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# THE ANTERIOR CINGULATE CORTEX

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*Abstract* — The anterior cingulate cortex (ACC) has a role in attention, analysis of sensory information, error recognition, problem solving, detection of novelty, behavior, emotions, social relations, cognitive control, and regulation of visceral functions. This area is active whenever the individual feels some emotions, solves a problem, or analyzes the pros and cons of an action (if it is a right decision). Analogous areas are also found in higher mammals, especially whales, and they contain spindle neurons that enable complex social interactions. Disturbance of ACC activity is found in dementias, schizophrenia, depression, the obsessive-compulsive syndrome, and other neuropsychiatric diseases.

*Key words*: Anterior cingulate cortex, limbic system, error detection, prefrontal cortex

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## INTRODUCTION

An important question in neuroscience is: which brain structures control human activity? Is the situation completely different or similar to that in other higher mammals? Prefrontal areas are the most important in initiating, monitoring and modification of human actions. The highest level of control is most probably executed by the ventromedial prefrontal cortex and especially the anterior cingulate cortex (ACC). Some analogous structures are found in higher primates and marine mammals. They are part of the limbic system and are named the "animal brain" because gyrification in the cingulate cortex is parasagittal (as in animals), not transverse (as in other regions of the human brain). In experimental animals, an analog of the human subgenual ACC participates in the visceromotor network that modulates autonomic and endocrine responses to reward, fear, and stress (Drevets and Savitz, 2008).

The first ideas about the ACC were that this is an old structure in mammals, defined in MacLean's (1949) concept of the "triune brain". According to his view, the mammalian brain evolved in concentric shells around a "reptilian brain", of which the ACC would be a part. Later Allman et al. (2001) suggested that the ACC is a novel structure that emerged as a specialization of the neocortex.

## ANATOMY OF THE ANTERIOR CINGULATE CORTEX IN HUMANS

The cingulate cortex is part of the limbic system, which can be divided into caudal and rostral parts. The rostral limbic system includes the ACC, which occupies part of the medial prefrontal cortex, amygdala, septum, orbitofrontal cortex (OFC), anterior insula, nucleus accumbens (ventral striatum), and periaquaductal gray matter and is involved in affective behavior and response selection (Devinsky et al., 1995).

The cingulate cortex wraps around the corpus callosum and consists of anterior and posterior subdivisions based on cytological and functional characteristics. The cortex of the gyrus cinguli is histologically agranular, with a pronounced fifth layer having a function in output (Vogt et al., 1995). The main anatomo-functional divisions of the ACC are the dorsal, cognitive area (Brodmann area – BA, 24b-c and 32); and the rostral/ventral, affective area (BP 24a-c and 32, and ventral areas 25 and 33), subdivided into executive (anterior), evaluative (posterior), cognitive (dorsal), and emotional (ventral) zones (Bush et al., 2000). The anterior cerebral artery irrigates the ACC.

The main connections of the ACC are to the prefrontal cortex, parietal cortex, motor system, and frontal eye fields (Posner and DiGirolamo, 1998). The dorsal part of the ACC has connections with parietal, prefrontal, and supplemental motor areas. It is active in demanding cognitive tasks. The rostral part is connected with the OFC, amygdala, hippocampus, and periaqueductal gray matter and is activated in tasks demanding processing of affective information and correlated with vegetative responses during execution of cognitive tasks (Critchley et al., 2005). The subgenual ACC (BA 25) is involved in regulation of emotions.

The subiculum sends efferents to mammillary neurons. Through mamillo-thalamic projections, these neurons connect further with the anterior thalamic nucleus and ACC, which sends axons back to the anterior nucleus and through the cingulum to other limbic areas.

Motor areas of the caudal ACC are connected with the spinal cord and red nucleus and are involved in premotor function, response choice, and information processing, while the rostral part has rich connections with the amygdala (regulation of emotions), ventral striatum (nucleus accumbens, putamen, etc.), periaqueductal gray matter, autonomous motor nuclei of the brain stem, lateral prefrontal cortex, insula, and OFC (Fitzgerald et al., 2005; Zimmerman et al., 2006).

## VON ECONOMO NEURONS

A special type of neurons are the spindle cells or von Economo neurons (VEN), organized in groups of 3-6 cells, that can be found only in the ACC and fronto-insular (FI) cortex (part of the OFC) (Nimchinsky et al., 1999). They are found in the Vb layer of the cerebral cortex in Brodmann subareas 24a, 24b, and 24c, making the medial wall of the gyrus cinguli. Besides in humans, these cells are also found in great apes (Pongidae) and humpback whales. Moreover, they were recently found in the African elephant, a species with highly developed social structure and cognitive activity. Spindle neurons are bipolar with one dendrite and long-distance projections. Rich in filaments, they convey socially relevant signals in the brain. The cell body of VEN is four to five times larger than in pyramidal neurons. The thick axons of VEN quickly disseminate information from the ACC and FI cortex to other brain areas.

