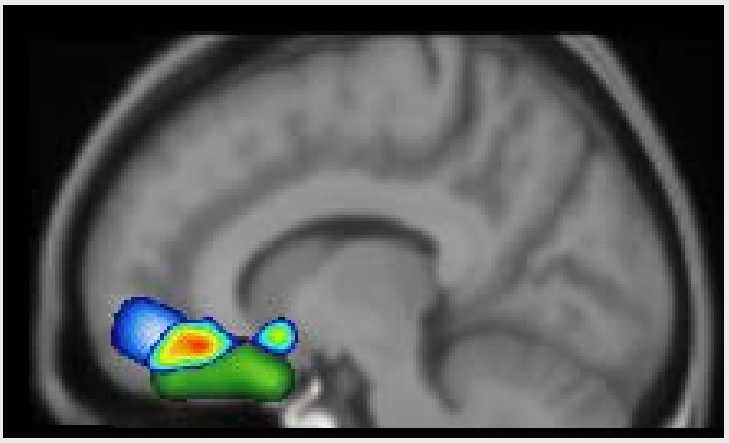
Functions of the Medial Frontal Cortex

A Model of Monoaminergic Modulation



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Aarhus Universitet den 6. juli 2009

Søren Mogensen, dekan

The thesis is based on the following papers:

1. Geday J, Gjedde A: Attention, Emotion, and Deactivation of Default Activity in Inferior Medial Prefrontal Cortex. *Brain Cogn*. 2009 Mar;69(2):344-52. Epub 2008 Oct 23.

2. Geday J, Gjedde A: Emotional impact in the inferomedial prefrontal cortex. *Synapse*. 2009 Feb;63(2):160-6.

3. Geday J, Ostergaard K, Johnsen E, Gjedde A. STN-stimulation in Parkinson's disease restores striatal inhibition of thalamocortical projection. *Hum Brain Mapp*. 2009 Jan;30(1):112-21ePub 2007 Nov 27.

4. Geday J, Kupers R, Gjedde A. As time goes by: Temporal constraints on emotional activation of inferior medial prefrontal cortex. *Cereb Cortex. 2007* Dec;17(12):2753-9. Epub 2007 Mar 1.

5. Geday J, Ostergaard K, Gjedde A. Stimulation of subthalamic nucleus inhibits emotional activation of fusiform gyrus. *Neuroimage*. 2006 Nov 1;33(2):706-14. Epub 2006 Sep 7.

6. Geday J, Hermansen F, Rosenberg R, Smith DF. Serotonin modulation of cerebral blood flow measured with positron emission tomography (PET) in humans. *Synapse*. 2005 Mar 15;55(4):224-9.

7. Geday J, Gjedde A, Boldsen AS, Kupers R. Emotional valence modulates activity in the posterior fusiform gyrus and inferior medial prefrontal cortex in social perception. *Neuroimage*. 2003 Mar;18(3):675-84.

8. Smith DF, Geday J. PET neuroimaging of clomipramine challenge in humans: focus on the thalamus. *Brain Res.* 2001 Feb 16;892(1):193-7. Erratum in: *Brain Res.* 2001 Jun 8;903(1-2):269.

Acknowledgement

This thesis is based on experimental studies carried out from 1999 to 2007 mainly during my employment as a “divided child” between the PET center and the Neurological Department at Aarhus University Hospital. Half of my time I worked as a scientist, half as a clinical neurologist.
This was a period in my professional carrier that I enjoyed a lot and I can only recommend this blend of science and clinic to anybody else, who like me would like to pursue a scientific idea, but still wants to keep working as a physician without loosing the daily patient contact.

I would like to thank my superiors, colleges and co-workers at the PET center and at the Neurological Department for their support during this process, as well as the laboratory staff at the PET center for their patience in teaching me how to work safely with radioactive tracers. But in particular I have to express my deepest gratitude to Professor Albert Gjedde. Without his support this thesis would probably never have been written.

Finally, thanks to my wife Dorthe for still believing in me all the times when I myself ceased to believe anything.

Jacob Geday

Introduction

Never express yourself more clearly than you are able to think.

Niels Bohr

The medial frontal cortex (MFC), and particularly the orbitofrontal part (also called the ventromedial frontal cortex, vMFC, or inferomedial prefrontal cortex, IMPC), is important to normal social behavior. The importance was first recognized by James Harlow (1848, 1868). He described the damage inflicted on Phineas Gage's brain and the profound consequences for Gage's personality and social conduct. The discovery largely went unnoticed for almost 100 years. For these many years, neuroscientists considered the orbitofrontal cortex to be more or less a "terra ignota". In a review of 275 PET and fMRI studies reported in the period 1988-1998, Cabeza and Nyberg (2000) included less than ten that described activations or deactivations in this region. In the last 15 years, however, neuroscientists and psychologists rediscovered this part of the brain and now have begun to understand its significance. In a review in 2001, Miller and Cohen suggested that the prefrontal cortex controls the rest of the brain. According to these authors, the area is responsible not only for a focus on the task at hand but also for working out what other areas need to do in order to solve a problem. Five years later, Amodio and Frith (2006) hypothetically explained how this responsibility could be subdivided among the areas of the MFC. However, the details of the functions of the MFC remain to be established.

Patients with lower medial frontal lesions present with characteristic neuropsychological symptoms of grossly altered social and emotional behavior but generally preserved perception, language, memory, and executive function (Bechara 2000; Damasio 1994; Rolls 2000). The symptoms some-

times even have aspects in common with the symptoms of several psychiatric conditions, including psychopathy (Lapierre 1995), bipolar disease (Wessa 2005), schizophrenia (Ritter 2004), and substance abuse (Bechara & Damasio, 2002).

Clinical observations reveal that the normal functions of the MFC as a whole can be compromised by a variety of causes, including tumors, head trauma, stroke, neurological diseases, and dementia that directly affect the frontal lobes. Patients with diseases involving the basal ganglia such as progressive supranuclear palsy or Parkinson's disease also may suffer from impaired function of the MPFC (Cordato 2005, Saint-Cyr 1995, Brand 2005).

The goal of this survey is the formulation of a model of the functions of the MFC, with full knowledge of the fact that no model possibly can do justice to the vast complexity of the work of the human brain. In order to address this goal, the model must explain not only how signals enter the MFC, but also how the processing of the signals is likely to proceed and to be regulated. I compose the model from evidence collected from the literature and from the work reported in the present publications. To allow further experimental testing, the model is intended as an integration of the following four basic claims of MFC function:

1. Defined from the anatomical connections, the medial frontal cortex has two major subdivisions, an upper dorsal part with primary connections to the cingulate and the motor and premotor cortices, and a lower ventral part with primary connections to limbic and sensory cortices.

2. The medial frontal cortex is the key to the mechanism of attention that delegates cognitive tasks to the subdivisions of the MFC, as defined by the anatomical connections. The connections facilitate a functional distinction between the upper and lower MFC. The upper, dorsal

MFC (dMFC) primarily serves the extroverted attention of someone who monitors an ongoing task, selects the appropriate response, and suppresses the inappropriate responses. The lower, ventral MFC (vMFC) serves the introverted perspective of someone who attends to emotions and directs attention to current feelings of reward or punishment. The region between the upper dorsal part and the lower ventral part of the MFC, recognized as the anterior MFC (aMFC), serves the intermediate function of social cognition to which the emotional value and performance accuracy of a task are equally important.

3. The mechanism of attention in the MFC depends on the operation of lateral (surround) inhibition from GABAergic interneurons. The interneurons innervate the glutamatergic neurons that receive information about stimuli processed in other brain regions and project the information onto the prefrontal cortex, thus enabling the person to recognize the most salient objects of attention and eventual action. The default activity of the MFC defined by Raichle et al (2001) is the idling of a dedicated network in which receptive neurons are mutually inhibited by matching spontaneous activity in respective interneurons, when no external signals are sufficiently salient to inhibit the entry of competing signals. Measured as blood flow or glucose consumption, activity in the MFC as a whole is higher in the default mode than in the mode of activity of a single cluster of neurons targeted by direct salient input, because the single cluster causes GABAergic interneurons to inhibit the activity of neighboring clusters.

4. Neuronal activity in the MFC is modulated by monoaminergic innervation as defined by the densities of inhibitory and excitatory receptors in the subdivisions of the MFC, and by the concentrations of the respective monoamines. In the MFC, monoamines have at least two pharmacologically and pharmacokinetically distinct receptors. The monoamines have specific excitatory and inhibitory receptors with different affinities towards the transmitter. Serotonin modulates attention. Low concentrations of serotonin favor the function of introverted emotional attention implemented in the vMFC, while increased levels favor the function of extroverted task-oriented attention implemented in the dMFC. More moderate increases of noradrenaline generally facilitate attention, while greater elevations of noradrenaline inhibit frontal functions, including that of attention. Dopamine adjusts the extent to which inputs are processed and transmitted to premotor cortices. Low levels of dopamine

favor less intense processing that leads to a passive, conservative behavior, while higher levels of dopamine favor more intense processing that leads to proactive and sensation-seeking behavior. Personality-building differences among people and accompanying changes of mood, performance, and behavior of individuals, relate to individual characteristics of serotonergic (extroversion vs. introversion), noradrenergic (focus vs. no focus) and dopaminergic (reaction vs. proaction) neuromodulatory systems.

This model of MFC function, admittedly audacious in its simplicity, is intended as a basis for future investigations. It casts light on the healthy experience of, and reaction to, the ”umwelt”, and it explains how therapeutic agents may help those who fail in these respects because of disease.

Anatomy of the Medial Frontal Cortex

In order to understand the inner workings of a specific brain region or area, the physical basis in architecture and connectivity must be considered. The medial frontal cortex (MFC), consisting of the medial prefrontal cortex (MPFC) and the anterior cingulate cortex (ACC) is a multimodal area that receives input from multiple areas through dense reciprocal connections. Thus, from a purely anatomical point of view, the MFC is an ideal candidate for a role as coordinator of higher processing of, and attention to, internal as well as external stimuli.

Phylogenetically, the dorsolateral and orbital prefrontal cortices are recently evolved regions of the neocortex derived from paleocortex with increasing cytoarchitectonic differentiation, the most recent also being the most differentiated (Barbas & Pandya, 1991). Dorsolateral prefrontal cortex (DLPC) originated from the cingulate gyrus, and the two structures maintain close reciprocal connections, whereas orbitofrontal cortex stems from the olfactory cortex and maintains relations with the limbic system.

The MFC can be separated from motor areas in the caudal part of the anterior cingulate by a vertical plane located 10 mm anterior (Talairach y =10) to the anterior commissure (Koski and Paus, 2000). The lower part of the MFC, the ventral MFC (vMFC), is defined as the part of the MFC below the z-Talairach coordinate of 2 mm and consists of the rostral and subcallosal parts of the anterior cingulate gyrus (Brodmann area (BA) 24, 25, 32), the medial portion of the orbitofrontal cortex, and the area in between (see figure below). Anatomically the latter is the part of the prefrontal cortices that receives projections from the magnocellular part of mediodorsal thalamus (Fuster 1997). Cytoarchitectonically, the orbitofrontal cortex is more difficult to classify. In humans, Brodmann

(1905, 1909) said that the area incorporates BA 10, 11 and 47; however there were some inconsistencies compared with his own studies in primates. We know now that the human orbitofrontal cortex is far more heterogeneous than Brodmann thought, with huge variations from person to person (Chiavaras and Petrides 2000) and the consensus now follows the suggestion of Petrides and Pandya (1994) that divides the orbitofrontal cortex in BA 10, 11, 47/12, 13 and 14, with a further subdivision of the different Brodmann areas based on their connectivity.

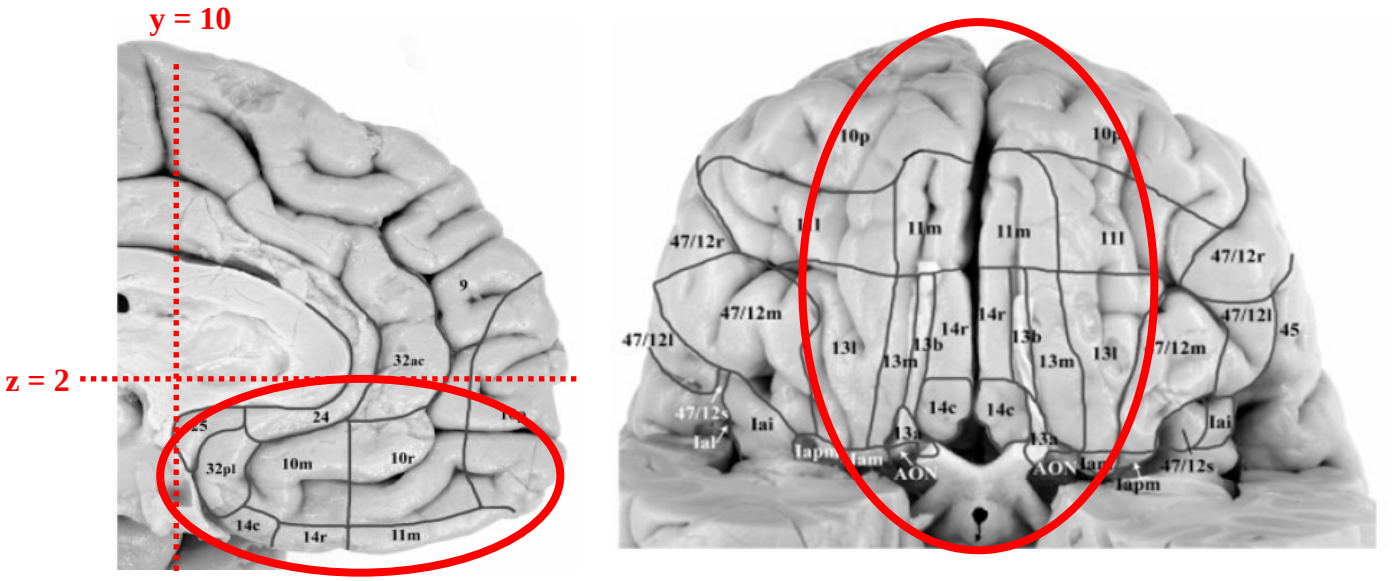


Fig. 1. The vMPFC as outlined by Öngür et al, (2003) in the Journal of Comparative Neurology 460:425–449)

Encompassing the upper part of the limbic system, the cingulate gyrus has dense reciprocal connections with the amygdala (Porrino et al 1981), insula, hypothalamus, periaqueductal gray matter, and the caudate nucleus as well as the accumbens (Morecraft et al 1993). All traffic in these connections can be shared with the medial orbitofrontal cortex, to which the cingulate gyrus is equally closely connected (Carmichael & Price 1995).

The orbitofrontal cortex in itself receives input from all sensory modalities; sight, taste, hearing, smell, and touch as well as visceral input (directly or through anterior cingulate gyrus). Gustatory information reaches the lateral part of BA 13 from the ventro-postero-medial thalamus (Rolls et al 1990), whereas olfaction is transmitted more anteriorly to BA 13 and BA 11 (Rolls et al 1994). Visual input is projected to lateral orbitofrontale cortex BA 47/12 (Barbas 1988, Booth & Rolls 1998) primarily through the ventral, object-orientated stream (Mishkin & Pribram 1954, Mishkin & Ungeleider 1982) from the inferior temporal cortex together with projections from fusiform gyrus and temporal pole, both being associated with recognition of facial expression and emotion (Hasselmo et al 1989, Dolan et al 1996, Geday et al 2003). Auditory inputs are projected from the upper part of the temporal lobe to BA 11 og 47/12 (Barbas et al 1999). Sensory input from BA 1 og 2 and SII ends in BA 47/12 while visceral information reaches the agranular cortex in Ial og Iam (Öngür & Price 2000). Finally the orbitofrontal cortex is directly connected to the amygdala, which projects widely to the area, but predominately to BA 10, 13a, 13b 14 and 47/12.

Studies of patients suffering from brainstem apoplexy have established the importance of monoaminergic innervation for normal frontal function (e.g. Malhotra et al 2006, Nishiro et al 2007 and Andersen 1995). The structural basis is the connection of the MFC to the monoaminergic cell groups in the midbrain and brain stem. Via the medial forebrain bundle the MFC receives serotonergic projections from neurons in the rostral raphe nuclei, noradrenergic projections directly from the locus ceruleus of the lateral tegmental area, and indirectly via the medial forebrain bundle and the amygdala, as well as mesolimbic dopaminergic projections from the ventral tegmental area, also via the medial forebrain bundle (Heimer 1983).

Functional subdivisions within the MFC

The anatomy predicts that different areas of the MFC subserve functions defined by the different connections. Koski and Paus (2000) found that complex cognitive tasks concomitantly activate dorsolateral regions of the prefrontal cortex, such as those requiring conditional associative learning or working memory, and more dorsally located regions of the anterior cingulate cortex, whereas areas below the border between the supracallosal and subcallosal anterior cingulate cortex (ACC) at the horizontal plane located 2 mm above the anterior commissure (Z=2) have no such connections and primarily serve emotional behaviour by modulating autonomic or visceral aspects of emotion, for example; in anticipation of rewards and penalties (Bechara et al. 1996).

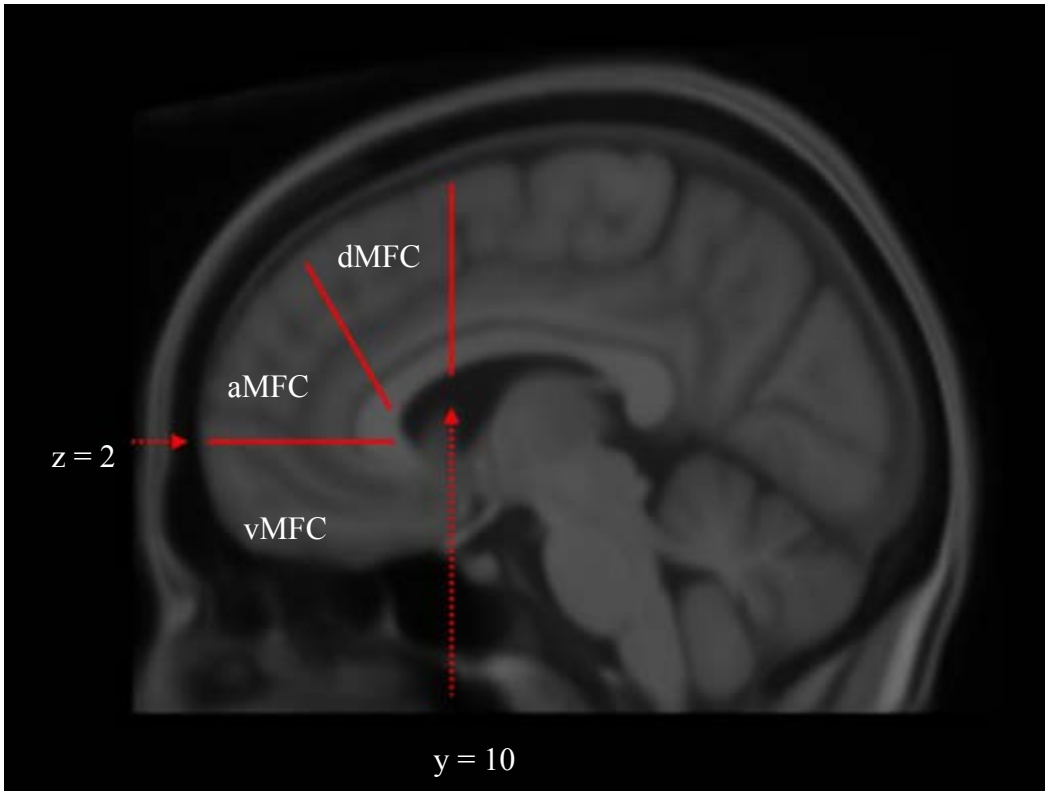


Fig. 2. The division of the MFC into the dorsal MFC (dMFC), the anterior region of the rostral MFC (aMFC), and the ventral MFC (vMFC), as suggested by Amodio and Frith (2006).

