

The medial frontal cortex and the subjective control of behaviour

Introduction

With the exception of scant insights from cerebral perfusion analyses and electrophysiology, the large cortical region on the medial side of the brain was barely understood in terms of its physiological significance prior to the beginning of this century. It was known that blood flow in the medial frontal cortex is particularly high under resting conditions, referred to as “hyperfrontality” [40]. The readiness potential had been discovered a few years previously. This brain electrical activity occurs in the medial frontal cortex up to 2000 ms before an intended movement and continues to build up until the movement is carried out [28, 38]. The pioneering work of Roland et al. [68] bore out this finding, showing that the supplementary motor area (SMA) located dorsally in the medial frontal cortex is not only involved in the performance of movements, but that it is also active in the conception of these movements. On the basis of these and other findings from human and experimental animal research on primates Passingham and co-workers [60] suggested that SMA is of critical importance in the internal generation of actions. The medial frontal cortex attracted attention—beyond its role in motor function—as a result of modern investigations with functional imaging (Excursus 1). Raichle and co-workers [27] observed that the spontaneously high activity in the medial frontal cortex is reduced by targeted performances in motor function and perception. Thus these authors coined the term “default mode”. In subsequent years,

numerous investigations using functional imaging were published showing the medial frontal cortex’s involvement in various perceptive, action-oriented, cognitive as well as emotional processes. In this context, it has been shown in meta-analyses that the ventral portion of the medial frontal cortex is important in the regulation of emotional behaviour [24, 25] and includes multiple sub-areas in its dorsal aspect which are associated with subjective perspective [74, 88] (see **Fig. 1**).

Human behaviour is based on perception and action. Since human action takes place in the context of social relationships, mental processes such as cognition and emotion also play a role. Cognition includes formal problem-solving, abstract logic and creative thinking and is closely associated with the concept of intelligence. Emotions are mental processes that cause moods and are perceived as affects. Moreover, man behaves according to individual values and wishes, as well as cultural norms [90]. This includes the acceptance of categories such as “good” and “bad” and moral codes like “thou shalt not kill” or “once a liar, always a liar”. In particular, humans experience the reaction of their environment to their actions either as the physical or mental laying down of boundaries or as positive reinforcement. For the individual acting in a social context, a third domain is also involved, i.e. the subjective evaluation of perceived information and the potential consequences of one’s own actions [76]. This third domain is based on the subjective value matrix and includes the valuation of information, subjective preference and the ensuing choice of alterna-

tive actions. Evaluating the intentions of one’s counterpart and how they will receive one’s own actions forms the core of social interaction.

Social interactions can be both linguistic and non-verbal. Non-verbal information can be transmitted to a counterpart via both facial expressions and gestures, or facial expressions and gestures can accompany verbal statements. These can also be expressed in isolation. Humans have the ability to understand facial expressions and the symbolism of gestures. Thus the “receiving agent” is able to perceive the emotional status of the “transmitting agent”. This process is referred to as empathy [83]. Furthermore, the receiving agent is able to put himself in the position of the transmitting agent and thereby understand the reasons for his behaviour. This process is known as “theory of mind” [19]. Thus, during these processes, not only are facial expressions and gestures observed—they are also evaluated, interpreted and internally simulated. The interesting question about the cerebral processing of these valuation processes represents the focus of this article, whereby it will be shown that the medial frontal cortex plays a vital role in this context.

The action-perception cycle

Human behaviour is seen as a cybernetic system made up of sensory input signals and motor functions in which a hierarchical system of anatomical connections links perception and action [22, 26]. Even higher brain functions, such as action planning and action conception, are



Fig. 1 ▲ Areas on the medial side of the brain which are associated with valuation functions. Dorsal areas according to a meta-analysis by Seitz et al. [74], ventral area according to a meta-analysis by Grabenhorst and Rolls [25]. SMA supplementary motor area, CA cingulate area, MD medial dorsal area, s superior, a anterior, VM ventromedial prefrontal cortex. Intercommissural lines through the anterior and posterior commissura and the coronary level through the anterior commissura are shown

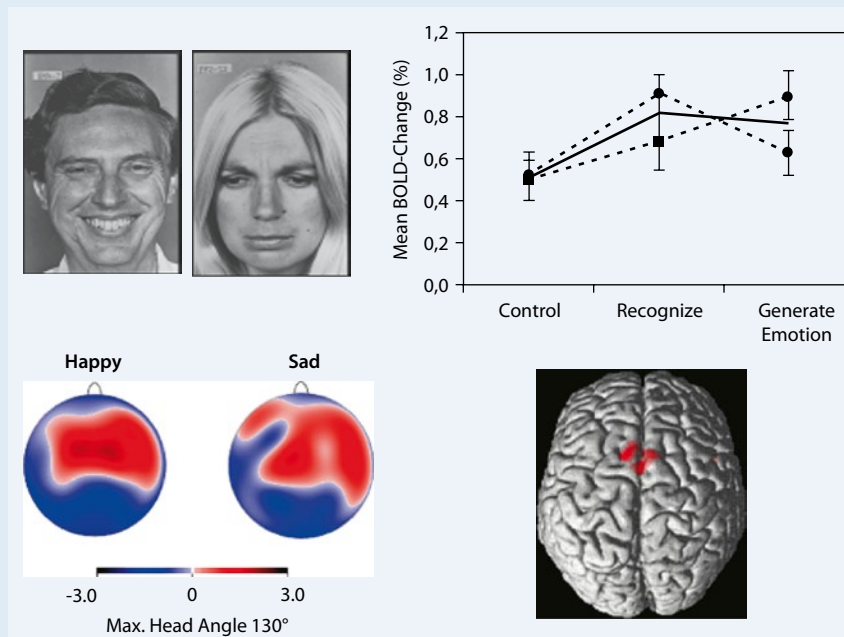


Fig. 2 ▲ Emotion recognition and empathy. **a** Sample faces. **b** Significant increase in the fMRI signal ($p < 0.05$) in the medial dorsal frontal cortex compared with when searching for an object while looking at the faces. **c** Significant change in EEG activity when empathizing with emotion in the time frame of 120–240 ms following exposure to the stimulus; colour coding according to the t-value scale. **d** Localization of activation from a dorsal perspective of the brain [75]

reconcilable with this model. The experimentally supported hypothesis of an overlap in motor conception and the performance of an action followed this model [35]. In this regard, the investigations by