Connections of VEN have not been well studied in humans, but in monkeys they project to the prefrontal area, OFC, insular and anterior temporal cortices, amygdala, hypothalamus, some thalamic nuclei, and periaqeductal gray matter (Allman et al., 2005). It is supposed that VEN are involved in anticipation of reward and punishment in uncertain conditions and formation of social bonds. One hypothesis is that VEN are an output of the ACC and FI cortex to the frontal and temporal association cortices, which are involved in the theory of mind (Hof and Van der Gucht, 2007). In cetaceans (whales, dolphins, and porpoises), VEN appear to mediate emotions and vocalization, as well as autonomic and alimentary behaviors. It seems that absolute brain size is more important for evolution of VEN than the encephalization quotient.

Receptors represented in VEN are vasopressin 1a (important for social bonding), dopamine D3 (signals the expectation of reward under uncertainty and provides cognitive flexibility), and serotonin 2b receptors (present only in VEN and the intestine, giving rise to "gut feelings" about danger or punishment) (Allman et al., 2005). Dopamine signals reward and serotonin punishment.

The average number of VEN is 6,950 in apes, 28,200 in human newborn and 193,000 in human adults, and they are 30% more numerous in the right FI cortex (Allman et al., 2005). The present estimate is that VEN evolved in the last 15 million years and that they convey fast intuitive assessment and reaction to complex situations (Allman et al., 2005). Predominance of VEN in the right hemisphere is possibly related to specialization for social emotions.

In humans, VEN appear around the fourth

month of age and gradually multiply during the second and third year of life, when feelings of guilt and discomfort arise. Too much stress has negative influence, and quality parental care leads to VEN multiplication (Allman et al., 2001). Social emotions associated with these structures are probably the base from which moral and thinking arose. They may be involved in the development of complex social networks and theory-of-mind, when fast intuitive judgments merge with slower judgments supported by the frontal and temporal cortices.

Up to 60% loss of VEN has been recorded in patients with Alzheimer's disease (AD) (Nimchinsky et al., 1995). In autistic patients, VEN are located in the wrong place. This shows the importance of VEN in social relations.

## WHALES – THE ANTERIOR CINGULATE CORTEX AND SOCIAL STRUCTURE

Whales, mammals of the order Cetacea, are distributed in two suborders, the Mysticeti and Odontoceti, with 13 and 72 species, respectively (Hof and Van der Gucht, 2007). Toothed whales (order Cetacea, suborder Odontocetes) possess brains that are significantly larger than expected for their body size and second only to modern humans (Marino et al., 2004). Cetaceans developed from terrestrial mammals some 50-60 million years ago, continuing their evolution in an aquatic milieu. Interestingly, they developed some brain structures that parallel those in the highest terrestrial mammals that lived in a completely different environment. This is a remarkable example of parallel evolution. Parallelism is particularly true of the ACC and VEN in humpback whales (*Megaptera novaeangliae*, order Cetacea, suborder Mysticetes) (Hof and Van der Gucht, 2007). Although humpback whales have a lower encephalization quotient than odontocetes and lower absolute weight, still they have large absolute brain size, extensive cortical gyrification, and complex morphology with VEN not found in odontocetes. Spindle cells are located in areas homologous to the human ACC and FI cortex. While in humans and great apes these neurons are restricted to layer Vb in BA 24 and 25, in humpback whales they are found in layer V (with some in layer III); in the crown of the gyri; in the subgenual, pregenual and supracallosal portion of the ACC; and in the frontopolar region (not seen in hominids and odontocetes).

Whales have rich social organization, complex communication and vocalization systems, cooperation in various activities, and group formation; moreover, they use tools and convey their experience to younger generations. Social structure has been extensively studied in killer whales (*Orcinus orca*) (Hoelzel et al., 2007).

Absolute and proportional brain size in the biggest whales and dolphins can be compared only with the human brain. The sperm whale (*Physeter macrocephalus*) has the largest brain (with average weight of 8,000 g), while the highest encephalization quotient (EQ – brain relative to body size) of over 4 is found in some dolphins (Marino et al., 2004). For comparison, the EQ in modern humans is around 7, and in nonhuman anthropoid primates the highest EQ is 3.3 (*ibid.*)

Along with humans and some great apes, whales are the only species to have VEN in their ACC and related structures. The most complex social relationships described among cetaceans are those of bottlenose dolphins from Shark Bay, Australia (Connor, 2007). They make alliances with imitative abilities, motion perception, and relationship uncertainty in a specific ecological niche. A larger brain in any species has to be supported by a high-quality diet. Evolutionary brain size enlargement is probably driven by inter-group competition and/or predators, which favored those groups with an extreme degree of mutual dependence (Connor, 2007).

Evolution of behavior in both whales and humans accompanied progressive encephalization. Examples of parallel behavioral abilities are mirror self-recognition, comprehension of artificial symbol-based communication systems, abstract concepts, and intergenerational transmission of behaviors (cultural) (Marino et al., 2004). Synchrony is a powerful social signal based on anatomical and functional development of areas for motion detection (Connor, 2007). This could be learned by copying, a more sophisticated version of "social mirroring". These abilities are not seen in non-human primates. It seems that one of the functions of the most advanced large brains is the ability to model the complexities of social circumstances and mentally rehearse the consequences of alternative social scenarios.