In a comprehensive review of functions of the medial frontal cortex, Amodio and Frith (2006) further divided the MFC into three areas; the posterior region of the posterior rostral (or dorsal) MFC: dMFC, the anterior region of the rostral MFC: aMFC, and the orbital, or ventral MFC: vMFC, as illustrated in figure 2 .

The posterior region of the rostral MFC (dMFC) is defined as the region in front of a vertical plane at the Talairach position y = 10 (see figure above). The area is incrementally active during response inhibition. As an important component of normal behavioural regulation, response inhibition is defined as the withholding of a habitual response when changing demands of a task require an alternative response. The "Stroop color-naming task" is well established as a way of studying response inhibition: the participants view words presented in colors (for example, red and blue) that are compatible (red written in red) or incompatible (red written in blue) with the meaning of the word. In incompatible trials, participants must inhibit the prepotent tendency to read the word's text in order to correctly report the color of the word. Cabeza and Nyberg (2000) claimed that the upper rostral part of the MFC serves attentional processes required to initiate a given behaviour and to suppress inappropriate responses, and that it receives cognitive/motor commands from relevant regions (for example, prefrontal cortex), and funnels them to the appropriate motor system. In concordance with this statement and the fact that dMFC is so closely connected to the motor system through the anterior cingulate cortex (ACC), Amodio and Frith (2006) suggested that the dMFC, and especially the dorsal ACC, is crucial to conflict monitoring, error monitoring, and response selection. In support of this claim, Walton et al (2004) observed an increase of activity in the dMFC with a peak at the Talairach coordinates (x,y,z) 0,18,36 mm when subjects monitored outcome of actions they decided themselves, but not when they monitored outcome of externally guided actions, just as Ravnkilde et al (2002) found Stroop interference to raise blood flow in the left anterior cingulate cortex.

Amodio and Frith defined the orbital, ventral MFC (vMFC) as the area of the MFC under the horizontal plane at Talairach coordinate z = 2 (see Figure above), approximating the split of the ACC between supracallosal BAs 24 and 32, and subcallosal BAs 24 and 14 as suggested by Koski and Paus (2000). Damasio (1994) and Bechara et al. (2000) claimed that the vMFC is critical to the integration of emotion and cognition by the use of so called "somatic markers". According to this hypothesis, marker signals related to body-state structure and regulation, including those which express themselves in emotions and feelings, consciously and non-consciously influence the cognitive processes of responding to external stimuli.

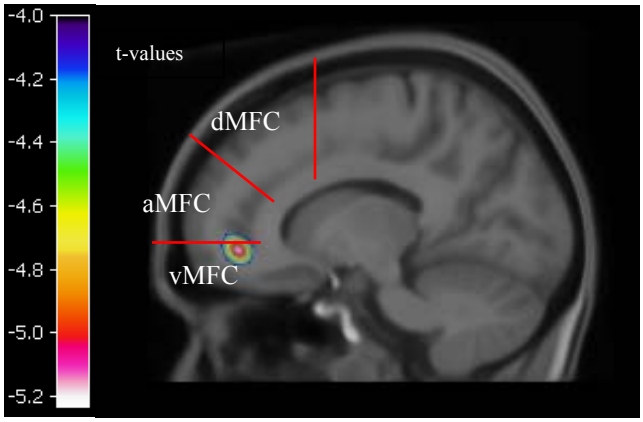


Fig. 3. The peak of the deactivation in the MFC as demonstrated by Geday et al (2003) elicited by a short presentation (3 s) of each image in a series of images with emotional contents

Rolls (1990, 2000), on the other hand, focused on the region's role in emotionally related learning and suggested that the main function of vMFC (a.k.a orbitofrontal cortex or IMPC) is to represent the magnitude of reward or punishment. Amodio and Frith (2006) proposed that the vMFC is involved in outcome monitoring, just as the dMFC represents and updates the value of possible future actions. However Geday et al (2003, 2006 and 2007) have in different setups demonstrated the area

just around z = 2 (se Figures 3 and 13) to be either deactivated or activated by images bearing an emotional content, depending on the presence of a concomitant task, in addition to being deactivated by attentional demand (Geday et al 2008a), and suggested within the framework of the default mode of brain function (Raichle et al 2001) that the area generally is involved in attentional processing, but especially so for emotional stimuli. The area between the dMFC and vMFC, the anterior region of the rostral MFC (aMFC), has access to both information about actions and outcomes; accordingly it may serve functions intermediate between those of the dMFC and vMFC. Amodio and Frith (2006) suggest that aMFC facilitates the reflection on values linked to outcomes and actions in addition to performing the high level representations that have a major role in social cognition. Accordingly; Burgess et al (2007a, 2007b) described activation of the anterior medial prefrontal cortex (aMPFC) in BA 10 during attention orientated towards external stimulus as well as during mentalization.

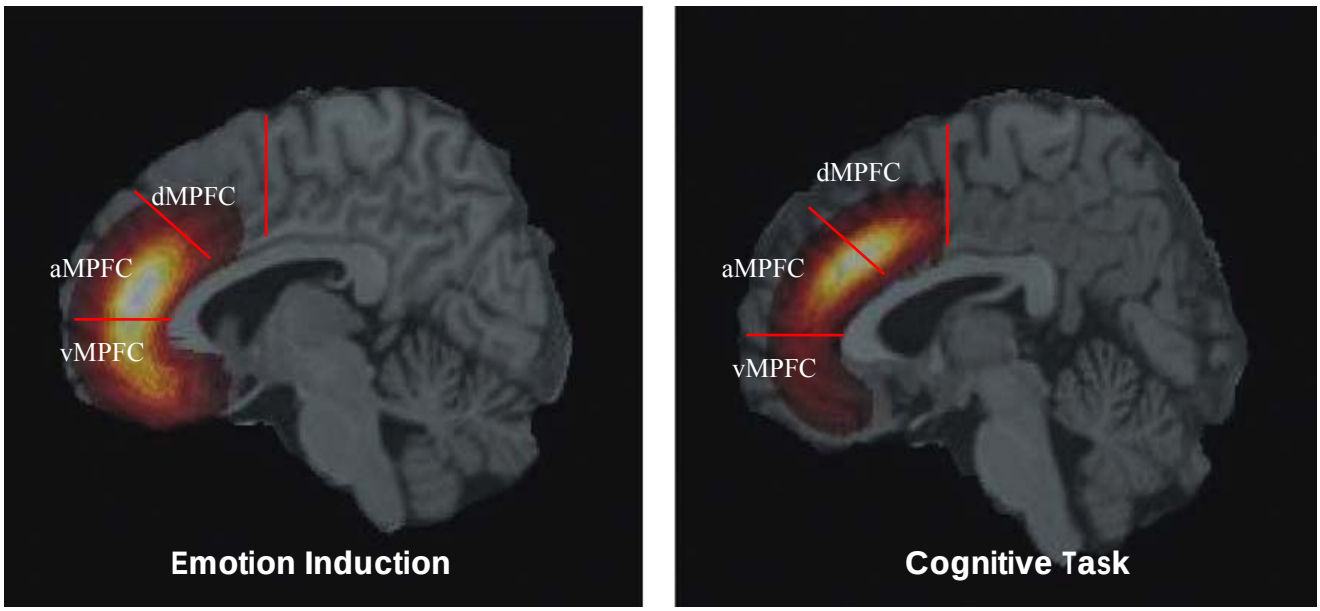


Fig. 4. Illustration of a continuum of activations in the MPFC (and the ACC) elicited by emotion or cognition. The likelihood of activation during emotion induction is the highest in ventral (v) and anterior (a) parts of the MPFC whereas the chance of getting activation during a cognitive task is best in the more dorsal (d) part. Adapted from Steele and Lawrie 2004¸ Neuroimage 21, 868–875)

Although the subdivision of the MFC in three functionally different parts may be helpful in a theoretical context, the reality is far more complex. Bush et al (2000) performed a meta-analysis of 132 data points from 64 studies reporting activation or deactivation of the anterior cingulate cortex (ACC) by an emotional or a cognitive task, showing that cognitive tasks preferentially activate the upper "cognitive division" of the ACC, whereas emotional tasks activate the lower "affective division". For deactivations, the complimentary pattern was found. However, for both activations and deactivations, an overlap existed in the anterior middle area between the two divisions. In a meta-analysis of 330 different emotion induction and cognitive task studies of normal subjects reporting prefrontal activation (including some activations of the ACC), Steele and Lawrie (2004) calculated a parametric map of the likelihood that a test of emotive or cognitive function would yield an activation of the MPFC, showing that the areas activated by emotion and cognition overlap more than for the ACC (Bush et al 2000), although on average a clear functional division still is present.

To further test whether the specialization of functionality in the MFC is absolute, Geday et al (2008a) did an experiment that is similar to that of Taylor et al (2003, described later). The subjects viewed series of neutral and emotional images presented for 3 s each, while they performed either a simple or a more complex attention task. In the simple task, subjects pressed any mouse button when the images changed. During the complex task, subjects pressed the left mouse button when the image showed the outdoors and the right button when the image showed the indoors. The authors expected to find reversible emotional deactivation, similar to the one demonstrated as a function of stimulus duration (Geday et al 2007), but there was no effect of emotional content in the MFC in any of the tasks. Instead, increasing complexity of the concomitant cognitive task, rather than the emotional content of the images, deactivated the vMPFC.

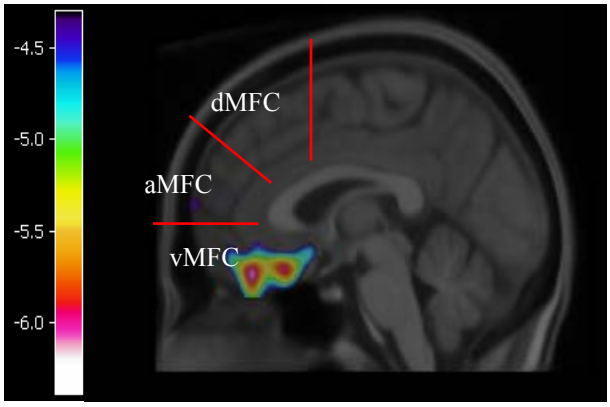


Fig. 5. The two peaks of deactivation in the vMPFC elicited by increasing the attentional demand of the task, as demonstrated by Geday et al (2008a)

A comparison with normalized activity values from Geday et al. (2003) (Figure 6), revealed that activity at the coordinates of significant deactivation during passive viewing of emotional content (Taliarach coordinates: 15, 51, -8; Geday et al 2003, 2006, 2007) was reduced more by execution of any concomitant task than by emotional content of the images.

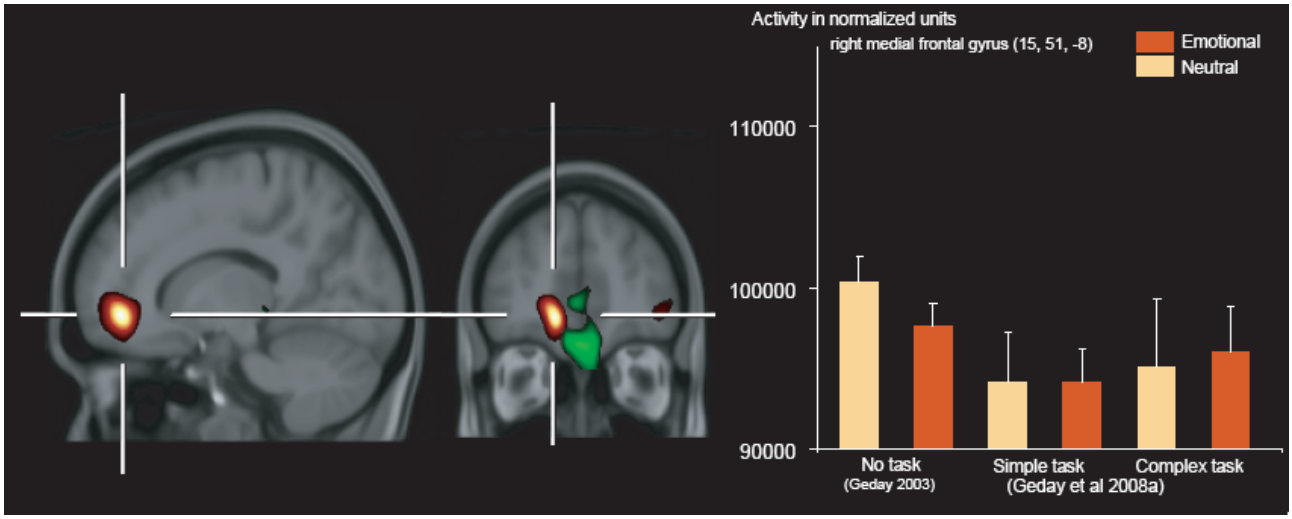


Fig. 6: The absent emotional interference with task-induced deactivation implied that processes in the inferior prefrontal cortex remain subservient to an external task rather than to external emotional distractions* (from Geday et al. 2008a).

In total, it may not be warranted to assign a specific part of the MFC to a specific emotion, or to the performance of a specific task, but rather more parsimoniously to attentional processing. Explaining behavior in terms of internal mental states, Olsson and Ochsner (2007) suggested that MFC processed emotional qualities, whereas the cognitive aspects preferentially are being processed in the dorsolateral prefrontal cortex. Without disregarding that such a lateral-medial distinction may also exist, I suggest that neurons in the orbital and anterior part of MFC primarily operate when attention is introverted and "emotional", whereas caudal neurons participate when attention is extroverted and "detached". In other words; when attention is maximally introverted and focused only on current reward or punishment, the MFC is most active in the orbital parts. On the other hand, if a subject must attribute a specific feeling to an experience, or actively describe this feeling to others, the activation moves more caudally and anteriorly. Likewise, if the individual attends to a decisively non-emotional task, activity rises in the "extroverted" caudal neurons of the dMFC, but more anterior neuronal groups assist if cooperation with other individuals is needed to perform the task, and anticipation of their reactions to, and beliefs about, the task therefore is necessary.

The neuronal basis of attentional processing in the MFC

"For to everyone who has, more shall be given"
Gospel according to Saint Matthew 25:29

Through the 1990's, neuroimages of brain functions primarily focused on areas of increased activity in response to a given task. Then, in 1997 Shulman and co-workers in St Louis published a report that focused on the frequent observations of declines of blood flow in the MFC and other brain areas in response to a visual task (Shulman et al 1997), with reference to a special issue on the neuropsychological perspectives of affective and anxiety disorders in the journal *Cognition and Emotion*. In this issue, Shulman's collaborators Drevets and Raichle (1998) demonstrated that the execution of an attentionally demanding cognitive task coincided with the decline of blood flow in areas of the brain that were known otherwise to be activated by emotions, and conversely that activity in areas subserving cognitive functions declined during experimentally or pathologically established emotional states.

Based on these and other findings Raichle et al. (2001, 2007) proposed the existence of a general state of activity in the cerebral cortex to which activity defaults (the "default" mode of brain function) when an individual is awake and alert but attends to no specific task. When attention is focused, activity is attenuated in a cortical network that includes the MFC together with several associative cortical areas. This attenuation is thought to reflect reallocation of resources from a more general to a more specific mode of information processing

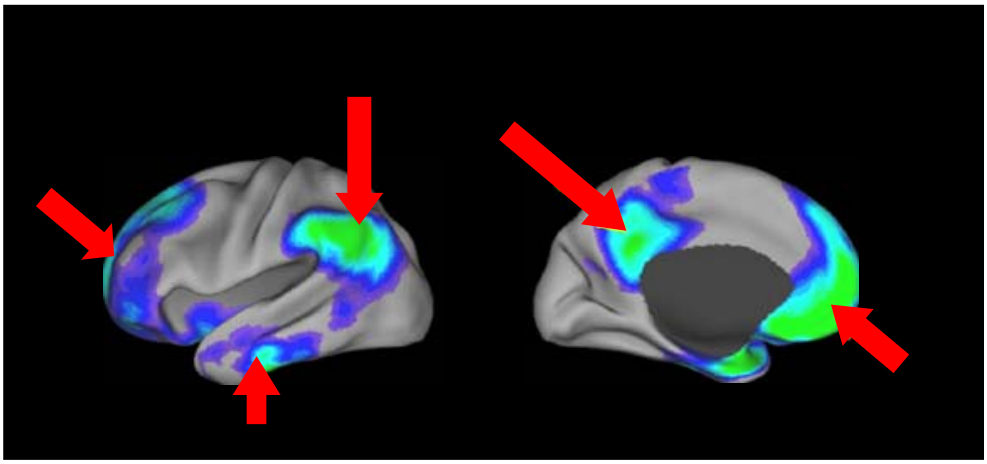


Fig 7. The default network, adapted from Raichle and Snyder 2007, based on data from Shulman et al. (1997), showing areas deactivated by focused attention. Arrows point to: 1) angular gyrus; 2) parahippocampal gyrus; 3) posterior cingulate/precuneus; 4) MFC

From the observations of spontaneous fluctuations in the BOLD* signal of alert but passive subjects, with eyes closed, open, or fixated on a cross-hair, Fox et al. (2005) found that activity in these four regions covary closely, suggesting that the regions, at least functionally, are connected.