Rizzolatti and co-workers [66] are of particular significance in that they were able to show that primate neurons in the pre-motor and inferior parietal cortex are active both in the performance of actions

and in the perception of these actions. Thus there is a link on the cellular level for sensory-guided action, as for example in tactile exploration. The human mirror neuron system is based on these findings [34]. According to Fuster, behavioural control takes place at the highest level in the frontal lobe [22], which comprises parts hosting motor functions and parts with complex behavioural control, the so-called prefrontal cortex (see Excursus 2).

Experimental investigations by Preston and deWaal [63] demonstrated that primates react to the behaviour of conspecifics with either affection or aversion and thus have insight into the emotional state of conspecifics. This ability is regarded as the capacity to understand the feelings of counterparts and is associated with the traditional concept of empathy [83]. Interestingly, empathy has been interpreted in this regard as a manifestation of the action-perception cycle [63]. Empathetic experiences are also seen in humans and can be qualified with scales [15]. Recent imaging investigations show that empathetic experience is associated with a significant increase in activity in the dorsal portion of the medial frontal cortex located close to the ventrally adjacent cingulate gyrus [74]. Even the recognition of emotional states in faces activates this region, whereby it has been shown using multi-channel electroencephalography that the medial frontal cortex alters its activity significantly as early as 120 ms after perceiving a face (■ Fig. 2). Empathy is also described as an emotional perspective [80]. Insight into the actions of another person involves understanding the reasons for their actions. This mental process is referred to as “theory of mind”, or cognitive perspective [19]. Using functional imaging it could be shown that the anterior medial frontal cortex is activated in this process [89]. This extra-activation is clearly related to the fact that the observed action is attributed to another person, an “actor”. An example of this is shown in ■ Fig. 3, where a person’s observation of a ball being caught by a third person significantly activates the anterior frontal cortex.

Thus in the human brain, subjective perspective is based on events in one’s environment and on one’s own inner workings. For this reason, the observation that

perceiving the mental self activates the medial frontal cortex is of great relevance [58]. In contrast, the tempo-parietal transition area plays an important role in the mediation of the sensory self when experiencing one's own body in the environment [19, 53, 61]. The mental self is based on social contexts; by reflecting on other targets and motives one simulates these as if they were one's own. This enables a person to evaluate and predict possible actions and reactions [53]. So-called self-awareness includes the exciting phenomenon whereby man is simultaneously the perceiver of his state of mind or his own mental world and the observer of this perception [59]. This function, which also includes metamemory, is associated with brain activity in the medial frontal cortex and may be impaired in neurological patients [59]. Thus the medial frontal cortex could make subjective evaluation as an autonomous function system possible in addition to the action-perception cycle.

Subjective evaluation

Man continuously evaluates his perceived sensory stimuli in order to adjust his actions in a social context. This evaluation function, which mediates a connection between perception and action, can be interpreted as a cognitive manifestation of the mirror neuron system [76]. In a social context, this evaluation is based primarily on the facial expressions and gestures of people in one's vicinity. A brief exposure to faces with emotional expressions lasting 400 ms induces extensive activations, including the fusiform gyrus, which is important to face perception [75]. Recognizing the emotional state observed in a face and empathizing with this emotional state leads to significant activation in the left side of the inferior frontal cortex as well as in the dorsomedial frontal cortex (■ Fig. 2). In this context, the observation that simply looking at emotional facial expressions and gestures is not the same as recognizing an emotion in emotional facial expressions and gestures is crucial. Whereas a person is an uninvolved observer in the first case, he is the receiver of non-verbally communicated emotional information in the second and thus also affected. Electroencephalographic re-

cordings in the same experimental person under the same experimental conditions have shown that brain activity alters significantly in the medial frontal cortex as early as 120 ms after being exposed to a face (■ Fig. 2). In contrast, evoked electrical potential in the occipital-parietal cortex during the perception of emotional facial expressions and gestures alters only after 150–170 ms [14, 71]. The observation that oscillatory gamma-band responses with a frequency of 30–80 Hz appeared as early as after 60–120 ms during asynchronous exposure to auditory and visual stimuli in the medial frontal cortex corresponds to the above findings on the one hand, whereas they first occurred in the occipital cortex after 60–120 ms [78]. This precision in temporal synchronicity induces an early cross-modal interaction in the medial frontal cortex. On the other hand, lesions in the medial frontal cortex impair recognition of emotional facial expressions, which in itself is associated with modified levels of event-related potentials following exposure to a face [71]. Thus the medial frontal cortex influences information processing in the visual cortex areas according to a “top-down” mechanism [51]. Indeed, multivariate image analyses have shown that the recognition of emotional facial expressions is based on a network of multiple cortical and subcortical areas [57]. Thus subjective evaluation influences how images or situations are perceived. For example, images of subjectively tranquil scenes lead to increased effective connectivity in the dorsal medial frontal cortex and auditory cortex compared to subjectively loud scenes, although the level of noise was comparable [32]. Ultimately, subjective evaluation is clearly relevant to behaviour, since, on the one hand, the observation of social exclusion causes activation of the dorsomedial frontal cortex, which has been associated with prosocial behaviour [50]. Activity in the medial frontal cortex in mental state attribution to sexually appealing images of women also correlated negatively with high sexist values in the male perceiver [6]. This was interpreted as a mechanism to dehumanize people. On the other hand, a visual choice paradigm demonstrated that incorrectly associated activity in the dorsomedial frontal cortex predicts

Abstract

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Abstract

The role of the cortex at the medial aspect of the frontal lobe for the subjective control of behaviour has been elaborated in recent years. As apparent from meta-analyses of functional imaging studies, the medial frontal cortex accommodates critical nodes in a caudo-rostral gradient that are involved in the evaluation of sensorimotor, empathic and abstract information. Brain electrical activity was found to be changed in the medial frontal cortex as early as 120 ms after stimulus presentation in relation to the modulation of perception. These functions become established during adolescence, mediating subjective perspective in a social context. They are most likely brought about by dedicated neurons of the mirror neuron system, but subcortical connections suggest a relationship to the reward system. While lesions of the medial frontal cortex such as brain infarction and brain tumours are rare, impairments of medial frontal cortex functions occur quite frequently in neurological, psychiatric and psychosomatic disorders. Essentially, the medial frontal cortex is closely connected to the concept of personality, opening up an approach for an interdisciplinary scientific discourse.