## FUNCTIONS OF THE ANTERIOR CINGULATE CORTEX IN HUMANS

Strategically located, the ACC is the central place for processing downstream and upstream stimuli and controlling other brain regions. It is crucial for affect and cognition. Activation of the ACC is registered in the early learning phase, problem solving, response selection, divided attention tasks, and verbal and motor response; in affective tasks such as emotional processing (enhanced activity leads to sadness); in feelings of anxiety, phobia, guilt, pain, embarrassment, deception, humor, trust, and empathy; in discrimination of emotional states of others, visceromotor control (autonomic reactions), bimanual coordination, eye movements, modulation of body arousal, spatial memory, self-initiated movement, and perception of pain and the emotional response to it; and in reward and goal-related activity (Devinsky et al., 1995; Bush et al., 2000; Allman et al., 2001; Siddiqui et al., 2008). For instance, the ACC detects mistakes and conflicting alternatives (as in go/no-go tasks) and has a role in conscious awareness of visceral activity (Craig, 2004).

**Hypotheses about ACC function**. Two main functions are postulated for the ACC: conflict monitoring and regulation (Roelofs et al., 2007). According to the conflict hypothesis, the ACC would be activated increasingly only when alternatives are incongruent. Activity in congruent and neutral tasks would be the same because in both cases there is no conflict. The ACC activates both when it detects an error and during the right response, more so as the stimulus competitiveness increases, testifying to the role of monitoring of conflict degree (Carter et al., 1998). Against this function is the finding of vast ASS lesions without significant neuropsychological deficits.

The regulatory hypothesis (outcomes-monitoring/decision-making) predicts that the ACC would be more active in incongruent than in neutral tasks and minimally active in congruent tasks because of less demand for regulation (the right response is already activated with a distracter in the same congruent task, as the word BLUE written in blue). These two hypotheses need not be mutually exclusive.

In antisaccadic tasks that demand suppression of a distracting signal (the target appears on the contralateral side of the space leading to conflict), there are two types of response. Correct task performance provokes activation of the rostral part, while the dorsal area activates in both the correct and the wrong response. Activation of the dorsal area reduces the error number, showing an effortful process. Wrong answers have longer latency than correct ones, probably because of the greater time needed for response evaluation.

Botvinick (2007) proposed a reconciliation of the conflict monitoring and outcomes-monitoring/decision-making theories. Conflict monitoring would lead to a form of avoidance learning based on past experience. It would bias future behavior away from tasks and strategies that can induce conflict and produce cognitively more efficient strategies that demand less effort. This is known in the psychological literature as "the law of least work" or a "drive for cognitive economy" (Botvinick, 2007).

**Conflict detection**. The ACC participates in error detection, task anticipation, motivation, and modulation of emotional processes (Posner and DiGirolamo, 1998; Bush et al., 2000; Nieuwenhuis et al., 2001). Functional neuroimaging shows that the ACC activates when there is a conflict that can lead to error. Single-cell recordings show involvement of the ACC in attention-demanding tasks (Davis et al., 2005). There is a group of cells that react only when a task has a high degree of conflict. The reaction to difficult tasks such as perception of pain and absorption of new information is similar. These reactions are mostly present in tasks with emotional content.

Typical conflict-inducing tasks are the Eriksen Flanker Task and Stroop Task. The first task consists of arrows that point to the left or to the right, with arrows on both sides that are distracters (compatible figure <<<<<, incompatible figure >><>>). The second task requires the subject to name the color with which are written the names of colors (congruent, i.e., RED written in red ink, and non-congruent, i.e., RED written in blue ink). Conflict arises in the Stroop task because reading of the written word interferes with the color that is not congruent. There are several variants of this test. This phenomenon can also be called distraction from desired outcome and has some correlations with Luria's concept of "the law of force".

Electrophysiological exploration revealed the phenomenon of error-related negativity (ERN), which appears in the ACC when an error occurs (Gehring et al., 1993). The ERN is greatest when the expected response differs from the actual response. It is supposed that optimization of this system depends on the dopamine level. There are two types of responses: when an error occurs and then when feedback information about the error is received. The rostral ACC is active when an error occurs, and it reacts to occurrence of the error, while the dorsal ACC is active in both situations (error occurrence and feedback information about the error), which indicates an evaluation function for the dorsal ACC. Evaluation is of an emotional nature and reflects the degree of distress coupled with a certain error (Bush et al., 2000). According to previous ERN studies, the ACC receives information about the stimulus, chooses an appropriate response, monitors the action and adapts behavior if the expectations are not met (Luu and Pederson, 2004).

**Cognitive control**. Decision making is a function of the lateral frontal, OFC, and ACC (Lee et al., 2007). The dorsal ACC follows the occurrence of conflict in information processing and, in accordance with that, guides compensatory adjustments in cognitive control (Botvinick et al., 2004). Besides decision making, it participates in reward-based learning. The dorsal ACC activates more in demanding situations, and out-of-routine situations although monitoring of cognition is a permanent function of this structure. The ACC assesses the amount of mental effort needed and generate the EEG theta rhythm in midline that characteristically appears in intensive concentration and connects cognition with accompanying changes in the autonomic nervous system. This cortical area analyzes the cost-benefit ratio for a given activity and regulates the process of choosing responses.