The covariation supports the claim by Raichle of the existence of a "default" network, defined as the network to which brain activity defaults, when other networks are inactive.

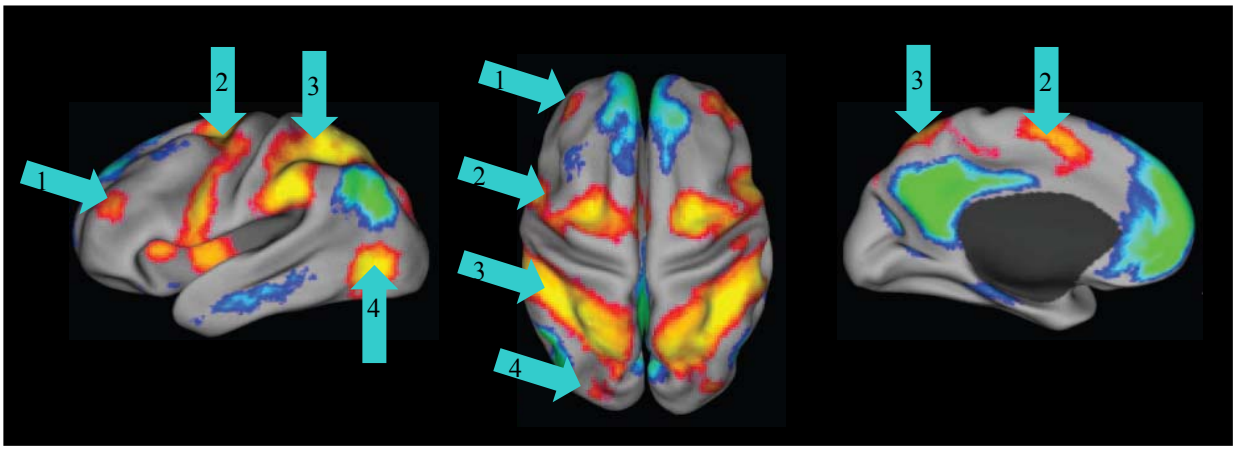


Fig. 8. Figure adapted from Fox et al. (2005) showing the areas where activity (marked in red/yellow colors)correlates negatively to activity in the default network (in green and blue colors). Arrows point to: 1) dorsolateral prefrontal cortex; 2) premotor cortex/frontal eye field; 3) sensory associative cortex; 4) occipitotemporal (visual ventral stream) cortex.

*) Blood-oxygen-level dependent, or BOLD, fMRI utilizes the difference in magnetic susceptibility between oxyhemoglobin and deoxyhemoglobin, and thus oxygenated or deoxygenated blood. This leads to magnetic signal variation which can be detected using an MRI scanner. Thus activity changes measured by BOLD reflect a combination of changes in blood flow and oxygen consumption.

Fox et al. (2005) introduced the concept of a complementary functional network (figure above), where the activity covaried inversely with the activity in the proposed default network. This "counter-balance" network may be defined as the network to which brain activity is diverted by an external stimulus sufficiently strong to disrupt the default state of brain function. Focused attention and goal-directed behavior previously were demonstrated to lower activity in the default network (Raichle et al 2001) and to raise activity in the anti-correlated task-positive network (Gusnard and Raichle 2001, Corbetta, et al 2002). In contrast, a lack of focus, defined as the emergence of stimulus-independent thought, is associated with increased activity in the default network and a trend toward decreased activity in the task-positive network (McGuire et al. 1996). The claim that "mind wandering" is the main mechanism of activity changes in default regions during attentional demand may be too simplistic. Gilbert et al (2006, 2007) reported that a stimulus orientated task (SOT) activated the upper part of vMFC in the BA 10 more than a stimulus independent task (SIT). However the finding may reflect an unaccounted division of attention between stimulus and concomitant motor task. During the SOT, the subjects were instructed to press different mouse buttons with either the index or middle finger corresponding to the nature of the stimulus, whereas during the SIT they only had to press the same button with their index finger when a SIT was performed. Thus an attentional split occurred during the SOT more often than during the SIT, which may explain their finding (see below, for further explanations).

The putative task-positive complementary network consists of multimodal association cortices, all known to participate in executive planning, motor function, and higher order sensory, auditory, and visual processing. Some of these areas will always be activated during any PET or fMRI activation paradigm, showing fluctuations of the baseline activity, caused by the processing of more random

associative processes elicited during the fMRI (physical discomfort, anxiety from slight claustrophobia, peripheral sensory nerve stimulation in high Tesla fields and noise from the scanner).

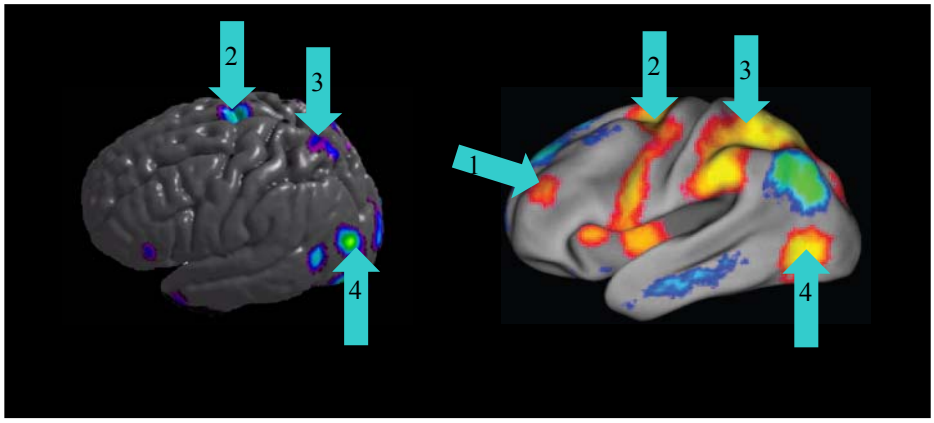


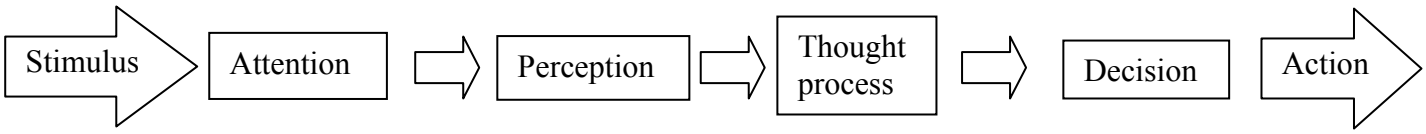
Fig. 9. Cortical areas activated by emotive visual stimuli in the studies by Geday et al. (2003 and 2007) compared to the "counter-balance" network as suggested by Fox et al (2005). Arrows point to: 1) dorsolateral prefrontal cortex (not activated in the studies by Geday et al (2003 and 2007), possibly because neither of those involved an active task) 2) premotor cortex/frontal eye field; 3) sensory associative cortex; 4) occipitotemporal (visual ventral stream) cortex

Thus, for the proposed anti-correlated task-positive functional network, emphasis possibly should be more on the functional aspect than on the network aspect, as the covariation may reflect different processes engaged by the different aspects of the same test situation, rather than by direct connections between the activated areas. Geday et al. (2003, 2007) demonstrated that emotive visual stimuli significantly activate the fusiform gyrus. When all activation clusters from these studies are projected onto the cortical surface the areas listed by Fox et al. appear activated, but the primary focus appears to be the occipitotemporal area.

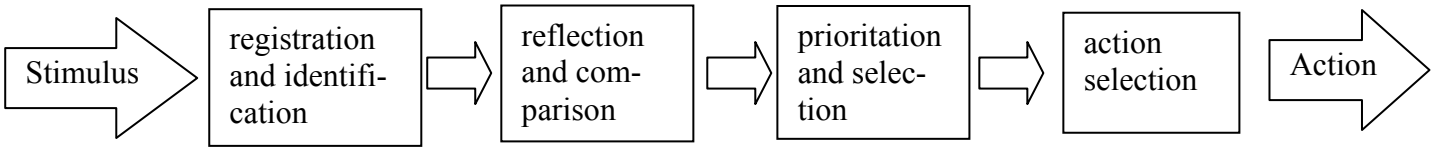
The claim that an apparent functional network activated by strong external stimulation is an ad hoc assembly of neurons rather than an exclusive band of connections also may be true for the original default network. The cortical areas in this network are activated or deactivated independently during specific tasks. To be sure the medial frontal cortex is engaged in attentional processing, possibly with a special role for the inferior medial prefrontal cortex (IMPC) in emotional processing. The

angular gyri are part of a distributed semantics system accessed by objects and faces as well as speech and written words (Price 2000). The parahippocampal gyri are engaged during very different tasks, such as listening to music with pleasant or unpleasant emotional valence and acts of spatial recognition (Eichenbaum et al. 2007), whereas the posterior cingulate and precuneus participate in episodic memory retrieval (Wagner et al. 2005). Indeed, findings of Geday et al. (2003, 2007) show that the IMPC is the only part of the default network that is deactivated by emotional content.

It may be useful for a moment to leave the concept of competing cortical networks, and instead focus on how the brain processes data. There are several cognitive psychological models of this mechanism, for instance the one below suggested by Eysenck and Keane (2005). It reveals the bottom-up processing of a stimulus that is first registered, then identified, and reflected upon, before the decision is completed about how to act.

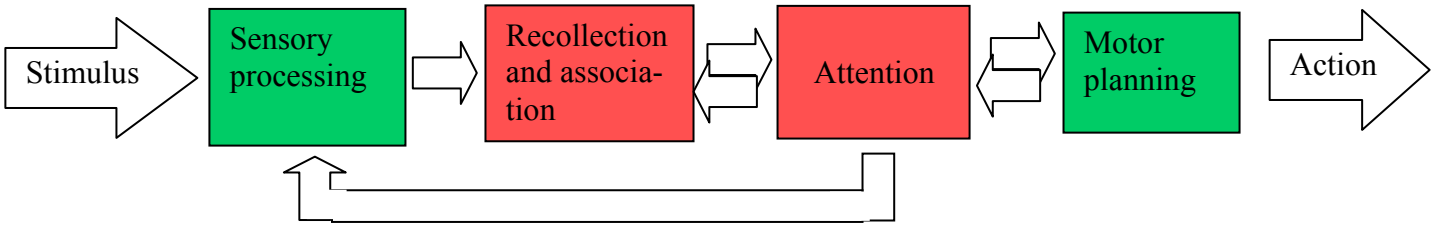


However, as this model uses rather broad terms and nomenclature, it is somewhat different from the one used here, and requires some refinement as follows:



In other words, the system registers the input, identifies the input, compares the input with previously experienced inputs, prioritizes among all coincident inputs, and selects the most salient input whereupon deciding which action to take and how to execute this action.

In terms of actual brain processes, a signal is sent from peripheral receptors to unimodal cortical sensory areas, where it is preprocessed and registered as an incoming signal (rather than as random sensory "noise") and then projected to sensory multimodal cortical areas as a potential percept. By comparison with previous experiences stored in parietal associative cortices, the best fitting percept is chosen as a candidate representation of the stimulus ("survival of the fittest"). The result of this process of elimination is among others weighted in the frontal lobes for gaining attention, before final projection to heteromodal and then unimodal motor areas for generation and execution of the percept and its course of action. As attention alternates between different associations of the percept and its consequent plans of action, the sensitivity for relevant external stimuli is adjusted. This co-existence of top-down and bottom-up modulation, as previously described for emotional attention (e.g. Compton 2003) or visual and sensory attention (e.g. Ship 2004, Macaluso et al 2002), is indicated by bidirectional arrows



The primary processes (marked green) may be described as threshold-dependent "go/no-go" logical nodes, where an incoming signal of sufficient salience is registered as a potential percept: The sight of an object is either registered or it is not. Thus the registration and identification, for example of a

white ball moving in the visual field, leads to an activation of neurons in primary and secondary visual cortex.

Based on the observer's previous experiences, the sight of a moving white ball may signify an on-going game of soccer on the television or a person playing soccer. If the observer is driving a car, the latter option seems the most likely, especially as there is a park to the left, where children are playing. In the presence of playing children, a ball in the street may be pursued by a running boy, and the ball becomes a valid object of attention as the observer has a wish not to hit the boy.

Rather than to reflect on a talk to be given in an hour, or to enjoy a favorite singer on the car radio, the observer addresses and selects among past experiences the relevant context of the moving white ball. He gives this signal priority over other signals as the one most deserving of attention. Consequently, during the fitting to and choice among templates in the precuneus, known to be involved in self-centred mental imagery strategies and episodic memory retrieval (Cavanna & Trimble 2006), poor fits are suppressed with a net decrease in the activity of the precuneus (marked red). Activity also decreases in the medial prefrontal cortex (also marked red), as the focus on the moving ball blocks all other candidates for attention.

At the same time the observer realizes that he must prepare to stop the car, and hence he moves the right foot from the accelerator to the brake. In the brain, the result of attentional processing in the medial frontal cortex is projected to the dorsolateral prefrontal cortex, where activity rises as he gets ready, leading to a subsequent raise in activity in unimodal premotor and motor cortices as the observer actually moves his foot (marked green).

The example above illustrates how different aspects of the same situation may lead to activity changes in different brain areas consistent with the action of two complementary networks, although physically such distinct networks need not exist. Rather there may be two complementary mechanisms of information processing in the brain: a thresholding mechanism, by which the stimulus must reach a certain degree of salience to depolarize the receptive group of neurons and subsequently raise activity, and a selection mechanism, by which all incoming signals are evaluated and prioritized by inhibition according to previous experiences and salience of the stimulus in question, leading to a net decrease of the number of neurons participating in this selection.

It is easy to understand intuitively how an incoming stimulus may lead to an excitation of a group of neurons; however it is less clear how selection among stimuli can lower activity. A plausible mechanism of such attenuation, elicited by the selection of a specific mode of processing over a more generalized mode, may be lateral inhibition. Lateral inhibition is a working principle of nervous system possessing of sensory impulses.

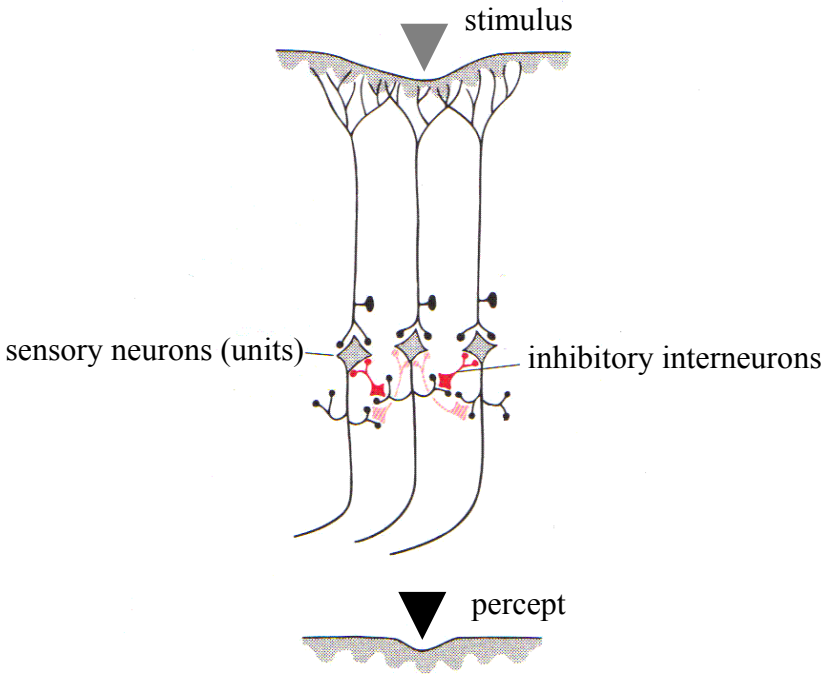


Fig. 10. Figure adapted from Brodahl (1995) illustrating, how the mechanism of lateral inhibition refines incoming signals by inhibiting activity in neighboring (less activated) neurons and thus improving contrast and minimizing intrinsic noise.

Lateral inhibition is well-established in the visual system (e.g. Hubel and Wiesel 1977) where interneurons in the primary visual pathways, particularly in the retina, commonly exhibit centre-surround antagonism within their receptive fields, as well as in the primary somatosensory system (e.g., Vallbo et al 1979). However, also central visual (Macknik 2006), auditory (Oswald et al. 2006), somatosensory (Favorov and Kelly 1994), olfactory (Mori et al. 1999), and likely also gustatory (Marui and Caprio 1982) cortices rely on lateral inhibition to process incoming sensory information.

Shortly after the onset of stimulation after a period of repolarization, the originally most activated center (see Figure below, marked in red) remains the only group of sensitive neurons in neighborhood. They are more easily depolarized than the surrounding neurons. When the original stimulation is repeated, new simultaneous and equipotent sensory impulses to neighboring neurons will be suppressed, in favor of the specifically predefined, salient stimulus.

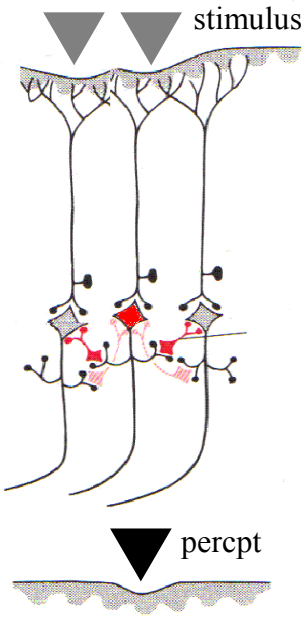


Fig. 11. Figure adapted from Brodahl (1995) illustrating, how the mechanism of lateral inhibition favors depolarization of recently depolarized neurons.

As demonstrated for the visual system, this mechanism of predictive coding enables an array of interneurons to transmit a larger number of distinguishable images, taking into account the templates of the existing, and hence expected, structures of the visual world (Srinivasan et al.1982). Just as for the sensory cortices, lateral inhibition is the working principle of the prefrontal cortex (Wilson et al 1994, Rao et al 1999, Krimer et al. 2001) and may therefore apply to the MFC and the rest of the proclaimed default network.

