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Derleme / Review

From Social Neurons to Social Cognition: Implications for Schizophrenia Research

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ABSTRACT

From social neurons to social cognition: implications for schizophrenia research

The term schizophrenia embraces a group of disorders that are characterised by a heterogeneous set of symptoms. Poor social cognition, including metacognitive dysfunction is present across all schizophrenia phenotypes, accounting for a large proportion of patients' social impairment. Metacognitive functioning is subserved by a distinct neural network of widely distributed regions of the brain, foremost areas of the prefrontal cortex, as well as, areas in the temporal and parietal lobes. While dysfunction of the metacognition neural network in schizophrenia has been well documented, the underlying neuronal correlates are only partially understood.

This review focuses on two distinct cell populations that evolved during primate evolution: The mirror neurons, and the von Economo neurons. Empirical evidence suggests that these cell types have a special role in social cognition and metacognitive functioning. However, only recent studies have addressed their potential role in schizophrenia.

In spite of current paucity of research on mirror neuron function in schizophrenia, it seems plausible to suggest that their functional properties are compromised, and contribute to aberrant imitation behaviour in schizophrenia. The potential impact of von Economo neurons in the pathophysiology of schizophrenia is even less clear, but future research may help to better understand the nature of this devastating group of disorders.

Key words: Schizophrenia, cognition, metacognitive, metacognition, theory of mind

ÖZET

Sosyal nöronlardan sosyal kognisyona: Şizofreni araştırmalarına etkileri

Şizofreni terimi, heterojen belirtilerle karakterize bir hastalık grubunu kapsar. Hastaların sosyal kaybının önemli bir bölümünden sorumlu olan metakognitif işlev bozukluğunu da kapsayan kötü sosyal biliş, tüm şizofreni fenotiplerinde vardır. Metakognitif işlevsellik, temporal ve parietal loblardaki alanlar kadar prefrontal korteksin önemli alanları gibi beynin birçok bölgesine yaygın şekilde dağılan ayrı bir sinir ağı ile desteklenmektedir. Şizofrenideki metakognisyon sinir ağındaki işlev bozukluğu daha önceden iyi tanımlanmış olmakla birlikte, altta yatan sinirsel bağlantılar yalnızca kısmen anlaşılabilmiştir. Bu gözden geçirme, primat evrimi boyunca gelişen iki ayrı hücre popülasyonuna odaklanmıştır: ayna nöronlar ve von Economo nöronları. Ampirik kanıtlar bize, bu hücre tiplerinin sosyal biliş ve metakognitif işlevsellik konusunda özel bir rolü olduğunu düşündürtmektedir. Bununla birlikte, sadece yakın zamandaki çalışmalar bunların şizofrenideki potansiyel rollerini tanımlayabilmiştir. Ayna nöron işlevlerine yönelik araştırmaların bazı eksikliklerine rağmen, bunların işlevsel özelliklerinin etkilendiği ve şizofrenideki anormal taklit davranışına katkıda bulunduğu fikri akla yatkın görünüyor. Şizofreninin patofizyolojisinde yer alan von Economo nöronlarının potansiyel etkisi hala yeterince açık değildir, fakat gelecek araştırmalar, belki bu yıkıcı hastalık grubunun doğasını daha iyi anlamamıza yardımcı olabilir.

Anahtar kelimeler: Şizofreni, kognisyon, metakognitif, metakognisyon, zihin teorisi

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INTRODUCTION

The term schizophrenia concerns a group of phenomenologically heterogeneous disorders that are characterized by cognitive and perceptual disturbances (e.g., thought disorder, delusions, hallucinations), affective signs and symptoms (e.g., lack of emotional resonance, affective flattening, abulia), behavioural symptoms (e.g., disorganization, catatonic features), as well as neurocognitive performance failures (e.g., impaired verbal memory, verbal fluency, and executive function deficits) (1). Recent research has suggested that specific impairments in social cognition (2) be included in the "core" symptomatology of schizophrenia (3). Social cognition embraces different domains such as social perception, social knowledge, emotion recognition, and the ability to represent mental states of self and others. This latter aspect of social cognition, termed "metacognition", includes the ability to use mentalistic information for effective social