Cognitive control pertains to regulatory processes that enable our thinking, memory, planning, and actions to be in accordance with our goals (Roelofs et al., 2006). Cognitive control allows us to resist temptations that interfere with actions to accomplish goals by constant monitoring of the congruency of our plans and actions with our intentions. The process of cognitive control involves the ACC, other medial prefrontal structures, the lateral prefrontal cortex, and parietal areas (Roelofs et al., 2006). The ACC is never activated entirely, which shows the complexity of its functions. Activation is greater in incongruent than in congruent tasks and demands more control.

Deactivation of the rostral ACC (with other default areas) is important for optimization of accomplishing an action, while increase in activity of the rostral and dorsal ACC is at the same time important for assessment of the accomplished action (Polli et al., 2005). Errors activate both parts of the ACC. The rostral part estimates the emotional aspect of error.

**Pain.** Pain has two components: pain sensation and unpleasantness caused by painful stimuli and the secondary pain-affect influenced by an individual's personality (Price, 2002). Nociceptive information reaches the ACC by two pathways: direct and indirect (cortico-lymbic). The ACC, especially BA 24, is always active during experiencing pain and mediates emotional aspects of pain. The central position of the ACC enables this area to integrate attentional and evaluative functions, establish the emotional valence, and determine response priorities. The ACC assesses the degree of danger and plans a reaction.

**Emotions**. The limbic system is known to participate in emotion. The core emotional regions in the human brain are the amygdala, the nucleus accumbens, the hypothalamus, the orbitofrontal cortex, and the ACC, while some other structures are less active during emotional processing (Pessoa, 2008). Metabolic activation was registered in the subgenual ACC near the pregenual area in sadness, selecting sad or happy targets, monitoring of internal states, and other tasks (Drevets and Savitz, 2008). These findings suggest that the ACC exerts automatic regulation of emotional behavior.

Activation of the rostral ACC and amygdala was registered in experiments where subjects were asked to imagine positive future events (Sharot et al., 2007). Normal function of the rostral ACC might be the integration and regulation of emotional and autobiographical information in optimistic expectation. Listening to pleasant music activates the subcallosal ACC, as well as the orbitofrontal and fronto-polar cortical areas (Blood et al., 1999).

Studies with positron emission tomography (PET) showed that a function of the right dorsal ACC is the capacity to correctly detect emotional signals from inside and outside the organism, while the rostral ACC is responsible for cognitive operations determining the content of emotions ("knowing how someone is feeling") (Lane, 2000). On the basis of these experiments, it was supposed that these areas are connected by the phenomenological experience of emotions and further processing of presentation of emotional events.

The rostral ACC is involved in the emotional response to error and is essential to self-confidence. In healthy individuals, the dorsal ACC is relatively deactivated during emotional tasks and the rostral during cognitive tasks, which represents resource economy in different cognitive processes. It would appear that the brain has its basic physiological activity as some kind of "default mode" that encompasses the medial cortical structures, dorsomedial and ventromedial prefrontal cortex, and posterior cingular cortex, which are active in the resting state, while their activity diminishes in goal-directed behavior (Wagner et al., 2008).

The ACC supposedly participates in regulation of the hypothalamo-pituitary-suprarenal axis (MacLullich et al., 2006). The hippocampus is involved in control of hypothalamic function. In this manner, the ACC regulates the endocrine system.

**Pain**. The ACC is involved in nociceptive modulation (Xie et al., 2009). It receives extensive input from the mediodorsal thalamic nucleus, as well as from the periaqueductal, gray, and other regions. The rostral ACC has been shown to be important in placebo analgesia. Painful stimuli activate the contralateral ACC and produce a sense of unpleasantness. This area has a role in responding to both somatic and visceral pain, and also in pain control. Neurotransmitters involved in pain modulation by the ACC are glutamate, dopamine, and opioids.

**Pain and emotions**. Pain and emotions are interlinked. Besides the pain caused by physical injuries, the ACC is also activated by hurt feelings (Frith, 2007). Physical pain is the most basic signal that something is wrong, while social rejection is a much higher signal, but both serve survival purposes (Vastag, 2003). The ventral prefrontal cortex dampens the emotional distress caused by pain, in contrast to the ACC, and is probably the structure responsible for the placebo effect. The ACC signals higher frontal areas to stop the pain, whether physical or emotional (Boes et al., 2008). Activity of the right ventral prefrontal cortex dampens the distress of both types of pain.

An important issue is the interconnection that exists between pain and depression. It is well known that chronic pain can cause depression, while depression can be accompanied by pain. Up to 80% of depressed individuals can really exhibit mainly physical symptoms (Kirmayer et al., 1993). These facts are also the fundamental principle behind application of tricyclic antidepressives in poorly defined pain syndromes. Normally serotonin and norepinephrine circuits suppress routine autonomic and somatic sensory input, ensuring that the brain does not waste energy on irrelevant details (Vastag, 2003). In depressed people, these sensations may become conscious because of increased ACC activity.