Keywords

Frontal cortex · Perception-action · Social context · Subjective perspective · Valuation

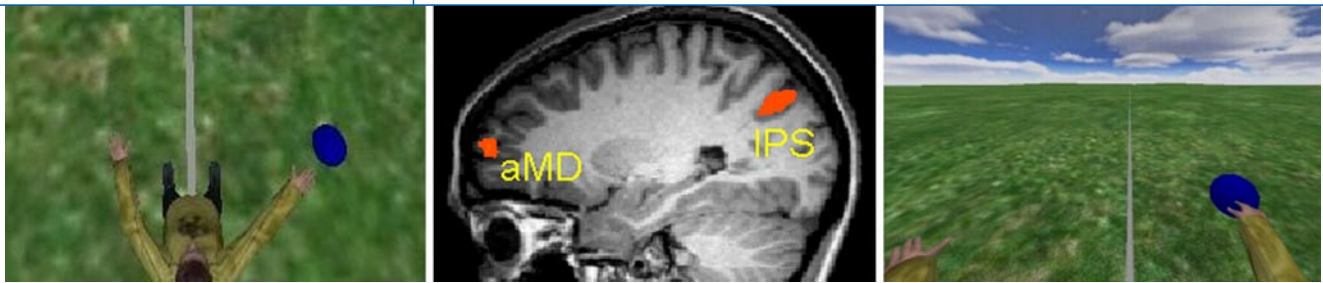


Fig. 3 ▲ Activation of the anterior medial frontal cortex (aMD) and the cortex around the intraparietal sulcus (IPS) while watching a ball being caught by a third person (left) compared with the observer's own perspective (right) [65]

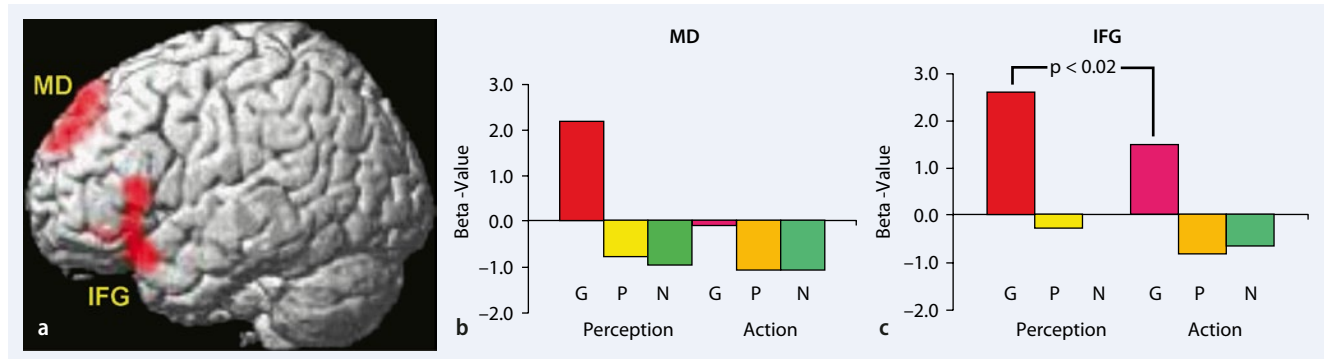


Fig. 4 ▲ **a** The perception of emblematic gestures with increased fMRI signal in the medial frontal cortex (MD) and the left inferior frontal gyrus (IFG). **b** Emblematic gestures (G) activate the MD during the perception process, while neutral gestures (N) and hand positions (P) fail to activate the MD during either the perception or the action process. **c** In the IFG, emblematic gestures during both perception and action processes lead to a significant increase in activity, which is likely an expression of the significance coding in the mirror neuron system [44]

an increased response in perceptive areas and reduced activity in motor areas [7].

The evaluation of emotionally laden, so-called emblematic gestures also leads to specific activation of the medial frontal cortex. As in language, there is a “transmitter”, who produces the emblematic gesture, and the “receiver”, who has to interpret the symbolic content of the gesture. Using MRI, it could be shown that transmitter and receiver activate different, yet partially overlapping, brain regions during this process [44]. However, when contrasting the brain activity of the receiver with that of the transmitter during the perception of emblematic gestures, two specific regions are distinct in the receiver, i.e. the left-sided inferior frontal cortex and the dorsomedial frontal cortex (■ Fig. 4). Regional analyses have showed that this activation in the inferior frontal cortex was specific for emblematic gestures, since it occurred in both the transmitter and the receiver, but not in the case of arbitrary, neutral gestures, nor in the case of hand positions. In contrast, activation of the medial frontal cortex was specific to the receiver of emblematic ges-

tures (■ Fig. 4). This clearly indicates that the medial frontal cortex is critical to the information content in the physical expression of emotional states.