problem-solving (4,5), and this particular capacity seems to be frequently impaired in schizophrenia (reviewed in 6-10). The concept of metacognition broadly overlaps with those of "theory of mind" (11), "metarepresentation" (12), "mentalizing" (13), "mental state attribution" (14), and "cognitive and affective empathy" (15). Irrespective of terminological questions, metacognitive dysfunction in schizophrenia has profound consequences for everyday social functioning. In fact, evidence supports the view that poor metacognition in schizophrenia accounts for a considerable proportion of variance of poor social functioning (reviewed in 16).

Metacognitive abilities are thought to be represented in an extended neural network comprising cortical midline structures, in particular the medial frontal cortex (mPFC), the anterior cingulate cortex (ACC), the precuneus, as well as lateral areas of the middle temporal lobes (MTL), the temporoparietal junction (TPJ), the superior temporal sulcus (STS) and the temporal poles (reviewed in 17-20). The area extending from the ACC to the anterior frontal pole, particularly the paracingulate cortex, is supposed to be engaged in self-reflection, person perception and in making inferences about others' thoughts (17). The mPFC and the ACC are also involved in distinguishing self from non-self, in error monitoring, and in differentiating salient from non-salient stimuli (21-23). The role of the precuneus is less well known, but this brain area seems to be important for the experience of agency and self-consciousness (24,25). The temporo-parietal junction (TPJ) contributes to reasoning about the contents of another person's mind (26,27), attribution of a character's true and false beliefs (20,28), recognition of cooperation versus deception (29) as well as self-other discrimination (30). Although hemispheric specialisation has been observed, the results are contradictory: while some studies found selective activity in right TPJ (31), others assumed left TPJ to be necessary for representing other persons' beliefs (32,33).

Several functional brain imaging studies have revealed that this neural network involved in metacognition is underactivated in schizophrenia. In a pioneering study using functional brain imaging technology, Russell et al. (34) found reduced activation in the left middle/inferior frontal gyrus and insula (BA 9/44/45) relative to healthy control subjects. Likewise, in a PET study, Brunet and co-workers (35) revealed that patients with mixed types of schizophrenia did not activate the medial prefrontal cortex during the execution of a metacognitive task, but instead, parts of the medial frontal cortex, medial occipital cortex, hippocampus and cerebellum that were qualitatively different from control activations. In a similar vein, Lee and colleagues (36) found that patients with acute episodes activated areas in the left mPFC to a lesser degree compared with healthy control subjects in a paradigm that required empathic responses. Similarly, Brüne et al. (37) studied metacognition in patients with schizophrenia who experienced "passivity" symptoms. They found that patients displayed a markedly diverging pattern of brain activation during performance compared with healthy controls in that the patient group showed significantly less activation of the right anterior cingulate cortex (ACC) and right insula compared with controls, but greater activation in dorsal areas of the medial prefrontal cortex, right temporal areas and left temporo-parietal junction. Finally, Walter et al. (38) revealed that patients with paranoid schizophrenia activated the ToM neural network to a lesser extent compared to controls, a finding that is in line with previous research. Most interestingly, patients showed higher activations in both the medial prefrontal cortex and temporo-parietal junction when observing cartoon drawings depicting physical causation of movements, which suggest an overattribution of intentionality in paranoid states (38). In summary, functional brain imaging studies support the idea of a divergent activation of the neural network involved in metacognition in schizophrenia that seem to be both state- and trait-dependent.