**Psychosocial stress**. There is a potential role of the perigenual ACC in connecting negative ideation and in increased risk of developing mental and somatic diseases. In individuals with low subjective social status (accompanied by subclinical depressive symptoms), a positive correlation was found with reduced volume of gray matter in the perigenual zone of the ACC, which is also supposedly a place for physiological reactivity to psychosocial stress (Gianaros et al., 2007). Along with the ACC, the hippocampus and amygdala would appear to be part of the neuronal network that coordinates behavior and neuroendocrine (hypothalamo-pituitary-adrenal) and autonomous (sympatoadrenal) functions in adaptive overcoming of emotionally important social and psychological challenges. Various stress events cause structural changes in these three structures. Stress increases N-methyl-D-aspartate glutamatergic receptor stimulation and glucocorticoid secretion and might be even more increased in impaired ACC function. Glucocorticoid receptors in the ventral ACC are involved in the negative feedback loop. Another predisposing factor may be serotonin transporter-promoter polymorphism (Drevets and Savitz, 2008).

**Social behavior**. The OFC and ACC mediate decision making, as well as emotional and social behavior (Rushworth et al., 2007). Both areas guide behavior by reinforcement with actions (ACC) and stimuli (OFC). The OFC is important for the representation of preferences. The ACC has greater access to spatial and motor systems and OFC to information about stimuli, especially visual. In that respect, the ACC has action-reinforcement representations and is involved in generation of actions and exploration of action values, effort-based decision making, and social behavior. Action selection is critically dependent on the anterior part of the cingulate sulcus and is based on the reward history of previous actions.

**Executive attention**. The ACC participates in vocalization and mimic control, as well as attentional processes during an action (Luu and Pederson, 2004). This process is called executive attention: during an action, a volitional process can overcome or modify automatic processes. Executive attention switches on when routine functions are not sufficient or when actual behavior has to be adapted to environmental demands (Posner and DiGirolamo, 1998).

**Motor control**. A less explored role of the ACC is motor control. Activation of the posterior ACC is coupled with complex bimanual tasks when movements of one hand are different from movements of the other hand, i.e., they are not of the "mirror type", which demands much less effort (Wenderoth et al., 2005). At the same time, there is activation of the anterior-dorsal precuneus, probably because of moving of the spatial attention necessary for spatial organization of the movements. The caudal ACC itself probably modulates other cortical motor areas and suppresses their more or less automatized movements.

Gigantopyramidal cells are another type of neuron characteristic of the ACC (Braak and Braak, 1976). They are located posterior to the VEN area, deep in the cingular sulcus in layer Vb and have motor function. In functional MRI studies, this cingulate motor area was activated in precision grasping movements of the thumb and index finger, but also in the mental imagery of such movements (Ehrsson et al., 2001).

**Behavior monitoring**. Experiments with functional magnetic resonance (fMR) showed that error detection is not the main ACC function, which instead is the constant monitoring and evaluation of behavior and its adaptation in order to avoid losses (Magno et al., 2006). Thus, adaptable behavior is a function of the ACC, which is one of the few cerebral control centers that maintain a high level of functioning (ACC, insula, dorsolateral prefrontal cortex, nucleus accumbens). The mesolimbic dopaminergic system that projects to the nucleus accumbens enables us to overcome difficulties in achieving a greater reward (Salamone et al., 1997). Prefrontal dopamine is necessary for cognitive processes and regulates working memory and attention through D1 receptors, and set shifting mediated by D1 and D2 receptors mediates mental flexibility (Schweimer and Hauber, 2006).

Together with the ACC, the nucleus accumbens mediates processes involved with reward and reacts when the expected reward is not received, with temporary depression of mesencephalic dopaminergic neurons. Coactivation of the dorsolateral prefrontal cortex and the nucleus accumbens is obtained during monitoring of one's functioning and both areas are involved in executive functions. The dorsolateral cortex maintains target-specific activity necessary for assessment of inadequate behavior and correct behavior to avoid new error. Responding specifically to error is a function of the insula, which is activated in such cases.

**Sex differences**. Examination with fMR showed sex differences in activity of the ventral (subgenual) ACC (BP 25) in the demanding task of metal rotation with complex visuospatial information processing (Butler et al., 2007). More ventral ACC activation was found in women than in men during negative emotions. It seems that the suppression of the ventral ACC seen after strenuous cognitive activity and during negative emotions is present only in women.

The amygdala-cingulate feedback circuit critical for emotional regulation is influenced by the short allele of a functional 5' promoter polymorphism of the serotonin transporter gene (Pezawas et al., 2005). Subjects with this allele have reduced gray matter volume in the brain structures that mediate processing of negative emotions, mostly the perigenual cingulate and amygdala. The repercussion of these changes is genetic susceptibility to depression.

Individuals of male sex harboring the monoamine oxydase-A (MAO-A) gene L version express lower enzyme acitivity and higher levels of serotonin (Meyer-Lindenberg et al., 2006). This leads to susceptibility to aggression (impulsive violence), but only in men who were abused as children, as they have only one copy of this allele on the X chromosome, whereas women have two alleles, one of which is usually the H variant. Men with the L variant show reduction in gray matter in the ACC and amygdale, while volume of the orbital frontal cortex is increased. It is hypothesized that greater volume is due to deficient pruning. Greater activity was found in the amygdala, which mediates fear, while structures that regulate the amygdala (ACC, orbitofrontal and insular cortices) showed decreased activity. Thus, the ACC, the hub of a circuit that regulates impulsive aggression, is not able to inhibit behavioral impulses.