One particular aspect of the evidence is the extent to which an activation of GABAergic terminals cancels the metabolic and circulatory effects of inhibition of target neurons, and how this is reflected in measures of regional cerebral blood flow (rCBF) or metabolism. Buzsáki et al (2007) and Raichle and Mintun (2006) claim that GABAergic innervation raises metabolism and rCBF. It is difficult to correlate the deactivations described above with the consequences of increased GABAergic activity. However, the claim that GABAergic innervation raises rCBF is primarily based on the single human study of patients operated for Parkinson's disease with STN-DBS by Hershey et al (2003). The authors of this single study found the blood flow to the lateral posterior (LP) nucleus (x, y, z: -20, -22, 12 mm) of the thalamus, dorsal to the VL nucleus to be increased during STN stimulation when subjects rest. They suggested that the increase could be the result of increased GABAergic inhibition from the internal pallidum and reticular substantia nigra and therefore that it would indicate a deactivation of the thalamus. The increase was found in a restricted search of a volume of 3142 mm^2 (corresponding to eight 10 mm diameter globes centered on coordinates in the STN, internal pallidum , substantia nigra, and the thalamus), 72 degrees of freedom and filter size 15 mm The resulting P value corrected for multiple comparisons corresponded to a t-statistics of more than 3.84.

In contrast, Geday et al (2007b) reported that STN stimulation under similar circumstances reduces blood flow in the thalamus. The search of the whole brain including white and gray matter was unrestricted with a significance corrected for multiple comparisons $P < 0.01$ for at t statistics of 5.46. The reported peak deactivation by Geday et al in 2007b happened closer to the VA-VL nuclei than the LP peak activation of the thalamus reported by Hershey et al in 2003. The VA-VL nuclei are parts of thalamus that are likely to be affected by STN stimulation because they are engaged in mo-

tor tasks, whereas the LP nucleus is thought to process and relay multimodal information to cerebral cortex by projecting to higher-order visual and association areas in the occipital, parietal, and temporal lobes. Thobois et al. (2002) reported bilateral rCBF increases in the thalamus with significance below the theoretical t-threshold for $P < 0.05$ in a global search that makes it difficult to draw conclusions from this evidence. Hilker et al. (2004) reported an activation cluster composed of thalamus in both hemispheres and reaching as far down as midbrain where the reported increase of glucose metabolism may reflect increased activity in the STN rather than in the thalamus metabolism. In 2006, Asanuma et al. reported increased glucose metabolism in the left VL nucleus of the thalamus but this cluster of voxels included the subthalamic region in addition to the ventrolateral thalamus.

Early PET studies suggested that blood flow measures might fail to distinguish between increased GABAergic inhibition and increased glutamatergic excitation, as both require energy and both may benefit from increased blood flow (Ackermann et al.1984). However, more recent evidence suggests that increased blood flow is less likely to indicate increased GABAergic inhibition; on the contrary, several recent studies suggest that GABAergic inhibition lowers blood flow in the target area (Chen et al. 2005; Roland and Friberg 1988; Takano et al. 2004; Xi et al. 2002). The neurophysiological coupling between regional blood flow and neuronal activity is the basis for the functional interpretation of flow signals recorded by neuroimaging (Iadecola, 2002; Lauritzen and Gold, 2003; Lauritzen, 2001; Logothetis et al. 2001; Shmuel et al. 2006). Although the results published by Mathiesen et al. in 1998 sometimes are taken to imply that increased GABAergic activity raises blood flow in cerebellar cortex, the authors themselves actually interpreted the increase as a consequence of the activation of the GABAergic neurons themselves, and not as an effect of the release

of GABA on other (glutamatergic) neurons. In summary, the bulk of the evidence supports the claim that GABAergic inhibition of target neurons lowers metabolic activity and blood flow.

This interpretation is not contradicted by Rolls' neurophysiological demonstration of activation rather than deactivation of specific neurons in the inferior frontal cortex by stimuli of emotional valence (Rolls 2000). Indeed, marked activation of a few single neurons is necessary to depolarize their inhibitory GABAergic interneurons and thus reduce excitability and activity in all neighboring neurons of the whole area. In 2007, Northoff et al. tested this interpretation by combining fMRI of emotional processing with resting-state magnetic resonance spectroscopy. In this experiment the concentration of GABA in the ACC specifically matched the negative BOLD responses elicited by emotional stimulation (Northoff et al. 2007).

In contrast to neurophysiological single-cell recordings, PET and fMRI focus on larger groups of neurons. These methods demonstrated consistently medial prefrontal cortex activation during emotional processing. For the neuronal network in the MFC to employ a mechanism of lateral inhibition the opposite would be expected; namely that emotions deactivated the larger group of neurons targeted by PET and fMRI. The resolution of this apparent inconsistency may lie in the methodology of PET and fMRI studies of emotion, especially in the stimulus presentation. Although the vast majority of studies result in activations, Paradiso et al (1999) and Geday et al. (2003) found that visual stimuli of emotional content deactivate the MFC: Besides from both being PET flow studies using a block design, the studies have two things in common, first; that subjects attended to no explicit concomitant task while viewing the series of stimuli (photographic images), and second; that each stimulus appeared for 3 seconds or less without intermission between the images.

Attention is divided between the emotional content and the task at hand, if an emotional stimulus appears when a subject performs a cognitive task. Instead the subject can focus relatively undisturbed on the task during the presentation of a neutral stimulus. If the major task of the MFC is to maintain attention and facilitate the entry into consciousness of salient inputs from other brain areas as proposed by Raichle et al. (2001) (see also Drevets and Raichle 1998; Simpson et al. 2001a, 2001b), divided attention must be linked to higher activity in the MFC than undivided attention. This is possible because two coincident salient inputs disrupt the default state less efficiently than a single input. Through the mechanism of surround inhibition simultaneous inputs to neighboring target neurons are mutually inhibitory, yielding relative disinhibition compared to the single input case (see Figure 28). This means that the activity in the medial frontal cortex, including the anterior cingulate as well as the medial and dorsomedial prefrontal cortex, is higher when subjects assign ratings to images with emotional content, rather than just passively view them (Taylor et al. 2003).

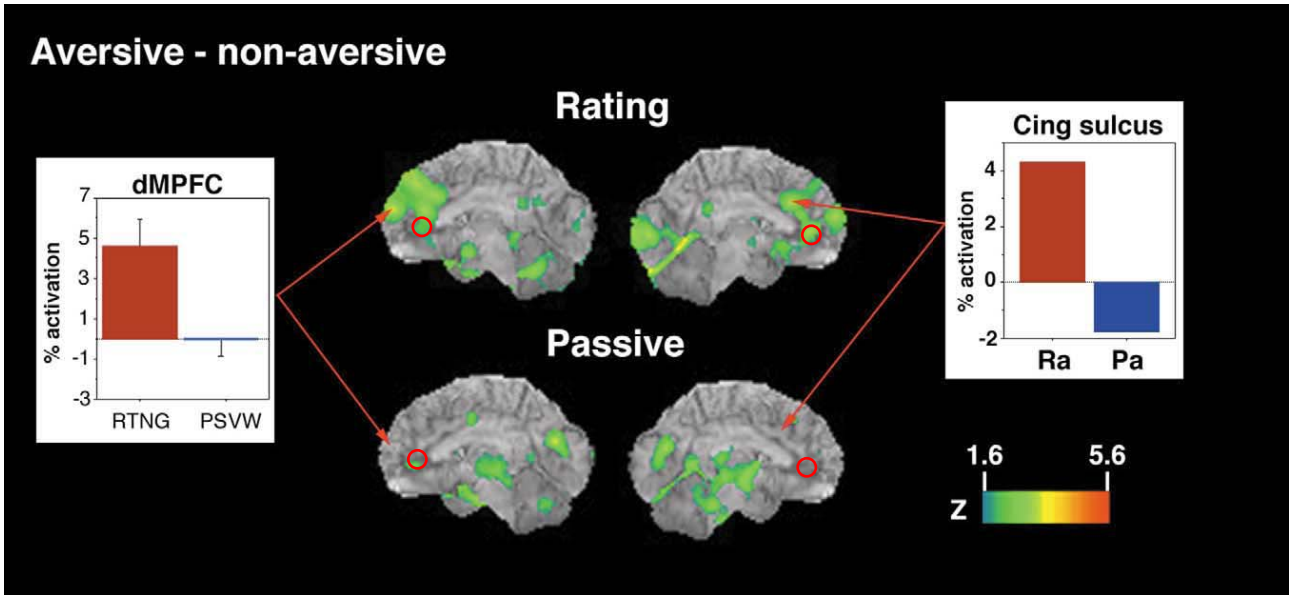


Fig. 12. Activation foci are mapped onto the right mesial surface (left column) and left medial surface (right column) surface renderings of a reference MRI brain in Talairach and Tournoux coordinates (figure from from S.F. Taylor et al. / NeuroImage 18 (2003) 650–659). The approximate y and z coordinates of the emotional deactivation, demonstrated by Geday et al (2003, 2007) are indicated by the red circles.

The task need not be explicit. Longer durations of emotional stimulation yield activations of the MFC. Previous physiological studies indicate that stimuli of durations of more than 3 s can be processed differently from stimuli of shorter duration. During 6-s presentations of affective images, blink inhibition wanes after 3 s (Bradley et al. 1993), and startle reflex potentiation by briefly (500 ms) displayed aversive pictures reaches maximum in 3 s (Codispoti et al. 2001). Pöppel (1997, 2004) concluded that attention to a stimulus allows entry of stimulus-related information for no longer than 2-3 s. When presentation persists, associations begin to compete for access to consciousness, and Pöppel claims that an endogenously generated question, ‘‘what is new?’’ arises every second to third second. To be consistent with Pöppel’s conclusion, any stimulus presentation that exceeds 3 s necessarily involves the implicit alternative cognitive tasks of interpretation and association evoked by the stimulus. During prolonged presentation of an emotional stimulus, the subject divides attention among the emotions evoked by the stimulus and their secondary cognitive associations. Geday et al. (2003) speculated that MFC deactivation during 3 s emotional stimulus presentation reflects involvement of MFC in attention rather than the processing of the emotional stimulus itself. Subsequent testing of this theory by extension of the stimulus duration from 3 to 6 s in half of the tomography sessions reverted the deactivation of the MFC elicited by the short duration emotional stimulation (Geday et al 2007).

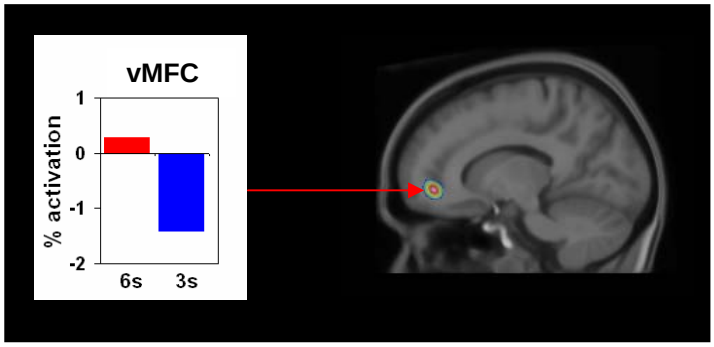


Fig. 13. The peak of the reversible emotional deactivation demonstrated by Geday et al (2007) laterally for, but close to, the clusters demonstrated by Taylor et al (2003) to be activated during rating of emotional content.

Thus, the current evidence from neuroimaging studies of emotional and cognitive processing suggests that the medial frontal cortex, through a mechanism of surround inhibition, selects the focus of attention among simultaneously arriving stimuli, projected to the frontal cortex from other brain areas. The activity of the MFC as measured by PET or fMRI in turn increases or decreases depending on the winning input, i.e., input that is sufficiently salient to inhibit the entry of other signals entering the area.

Monoamines and the MFC

In studies with PET or fMRI it is a frequent observation that examination of several subjects is needed to obtain a significant finding, as subjects have a considerable variation of the extent, to which a given paradigm activates or deactivates the brain area under study. This variability is particularly pronounced in the ventromedial prefrontal cortex (vMPFC), as revealed below by the sd-parametric map, calculated from the data of emotional perception published by Geday et al. in 2003.

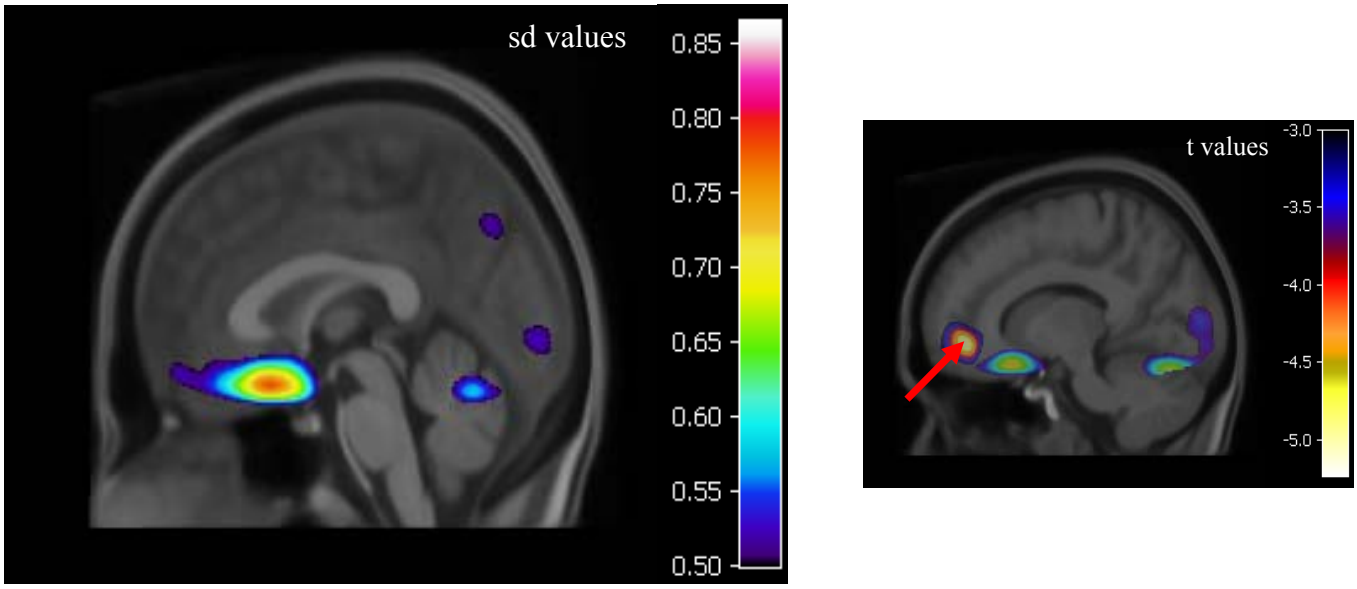


Fig. 14. Parametric map of the distribution of the standard deviations of rCBF measured by $H_2{}^{15}O$ PET in nine healthy male subjects while they passively view brief presentations of emotive or neutral images. As indicated on the small image; the area of maximum variation is situated just medial and rostral for the area in the right inferior medial prefrontal cortex (indicated by red arrow) reported as deactivated during the viewing of emotive images. Re-analysis of data from Geday et al 2003.

As an example, a region-of-interest analysis of a 10 mm diameter sphere, centred on the peak coordinates of emotional deactivation (Talairach coordinates 15, 51, -8 mm, Geday et al 2003) in 14 healthy subjects who view emotive or neutral images while they press a mouse button when images change every third second, shows that the co-existence of a simple and attentionally undemanding task during emotive stimulation, in five of the 14 subjects reverted the emotional deactivation found

in three previous studies (Paradiso et al 1999, Geday et al 2003, 2006 and 2007) to an activation.

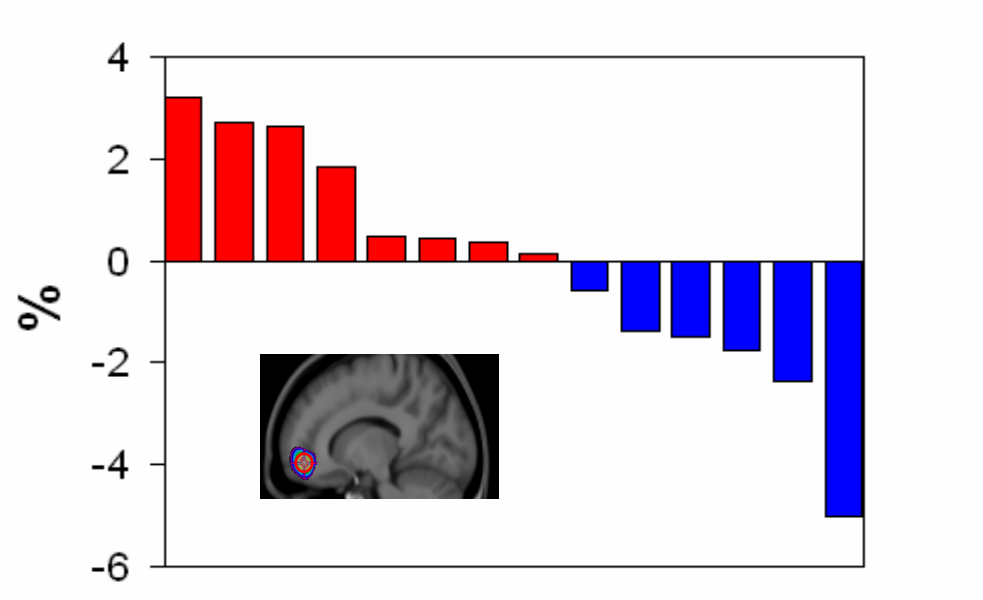


Fig. 15. Difference in rCBF as a percentage of normalized blood flow in 14 healthy subjects in a 10 mm diameter sphere, centred on the Talairach coordinates 15, 51, -8 mm indicated in the image, when emotive and neutral stimulation are compared (emotive – neutral). Data from Geday and Gjedde 2008a

Depending on the design of the study, the same stimulation in one subject may powerfully disrupt of the default activity, while in another, this does not happen. Thus activity in the MFC is influenced by individually variable factors other than emotional stimulation and attentional demand. Differences of monoaminergic innervation of the MFC may be such a factor.

As noted in the discussion of the anatomy, the medial prefrontal cortex (MPFC) receives projections from three monoaminergic systems. The monoamines serotonin, noradrenalin, and dopamine have different effects on MFC function (as described later), but the receptor systems share important functional characteristics. In the MFC monoamines have at least two pharmacologically and pharmacokinetically different receptors, in the form of specific excitatory and inhibitory receptors with different affinities towards the transmitter.