While functional brain imaging has greatly advanced our knowledge of how the brain deals with metacognitive processes in healthy subjects and patients with schizophrenia, these studies inform us – strictly speaking – at best about changes in oxygenation of blood, but very little with regard to what happens at the neuronal level. The latter question can only be addressed using

other methods, including comparative studies in nonhuman animals, as well as electroencephalography, transcranial magnetic stimulation, and magnetoencephalography in human subjects. Most interesting in this respect are two types of cell populations which seem to be largely specific to primates, and can partly be targeted by electrophysiological or anatomical means. One type of neuron is referred to as "mirror neuron" (MN) for its unique properties to discharge during both the execution of an action or by the mere observation of the same behaviour in others (39). The other cell type, first discovered by von Economo (40), and hence called "von Economo neuron" (VEN), is located in the anterior part of the ACC and in the anterior insula of apes and humans, but apparently absent in monkeys (41). Both MNs and VENs are likely to be functionally involved in metacognition (42,43), and thus, a target for scientific inquiry in schizophrenia research focussing on the question whether or not MNs and VENs play a role in the pathophysiology of schizophrenia and, if so, how dysfunction relates to metacognitive functioning. Accordingly, the present article aims at reviewing the evidence for MN dysfunction and VEN pathology in schizophrenia.

Mirror neuron system

In the 1990s, a ground-breaking study suggested the existence of MNs. In essence, di Pellegrino and colleagues (44) observed in monkeys that some neurons in the inferior premotor cortex not only discharged when executing specific movements, but also during the observation of similar movements performed by humans. MNs were subsequently localised in the ventral premotor cortex of macaque monkeys, an area that is possibly homologous to Broca's area in humans (39). In macaques, the same region contains MNs with audiovisual properties, which are activated when actions are detected by their acoustic properties (45). In humans, multiple brain regions including the premotor cortex, the inferior parietal lobule as well as the supplementary motor area, the somatosensory cortex and cerebellum have been linked to the MN system (46). In an experiment using transcranial magnetic stimulation (TMS), Fadiga et al. (47) showed that the observation of a goal-directed hand movement elicited enhanced motor evoked potentials in the test subject's corresponding hand muscles. Moreover, Chong and co-workers (48) demonstrated activation of the right inferior parietal lobe which turned out to be diminished if subjects had observed a movement they performed earlier in relation to ones they only observed but did not perform in person. Direct in vivo observation of human neurons with MN characteristics has recently been conducted by Mukamel et al. (49) using electrophysiological recordings in patients undergoing surgery for intractable epilepsy. According to this study, neurons putatively linked to the MNS are more widely distributed than previously thought, and seem to be localized throughout the medial frontal cortex and medial temporal cortex (e.g. supplementary motor area, hippocampus and entorhinal cortex). In addition to simple action-observation activity, animal experiments have revealed that MN selectively fire when monkeys observe a hand movement of which the terminal part is hidden from their view. This suggests that MNs have properties to predict the outcome of a partially invisible action (50). Taken together, MN activity offers an explanation of how the ability to imitate the actions of others could have evolved into the capacity to simulate the mental states of other individuals, a crucial aspect of metacognitive skills (51).

In light of these findings, Gallese (42) proposed the "shared manifold hypothesis" suggesting that MNs are part of a neural network not only involved in linking action with observation, but also in forming a neural correlate for interpersonal experience. Accordingly, the mirror neuron system (MNS) could represent social cognition and empathy at a cellular level (52).

From a clinical point of view, it has been argued that dysfunction of the MNS might not only be fundamental to explaining behavioural symptoms of autism (53-55), but also to the understanding of psychotic symptoms (56). For example, Arbib (57) suggested that misattribution of manual actions as well as inner speech to other persons could emerge from a dysfunction of the MNS. He postulated that a lack of memorizing

actions or speech might cause the subject to misinterpret them as external. Similarly, echopraxia, the pathological imitation of behaviours seen in patients with catatonic syndromes or Tourette syndrome, may occur due to a pathologically enhanced "mirroring effect" associated with behavioural disinhibition (58). It could therefore be fruitful to further examine the relationship of the MNS with psychotic symptoms, such as passivity symptoms and catatonia. However, to date, the evidence for a dysfunction of the MNS in schizophrenia and other psychotic disorders is limited.