When perceiving emotional facial expressions and emblematic gestures, the question naturally occurs to the receiver in a social context as to why he is confronted with these emotions. Aspects of the theory of mind come into play here. Thus there is modality-independent yet emotion-specific activation in the anterior medial frontal cortex when faces, physical movements and vocal intonation are examined [61]. A comparable anterior region in the medial frontal cortex additionally encodes subsequent preferences for objects/products shown, irrespective of whether they were perceived consciously or less consciously [85]. The subjective evaluation of risks and rewards, which can vary in the course of a lifetime, is associated with prefrontal activation in the ventral prefrontal cortex [24, 69, 73]. The ventromedial frontal cortex is involved in the discrimination of pleasant and unpleasant stimuli and rewards, i.e. expectancy values in the future (■ Fig. 1; [24, 25]). The asso-

ciations discussed here can also be seen in the underlying features of economic evaluation and decision-making, whereby in this context the reward in the form of expectancy value for future events is of particular relevance [54].

From evaluation to action

The medial dorsal frontal cortex plays a central role in the planning, initiation and sequencing of actions, as has recently been confirmed by electrophysiological imaging and anatomical connectivity studies [60]. These areas in the dorsomedial frontal cortex, which are so critically involved in the subjective evaluation of internal and external perceptions, overlap in their localization with the SMA and the so-called pre-SMA (■ Fig. 1). However, there are clear differences between the pre-SMA and the SMA: In contrast to the SMA, neurons in the pre-SMA indicate motivation to and reward for an action, but not whether the action will be performed or not [41, 70]. The pre-SMA and SMA receive extensive projections from the cerebellum and the basal ganglia, whereby the

projection neurons to the SMA belong more to the caudal and ventral sensorimotor territory of the pallidum, while the neurons which project to the pre-SMA lie in a rostral associative region [1]. A similarly distinct topography is also seen in projection neurons of the cerebellar dentate nucleus [1]. Ultimately, cortical connections to the pre-SMA come from the prefrontal cortex and the anterior premotor cortex, while connections to and from the SMA to the sensorimotor areas exist [48]. Any functional distinction of these regions is still rudimentary and needs to take cognitive functions into consideration [56].

A person can only perform one action at a given point in time and typically has to choose between two possible action alternatives. Although one can organize actions sequentially, as in the Tower of Hanoi, only one action per point in time can be performed leading to an overall result. When planning actions, complex situations are correspondingly reduced to one solution or one target. In this process, the information to be evaluated is reduced to a subjective view, with varying grades of subjective certainty (I think, I find, I believe, I'm sure, I notice, I know). Simple gauges include space, time and dichotomous qualities such as right/left, good/bad, full/hungry, familiar/strange. Reducing factors to a main feature enables a rapid decision. There is a clear association here between the ambiguity of action alternatives and the level of fMRI signals [86]. The higher a person's formal intelligence, the easier it is for him to whittle complex stimuli down to their characteristic features and thereby justify subjectively plausible decisions [11]. Decisions of this type evoke particularly strong activation of the dorsolateral prefrontal cortex [10]. Using fMRI, we recently attempted to identify the part of the brain responsible for distinguishing between positive and negative facial expressions and emblematic gestures [77]. In this context, we found that categorizing stimuli into positive and negative leads to specific activation of the right hemispheric dorsolateral prefrontal cortex, while activity in the medial dorsal frontal cortex correlates with the valence of faces. These findings support a role for the medial dorsal frontal cortex in

the evaluation of physical expressions of emotional states on the one hand, while showing on the other that mediation of the decision made in this process takes place in the dorsolateral prefrontal cortex. The question of to what extent evaluations of this kind are a conscious weighing up of factors or whether they can take place more as spontaneous "gut reactions" remains an interesting one.

Subjective evaluation modified by pathology

The topography of structural brain lesions and functional impairments validates the cognitive scientific results achieved in healthy test subjects. For example, prefrontal lesions are associated with an inability to experience emotions, referred to as alexithymia [31]. Lesions in the medial frontal cortex impair processing of emotional facial expressions in the fusiform gyrus [71]. Similarly, lesions in the right inferior fronto-occipital fasciculus can impair facial affect recognition in the form of a disconnection syndrome [62]. In the case of multiple sclerosis, the recognition of emotional facial expressions is likely impaired as a result of axonal demyelization [64]. Recordings from event-related potentials also indicate that the N200 and P300 potentials for new acoustic stimuli are reduced in prefrontal lesions [37]. Finally, patients with Parkinson's syndrome who demonstrate subcortical damage in the basal ganglia are impaired in their affective and cognitive perspectives, which is associated with a reduction in quality of life [4]. However, lesion studies are often only able to show which lesion interferes with which function. In the case of emotional facial expression recognition, for example, it is often the case that patients recognize that they are looking at a face, but can no longer say who the person being shown is. Thus an associative agnosia due to disrupted communication between the areas responsible for face recognition and the memory pool of known faces, i.e. faces that have already been seen, is present. In the case of complete prosopagnosia face representation itself can be disrupted. However, a blindsight-type, intuitive emotional reaction to the known face can remain, although explicit attribution is no

longer possible. This raises the interesting question of how many different representations are sufficient in order for the evaluation of an emotional facial expression to take place. In this context, the role of the medial frontal cortex remains crucial; patients who had recovered from an acute schizophrenic episode showed increased activity in the medial frontal cortex, whereby this correlates with the increase in patients' cognitive faculty and social competence [42].

The development of subjective evaluation

The medial frontal cortex and the ventrally adjacent paracingulate cortex mediate social event knowledge by integrating it into a network which also comprises limbic structures and posterior brain regions [39, 92]. There is a caudal-rostral axis involved in this mechanism, which is responsible for aspects of self-schemata, people and mental phenomena. Interestingly, there is an early, attention-independent reaction (40–140 ms) in the amygdala to emotional stimuli and a late, attention-dependent reaction (280–410 ms) [47]. Animal experiments in which individual recordings were taken in macaques showed that the medial prefrontal cortex has neurons that encode the result of behavioural responses. In particular, these neurons encoded the animals' intentions and the quality of results [46]. In addition, reward and subjective exertion, as well as various aspects of evaluation, including the cause of subjective values, were encoded [36]. Thus neurons that mediate complex evaluation functions were identified in the medial frontal cortex. Presumably, in subjective evaluation, iterative neural processes occur between sensory-fugal connections, which provide information on the physical nature of environmental events, and sensory-petal connections, which originate primarily from the prefrontal cortex and describe the nature of events by means of a top-down mechanism [51]. During this process, memory contents are encoded. Thus the recognition of congruent visuotactile stimuli is associated with increased activity in the dorsomedial frontal cortex compared with incongruent visuotactile stimuli, whereby congruent visuotac-

tile stimuli were remembered better [87]. This shows the frontal cortex's integration mechanisms, which function in a cross-modal manner [78]. In contrast, episodic memory retrieval deactivates the parietal cortex [79].

