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S.26. Imaging the serotonergic transmitter system in humans: a multimodality approach

S.26.01 Structural imaging of development in serotonergic brain systems

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In separate studies of adults and children, conducted by our research groups in Denmark and in the U.S., we have observed associations between high negative affectivity and the neural architecture of cortico-limbic systems. The results suggest that aspects of the neural architecture that may be relevant to the behavioral differences include cortical arealization, cytoarchitecture, and structural characteristics of fiber tracts, as well as the degree of hemispheric asymmetry present in these parameters. Here we describe developmental change in components of brain systems in which prominent serotonergic receptor density has been demonstrated, including ventromedial prefrontal cortex, medial temporal lobe, striatum, and the fiber tracts connecting these structures. Magnetic resonance imaging techniques were used to measure cortical areas and thicknesses, as well as aspects of proton diffusion that may index microstructural variability in subcortical nuclei and white matter tracts. A complex pattern of fronto-limbic development occurs throughout childhood, during which surface areas of the cortical components can be shown to peak early while biological alterations in cortex and the underlying white matter continue for a protracted period. Concurrent age-related biological alterations in subcortical nuclei can also be detected during adolescence. A lateralized pattern within the neural architecture of these fronto-limbic structures can be linked to an anxious affective phenotype that is present in adolescents, but the roles that genetic, experiential, and neuro-adaptational factors may play in the observed associations are still unclear.

S.26.02 Molecular imaging of the serotonin system

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Serotonin (5-HT) is a critical neurotransmitter in the generation and regulation of emotional behaviour and it plays a prominent role in the inhibition of impulses. Molecular neuroimaging with the use of appropriate radioligands has enabled us to quantify key aspects of 5-HT neurotransmission in vivo in humans, most notably the 5-HT transporter and 1A, 1B, 2A, and 4 receptors. This allows us to combine functional measures of brain function in, e.g., impulsivity and punishment with measures of 5-HT neurotransmission. In addition, pharmacological challenges of the 5-HT system may interact with the individuals pre-existing cerebral serotonergic setting. This raises the pertinent question whether measurements of the cerebral 5-HT system can be regarded as a trait or state markers.

There are observations to support both views. Molecular imaging studies have shown that the cerebral 5-HT_{2A} receptor [1] and 5-HT transporter [2] binding are genetically determined. Yet, ageing effects on the 5-HT system are evident but the effect is variably expressed among the different 5-HT markers. Finally, there is a genotype $\times$ environment effect to consider: the number of daylight minutes at the time of scanning correlates negatively with SERT binding in striatal regions, with a negative correlation between 5-HTT binding and daylight minutes in carriers of the short 5-HTTLPR allele, but not in homozygote carriers of the long allele [3]. These effects and their importance for multimodality neuroimaging studies will be discussed.

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S.26.03 Links between reward processing and the serotonergic system: pharmacological fMRI using serotonergic challenges

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Avoiding punishment is a major source of motivation when facing risky decisions. Here we used functional magnetic resonance imaging (fMRI) to test the hypotheses (i) that the brain response to punishment depends on the motivational context during decision making (i.e., loss avoidance) and (ii) that serotonergic neurotransmission links negative outcomes to loss-avoiding decisions. In healthy volunteers, we increased central serotonin (5-HT) levels by intravenous administration of the selective serotonin reuptake inhibitor (SSRI) citalopram or reduced 5-HT levels by an amino acid drink leading to acute tryptophan depletion (ATD). The pharmacological effect on neural processing of negative outcomes was studied with fMRI while participants performed a gambling task which required subjects to make risky decisions that varied in terms of risk level. Compared to a control condition without pharmacological manipulation, the two serotonergic challenges exerted opposite effects on loss-related activity in medial prefrontal cortex (mPFC) and amygdala without influencing reward-related activity or risk choice behaviour. ATD increased and SSRI decreased loss-related activity in mPFC and adjacent anterior cingulate cortex. The opposite pattern was found in left amygdala where SSRI increased and ATD decreased loss-related activity levels. Critically, both pharmacological manipulations influenced loss processing only if the loss was caused by a low-risk decision but not by a high-risk decision. The data indicate that 5HT is specifically involved in processing negative outcomes caused by loss avoidance (“trying to play it safe, but being punished for it”), pointing to a specific role of serotonin in the control of aversive motivational behaviour.