Indirect hints come from studies that have used imitation paradigms in schizophrenia. For example, in healthy subjects it has been shown that viewing facial expressions of emotions elicits brain activity in those areas that are also active when displaying these nonverbal expressions akin to MN activity (59). Such noninvasive approaches can clearly inform potential abnormalities in schizophrenia. In accordance with these theoretical considerations, it was shown in a behavioural study that patients were found to be less well able to imitate facial expressions from still photographs (60). In a paradigm using contagious yawning as stimulus, patients with schizophrenia showed reduced contagiousness compared to nonclinical controls when video clips of yawning persons were presented, suggesting reduced MN activity (61). In a similar vein, Varcin et al. (62) examined differences in fast and involuntary reactions of facial muscles to the presentation of happy and angry faces using electromyographical recordings of facial muscle activity. During those tasks, rapid mimicry-like reactions of two facial muscle regions (m. corrugator supercilii and m. zygomaticus major) were detected in healthy controls. In contrast, schizophrenia patients did not show these involuntary facial responses upon the presentation of happy or angry faces. Interestingly, when recording facial movements using ultrasonic markers attached to the skin (over mm. zygomatici, m. risorius and m. depressor anguli oris), Juckel and colleagues (63) found abnormally rapid initial movements in schizophrenia patients when spontaneous laughing was evoked by slapstick movies, and such "rapid facial reactions" have been linked to the MNS (64,65).

Other sources of indirect evidence have made use of transcranial magnetic stimulation (TMS), magnetoencephalography (MEG), or magnetic resonance tomography (MRI). Enticott et al. (66), using transcranial magnetic stimulation (TMS), found that schizophrenia patients showed decreased motor facilitation compared to healthy control subjects, when observing thumb movements on video. The decreased motor facilitation had been quantified by registration of motor evoked potentials of m. abductor pollicis brevis. Their findings might indicate a deficit of the MNS. In an MEG study, Schürmann et al. (67) reported a decreased response of the motor cortex in patients compared with their non-schizophrenic twins during both observation and execution of actions. In addition, difficulties of patients with schizophrenia with the evaluation of positive behaviours might also at least partly be caused by impairments of the MNS (68). In an fMRI-study, Park and colleagues found reduced activations of the ventral premotor and the inferior frontal cortex in response to happy facial expressions in a group of patients with schizophrenia. Consistent with previous findings that schizophrenic subjects exhibit problems in processing facial expressions, increased activation of brain areas linked to the MNS (motor and pre-motor cortex) in functional magnetic resonance imaging after the presentation of facial stimuli has been described by Quintana et al. (69). Patients had shown relatively more activation in those brain areas when facial stimuli were presented than when simple coloured dots were shown. Likewise, Bertrand et al. (70) proposed that deficits of the MNS contribute to the known deficits of schizophrenic patients in social cognition, based on the observation that grey matter density in brain areas corresponding to the localisation of the MN was decreased in patients with low social cognition performance (assessed using the Four Factor Test of Social Intelligence).

In summary, to date, a few studies seem to indirectly suggest dysfunctional MN activity in schizophrenia. We propose in the discussion, how these approaches can be advanced in future research.

Von Economo neurons

Frith and Frith (71,72) have pointed out that the representation of goal-directed actions is necessary, but not sufficient to fully explain metacognitive abilities in humans. Instead, it is crucial to be able to distinguish between behaviours generated by oneself or by others. This ability seems, at least in part, be represented in the ACC, a brain area that belongs to the greater limbic lobe (73). The ACC receives input from the motor cortex and the spinal cord, from the ipsilateral prefrontal cortex, and from the thalamus and brainstem nuclei. The ACC is therefore conceived of as an "interface" of motor control, cognition, and arousal regulation (74). From an evolutionary point of view, the ACC is an interesting region, because it has undergone adaptive changes during recent human evolution, which include the formation of a paracingulate gyrus that can be found in about 50% of humans (74), and because it contains a specific type of pyramidal neuron that is conspicuous for its elongated apical dendrite and "spindle"-shaped soma, hence referred to as "spindle cell" or "von Economo neuron" (VEN) after its discoverer Constantin von Economo (40). In comparative perspective, it was believed until quite recently that VENs are specific to apes and absent in lesser primates and other animals; however, VENs have recently been detected in whales and elephants, which is notable, because these species are highly social (75,76).

