anxiety disorders. The serotonergic system is widely distributed throughout the brain. Serotonin is released by one neuron and taken up by other neurons. Part of these serotonergic transmitters is reabsorbed by the neuron that released them. SSRIs prevent this reuptake, leading to an increased amount of serotonin that is available to other neurons.

Despite the immediate neural changes after administration of an SSRI, improvements in mood and cognition usually begin only after a few weeks. Better understanding of the neuronal processes prior to these behavioural changes requires a method that takes into account the large-scale nature of the serotonergic system. With resting-state functional magnetic resonance imaging (RS-fMRI) it is possible to investigate whole-brain connectivity. RS-fMRI detects brain areas that exhibit correlating activation patterns during rest. These regions are functionally connected to each other and form a network. There are multiple resting state networks in the brain that pertain to different brain functions. One typical example is the default mode network. Regions of this network are more active at rest as opposed to during the performance of goal-oriented tasks.

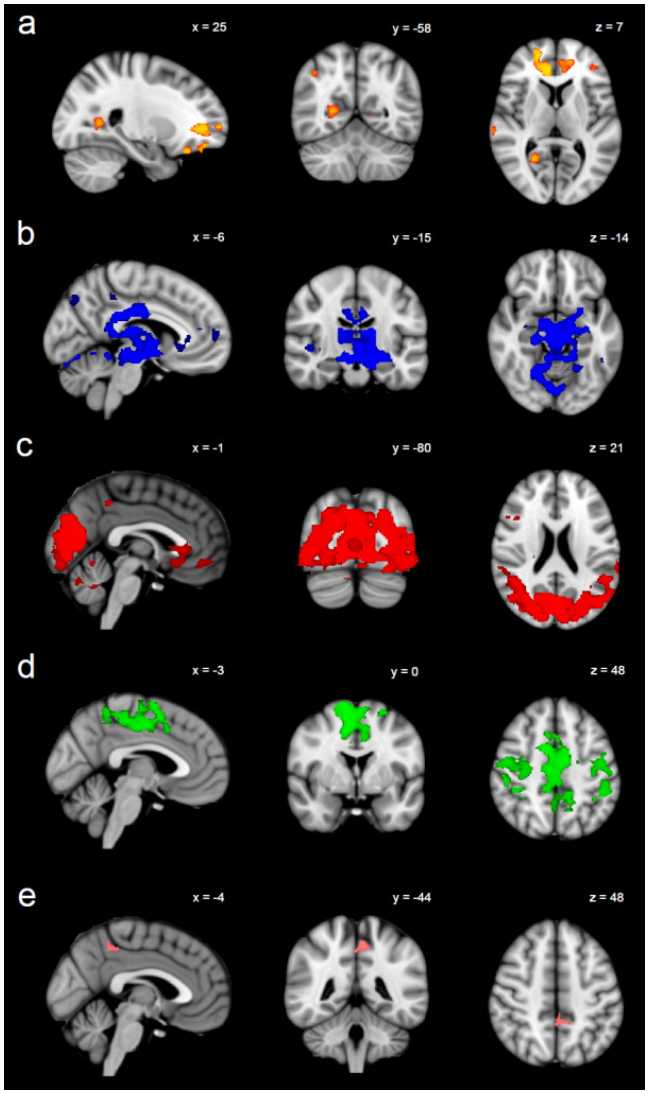

Illustration of sertraline-induced (a) decreases in functional connectivity between orange regions and the default mode network; (b) decreases in functional connectivity between blue regions and the executive control network; (c) decreases in functional connectivity between red regions and the visual networks; (d) decreases in functional connectivity between green regions and the sensorimotor network; (e) increases in functional connectivity between pink regions and the auditory network.

Resting state networks are representative of interactions between different brain areas and therefore suitable to measure changes in neurotransmission. We used this non-invasive neuroimaging technique to examine acute pharmacological effects of the SSRI sertraline (75 mg) in 12 healthy young volunteers. RS-fMRI scans were acquired before and 3, 5, 7 and 9 hours after drug administration. In addition, cognitive and subjective measures were taken to investigate

changes in mood, alertness, calmness, memory, emotional processing, executive functioning and reaction time. As expected, sertraline did not affect any of the cognitive and subjective measures compared to a placebo. However, sertraline induced widespread effects on functional connectivity with multiple functional networks; the default mode network, the executive control network, visual networks, the sensorimotor network and the auditory network.

The default mode and executive control network have been associated with passive and active emotional processing, respectively. In depressed patients, increased connectivity has been found for both networks, which might refer to rumination, the preoccupation with inner thoughts and feelings, and excessive alertness for arousing triggers. In our study, sertraline induced a decrease in connectivity, suggesting that SSRIs correct dysfunctional pathways as seen in depression. The observed alterations of the auditory, visual and sensorimotor networks indicate that serotonin is involved in visual and auditory processing and motor control as well. Emotion, perception and action are intertwined concepts; our mood affects the way we perceive our environment and act throughout the world. It is therefore not unlikely that SSRIs alter related neural processes, even in the first few hours after a single-dose administration. It just takes some time for our brain to adapt to the world and process information differently.

The results of this study verify that serotonergic tracts cover a substantial part of the brain and suggest that serotonin is implicated in processing emotional information, conscious coordination of motor behavior and higher-level perception of the environment. We propose the RS-fMRI technique as a very sensitive and specific method of drug investigation, which in the future may also be used to predict treatment success in depressed patients and/or characterize new drugs under development.

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Publication

Single-dose serotonergic stimulation shows widespread effects on functional brain connectivity.
Klaassens BL, van Gorsel HC, Khalili-Mahani N, van der Grond J, Wyman BT, Whitcher B, Rombouts SA, van Gerven JM
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