From childhood through to adulthood there is an increase in the number and strength of connections in the frontal cortex to other brain areas and subcortical structures, as shown in a network analysis of fMRI data on the inhibitory control of eye movements [33]. The default network does not develop until adolescence [13]. The acoustically evoked potential N1B in the medial frontal cortex develops from the age of 12, permitting rapid sensorimotor coupling thereafter [3]. This N1 response has a latency of approximately 100 ms. Similarly, theory of mind improves in late adolescence and shows increasing interaction with executive functions [9]. A positive correlation between the strength of medial dorsal frontal cortex activation when performing tasks with subjective perspectives and age between 9–16 years was even observed [55]. Finally, it could be shown that, in adolescence, there is greater functional connectivity between the frontal cortex and the posterior brain area in the perception of feelings of guilt and shame than in adults [5]. This demonstrates the age-related development of cognitive and emotional perspective ability.

Perspective

Research into the link between subjective behavioural control and the medial frontal cortex opens up new perspectives for cognitive research and clinical neuroscience. Many neurobiological questions are raised here, relating not least to the neurotransmitter systems involved and pharmacotherapeutic possibilities. In the systems physiological context outlined here, it should be explicitly borne in mind that perception includes the mental processing of sensory stimuli and action includes the mental conception of the action to be performed. Thus in the human brain there is a profound and indissociable interaction between physical and mental events [21]. For the person functioning in a social context, however, there is a third area of equal

importance, i.e. the 'valuation' function, which is what raises humans to the level of people [76]. In addition to the evaluation of perception in the narrower sense, evaluation also includes distinguishing between various inner and outer perceptions as a prerequisite of being able to act appropriately and justifiably. In this regard, the individual is in constant exchange with the cultural context and influenced by social interactions [90]. The concept of the evaluation function presented here has many points of contact with the so-called creditions, which were recently postulated as the third psychological realm alongside cognition and emotion and which are suggested to influence individual human behaviour [2]. Contrary to the notion widely held today, Descartes already recognized the realm of emotions as an important human criterion, prompting him to suggest a link between the mental and physical spheres [30]. Thus it is clear that an interdisciplinary discourse between the neurosciences and the humanities can evolve.

Excursus 1

Mapping human brain function

1. Functional imaging

Human brain function is based on millisecond changes in neuronal potentials. Depolarization and repolarization processes require metabolic processes, which take place in an interaction between neurons and astroglial cells [49]. Neuronal synaptic activity results in an increase in regional brain perfusion, which markedly exceeds local oxygen consumption [20]. Field potentials as an expression of synaptic activity in neuronal clusters correlate temporally and spatially to changes in cerebral perfusion, as can be measured using functional magnetic resonance imaging (fMRI) [45]. In this process, the change in the magnetic characteristic of hyperoxygenated blood compared with venous deoxygenated blood is recorded locally and temporally. Event-related MRI signals take advantage of the dynamics of these local changes.

Functional imaging is able to anatomically depict the topography of brain activations by means of reference systems. In this process, mapping is achieved by using

stereotaxic coordinates in the Talairach space, which enables mapping of the human brain with precision in the millimetre range [84]. By appropriately designing experimental activation and control conditions, specific aspects of a physiological process can be isolated and a selected area of activation enhanced. In addition to topographic analyses, there are also multivariate analyses, which are able to depict the network-like interaction between various areas of the brain [18]. Emphasis must be put on the fact that changes in normal brain activity are limited by the temporal resolution of fMRI, which is determined by hemodynamics in the range of seconds.

2. Bioelectric brain activity

Millisecond neuronal signals can be recorded using electroencephalography (EEG) and magnetoencephalography (MEG). Bioelectric brain activity covers various frequency spectra in the alpha [8–12 Hz, beta- (13–20 Hz)] and gamma range (ca. 40 Hz). Recordings of sum potentials taken from the surface of the head are based on assumptions in terms of the localization of their electrical sources and ambiguous due to the inverse problem; thus they become more unreliable with increasing depth [29]. Investigating brain activity in terms of event-related potentials enables the temporal determination of when stimulus-related changes in brain activity occur. Inter-regional analyses are able to show the correlation of frequency spectra and enable oscillations in the neuronal network to be measured. The "binding" phenomenon of oscillations over various brain areas is considered the basis of sensory awareness [12].

Excursus 2

The human frontal cortex

The human frontal lobe is considered the highest structure in behavioural organization [22]. It enables a cognitive control function by actively sustaining activity patterns which represent the targets and the routes by which these targets can be reached [52]. It has shown a particularly marked volume increase during phylogenesis, whereby its size is associated with the evolution of social behaviour

and, in humans, involves primarily the left cerebral hemisphere [81, 82]. The human frontal cortex can be divided into an orbitofrontal, inferior, dorsolateral and medial part. Adjacent to the central sulcus, the anatomical border of the frontal lobe, lies the motor cortex, which plays a central role in movement execution and, in the case of lesions, is associated primarily with brachiofacial paralysis [16]. The clinical-neurological investigation of frontal lobe function is challenging, since lesion topography and deficit syndrome are apparently less specific outside the motor regions than in parietal lobes. Thus frontal dysfunctions are challenging to identify without neuropsychological testing and are not observed in daily routine.