The conundrum of multiple receptor subtypes serving the same transmitter in the same region of the brain may be resolved by consideration of the concentration-dependent differential reactivity afforded when receptor subtypes of different density, affinity, and action (inhibitory and excitatory) coexist. The binding potential is an estimate of receptor availability, i.e.,

$$BP_{ND} = \frac{B}{C} = \frac{B_{max} - B}{K_d} = \frac{B_{max}}{K_d + C}$$

while the reactivity of a receptor system is the incremental binding of neurotransmitters obtained with a unit increase of transmitter concentration, in the simplest case equal to the slope of the Michaelis-Menten curve at any concentration. The reactivity is the magnitude of this slope,

$$R = \frac{dB}{dC} = B_{max} K_d / \left(K_d + C\right)^2 = BP_{ND} \frac{K_d}{K_d + C}$$

where R is the reactivity, B_{max} the receptor density, K_d is the affinity towards the transmitter, and C is the transmitter's concentration (from Geday and Gjedde 2008b). Thus, incremental binding leads to increased excitation if the receptor subtype mediates excitation, in addition to increased inhibition if the receptor subtype mediates inhibition. If two kinetically different receptor subtypes of opposite action both respond to the same transmitter, and if the maximum binding potentials are not the same, then the net effect of an increase in transmitter concentration will depend on the original concentration of the transmitter. At a specific threshold concentration (C_0), the effect of inhibitory and excitatory actions would then be expected to be equally large. The magnitude of this concentration is:

$$C_0 = K_e \frac{\sqrt{R_B R_K} - R_K}{1 - \sqrt{R_B R_K}}$$

where C_0 is the threshold concentration of the transmitter, K_e is the affinity of the lower affinity receptor, in this case the receptor mediating excitation, R_B is the ratio of inhibitory to excitatory receptor densities, and R_K is the ratio of inhibitory to excitatory receptor affinities (from Geday

and Gjedde 2008b). When the density of the receptors is the same, the effect of a transmitter surge below C_0 reflects the action of the high affinity receptor, while above this concentration the effect reflects the action of the low affinity receptor. The possible roles of each of the monoamines in controlling MFC reactivity is discussed below:

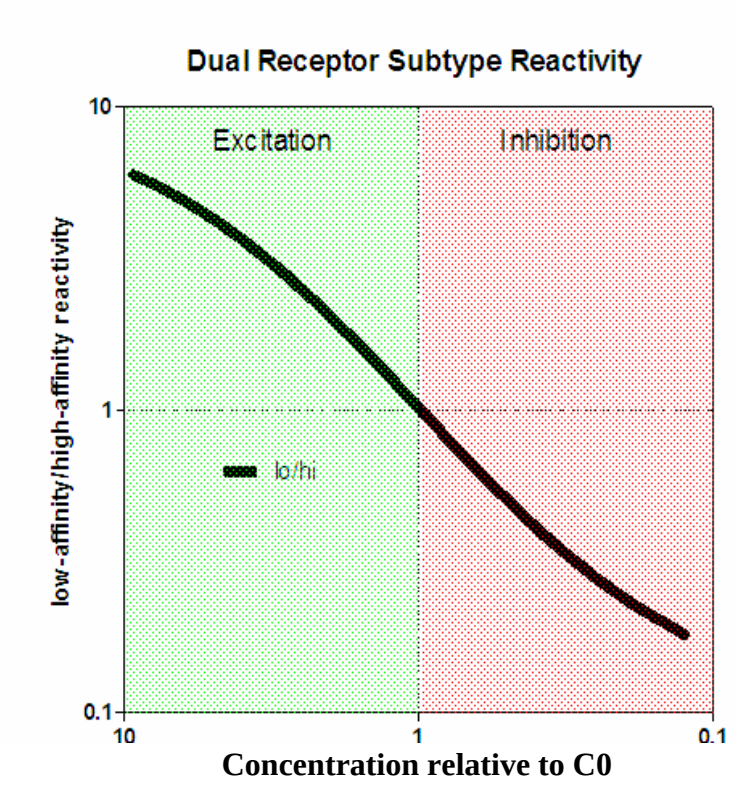


Fig. 16. If the high affinity receptor is inhibitory, and the low affinity receptor is excitatory, the net effect (inhibitory or excitatory) will depend on the transmitter concentration as illustrated on the figure (from Geday and Gjedde 2009)

SEROTONIN

There are seven main types of serotonin receptors (5-HT_1 to 5-HT_7) with at least 17 subtypes, of which the majority are present in the human brain. With the exception of the 5-HT_3 receptors, the serotonin receptors all belong to the G-protein coupled 7-transmembrane domains group of metabotropic receptors. Activation of these receptors trigger a postsynaptic cascade of intracellular

mechanisms, resulting in altered gene expression. The main effects and distributions of the majority these receptors are briefly summarized below.

The 5-HT_1 receptor group generally is inhibitory.

The density of 5-HT_{1A} binding sites is high in limbic brain areas, notably hippocampus, lateral septum, cortical areas (particularly cingulate and entorhinal cortex), and the mesencephalic raphe nuclei (both dorsal and median raphe nuclei). The receptors are located both postsynaptically in glutamatergic and cholinergic neurons in forebrain regions, and presynaptically as autoreceptors on the soma and dendrites of the 5-HT neurons in the mesencephalic and medullary raphe nuclei. (Barnes and Sharp 1999).

The 5-HT_{1B} receptors are situated presynaptically and postsynaptically in the basal ganglia, postsynaptically on glutamatergic neurons, and presynaptically on the 5-HT neurons as autoreceptors as well as on dopaminergic neurons as heteroreceptors modulating release of dopamine (Boschert et al., 1994, Castro et al., 1997).

The 5-HT_{1D} receptors are present in the basal ganglia (globus pallidus and substantia nigra) as well as in specific regions of the midbrain (periaquaductal grey) and spinal cord, located predominantly on axon terminals both of serotonergic and cholinergic neurons, where they function as autoreceptors and heteroreceptors (Castro et al., 1997).

The 5-HT_{1E} receptors are located postsynaptically in the cortex (particularly entorhinal cortex), caudate putamen and claustrum and have been detected in other areas, including the hippocampus and amygdala (Bruinvels et al., 1994).

5-HT_{1F} receptors inhibit excitation of cortical and hippocampal areas, claustrum and the caudate nucleus, but the receptors can be barely detected in the substantia nigra (Castro et al., 1997)

The 5-HT_2 receptors are largely excitatory.

Thus 5-HT_{2A} receptor activation results in neuronal excitation in many forebrain regions, particularly the neocortex, entorhinal and pyriform cortices, claustrum, caudate nucleus, nucleus accumbens, olfactory tubercle and hippocampus where the receptors are situated postsynaptically on glutamatergic and cholinergic neurons, but also on cortical GABAergic interneurons.

The 5-HT_{2B} receptors appear to be restricted to a few brain regions, particularly cerebellum, lateral septum, dorsal hypothalamus and medial amygdala (Duxon et al., 1997a+b).

The 5-HT_{2C} receptors (formerly 5-HT_{1C}) are excitatory in several brain regions including olfactory nucleus, pyriform, cingulate and retrosplenial cortices, limbic system (nucleus accumbens, hippocampus, amygdala) and the basal ganglia (caudate nucleus, substantia nigra) (Radja et al.1991). The receptor is predominantly postsynaptic, and mediates long-term effects by alteration of gene expression. (Barns and Sharp 1999)

For the 5-HT_3 receptors, it is known that the ligand-gated 5-HT_{3A} and 5-HT_{3B} receptors are excitatory, although little is known of their differences. Functionally, 5-HT_3 receptors are regarded as inhibitory because they stimulate GABAergic neurons in the prelimbic and cingulate areas of rats (Puig et al 2004). The highest levels of 5-HT_3 receptor binding sites exist within the dorsal vagal complex in the brainstem, and the 5-HT_3 receptor expression is low in the forebrain. Behavioural,

neurochemical and electrophysiological investigations indicate that the 5-HT_3 receptor modulates dopaminergic activity in the brain.

The 5-HT_4 receptors reside in the nigrostriatal and mesolimbic systems of the brain where they increase neuronal excitability and slow the repolarisation of cholinergic and dopaminergic neurons, but also the serotonergic neurons in the hippocampus region are subject to presynaptic 5-HT_4 receptor modulation (Barnes and Sharp 1999)

The 5-HT_{5A} receptors are inhibitory (Nelson 2004) and are distributed in the neocortex and hippocampus as well as predominantly in the Purkinje cells of the cerebellum in the dentate nucleus and, at a lower level, in the granule cells (Pasqualetti et al 1998). Their primary function may be that of presynaptic autoreceptors (Thomas 2006)

The 5-HT_6 receptors are excitatory, but like the 5-HT_3 receptors they may be functionally inhibitory as they are primarily expressed on GABAergic neurons (although there may be 5-HT_6 receptors on glutamatergic neurons in the hippocampus). The receptors are located in the striatum, nucleus accumbens, olfactory tubercle, and cortex, with moderate expression in the amygdala, hypothalamus, thalamus, cerebellum, and hippocampus. 5-HT_6 receptors appear only to be postsynaptic (Mitchell and Neumaier 2005)

The 5-HT_7 receptors are excitatory (both 5-HT_{7A} and 5-HT_{7B}), with relatively high expression is within regions of the thalamus, hypothalamus and hippocampus with generally lower levels in areas such as the cerebral cortex and amygdala. However little is yet known about the exact distribution.

When the general functions of the many 5-HT receptors are considered, the 5-HT_1 and 5-HT_{5A} receptors are inhibitory, whereas the rest are excitatory, although the 5-HT_3 and 5-HT_6 receptors re-

siding on GABAergic neurons may be functionally inhibitory as well.

The distributions of 5-HT receptor subtypes vary throughout the CNS, and individual brain regions have their own unique complement of 5-HT receptor subtypes, implying that the threshold concentration (C_0) defined above probably differs from region to region, and therefore that a uniform serotonin concentration as well as superimposed increases above the baseline in separate parts of the brain may have very different effects on neuronal activity.

For the medial prefrontal cortex the inhibitory 5-HT_{1A} and the excitatory 5-HT_{2A} receptor subtypes appear to dominate. As serotonin enjoys 50-1000 times greater affinity for $5HT_{1A}$ than $5HT_{2A}$ sites (Peroutka and Snyder 1983), the possibility of a variable effect of increases or decreases in baseline serotonin, as stated above, is clearly present in the MPFC.The 5-HT_{1A} receptors are unevenly distributed in the MPFC, and binding potentials (pB) are progressingly lower in the direction vMPFC > aMPFC > dMPFC (Bailer et al. 2007) as illustrated below.

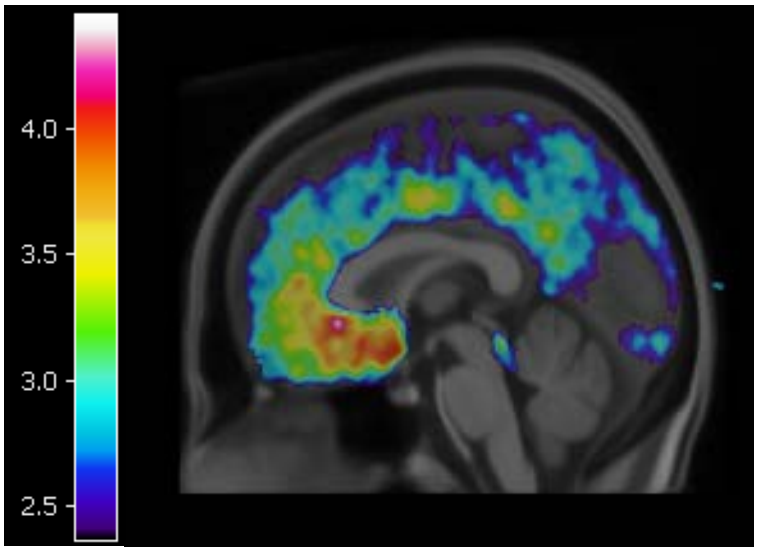


Fig. 17. Average [^{11}C]WAY100635 PET brain image of 5-HT1A receptors in 7 healthy young volunteer (reconstructed from Møller et al 2007).

Others have confirmed this distribution; Bailer et al (2007) found the binding potentials of [^{11}C]WAY100635 binding to 5-HT$_{1A}$ receptors to be highest in the subgenual cingulate/medial orbital cortex > pregenual cingulate > supragenual cingulate, as indicated on the figure above.

For the 5-HT$_{2A}$ receptors the distribution is slightly different;

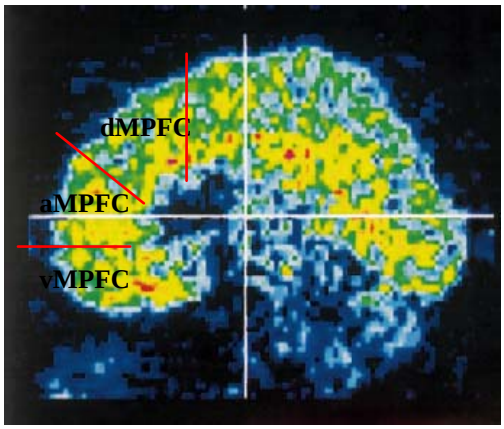


Fig. 18 Unquantified [^{11}C]MDL 100907 brain image of 5-HT$_{2A}$ receptors measured as specific binding relative to unspecific binding in the cerebellum. Red colors indicate the highest binding. From N.M. Barnes, T. Sharp : Neuropharmacology 38 (1999) 1083–1152

Bailer et al. (2007) also found the order of the magnitude of the binding of [^{18}F]altanserin to 5-HT$_{2A}$ receptors to be the highest in the subgenual cingulate or medial orbital cortex > pregenual cingulate > supragenual cingulate,with the highest variation among subjects in the inferior subgenual or orbital region although differences of binding potentials between the areas were smaller than for [^{11}C]WAY100635. The ratio of binding of [^{11}C]WAY100635 to binding of [^{18}F]altanserin is an approximation to the 5-HT$_{1A}$ to 5-HT$_{2A}$ receptor ratio.

When calculated from the findings from Bailer et al 2007, it appears that there is a 5% difference from the highest to the lowest ratio in the MFC, indicating the possibility of a variable C_0 within the area. With a high density of both inhibitory and excitatory receptors in MFC, especially when the baseline concentration of serotonin is near C_0, it is difficult to predict how a surge of serotonin, elicited by a pharmacological challenge with a serotonin reuptake inhibitor, may affect neuronal activ-

ity, as measured by changes of cerebral blood flow and glucose metabolism. Fenfluramine raises cerebral blood flow and glucose metabolism in the MFC (Kapur et al 1994, Meyer et al 1996, Mann et al 1996) as does clomipramine (Smith and Geday 2001). However the SSRI citalopram lowers both glucose metabolism in the MFC (Smith et al 2002), and blood flow significantly more than clomipramine when the effects of the two are directly compared (Geday et al 2005). The results of these studies are shown in the figure below:

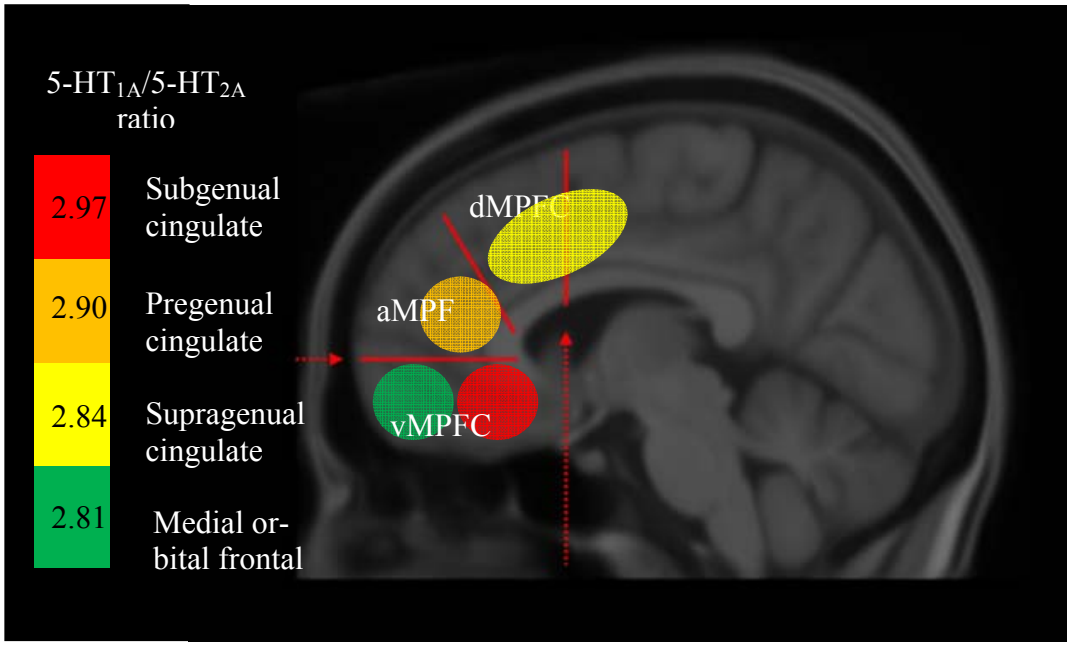


Fig 19. Estimates of 5-HT$_{1A}$/5-HT$_{2A}$ ratios based on the results reported by Bailer et al 2007, the largest differences in ratios are found in vMFC between cingulate and orbital cortex.

These rather dispersed sites may reflect diverse selectivity for serotonin (clomipramine is a dual serotonin- and noradrenalin reuptake inhibitor)) of the three serotonin reuptake inhibitors, dissimilar side effects (Geday et al 2005 reported nausea as a side effect for citalopram), or different magnitudes of the serotonergic surge elicited from fenfluramine, clomipramine, and citalopram.

More importantly, the variation among individual subjects is less for the binding of [^{18}F]altanserin than for the binding of [^{11}C]WAY100635. In Figure 21, the percentage coefficient of variance (COV) of binding potentials of [^{11}C]WAY100635 and [^{18}F]altanserin indicate the variations of 5-HT1A and 5-HT2A receptor densities within the brains of normal young (female) subjects based on the values of the four areas of the MFC recorded by Bailer et al 2007.

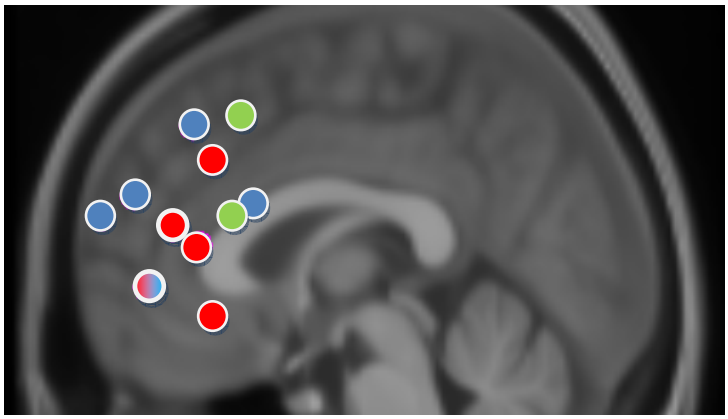


Fig. 20. Activity changes in the MFC measured by blood flow or glucose metabolism elicited by a pharmacological challenge of fenfluramine (Kapur et al 1994, Meyer et al 1996, Mann et al 1996, increases of activity, marked by red circles), clomipramine (Smith and Geday 2001, increases and decreases of activity, marked by thick circlelines, one is on top of a fenfluramine increase from Meyer et al 1996, marked with red and blue), citalopram (Geday et al 2005, decreases of activity, marked by blue circles) and finally the coordinates where citalopram decrease blood flow significantly more than clomipramine (marked with green circles). All points shown by y and z coordinates; projected to the x = 2 plane.