People who believe in God are less anxious and have less reactivity in the ACC (Inzlicht et al., 2009). A strong belief in God acts as a buffer against anxiety and minimizes the experience of error. Religion has been shown to provide better mental and physical health and lower mortality rates. Studies show that the ACC is a critical cortical structure for the inhibition of response that is seen in anxiety. This area signals every time when some behavioral modification is needed in response to an anxiety-producing event (commission of an error, detection of conflict or the experience of uncertainty). Religious conviction acts like an anxiolytic, reducing emotional reactions to errors or uncertainty, providing people with a meaningful system helping them to understand the complex and uncertain word that we live in (Peterson, 1999). Religion gives motivation, purpose, and meaning, providing people with standards upon which to act in life. In physiological terms, it reduces ACC activity and consequently distress.

**Summary of ACC functions**. It can be stated in summary that the ACC acts as a monitoring system that alarms us when the brain perceives (or predicts) physical or psychic pain, hunger, thirst, inconsistency, irritation, and cognitive discrepancy between current standards (environmental models) and perceived outcome (uncertainty, surprise, cognitive dissonance, conflict), and then reacts to adjust the ongoing behavior in order to fulfill a goal or improve the state of the subject. In such a way, it can change the frequency of some behaviors according to experience of reward or punishment (operant conditioning). It is also necessary for resolving complex cognitive tasks, but participates in difficult emotional matters as well. Regulation of autonomic and endocrine functions is another role of the ACC (Devinsky et al., 1995).

The ACC acts in cooperation with the dorsolateral prefrontal cortex, which maintains and manipulates reward-based environmental models, and the anterior prefrontal cortex, which estimates unobservable states (part of abstract thinking) along with the rostral limbic system, including the amygdala, periaqueductal gray matter, ventral striatum, and orbitofrontal and anterior insular cortices. This system assesses the motivational content of internal and external stimuli and regulates context-dependent behaviors (Devinsky et al., 1995).

## THE ANTERIOR CINGULATE CORTEX IN BRAIN DISEASES

Several neurological and psychiatric entities have a dysfunctional ACC. Most interest in this area is focused on depression and certain other diseases. Electrical stimulation of the subgenual ACC, i.e., BP 25, in some neurosurgical patients improved depression. Lesion of area 25 leads to difficulties in error detection, inability to resolve stimulus conflict (as in the Stroop task), emotional instability, disturbance of attention, and akinetic mutism (Posner and DiGirolamo, 1998; Bush et al., 2000).

**Dementia**. Lesions of the ACC are detected in AD (Nimchinsky et al., 1999). Cognitive decline in AD involve dysfunction in the medial temporal lobe and posterior cinculate gyrus, while behavioral and psychological symptoms reflect involvement of the ACC (Shinno et al., 2007). Examination with 99mTc-hexamethyl propyleneamine oxime single photon emission computed tomography (HMPAO-SPECT) showed selective hypoperfusion in the ACC in depressed patients with AD similar to findings in primary depression, which testifies against the reactive character of depression in this type of dementia (Liao et al., 2003). Apathy is the most frequent behavioral symptom in AD and is connected to dysfunction of the ACC and orbitofrontal cortex (Guimarães et al, 2008). This is understandable, as the ACC has a pivotal role in decision making. Autopsy findings reveal significant hypertrophy of neuronal cell bodies in the ACC and hippocampal CA1 area in asymptomatic AD patients (Iacono et al., 2008). Neuronal hypertrophy might be an early reaction to amyloid beta or tau protein or a compensatory mechanism.

Behavioral variant frontotemporal dementia (bvFTD) shows impairment of social and emotional functions with early focal degeneration of the ACC and FI cortex more prominent in the right hemisphere (Seeley et al., 2007). Both the ACC and FI are paralimbic agranular cortices with a prominent layer 5 and the only brain site of VEN, which are important for complex social networking. These patients lose self-conscious emotions, theory of mind, empathy, metacognition, and moral sensibility, precluding the representation of self and others and their use for guiding behavior, correlating with early von Economo neuron loss (Seeley, 2008).

Subcortical vascular dementia shows reduced glucose metabolism of the ACC on 18 F-FDG (fluro deoxy glucose) positron emission tomography (PET) images (Seo et al., 2007). Dementia in Parkinson's disease is significantly associated with alpha-synuclein and amyloid beta peptide deposition in the ACC (Kalaitzakis et al., 2009). It was shown that an alpha-synuclein burden in the ACC can differentiate demented from non-demented Parkinson patients with high accuracy. Amnestic mild cognitive impairment shows hypoperfusion in the bilateral medial temporal lobe, anterior cingulated cortex, and left orbitofrontal cortex (Nobili et al., 2009).