Additional information on the relevance of the frontal cortex has been gained from single-cell recordings in primates and imaging investigations in humans. The premotor cortex, which lies rostral to the motor cortex, performs central functions in the specification of movement synergies [67]. It has strongly differentiated cytoarchitectonic characteristics and cortico-cortical connections, which are likely associated with various aspects of movement control in distal and proximal arm movements, eye movements and hand-to-mouth movements. The dorsolateral prefrontal cortex is primarily discussed in relation to working memory operations [43, 10]. The inferior frontal cortex includes language function and higher motor control [17, 67]. The orbitofrontal cortex plays a prominent role in affect control and emotion processing [69]. Thus the premotor and prefrontal brain areas are crucially involved in the processing of environmental stimuli to which the individual is exposed.

The superior frontal gyrus, a large anatomical structure, lies on the medial side of the frontal lobe. At the furthest most dorsal point, the medial part of the Brodmann Area 4, with motor representation of the leg, is found. This is followed by the premotor cortex, Brodmann area 6, the size of which can vary widely between individuals [23]. Adjacent to this lies Brodmann area 8, which plays a crucial role in the control of saccadic eye movements [72]. This is followed rostrally by prefrontal Brodmann area 9 and, at the frontopolar

aspect, area 10 [84]. The cingulate gyrus, which is part of the limbic system, is adjacent to the superior frontal gyrus on the ventral side. This anatomic structure comprises several cytoarchitectonically characterized sub-areas and fulfils a series of functions related to attention control, the monitoring of actions and events, pain processing and the interhemispherical integration of information [8, 91]. Here again, isolated lesions in this portion of the brain are rare; however, new insights have been gained in recent years with the help of functional imaging.

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References

1. Akkal D, Dum RP, Strick PL (2007) Supplementary motor area and presupplementary motor area: targets of basal ganglia and cerebellar output. *J Neurosci* 27:10659–10673
2. Angel HF (2011) Ist das Konzept der Creditionen für die Religionspsychologie brauchbar? *Wege zum Menschen* 63:5–26
3. Bender S, Oelkers-Ax R, Resch F, Weisbrod M (2006) Frontal lobe involvement in the processing of meaningful auditory stimuli develops during childhood and adolescence. *Neuroimage* 33:759–773
4. Bodden ME, Mollenhauer B, Trenkwalder C, Cabanel N, Eggert KM, Unger MM, Oertel WH, Kessler J, Dodel R, Kalbe E (2010) Affective and cognitive theory of mind in patients with parkinson's disease. *Parkinsonism Relat Disord* 16:466–470
5. Burnett S, Blakemore S-J (2009) Functional connectivity during a social emotion task in adolescents and in adults. *Eur J Neurosci* 29:1294–1301
6. Cikara M, Eberhardt JJ, Fiske ST (2010) From agents to objects: sexist attitudes and neural responses to sexualized targets. *J Cogn Neurosci* 23:540–551

7. Danielmeier C, Eichele T, Forstmann BU, Tittgemeyer M, Ullsperger M (2011) Posterior medial frontal cortex activity predicts post-error adaptations in task-related visual and motor areas. *J Neurosci* 31:1780–1789
8. Devinsky O, Morrell MJ, Vogt BA (1995) Contributions of anterior cingulate cortex to behaviour. *Brain* 118:279–306
9. Dumontheil I, Apperly IA, Blakemore SJ (2010) On-line usage of theory of mind continues to develop in late adolescence. *Dev Sci* 13:331–338
10. Duncan J, Owen AM (2000) Common regions of the human frontal lobe recruited by diverse cognitive demands. *Trends Neurosci* 23:475–83
11. Duncan J, Seitz RJ, Kolodny J, Bor D, Herzog H, Ahmed A, Newell F, Emslie H (2000) A neural basis for general intelligence. *Science* 289:457–460
12. Engel AK, Singer W (2001) Temporal binding and the neural correlates of sensory awareness. *Trends Cogn Sci* 5:16–25
13. Fair DA, Cohen AL, Dosenbach NUF, Church JA, Miezin FM, Barch DM, Raichle ME, Petersen SE, Schlaggar BL (2008) The maturing architecture of the brain's default network. *Proc Natl Acad Sci USA* 105:4028–4032
14. Flaisch T, Schupp HT, Renner B, Junghöfer M (2009) Neural systems of visual attention responding to emotional gestures. *Neuroimage* 45:1330–1346
15. Franz M, Schneider C, Schäfer R, Schmitz N, Zweyer K (2001) Factorial structure and psychometric properties of the German version of the Toronto Alexithymia Scale (TAS-20) in psychosomatic patients. *Psychother Psychosom Med Psychol* 51:48–55
16. Freund HJ (1987) Abnormalities of motor behavior after cortical lesions in humans. *Philadelphia, USA American Physiological Society*, 763–810
17. Friederici AD (2006) Broca's area and the ventral premotor cortex in language: functional differentiation and specificity. *Cortex* 42:472–475
18. Friston KJ (1997) Imaging cognitive anatomy. *Trends Cogn Sci* 1:21–27
19. Frith U, Frith CD (2003) Development and neurophysiology of mentalizing. *Phil Trans R Soc Lond B* 358:459–473
20. Frostig RD, Lieke EE, Ts'o D, Grinvald A (1990) Cortical functional architecture and local coupling between neuronal activity and the microcirculation revealed by in vivo high-resolution optical imaging of intrinsic signals. *Proc Natl Acad Sci USA* 87:6082–6086
21. Fuchs T (2009) Embodied cognitive neuroscience and its consequences for psychiatry. *Poesis Prax*, DOI 10.1007/s10202-008-0068-9
22. Fuster JM (2000) Executive frontal function. *Exp Brain Res* 133:66–70
23. Geyer S, Matelli M, Luppino G, Schleicher A, Jansen Y, Palomero-Gallagher N, Zilles K (1998) Receptor autoradiographic mapping of the mesial motor and premotor cortex of the macaque monkey. *J Comp Neurol* 397:231–250
24. Gilbert SJ, Spengler S, Simons JS, Steele JD, Lawrie SM, Frith CD, Burgess PW (2006) Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. *J Cogn Neurosci* 18:932–948
25. Grabenhorst F, Rolls ET (2011) Value, pleasure and choice in the ventral prefrontal cortex. *Trends Cogn Sci* 15:56–67
26. Guillery RW (2005) Anatomical pathways that link perception and action. *Prog Brain Res* 149:235–256
27. Gusnard DA, Akbudak E, Shulman GL, Raichle ME (2001) Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc Natl Acad Sci USA* 98:4259–4264