	Supragenual cingulate cortex	Pregenual cingulate cortex	Subgenual cingulate cortex	Medial orbital cortex
[^{11}C]WAY100635	0,918/3.738 = 24.6%	1.186 /4.543 = 26.0%	1.221/4.700 = 26.0%	1.245/4.667 = 26.7%
[^{18}F]altanserin	0.253/1.317 = 19.2%	0.265/1.566 = 16.9%	0.299/1.584 = 18.9%	0.284/1.662 = 17.1%

Figure 21. For the four areas in the MFC investigated by Bailer et al (2007) percentage COV of binding potentials for [^{11}C]WAY100635 and [^{18}F]altanserin are calculated as percentages of the mean. The difference of variation of binding potentials of the two ligands is highly significant ($p < 0.001$). Based on the results reported by Bailer et al 2007.

The dissimilar variations of the 5-HT_{1A} and 5-HT_{2A} receptor density imply considerable individual variation of the ratio between inhibitory and excitatory 5-HT receptors in the MFC, especially in the inferior medial prefrontal cortex (IMPC). Accordingly the vMFC and dMFC threshold concentrations (C_0) may be different for different subjects.

As the IMPC becomes more or less activated when a person is engaged in a task of identification or experience of emotions, the interpersonal variability of reactivity to an emotional stimulation may relate to the formal IMPC reactivity determined for the serotonergic system by the ratio of 5-HT_{1A} to 5-HT_{2A} receptors and the baseline level of serotonin.

Geday and Gjedde (2008b) tested the emotional reactivity of nine subjects who previously had PET of blood flow changes after IV infusion of clomipramine. All subjects rated images of the standard series of emotive images (Empathy Picture System), with four pleasant, four neutral, and four unpleasant (aversive) image series (see Geday et al 2002, 2003 and 2006) on a scale from -3 for the most unpleasant to +3 for the most pleasant.

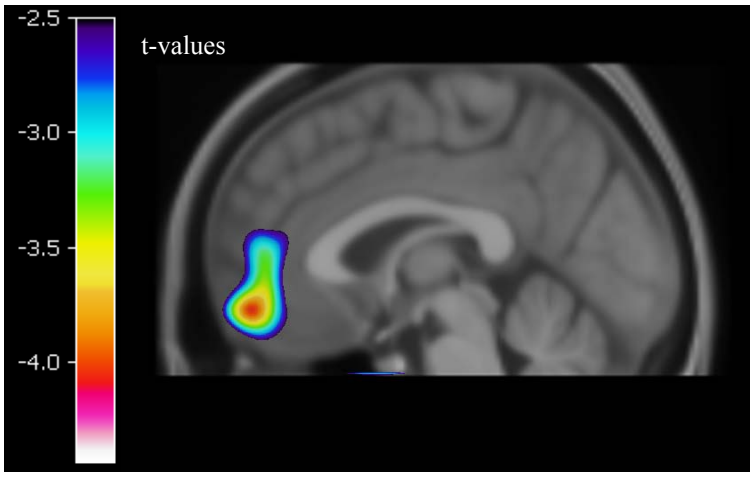


Fig. 22. The area of the IMPC where there is a significant interaction between emotional impact and blood flow changes elicited by a surge of clomipramine (from Geday and Gjedde 2008b)

To measure emotional impact, the average individual score of pleasant images series was subtracted from the average score of unpleasant images. For each person, the emotional impact scores were used as regressors for this person against the changes of cerebral blood flow elicited by a previous challenge with clomipramine. The analysis revealed that emotional impact is inversely and significantly correlated with the effect of a serotonin-noradrenaline reuptake inhibitor on blood flow in Brodmann's area 11 of the inferomedial prefrontal cortex (IMPC), in the part of the vMPFC (medial orbital cortex). As described above, this is a site where there is a considerable difference in the COV between the 5-HT_{1A} and 5-HT_{2A} receptors, and thus a site where on the potential for individual differences of the ratios between the two receptors is the greatest.

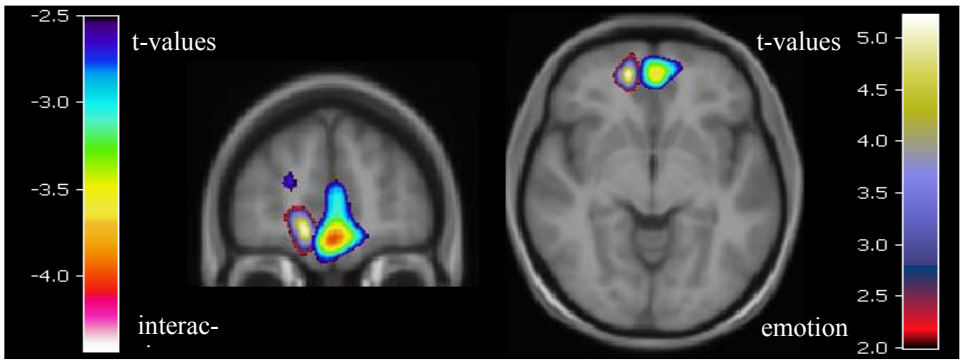


Fig. 23. The area of interaction between emotional impact and blood flow is right next to the area deactivated by emotive images from the very same EPS-series (Geday et al 2003, 2006 and 2007)

The actual changes of blood flow at this site, measured with PET as normalized $H_2{}^{15}O$ radioactivity, show that subjects with a low emotional impact increase regional cerebral blood flow (rCBF) in the IMPC after increase of monoamine; whereas high responders decrease rCBF after the clomipramine challenge. The inverse relationship suggests that the personal trait of affective impact of emotive stimuli is closely related to the specifics of monoaminergic receptors in the prefrontal cortex. The findings are evidence that individual differences of the ratio between inhibitory 5-HT_{1A} receptors and excitatory 5-HT_{2A} receptors in the IMPC may be an important predictor of this personality trait. This need not be the only example of the role of monoaminergic neuromodulation. Differences in the baseline concentration may play another important role.

Fig. 24. The relationship between emotional impact of the EPS series (x-axis) in nine healthy individuals and changes of blood flow elicited by a surge of clomipramine (y-axis). On average EPS has an emotional impact of 2.75 on normal controls, leading on average to a decrease of rCBF. From Geday and Gjedde 2009.

Pathological crying is a state of extreme emotional reactivity, in which patients react disproportionately by weeping when faced with stimuli that are trivial or of little emotional impact by their own admission. This condition is often seen after stroke and other cerebrovascular incidents and is most likely caused by central depletion of serotonin. The syndrome is reversed by administration of a selective serotonin re-uptake inhibitor (SSRI) with apparent dramatic and immediate effect (Andersen et al 1993, House et al 2004).

For stroke patients with pathological crying Møller et al (2007b) demonstrated a higher occupancy of 5-HT_{1A} receptors in the IMPC after effective treatment with SSRI than before treatment, which is possibly due to an increase of the concentration of available serotonin. The change of baseline serotonin from a pathologically low level below C_0 towards the normal level, shifts the patients' emotional reactivity from a condition of excessive reactivity to more normal reactions as predicted from the pharmacodynamical dual-receptor model.

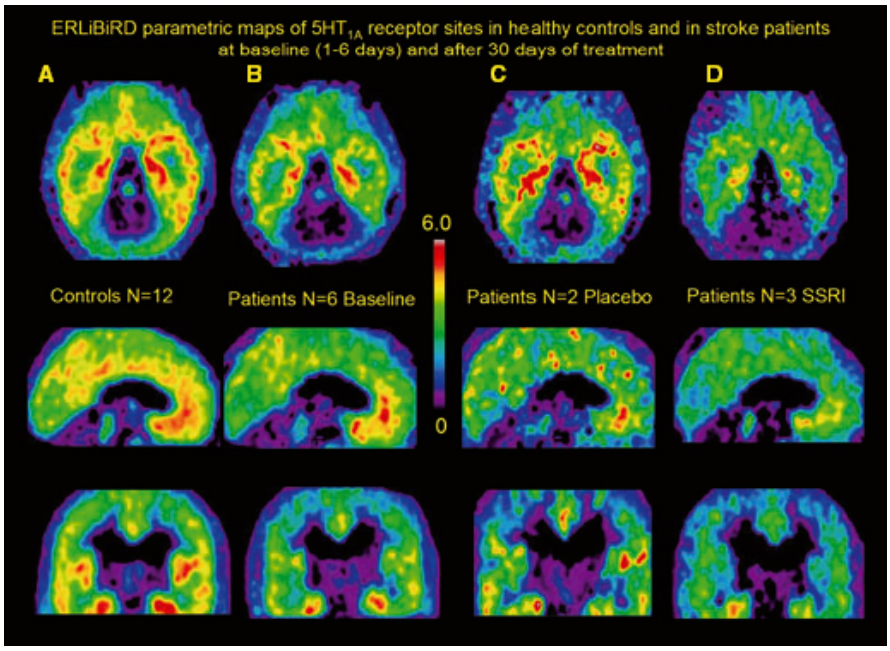


Fig. 25. Parametric maps of binding potentials (pB) of radioligand [carbonyl–11C]WAY-100635 before and after treatment with citalopram (SSRI) of six patients with pathological crying, compared with 12 healthy age-matched controls (from Møller et al. Acta Neurol Scand. 2007 Aug;116(2):83-90)

Constitutional susceptibility may share a mechanism with this dual-receptor concept. Variations of the serotonin transporter gene may contribute to this. In normally healthy subjects, the frequencies of the alleles "long" (l) and "short" (s), in a variable repeat sequence in the promoter region (SLC6A4) of the serotonin transporter (5-HTT) gene, have been implicated in traits of personality (Greenberg, 1996). Cultured lymphoblasts that are homozygous for the l allele (l/l) have a higher concentration of 5-HT transporter mRNA and express a nearly twofold increased 5-HT reuptake capacity compared to cells having either one (l/s) or two copies (s/s) of the s allele (Lesch et al., 1996), implying that the extracellular baseline concentration of serotonin may be lower in l/l subjects and higher in s/s and s/l subjects. Graff-Guerrero et al (2005) found that glucose metabolism is higher in Brodmann area 10 and 11 of the inferomedial prefrontal cortex for s/s than for l/l or s/l. This finding could reflect differences of the concentration of serotonin, as a lower concentration would favor activation of the high affinity inhibitory 5-HT_{1A} receptors. However, it remains to be established to which extend differences in baseline concentrations of serotonin play a role in the emotional perception and reactivity of normally healthy subjects.

NORADRENALINE

As no completely selective PET adrenoceptor tracers yet exist for human in vivo studies, the neuroimaging evidence of noradrenaline is sparse compared to serotonin and dopamine. There are three main types of noradrenergic receptors; α_1, α_2 and β, each subdivided into three subtypes.

Adrenoceptors belong to the 7-transmembrane domains group of metabotropic receptors. The α_1–receptors are excitatory and cause depolarization of neurons; however, the subcellular localization of these receptors is not yet established. There are three subtypes: α_{1A}, α_{1B}, and α_{1D} (Ramos 2007). Compared to the rest, the α_1–receptors have an intermediate affinity for noradrenaline with an EC_{50} of 330 nM, according to Ramos and Arnsten (2007). The α_{1A} and α_{1D} receptors

are most prominent in rodent PFC (Pieribone et al., 1994), but the functional differences of the subtypes remain to be established. In primate PFC, α_1 receptors are concentrated in the superficial layers of the cortex (Goldman-Rakic et al., 1990), as are the α_2 receptors.

The α_2–receptors are inhibitory with three subtypes, α_{2A}, α_{2B} and α_{2C} . The α_{2A}, and α_{2C} adrenoceptors are presynaptic on noradrenergic neurons and terminals as autoreceptors, and all three subtypes are found post-synaptically (MacDonald et al. 1997). The α_2–receptors have six–fold the affinity of the α_1–receptors for noradrenaline with an EC_{50} of 56 nM (Ramos and Arnsten 2007). In rodents as well as primates, the α_{2A} receptor is the most common subtype in the PFC (Aoki et al., 1994). In pigs, the distribution of α_{2A} receptors in the MPFC measured by binding of [^{11}C] yohimbine (Jakobsen et al 2006) differs from the inhibitory 5-HT_{1A} receptors measured by [^{11}C]WAY-100635 (Cumming et al 2007) by being more homogeneous in the prefrontal cortex, without tendency towards maximal receptor density in the most rostral parts. As the distribution of 5-HT_{1A} receptors is similar in the prefrontal cortex of pigs and humans, it is not unlikely that α_{2A} receptors are also more homogeneously distributed in the MPFC than their serotonergic counterpart in humans. However future [^{11}C]yohimbine studies in humans may clarify this.

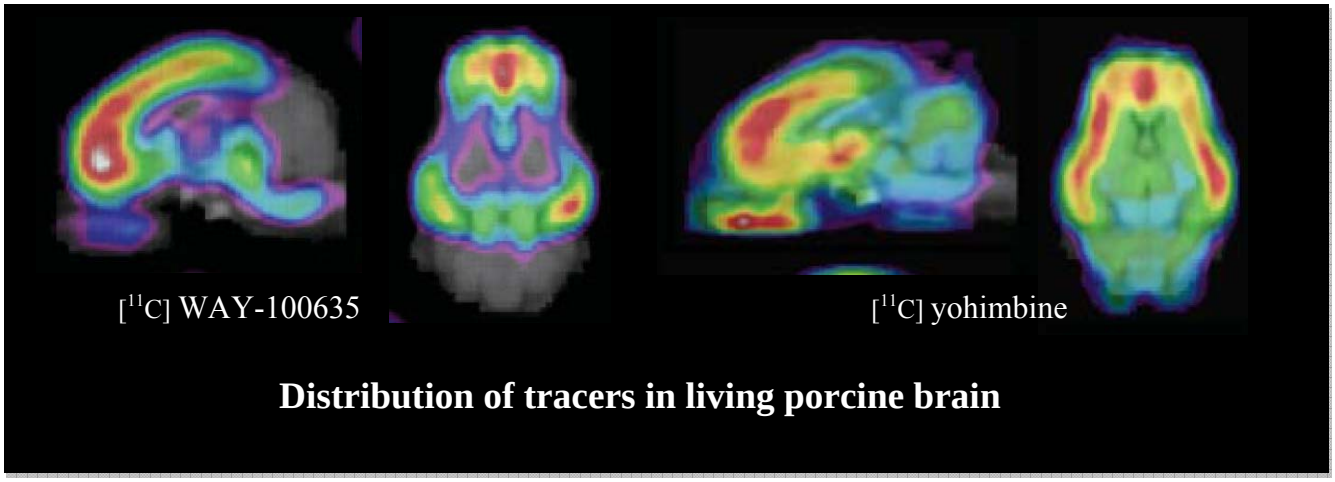


Fig. 26. Parametric maps of [^{11}C]WAY-100635 and [^{11}C] yohimbine binding in living porcine brain. Note that the distribution of [^{11}C]WAY-100635 in the MPFC is very similar to that found in humans. From Cumming et al 2007 and Jakobsen et al 2006.

The β–receptors are excitatory. There are three subtypes, β_1 (located mainly in the heart), β_2 (located mainly in the lungs), and β_3 (located mainly in the stomach). All subtypes are also found in the central nervous system. The β receptors have a low affinity for noradrenaline with an EC_{50} of 740 nM according to Ramos and Arnsten (2007). In the PFC, the β1 and β2 adrenoceptors are most prominent in the intermediate layers (Goldman- Rakic et al., 1990) where thalamic inputs converge. There are further β–receptors in the amygdala and hippocampal formation where they play a critical role in memory consolidation.

I suggested above that the main function of the MFC could be the choice among incoming signals and the selection of the most salient by GABAergic surround inhibition mechanism of the less salient input (Wilson et al 1994, Rao et al 1999). An attenuation of glutamatergic neuronal activity consequently will facilitate this selection process by inhibition of the less salient inputs, while increasing neuronal activity has the opposite effect. Assuming the baseline concentration of noradrenaline to be below C_0, from the theory above it follows that a minor increase of available noradrenaline sustains frontal function during attention to a demanding task (Arnsten 2006) by preferentially stimulating inhibitory α_2–receptors with the highest affinity for noradrenalin. The PET-deactivation of the vMPFC elicited by increasing task complexity, described by Geday et al in (2008a) could be a consequence of such increased α_2–receptor binding of noradrenaline.

In contrast, a huge stress-induced noradrenergic surge raises the concentration of noradrenaline above C_0 and engages frontal low-affinity α_1 and β receptors, overriding the otherwise dominant high-affinity α_2–receptors with the opposite effect and compromise of frontal function as stated by Ramos and Arnsten (2007):

"The PFC successfully guides behavior under nonstressful conditions when we feel in control. However, there is abundant evidence that the PFC goes "off-line" during stress. Our emerging picture suggests that the PFC may be modulated differently than other than brain regions, and that the neurochemical conditions that are optimal for PFC are suboptimal for posterior cortical and subcortical regions, and vice versa."

The noradrenaline level is high, during stress-full situations. The elevation favors the function of brain areas where excitation rather than inhibition is crucial for optimal function, such as the amygdala, hippocampus, sensory-, and motor cortices and cerebellum. The increase allows more habitual or reflexive mechanisms to regulate behavior in dangerous situations, and hence to have a survival value in situations with little or no time for careful consideration.

DOPAMINE

Dopamine receptors belong to the 7-transmembrane domains group of metabotropic receptors. There are five types in the human brain (D1 to D5) in two subgroups of opposite actions: The high affinity excitatory D1-like receptors (D1 and D5) are positively coupled to adenylate cyclase, and the low affinity inhibitory D2-like receptors (D2, D3 and D4), inhibit adenylate cyclase.