**Schizophrenia**. Dysfunction of the ACC was found in patients with schizophrenia (Posner and DiGirolamo, 1998). For successful accomplishment of demanding tasks, it is necessary to assess outcome in order to learn from mistakes. The neural mechanism of the ACC makes possible error detection, its assessment, and adequate correction of behavior. The dorsal ACC participates in learning, while the rostral ACC (along with the amygdala and insula) assesses the affective or motivational importance of error (Polli et al., 2008). Theoretically, the dorsal ACC uses dopaminergic input to modify the intensity of stimulus-response mapping in response to detected error and in this way corrects behavior. Errors cause phasic suppression of dopamine and increased activity of the dorsal ACC. Patients with schizophrenia show rigid, perseverative behavior that is not adequately corrected based on errors. Studies have shown decreased activity in both parts of the ACC, coupled with lack of effect of error in assessment and correction of behavior. Reaction to error is thereby damped in these patients, causing disturbance of normal adaptive behavior. Dysfunction in the dorsal ACC results in disturbance of conditional learning, while dysfunction in the rostral ACC causes affective bluntness for the effects of behavior (Polli et al., 2008). These patients detect errors normally. Disturbance of responding to error is registered in the substantia nigra as one more part of the system involved in operant learning. It is possible that the striatum detects incongruity between correct (intended) and wrong (actual) outcome. This causes phasic diminution of mesencephalic dopaminergic signals, which leads to disinhibition of the dorsal ACC. The role of the insula in emotional experience is probably that of conveying to consciousness the state of the organism from visceral and autonomous information. The amygdala detects salient and/or aversive stimuli and events. Diminution of normal activation of the rostral ACC, which is part of this system in patients with schizophrenia, reflects decreased affective and interoceptive sensibility to errors.

**Attentional deficit hyperactive disorder**. Patients with attentional deficit hyperactive disorder (ADHD) have decreased activation of area 25 in the Stroop test (Bush et al., 1999). In patients with obsessive-compulsive disorder, a lowered level of glutamate was found in the ACC and an increased level in other brain areas (Pittenger et al., 2006). The rostral ACC is hyperactive in obsessive-compulsive disorder (OCD), with increased error sensitivity to the extent that patients perceive error where there is none (Fitzgerald et al., 2005). This is linked with affective response to error. The given area participates in emotions and motivation. Some trials of operative treatment of OCD and chronic pain by medial caudal cingulotomy were controversial (Davis et al., 2005).

**Anxious disorders and depression**. Increased reaction to error is observed in anxious disorders and depression. Patients can observe error when there is none and exhibit increased ACC activity. This can be based of an early stress that predisposes the ACC and related structures to react with anxiety.

Acitivity in the subgenual (subcallosal) ACC is increased in patients with major depressive disorders and normalizes with antidepressant therapy (Drevets and Savitz, 2008). The most prominent methabolic changes were detected in familial pure depressive disease. This area is represented by BA 24b and BA 24a anteriorly and BA 25 posteriorly. Deep brain stimulation in area 25 showed improvement in eight out of 12 patients with resistant depression (Mayberg et al., 2005). The authors concluded that area 25 is the main connection between the frontal cortex as the site of thinking and the central limbic area as the site of emotions. In elderly subjects with major depression, there is an increased prevalence of neuroimaging signs of cerebrovascular disease without focal ACC atrophy (Drevets and Savitz, 2008). In successfully treated patients, the posterior subgenual ACC (BA 25) volume may even increase (Drevets and Savitz, 2008).

Individuals with depression cannot suppress negative thoughts and tend to focus their attention on negative emotional stimuli (Wagner et al., 2008). Depression is also accompanied by cognitive control disturbances and disturbance of the decision-making system. The ventrolateral prefrontal cortex (BP 44, 45), dorsolateral prefrontal cortex (BP 9, 46), and ACC (BP 24, 25, 32) have a crucial role in target-oriented flexible behavior such as selection and activation of adequate responses (ventrolateral prefrontal cortex), conflict monitoring and activity outcome (ACC), and cognitive inhibition of responses that are irrelevant for task completion (dorsolateral prefrontal cortex) (Wagner et al., 2008). Functional MR showed reduced activation of the prefrontal cortex and ACC in patients with depression and dysexecutive syndrome. It was shown that these patients have disturbed ability to inhibit cognitive interferrence in emotional states. For instance, when confronted with a conflict situation in the Stroop test, depressed individuals spend more time inhibiting the wrong answer than do healthy subjects (Wagner et al., 2008). This is accompanied by inability to deactivate the rostral or affective ACC, which may be a consequence of disturbance of the normal cerebral "default mode". It is hypothesized that there is a disturbance in structure and function of the ventromedial prefrontal cortex, which with the rostral

ACC (together forming the medial perigenual area), is part of the „default network". Loss of deactivation of this system might create a depressive ideation of self.

**Structural brain changes in depression.** Individuals with major depression have reduced volume of the hippocampus and cingulate cortex, as well as reduction of the glia and neurons in the OFC and dorsolateral prefrontal cortex (Wagner et al., 2008). Magnetic resonance imaging studies showed reduction in volume of the left amygdala and hippocampus, mostly the subiculum, and the left middle frontal gyrus (BA 8, 9), subgenual cortex (BA 25), and gyrus rectus bilaterally (BA 11) (Wagner et al., 2008). This is confirmed in the majority of studies. It seems that anatomical characteristics of the rostral ACC predispose occurrence of depression already in childhood. Volume of the rostral ACC is significantly diminished, especially on the left side, in boys with subclinical depression compared to boys that are not depressed (Boes et al., 2008).

Depressed patients have an increased level of activity in the subgenual ACC in the resting state compared to control subjects (Greicius et al., 2007). The higher level of increased activity would supposedly make the default system refractory to antidepressants. A higher level of activity in the subgenual ACC and thalamus correlated positively with better outcome of anterior cingulotomy in patients with refractory depression.