28. Hallett M (2007) Volitional control of movement: the physiology of free will. *Clin Neurophysiol* 118:1179–1192
29. Hari R (1994) Human cortical functions revealed by magnetoencephalography. *Prog Brain Res* 100:163–168
30. Harrison P (2009) Myth 12—that René Descartes originated the mind-body distinction. In: Numbers R (ed) *Galileo goes to jail and other myths about science and religion*. Harvard University Press, pp 107–114
31. Hornak J, Bramham J, Rolls ET, Morris RG, O'Doherty J, Bullock PR, et al. (2003) Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain* 126:1691–1712
32. Hunter MD, Eickhoff SB, Plesent RJ, Douglas MJ, Watts GR, Farrow TFD, Hyland D, Kang J, Wilkinson ID, Horoshenkov KV, Woodruff PWR (2010) The state of tranquillity: subjective perception is shaped by contextual modulation of auditory connectivity. *Neuroimage* 53:611–618
33. Hwang K, Velanova K, Luna B (2010) Strengthening of top-down frontal cognitive control networks underlying the development of inhibitory control: a functional magnetic resonance imaging effective connectivity study. *J Neurosci* 30:5535–5545
34. Iacoboni M, Mazziotta JC (2007) Mirror neuron system: basic findings and clinical applications. *Ann Neurol* 62:213–218
35. Jeannerod M (1995) Mental imagery in the motor context. *Neuropsychology* 33: 419–432
36. Kennerley SW, Wallis JD (2009) Evaluating choices by single neurons in the frontal lobe: outcome value encoded across multiple decision values. *Eur J Neurosci* 29:2061–2073
37. Knight RT (1984) Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalogr Clin Neurophysiol* 59:9–20
38. Kornhuber HH, Deecke L (1965) Brain potential changes with voluntary movements and passive movements of man: readiness potential and reafferent potential. *Pflügers Arch Physiol* 284:1–17
39. Krueger F, Barbey AK, Grafman J (2009) The medial prefrontal cortex mediates social event knowledge. *Trends Cogn Sci* 13:103–109
40. Lassen NA, Ingvar DH (1972) Radioisotopic assessment of regional cerebral blood flow. *Prog Nucl Med* 1:376–409
41. Lee D (2004) Behavioral context and coherent oscillations in the supplementary motor area. *J Neurosci* 24:4453–4459
42. Lee K-H, Brown WH, Egleston PN, Green RDJ, Farrow TFD, Hunter MD, Parks RW, Wilkinson ID, Spence SA, Woodruff PWR (2006) A functional magnetic resonance imaging study of social cognition in schizophrenia during an acute episode and after recovery. *Am J Psychiatry* 163:926–1933
43. Levy R, Goldman-Rakic PS (2000) Segregation of working memory functions within the dorsolateral prefrontal cortex. *Exp Brain Res* 133:23–32
44. Lindenberg R, Uhlig M, Scherfeld D, Schlaug G, Seitz RJ (2011) Communication with emblematic gestures: shared and distinct neural correlates of expression and reception. *Human Brain Mapp*. Epub ahead of print
45. Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. *Nature* 412:150–157
46. Luk C-H, Wallis JD (2009) Dynamic encoding of responses and outcomes by neurons in medial prefrontal cortex. *J Neurosci* 29:7526–753
47. Luo Q, Holroyd T, Majestic C, Cheng X, Schechter J, Blair RJ (2010) Emotional automaticity is a matter of timing. *J Neurosci* 30: 5825–5829
48. Luppino G, Matelli M, Camarda R, Rizzolatti G (1993) Corticocortical connections of area F3 (SMA-proper) and area F6 (pre-SMA) in the macaque monkey. *J Comp Neurol* 338:114–140
49. Magistretti PJ, Pellerin L (1999) Cellular mechanisms of brain energy metabolism and their relevance to functional brain mapping. *Philosoph Trans Royal Soc Lond B* 354:1155–1163
50. Masten CI, Morelli SA, Eisenberg NI (2011) An fMRI investigation of empathy for “social pain” and subsequent social behaviour. *Neuroimage* 55:381–388
51. Mesulam M (2008) Representation, inference, and transcendent encoding in neurocognitive networks of the human brain. *Ann Neurol* 64:367–378
52. Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 24:167–202
53. Molnar-Szakacs I, Arzy S (2009) Searching for an integrated self-representation. *Communicative Integrative Biology* 2:365–367
54. Montague PR (2007) Neuroeconomics: a view from neuroscience. *Function Neurol* 22:219–234
55. Moriguchi Y, Ohnishi T, Mori T, Matsuda H, Komaki G (2007) Changes of brain activity in the neural substrates for theory of mind during childhood and adolescence. *Psychiatr Clin Neurosci* 61:355–363
56. Nachev P, Kennard C, Husain M (2008) Functional role of the supplementary and pre-supplementary motor areas. *Nat Rev Neurosci* 9:856–869
57. Nomi JS, Schäfer R, Scherfeld D, Friederichs S, Schäfer R, Franz M, Wittsack H-J, Azari NP, Missimer J, Seitz RJ (2008) On the neural networks of empathy: a principal component analysis of an fMRI study. *Behav Brain Funct* 4:41
58. Northoff G, Heinzel A (2006) First-person neuroscience: a new methodological approach for linking mental and neuronal states. *Philos Ethics Humanit Med* 1:1–10
59. Pannu JK, Kasniak AW (2005) Metamemory experiments in neurological populations: a review. *Neuropsychol Rev* 15:105–127
60. Passingham RE, Bengtsson SL, Lau HC (2010). Medial frontal cortex: from self-generated action to reflection on one's own performance. *Trends Cogn Sci* 14:16–21