D1-like receptors. The D1 and D5 receptors are widely distributed in the central nervous system, albeit not to the same extent everywhere. In the striatum and nucleus accumbens, the D1 receptors are most prominent, and exclusively reside on GABAergic neurons, while the D5 receptors appear to dominate elsewhere, particularly on cholinergic neurons in the basal forebrain, where the highest density of D5 receptors is found (Ciliax et al 2000), but also in the globus pallidus and the thala-

mus, where the D1 receptors are sparse (at least in monkeys). The D5 receptor frequently is described as less abundant than the D1 receptor; but most studies used estimates of mRNA expression. In more direct measurements, Khan et al (2000) found that D1 receptor antibody immunoprecipitates only 35% of the D1-like receptors in the rat cortex. It is noteworthy to observe that dopamine (DA) is ten times more potent at the D5 receptor than at the D1 receptor (Sunahara et al 1991). For that reason the D5 receptor may functionally be the dominant receptor in the prefrontal cortex (PFC) where the two receptors are equally expressed on both glutamatergic and GABAergic neurons (Bergson et al 1995, Ciliax et al 2000). The D5 receptors are diffusely distributed in all cortical layers of the PFC with the strongest expression in layer V (Lidow et al 1991). The D1 receptors are distributed in a laminar pattern; predominately in the supragranular layers II and upper part of III and layers V-VI (Bergson et al 1995, Ciliax et al 2000, Khan et al 2000). All these layers are characterized by a horizontal fiber direction, primarily derived from numerous GABAergic interneurons connecting neighboring groups of glutamatergic output neurons, as opposed to the primarily ascending or descending (pyramidal) fibers in the lower part of layer III and layer IV.

The subcellular distribution of the D1-like receptors is complex: postsynaptically, D1 receptors are abundant on the dendritic spines with glutamatergic input; whereas D5 receptors dominate on the shafts of dendrites with glutamatergic and GABAergic synapses. Presynaptically, D1 receptors are found in the prefrontal cortex on 13% of the axons forming glutamatergic synapses, whereas D5 receptors are present on 31%. GABAergic axons have only few D1 and D5 receptors (Paspalas and Goldman-Rakic 2004). In general, novel and salient stimuli activate the mesocortical dopaminergic system, probably reflecting attention-inducing properties of these stimuli (Schultz 2002). During a dopaminergic surge, D1 and D5 facilitation of the plateau depolarization of glutamatergic neurons opens a temporal window in which the prefrontal pyramidal neurons are synchronized and

"readied to fire" if further input indicates that this is necessary (Tseng and O'Donnel 2005). Activation of D1 and D5 receptors is critical for memory encoding in the hippocampus (O'Carrol et al 2006). In the prefrontal cortex D1 and D5 receptor facilitation of long term potentiation (LTP) is important in working memory (Gurden et al 2000). There is evidence that the number of D1 receptors on glutamatergic pyramidal neurons increases significantly during puberty. This increase in dopaminergic excitation of glutamatergic NMDA receptors (and thereby long-term potentiation) may be critical for the neuroplasticity that underlies normal maturation of cognitive abilities (Tseng and O'Donnell 2005).

D2-like receptors: The highest concentration of D2 receptors is found in the striatum, and cerebral cortex has 10-fold lower levels. In the cortical areas, the temporal cortex has higher levels of D2 receptors than the motor and somatosensory cortices surrounding the central sulcus (Lidow et al 1998). The D3 receptors are present in equally low concentrations in striatum and cerebral cortex, but within these areas, motor and somatosensory cortices and caudate nucleus have relatively higher concentrations (Schmauss et al., 1993). The D4 receptor is the dominant D2-like receptor in the cortex, particularly in the temporal, entorhinal, and prefrontal cortices (Primus et al 1997). In the frontal cortex, the D2-like D4 receptors modulate activity of GABAergic and glutamatergic neurons (Mrzljak et al 1996). The D2 receptors activate fast-spiking GABAergic interneurons after, but not before, adolescence, indicating that D2 receptors attenuate local excitatory synaptic transmission in the adult PFC, and this effect of D2 is obtained by recruitment of local GABAergic activity (Tseng and O'Donnell 2007).

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) may offer glimpses of the dopaminergic system. The effect of STN-DBS in patients with Parkinson's disease (PD) is somewhat

controversial: On basis of experiments on rats Benazzouz and Hallett (2000) claimed, that STN-DBS increases the release of glutamate and dopamine in the substantia nigra and striatum, respectively. Meissner et al (2002) confirmed the finding, also in rats, and explained the finding by STN-DBS disinhibition of neurons in substantia nigra pars compacta by inhibition of GABAergic neurons in substantia nigra pars reticulata. With [^{11}C]raclopride-PET of patients with PD, Hilker et al (2003) found no evidence of increased striatal dopamine in effective STN-DBS, and concluded that modulation of dopaminergic activity is not critical to STN-DBS's mechanism of action. Yet, two years later, with [^{11}C]raclopride-PET, Nimura et. al (2005) found that STN-DBS did modulate dopaminergic activity. Low DA concentrations (< 1 μM) preferentially activate D1-like receptors; whereas higher concentrations activate D2-like receptors (Trantham-Davidson et al 2004). As [^{11}C]raclopride targets lower affinity inhibitory D2/D3 receptors, preferentially found on tonically firing medium spiny GABAergic neurons of the striatopallidal "indirect" pathway (Gerfen et al., 1990, Ade et al 2008), it is possible that the baseline concentration of DA is so low in some PD patients, that the increase in DA elicited by the STN-DBS is insufficient to alter the occupancy of the D2/D3 receptors significantly, and thus undetectable in PET studies with [^{11}C]raclopride of these patients. Therefore, STN-DBS may raise dopaminergic activity in patients with PD, and increase DA concentration within the low range (< 1 μM), and facilitate movement, by activating high affinity excitatory D1 receptors on phasically firing medium spiny neurons of the striatonigral "direct" pathway (Gerfen et al., 1990, Ade et al 2008).

The fusiform gyrus in the inferior temporal lobe is part of the ventral stream associated with object recognition (Macko et al., 1982), and is robustly activated by emotive visual stimuli (Phan et al., 2002, Geday et al. 2001, 2003, 2007 and 2008a). This region is a target of basal ganglia output from striatal, "direct" pathway, GABAergic, medium spiny neurons, expressing D1 receptors, via the

substantia nigra pars reticulata and the thalamus (Gerfen et al. 1990; Middleton and Strick 1996). In patients with Parkinson's disease, deep brain stimulation of the subthalamic nucleus (STN-DBS) is known to impair their ability to correctly identify facial expressions of negative emotions (Schroeder et al., 2004; Dujardin et al., 2004; Biseul et al., 2005). Geday et al. (2006) showed that PD patients rated facial expressions in general as less pleasant on STN-DBS than off STN-DBS. They found STN-DBS to inhibit the increase of activity in the lateral fusiform gyrus normally induced by emotive stimulus relative neutral stimulus, by a non-physiological rise of activity in the area during neutral stimulation. They deducted that the STN-DBS induced increase in fusiform activity during neutral stimulation was caused by a D1 receptor driven output from the striatonigral pathway and that this explained the diminished ability by STN operated PD patients to recognize emotions expressed in faces.

High frequency stimulation of the subthalamic nucleus significantly inhibited the normal decrease of blood flow in the vMFC of patients with Parkinson's disease, who view images of varying emotional contents (Geday et al 2006, see Figure 27). This change in rCBF need not be an indirect consequence of the reduced emotional fusiform output to the vMFC as described above, but can also be the result of a minor STN-DBS induced increase in prefrontal dopaminergic innervation, directly stimulating D1/D5 receptors on GABAergic interneurons. In the presence of a emotional stimulation during eight of the 12 scans, with active glutamatergic pyramidal output neurons in the lower parts of the PFC, further dopamine-dependent activation engages the center-surround inhibition by GABAergic interneurons, as described above, leading to the net decrease in rCBF. The explanation may also simply be that adrenoceptors also respond to dopamine. The affinity (EC_{50}) of DA for α_1 receptors is 5 μM (Rey et al 2001), against the affinity for NE of 1.7 μM (Hieble and Ruffolo 1996), and for α_2 receptors of 40 μM (Cornil et al 2002), against the NE affinity of 56 nM

(Ramos and Arnsten 2007). For β receptors, the affinity for DA is 10 μM (Swaninath et al 2004), against 740 nM for NE (Ramos and Arnsten 2007). Theoretically the deactivation can be a consequence of further attenuation of vMFC neuronal activity elicited by dopaminergic stimulation of α_2-receptors on neurons, deactivated by emotional content. However as the α_2 receptor affinity for DA is as low as 40 μM, this explanation seems less likely.

The part of vMFC deactivated by STN-DBS (data from Geday et al 2007) is situated next to the area previously deactivated by emotional contents (Geday et al 2003, 2007). There is a significant interaction between patients' individual emotional reactivity, measured off STN-DBS, and the effect of STN-DBS on rCBF in the overlapping area, similar to what is seen for a surge of clomipramine and emotional reactivity. Therefore it is possible that also dopamine, regardless of the receptors involved, modulate emotional perception.

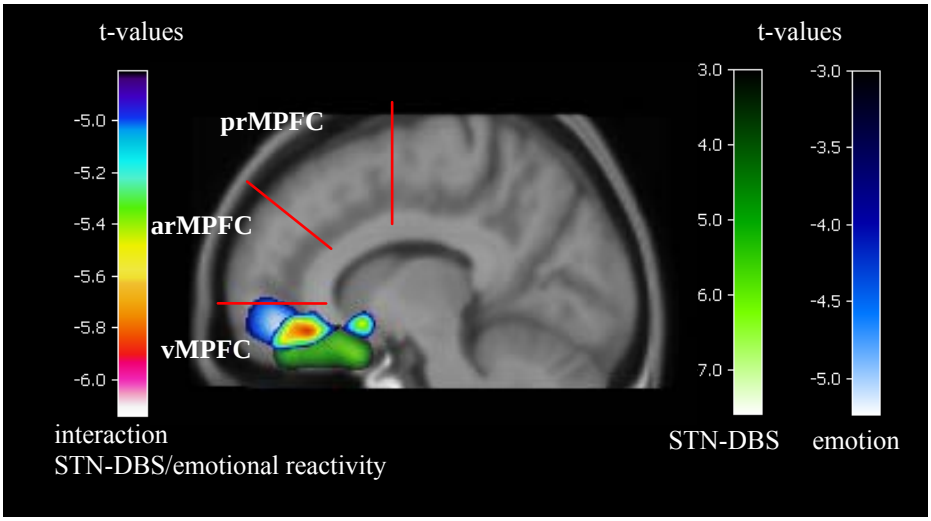


Fig. 27. Parametric maps of significant changes in rCBF. To the right elicited by STN-DBS (green bar, data from Geday et al 2007) and viewing of emotive contents (blue bar, data from Geday et al 2003). To the left the interaction between STN-DBS elicited changes in rCBF (data from Geday et al 2007) and emotional reactivity measured while the patients were of STN-DBS (data from Geday et al 2006)

To summarize the effects of monoaminergic stimulation of the MFC: serotonin and noradrenalin, where the receptors primarily are localized postsynaptically on glutamatergic neurons, mainly modulate the entry of inputs into attentional focus.

The different ratios between inhibitory $5HT_{1A}$ and excitatory $5HT_{2A}$ receptors, may cause lower concentrations of serotonin to favor attentional processing in the inferior orbitofrontal parts of MFC involved in emotions, rewards and punishments, whereas higher concentrations support processing in the upper parts of MFC, engaged in motor planning and outcome monitoring. Lower serotonin levels tend to shift attention inward, thus introverting the individual, whereas higher concentrations favor extroversion and outward attention.

Many people experience seasonal mood changes. In the winter when serotonin levels are lower some people tend to be more reserved, passive and even depressed (Neumeister et al 2001, Levitan el al 2004), than in the summer when serotonin levels are higher. This mechanism makes sense from an evolutionary point of view: When it is cold and there is not much food, it is important to be conservative, to stay in the warm cave, and pay attention to yourself and those close to you, rather than to the unfriendly world outside. This is in contrast to the summer, when it is important to expand the territory, conceive children, gather supplies and make preparations for the coming winter. As the variation of the density of $5HT_{1A}$ receptors is higher than of $5HT_{2A}$ receptors, individual differences in the ratio between the two may be considerable and may be an important factor determining a person‘s introversion or extroversion (Borg et al. 2003)

When regarding noradrenalin a similar but slightly different pattern pertains: A small surge of

noradrenaline activates preferentially inhibitory α_2-receptors but a huge surge activates excitatory β- and α_1 receptors. Low levels of noradrenaline help focusing attention, whereas high levels have the opposite effect. There is a small phasic increase of noradrenaline when an attentionally demanding task is performed. The consequent attenuation of neuronal activity helps remove "noise" from irrelevant inputs, and assists the focus on the task at hand. As opposed to the "fight-and-flight" situations when adrenaline and noradrenaline rise rapidly to high levels, the β- and α_1 receptor mediated increase of MFC neuronal excitability eliminates the GABAergic (attentional) surround inhibition, leading to functional arrest of the frontal lobes. In areas where excitation rather than inhibition is crucial for optimal function, such as the amygdala, hippocampus, sensory, and motor cortices, and cerebellum, the function is enhanced, allowing habitual and reflexive mechanisms to control behavior. The cave-man above now goes bear hunting: when he tracks and stalks the bear, his attention is focused on small traces and signs. In this situation, a small noradrenergic surge enables the required processes in the upper part of the MFC. Suddenly and unexpectedly, the bear turns around and attacks the caveman. Now the situation has changed dramatically and there is no time for careful consideration. Noradrenaline rises and the posterior parts of the brain take over: our caveman panics and flees head over heels as fast as he can, getting far away from the danger, without bothering to speculate about which direction is the better, or how his less fortunate mates are faring.

Dopamine (DA) differs from the other main monoamines by its role in adjusting activity in GABAergic interneurons and hence by the subsequent handling of input permitted by the serotonergic and noradrenergic gating mechanisms proposed above. Psychotic patients loose contact with reality and react inappropriately to external stimuli. The classical dopamine hypothesis of psychosis is a model attributing psychotic and manic symptoms to hyperactive dopaminergic signal transduc-

tion (Seeman 1987). The model draws evidence from the observation that a large number of antipsychotic drugs have DA-antagonistic effects, just as drugs like amphetamine and cocaine that increase levels of dopamine in the brain can cause psychosis, particularly after large doses or prolonged use. It is fair to claim that the level of extracellular dopamine plays a critical part in determining whether, and how, a given input leads to a reaction. Like serotonin, dopamine has seasonal and circadian rhythms (Levitan el al 2004) indicating a possible reciprocity of the two monoamines. The explanation possibly is an evolutionary advantage similar to the one suggested for serotonin: In times of limited sunlight, (nights and winter) the need for action is limited and the level of dopamine falls (Partonen 1996) promoting energy-conservative, risk evasive, passive and perseverating behavior, whereas it rises during the day and in the summer where many things need to be done. The existence of several serotonergic receptors with a direct or indirect effect on the activity of dopaminergic neurons (see above) supports this interpretation.

Discussion

It is well-documented that the medial frontal cortex is a significant and important node in the neuronal network involved in attention. The function of the MFC enables the individual to select the focus of attention among stimuli received in parts of the brain that project to the prefrontal cortex. Current evidence indicates that the choice is made by means of a mechanism of lateral inhibition, by which GABAergic interneurons in the MFC modulate excitability and activity of the pyramidal neurons that receive the signals from other brain areas.

All areas of the brain have a specific baseline, i.e., a resting condition to which the activity defaults when no task worthy of attention is in focus. In any area of the brain, the energy turnover measured as PET or fMRI estimates of blood flow or metabolism, matches the neuronal activity in that area. When a test situation raises excitatory neurotransmission by increased depolarization, compared to baseline, net energy turnover rises. If a test situation raises inhibitory neurotransmission compared to the baseline, net energy turnover falls. Although excitation of an inhibitory neuron demands as much energy as the excitation of an excitatory neuron, the vast majority of neurons in neocortex are excitatory, as few as 1/4 of the neurons in human prefrontal cortex are inhibitory. Therefore reduced repolarization of excitatory neurons saves more energy than expended by the depolarization of GABAergic neurons, particularly in an area such as the MFC, where the normal default is a high rate of energy turnover.

From these observations I conclude that changes of blood flow and glucose consumption in the MPFC depend on whether the test situation compared to the baseline introduces a signal that is sufficiently salient to inhibit the entry of competing signals to region (See Figure 28 below).

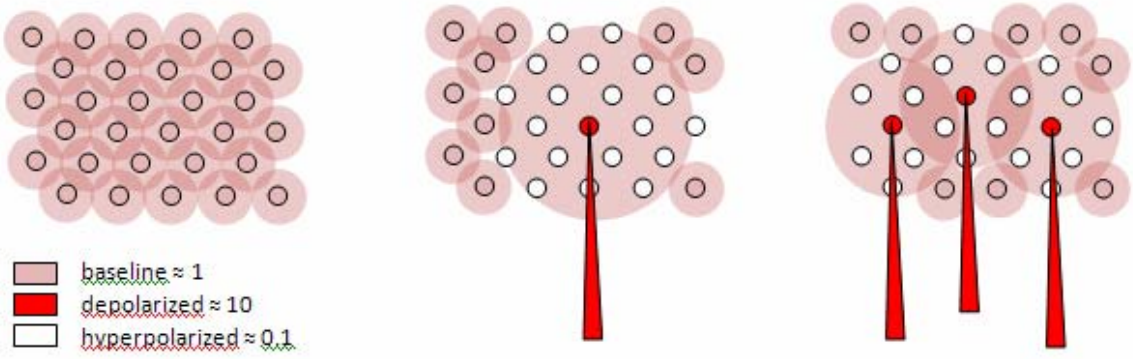


Fig. 28. To understand the principle of lateral inhibition in a neuronal network, assume that the average baseline metabolism of a single neuron increases or decreases 10-fold upon depolarizion or hyperpolarizion. Left: In the default state all 30 neurons receive external signals of uniform, little or no salience. The tone of lateral inhibition is then small for each neuron. Middle: One neuron receives a strong signal and depolarizes, initiating lateral inhibition of neighboring neurons. Compared to baseline, net energy turnover falls from 30 to 21.9. Right: Three neurons now receive strong signals and depolarize, still leading to lateral inhibition of neighboring neurons, but the respective areas of inhibition cancel each other compared to baseline and the net energy turnover rises from 30 to 39.9

The relationship illustrated in the figure above, clarifies how a robust increase neuronal activity in MFC measured by single cell recordings, may fail to show activation or a deactivation by PET or fMRI, depending on the specifics of the test. Importantly, it explains how the introduction of an explicit or implicit, possibly unintended, task during emotional stimulation completely may alter the effect of the emotions studied.