Magnetic resonance spectroscopy showed a lower level of gamma-amino-butyric acid (GABA) in the occipital lobe and ACC in patients with depression (Bhagwagar et al., 2008). Levels of GABA increased with therapy, but were still lower than in control subjects. It is supposed that there are fewer GABA-producing glial cells in the ACC of depressed patients. A lower level of GABA was also found in serum and cerebrospinal fluid of individuals with depression. Inadequate functioning of area 25 allows intrusion of negative emotions that overflow thinking.

**Bipolar disorder**. The volume of mean gray matter in the subgenual ACC is reduced in patients with bipolar disorder (BD) irrespective of mood state (Drevets and Savitz, 2008). In the early stages of BD, there are already changes in volume of BA 25 and part of 24 (Fountoulakis et al., 2008). This might be a consequence of neuronal and glial depletion or lesions of white matter connections. Left BA 25 activity is increased in the manic and decreased in the depressive phase. One possible mechanism is confirmed deficient GABA-ergic activity in the ACC. Individuals with familial occurrence of BD show reduction of gray matter in the left subgenual ACC. Reduced volume of the left ACC was found in children with BD (Chiu et al., 2008). The volume of this area can be influenced by age, drugs, and intelligence. Measurements of the ACC would be a potential marker of BD.

On the other hand, chronic lithium treatment has measurable neurotrophic effects in animals, such effects leading to increased gray matter volumes in several prefrontal areas (Drevets and Savitz, 2008). In humans with BD, lithium treatment correlated with increased concentrations of N-acetylaspartate, which is a marker of neuronal integrity (Moore et al., 2000).

**Autism**. Spindle neurons are possibly dysfunctional in autism which might lead to defective intuition and spontaneous adaptation (Allman et al., 2005). Magnetic resonance imaging studies showed reduced volume of the right ACC (containing VEN) in autistic individuals (Haznedar et al., 2000). There are also other anomalies in these structures in these patients.

**Anorexia nervosa**. Decrease of ACC gray matter was found in patients with anorexia nervosa in remission MR vowel-based morphometry (Mühlau et al., 2007). The level of gray matter loss correlated with the severity of anorexia nervosa. Lesions of the ACC supposedly cause alexithymia (Lane, 2000).

**Dissociative (conversion) disorders.** Patients with conversion paralysis activate the premotor cortex, right orbitofrontal cortex, and right ACC when attempting to move their "paralyzed" limb (Marshall et al., 1997). A possible explanation is that activation of the right (nondominant) ACC and OFC is a sign of unconscious inhibition of movement. Similar results are obtained in hypnotically-induced paralysis.

**Obsessive-compulsive disorder**. Patients with obsessive-compulsive disorder have elevated activity along the frontal-subcortical axis: the orbitofrontal cortex, caudate nucleus, thalamus, and ACC (Saxena et al., 1998). Symptoms decrease in response to treatment with serotonin reuptake inhibitor medications or cognitive-behavioral therapy (Saxena et al., 2009). Clinical effects are accompanied by decreased activity in both thalami and increased activity in the right dorsal ACC. It is supposed that the dorsal ACC is important in suppression of negative emotions. This same area is more active after successful therapy for major depression.

**Hyper- and hypoactivity of the ACC**. Epileptic discharges in the ACC disturb consciousness and emotions and lead to motor and autonomous activities (Devinsky et al., 1995). These patients express psychopathic or sociopathic behaviors. Decrease of ACC activity leads to akinetic mutism, decreased self consciousness, depression, motor neglect, disturbance of initiations of movements, decreased pain sensitivity, and disturbance of social behavior (Devinsky et al., 1995).

## CONCLUSION

Studies so far show an important role for the ACC in all higher mammals. This structure participates in attention, analysis of sensory information, behavior, interference, discovering what is novel to the individual, reward expectation, decision making, empathy, emotions and autonomous functions such as regulation of heart rhythm and blood pressure, digestion, voice production, and mimic expression. It is supposed that the ACC coordinates emotions, cognition, and emotional self-control. This cortical area is the site of awareness, feelings of free will, social emotions, and feelings of morality. The ACC monitors performance, recognizes errors, and adapts to changes of conditions, which are the marks of intelligent behavior.

This area is part of numerous neuron networks and is active whenever a person experiences some emotions or resolves a problem where there is a conflict of reward. This permits analysis in favor or against an action, i.e., if this decision is right. The ACC is linked with conscious experience. Emotional awareness is connected with increased recognition of emotional signs and activates area 25.

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## ПРЕДЊА ЦИНГУЛАРНА КОРА

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Предња цингуларна кора има улогу у пажњи, анализи сензорних информација, препознавању грешке, решавању проблема, откривању оног што је ново за јединку, понашању, емоцијама, социјалним релацијама и когнитивној контроли као и регулацији аутономних функција. Ова ареа је активна кад год особа доживљава нека осећања или када решава неке проблеме и врши анализу за и против неке акције односно да ли је одлука исправна. Аналогне области су нађене и код виших сисара, нарочито китова и код свих постоје вретенасти неурони које омогућавају сложене социјалне интеракције. Поремећај функције предње цингуларне коре се виђа у деменцијама, схизофренији, депресији, опсесивно-компулсивним поремећајима и другим неуропсихијатријским болестима.