61. Peelen MV, Atkinson AP, Vuilleumier P (2010) Supramodal representations of perceived emotions in the human brain. *J Neurosci* 30:10127–10134
62. Philippi CL, Mehta S, Grabowski T, Adolphs R, Rudolph D (2009) Damage to association fiber tracts impairs recognition of the facial expression of emotion. *J Neurosci* 29:15089–15099
63. Preston SD, de Waal FG (2002) Empathy: its ultimate and proximate bases. *Behav Brain Sci* 25:1–20
64. Prochnow D, Donell J, Schäfer R, Jörgens S, Hartung HP, Franz M, Seitz RJ (2011) Alexithymia and impaired facial affect recognition in multiple sclerosis. *J Neurol* 258:1683–1688
65. Prochnow D, Badia SB, Schmidt J, Duff A, Brunheim S, Kleiser R, Seitz RS, Verschure PF (2011) Rehabilitation gaming system—neural correlates of visuo-motor transformations in actual and imagined target catching. *Neurosci Abstracts* 815.13
66. Rizzolatti G, Fadiga L, Gallese V, Fogassi L (1996) Premotor cortex and the recognition of motor actions. *Brain Res Cogn Brain Res* 3:131–141
67. Rizzolatti G, Luppino G, Matelli M (1998) The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol* 106:283–296
68. Roland PE, Larsen B, Lassen NA, Skinhøj E (1980) Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J Neurophysiol* 43:118–136
69. Rolls ET (2006) Brain mechanisms underlying flavour and appetite. *Philos Trans R Soc Lond B Biol Sci* 361:1123–1136
70. Scangos KW, Stuphorn V (2010) Medial frontal cortex motivates but does not control movement initiation in the counterdemanding task. *J Neurosci* 30:1968–1982
71. Schäfer R, Popp K, Jörgens S, Lindenberg R, Franz M, Seitz RJ (2007) Alexithymia-like disorder in right anterior cingulate infarction. *Neurocase* 13:201–208
72. Schlag JD (2002) Neurons that program what to do and in what order. *Neuron* 34:177–118
73. Schultz W (2010) Subjective neuronal coding of reward: temporal value discounting and risk. *Eur J Neurosci* 31:2124–2135
74. Seitz RJ, Nickel J, Azari NP (2006) Functional modularity of the medial prefrontal cortex: involvement in human empathy. *Neuropsychology* 20:743–751
75. Seitz RJ, Scherfeld D, Friederichs S, Popp K, Wittsack H-J, Azari NP, Franz M (2008) Valuating other people's emotional face expression: a combined fMRI and EEG study. *Neuroscience* 152:713–722
76. Seitz RJ, Franz M, Azari NP (2009) Value judgments and self-control of action: the role of the medial frontal cortex. *Brain Res Rev* 60:368–378
77. Seitz RJ, Prochnow D, Höing B, Müller-Schmitz K, Lindenberg R, Schäfer R, Franz M (2011) Frontal cortex activation related to valuation and categorization of emotional face expressions and gestures. *Neurosci Abstr* 299.22
78. Senkowski D, Talsma D, Grigutsch M, Hermann CS, Woldorff MG (2007) Good times for multisensory integration: effects of the precision of temporal synchrony as revealed by gamma-band oscillations. *Neuropsychologia* 45:561–571
79. Sestieri C, Corbetta M, Romani GL, Shulman GL (2011) Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. *J Neurosci* 31:4407–4420
80. Shamay-Tsoory SG, Tomer R, Goldsher D, Berger BD, Aharon-Peretz J (2004) Impairment in cognitive and affective empathy in patients with brain lesions: anatomical and cognitive correlates. *J Clin Exp Neuropsychol* 26:1113–1127
81. Shultz S, Dunbar R (2010) Encephalization is not a universal macroevolutionary phenomenon in mammals but is associated with sociality. *Proc Natl Acad Sci USA* 107:21582–21586
82. Smaers JB, Steele J, Case CR, Cowper A, Amunts K, Zilles K (2011) Primate prefrontal cortex evolution: human brains are the extreme of a lateralized ape trend. *Brain Behav Evol* 77:67–78
83. Stueber KR (2006) Rediscovering empathy. Agency, folk psychology, and the human sciences. MIT Press, Cambridge, USA
84. Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. New York, Thieme
85. Tusche A, Bode S, Haynes J-D (2010) Neural responses to unattended products predict later consumer choices. *J Neurosci* 30:8024–8031
86. Ullsperger M, Nittono H, von Cramon DY (2007) When goals are missed: dealing with self-generated and externally induced failure. *Neuroimage* 35:1356–1364

87. van Kesteren MTR, Rijpkema M, Ruiter DJ, Fernandez G (2010) Retrieval of associative information congruent with prior knowledge is related to increased medial prefrontal activity and connectivity. *J Neurosci* 30:15888–15894
88. van Overwalle F (2009) Social cognition and the brain: a meta-analysis. *Hum Brain Mapp* 30:829–858
89. Vogeley K, Bussfeld P, Newen A, Herrmann S, Happe F, Falkai P, Maier W, Shah NJ, Fink GR, Zilles K (2001) Mind reading: neural mechanisms of theory of mind and self-perspective. *Neuroimage* 14:170–181
90. Vogeley K, Roepstorff A (2009) Contextualising culture and social cognition. *Trends Cogn Sci* 13:511–516
91. Vogt BA, Vogt L, Laureys S (2006) Cytology and functionally correlated circuits of human posterior cingulate areas. *Neuroimage* 29:452–66
92. Walter H, Adenzato M, Ciaramidaro A, Enrici I, Pia L, Bara BG (2004) Understanding intentions in social interaction: the role of the anterior paracingulate cortex. *J Cogn Neurosci* 16:1854–1863
93. Wegner DM (2005) The mind's best trick: how we experience conscious will. *Trends Cogn Sci* 7:65–69