Neurons in the medial frontal cortex enjoy reciprocal connections with neighboring neurons in the region as well as in other brain areas, leading to a functional subdivision of the MFC defined by the nature of these connections. The superior part of the MFC, especially the anterior cingulate cortex primarily connects to motor and premotor regions and engages when attention reaches outward to monitoring, planning, and execution of tasks. The inferior, orbitofrontal part, connected to limbic and sensory areas, is more active when attention reaches inward; to feelings of reward or punish-

ment. The region between these two parts, the anterior medidal prefrontal cortex, serves an intermediate function that is crucial to higher-level representations in social cognition. Recruitment of the caudal part of the MFC facilitates extroversion; while recruitment of the rostral part facilitates introversion.

The monoamines serotonin, noradrenaline and dopamine modulate activity in the MFC with a complex mechanism of dual receptor antagonism. The modulation depends on the ratio and affinities of inhibitory and excitatory receptors in the specific parts of the MFC.

In the MFC, receptors for serotonin and noradrenalin primarily (albeit not exclusively) reside on excitatory neurons that receive projections from other brain areas. The parsimonious interpretation implies that both monoamines predominately serve input gating, by regulating the entry of stimuli into the prefrontal processing of attention and awareness. Levels of serotonin and the distribution of 5HT receptors define whether attention is extroverted or introverted. I suggest that the concentration of serotonin affects the individual's state of mind, low levels of serotonin favoring function in the lower part of the MPFC and introversion, high levels favoring function in the upper parts of the MPFC and extroversion. The ratio between the inhibitory and excitatory receptors on the other hand may define constitutional personality traits, and it may decide whether an individual generally is extroverted or introverted.

Noradrenergic neuromodulation adjusts the focus of attention: As stated by Ramos et Arnsten (2007) small increases of noradrenalin enhance prefrontal function and promote focus and reflection on specific inputs; whereas high levels of noradrenalin disrupt frontal attentional processing but supports function in posterior cortices, and facilitate a more reactive and instinctive behavior.

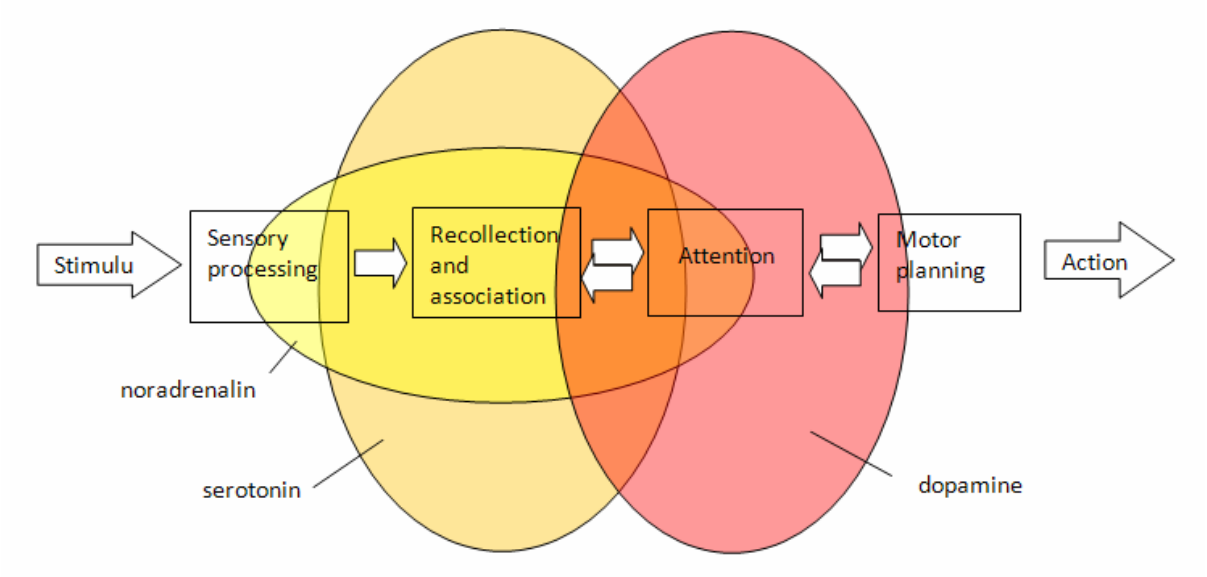


Fig. 29. A model of the actions of the monoamines and the extent to which they may affect specific brain processes. Serotonin defines the context of incoming stimuli: Is a given experience to be evaluated upon whether it seems rewarding, here and now – or should the perspective be broadened and attend to how the experience relates to the world around in general or future plans? Noradrenalin adjusts focus of attention: Is focus to be completely on the task at hand, leaving out all distractions, and only reacting to this - or is instinctive and fast reaction, without any deeper speculation on any, even the slightest input the most important? Dopamine determines the degree to which a stimulus that is allowed entry through the serotonin-noradrenaline gate is to be processed and the extent to which it leads to action.

Dopamine receptors reside on GABAergic interneurons in the MFC. Dopamine appears to modulate the processing of incoming stimuli are being processed. This may happen, by adjusting the activity of prefrontal neurons, or indirectly by adjusting activity in the basal ganglia loops that link the prefrontal cortex to other cortical areas.

To summarize shortly: the function of the MFC is to weigh, by lateral inhibition, the signals from other parts of the brain and then to select the signal to attend to and be conscious about. This process is modulated by the monoaminergic systems, in which the actions of noradrenaline and serotonin influence the signals that enter into attention and dopamine defines the learned processing and reaction to these signals.

Limitations and final considerations

The model of MFC function proposed in this review is only a framework intended for future research. The complexity of the serotonergic receptors of which this treatment considers only the actions of the two most dominant subtypes, regardless of their potential for being in a low-affinity or a high-affinity state, makes this limitation abundantly clear. The treatment completely omits any discussion of the role of the cholinergic system in MFC function, although there is evidence that this transmitter may benefit from a dual receptor antagonism similar to the monoamine effects on MFC function. The treatment only briefly mentions the important roles played by the basal ganglia and limbic structures, such as the amygdala and hippocampus, in cognitive and emotional processing. It also completely neglects the cerebellar and hypothalamic systems and the extensive feedback system from neocortex to brainstem.

Drugs that manipulate the action or the metabolism of monoamines are the cornerstones of modern psychiatric therapy. Until recently, much of this therapy was based purely on empirical observations of the effect of specific drugs, rather than on an understanding of the pathology of the neuronal systems and receptors involved and the subsequent design of a specific agent targeting this pathology. Happily it appears that the tide is turning and much development of drugs now utilizes findings from basic neuroscience.

Jacob Geday August 2008

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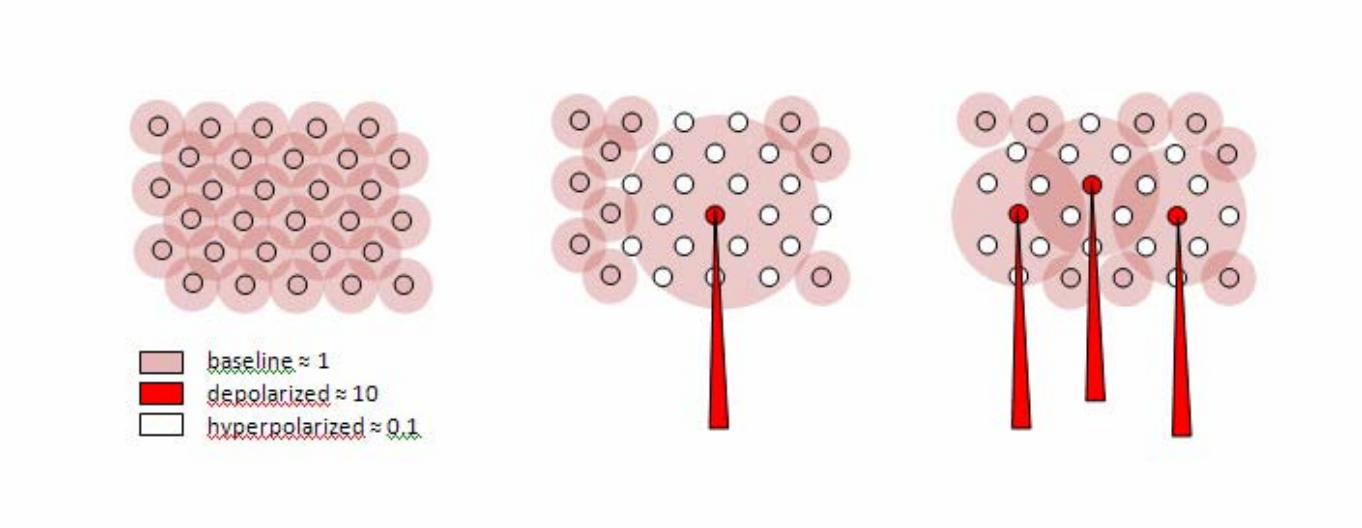
Dansk Resumé

Den mediale frontale cortex (MFC) er en vigtig del af det neurale netværk, der styrer vores opmærksomhedsfunktioner. MFC's styring gør det muligt at vælge fokus blandt flere konkurrerende input projiceret til den prefrontale cortex fra alle dele af hjernen. Sandsynligvis foregår dette valg af fokus ved hjælp af en mekanisme, hvor GABAerge interneuroner, gennem lateral inhibition, modulerer aktivitet og excitabilitet af de neuroner i MFC, der modtager signalerne fra de andre hjerneområder.

De forskellige dele af hjernen har deres egen hvileaktivitet, defineret som den aktivitet, der måles når forsøgspersonens fokus ikke er rettet mod noget bestemt. I hjernen matcher neuronal aktivitet energiomsætningen. Sidstnævnte kan estimeres ud fra PET eller fMRI målinger af blodgennemstrømning og metabolisme. Hvis et aktiveringsparadigme medfører excitatorisk neurotransmission med øget neuronal depolarisering sammenlignet med baseline, vil energiomsætningen stige. Hvis det medfører inhibitorisk neurotransmission i forhold til baseline, falder den.

Depolarisering af et inhibitorisk neuron kræver lige så meget energi som depolarisering af et excitatorisk neuron. Men da langt størstedelen af neuroner i neocortex er excitatoriske (kun ca. 25% af neuronerne i den menneskelige prefrontal cortex er hæmmende), vil den reducerede depolarisering af de excitatoriske neuroner spare mere energi, end hvad bruges under depolariseringen af de hæmmende GABAerge neuroner. Især i et område som MFC, hvor der normalt er en høj energi omsætning. Heraf kan konkluderes, at ændringer i blodgennemstrømning og glukoseforbrug i MFC vil afhænge af, om testsituationen i forhold til baseline medfører et signal, der er så stærkt at det kan hæmme bearbejdelsen af andre konkurrerende signaler til regionen (se nedenfor).



For at forklare hvordan lateral inhibition påvirker energiforbruget i et neuralt netværk, antages her, at den gennemsnitlige metabolisme i et enkelt neuron stiger eller falder 10-fold ved depolarisering eller hyperpolarisering. Venstre: I baseline tilstanden modtager alle 30 neuroner ensartede, svage signaler fra andre hjerneområder. Tonus af den laterale inhibition er lille i forhold til hvert neuron.

Midt: Et neuron modtager et kraftigt signal og depolariseres, hvilket fører til lateral inhibition af naboneuroner. I forhold til baseline, falder energiomsætningen fra 30 til 21,9.

Højre: Tre neuroner modtager nu ens stærke signaler og depolariseres lige meget. Dette fører stadig til lateral inhibition af naboneuronerne, men de respektive områders inhibition ophæver i en vis grad hinanden og energi omsætningen stiger fra 30 til 39,9 i forhold til baseline

Figuren ovenfor illustrerer, hvordan en stigning i neural aktivitet i en lille cellegruppe i MFC (f.eks. verificeret ved *single-cell recordings*), kan medføre aktivering - såvel som deaktivering - af et større område påvist med PET eller fMRI, helt afhængigt af hvilke andre områder det pågældende testparadigme stimulerer eller ikke stimulerer. Men særlig vigtigt forklarer dette princip, hvordan tilstedeværelsen af en eksplicit eller implicit, muligvis helt utilsigtet, opgave under en emotionel stimulation helt kan ændre effekten af denne stimulering målt med PET eller fMRI.

Neuronerne i den mediale frontale cortex har tætte gensidige forbindelser med hinanden såvel som med andre områder af hjernen. Man kan rent funktionelt ud af arten af disse forbindelser opdele MFC i to områder: Den øverste del af MFC (især anteriore cingulate cortex) er primært forbundet med motoriske og premotoriske områder, der inddrages når opmærksomheden er udadrettet mod overvågning, planlægning og gennemførelse af specifikke opgaver. De nederste, orbitofrontale dele modtager signaler fra limbiske og sensoriske områder, og er primært aktive, når opmærksomheden er rettet mod, hvorvidt man oplever sig belønnet eller straffet. Området mellem disse to dele, kaldet den forreste mediale prefrontal cortex, tjener en intermediær funktion og er afgørende for højere sociale, kognitive processer. Helt kort kan man sige; at processer i den caudale del af MFC favoriserer ekstroversion; mens den rostrale del favoriserer introversion.

Monoaminerne; serotonin, noradrenalin og dopamin modulerer aktiviteten i MFC gennem en kompleks dobbelt-receptor antagonistisk mekanisme. Nøjagtigt hvordan, afhænger af forholdet mellem hæmmende og eksitatoriske receptorer og deres placering på glutamaterge eller GABAerge neuroner i de enkelte dele af MFC.

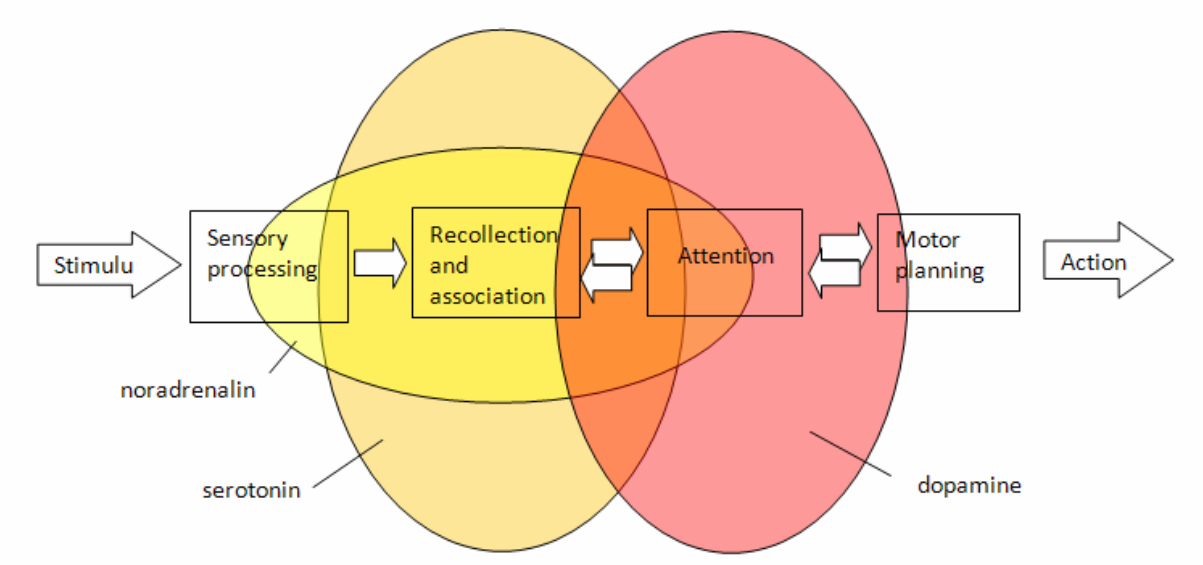
I MFC sidder receptorerne for serotonin og noradrenalin primært (men ikke udelukkende) på de excitatoriske glutamaterge neuroner, der modtager projektioner fra andre hjerneområder. Dette kan udlægges sådan at begge disse monoaminer overvejende tjener til *input-gating* ved at regulere, hvilke stimuli der "lukkes ind" i prefrontale cortex, hvor de bliver bearbejdet og bliver bevidste.

Serotonin niveauet definerer sammen med forskelle mellem den øverste og den nederste del af MFC i fordelingen af højaffine hæmmende og lavaffine exciterende 5HT receptorer, hvorvidt opmærksomheden rettes udad eller indad. Koncentrationen af serotonin påvirker den enkeltes mentale til-

stand: lave niveauer af serotonin favoriserer funktionen af den nederste del af MFC og dermed introversion, mens høje niveauer favoriserer den øvre del og ekstroversion. Forholdet mellem de hæmmende og exciterende receptorer kan definere medfødte personlighed træk, som hvorvidt en person i almindelighed er udadvendt eller indadvendt.

Noradrenerg neuromodulation justerer fokus: Små stigninger af noradrenalin fremmer funktionen i prefrontale cortex og hjælper dermed personen til at fokusere på specifikke input. Høje niveauer af noradrenalin forstyrrer denne funktion, men støtter så til gengæld processer i de posteriore corticale områder, og fremmer dermed en hurtigere, mere reaktiv og instinktiv adfærd, der i en truende situation kan være livreddende.

Dopamin receptorer findes fortrinsvist på GABAerge interneuroner i MFC. Ændringer i dopamin koncentrationen vil derfor modulere behandling af indkommende stimuli. Dette kan ske, ved at justere aktiviteten i de prefrontal neuroner, eller indirekte ved at ændre aktiviteten i de basal ganglie sløjfer der knytter prefrontal cortex til andre korticale områder.



Figuren viser en model af monoaminernes effekt på specifikke hjerne processer:

Serotonin definerer rammerne for behandlingen af indkommende stimuli: Skal et givent input bare evalueres på, om det medfører belønning her og nu - eller skal perspektivet udvides og inkludere hvad der sker i verden omkring i almindelighed?

Noradrenalin justerer fokus: Skal fokus være 100 % på den aktuelle opgave, idet alle distraktioner holdes ude, og man kun reagerer på det, der har med opgaven at gøre - eller er instinktiv og hurtig reaktion - selv på det mindste input, uden nogen dybere spekulationer, det vigtigste?

Dopamin bestemmer i hvilken grad de input, der "lukkes ind" via serotonin-noradrenalin gaten bliver behandlet, og i hvilket omfang de fører til handling.

For at opsummere kort: funktionen af MFC er at afveje ved lateral hæmning, signaler fra andre dele af hjernen og derefter for at vælge signalet til at deltage og blive bevidst om. Denne proces gradueres af de monoaminerge systemer, hvor noradrenalin og serotonin styrer hvilke signaler der når opmærksomheden og dopamin definerer i hvilket omfang disse signaler undergår indlært forarbejdning og medfører en reaktion.