Research has shown that in humans the local density and size of VENs have dramatically increased over evolutionary time, such that among apes, VENs in humans have reached the greatest density and size compared to chimpanzees, gorillas and orangutans (77,78). VENs are also present in the frontal part of the insula (FI), another region pertaining to the limbic system (40,73,79), and smaller numbers of VENs are located in the dorsolateral prefrontal cortex (80). These findings and the convergent evolution of VENs in other highly gregarious animals strongly suggest a special role in social cognition, perhaps metacognition (74,43). Even though their functional properties are unknown so far (81) and very difficult to verify, because single-cell recording is hardly feasible, there is some indirect evidence from functional brain imaging studies supporting speculations that VENs are part of the neuronal system that is involved in self-reflection (82), perception of unfairness (83), empathy (84,85), and complex negative emotions such as self-criticism (86), and feelings of being rejected and socially excluded (87), all of which can be regarded as a function of metacognitive skills.

Functionally, VENs are assumed to be specialised in rapid transmission of information over long distances (79). In humans, VENs are almost absent at birth (as opposed to the detection of VENs in chimpanzee foetuses (88). The density of VENs in humans reaches the adult figure around four years of age, suggesting a role in functional domains that mature slowly such as emotion regulation, motor control (78), and economic decision-making (43).

Additional evidence for a role of VENs in complex cognitive processes comes from studies in pathological conditions. VENs contain a high amount of neurofilament, which is why they are assumed to be affected in Alzheimer's disease (89). Moreover, VENs have been found to be selectively reduced in frontotemporal dementia (90), in corpus callosum agenesis (91), and it has also been speculated that VENs may play a role in the pathophysiology of autism (41). However, evidence for an alteration of the density of VEN in autism has been mixed. Whereas Kennedy et al. (92) found normal VEN density in the insular cortex of autistic subjects, Simms et al. (93) revealed a diverse pattern with increased VEN density in the ACC in some subjects and rarefication of VENs in others. A recent study demonstrated that individual VENs located in the anterior insula of children with autism are abnormal in size and shape (94).

In schizophrenia, the VEN density in the ACC does not seem to be altered per se; however, in a subgroup of patients with early onset schizophrenia, the density of VENs was significantly lower than in adult onset (95). Moreover, the density of VENs in the ACC correlated inversely with the duration of schizophrenia. This could be interpreted as evidence for a neurodevelopmental subtype of schizophrenia (96) in which the migration or maturation of VENs is impaired.

Consistent with this interpretation, though speculative, the association of low VEN density with early onset schizophrenia could also explain why patients with juvenile onset of the disorder are more often socially aloof and display more negative symptoms than late-onset patients (97). Put differently, if VENs have indeed a role in complex social emotion processing and self-reflection, a reduction in density or number could account for deficits in these cognitive domains in schizophrenia patients.

DISCUSSION

The term "schizophrenia" concerns a group of severe mental disorders of which poor social functioning is a hallmark. Research in the past two decades or so has revealed that poor social functioning is, at least to a considerable extent, caused by deficits in social cognition (3). Among several subdomains of social cognition, metacognition, the ability to represent own and others' mental states and to use this knowledge to cope with social problems (5,6), has been identified as a mediator of neurocognitive functioning and social skills in schizophrenia patients (10,11). Metacognition, which in a broader definition includes judgements about complex mental states such as empathetic feelings, fairness perception, moral norms and values, including shame and guilt (83-87), is profoundly impaired in schizophrenia (6,7,8), and two recent studies discovered that this failure includes the appreciation of moral values such as fairness (98,99). A number of functional brain imaging studies have demonstrated that several brain regions including cortical midline structures, the temporo-parietal junction, the inferior frontal gyrus, as well as parts of the greater limbic lobe, i.e. the ACC and the FI, not only subserve several of the above-mentioned complex metacognitive abilities, but also, that these regions seem to be involved in the pathophysiology of schizophrenia (34-38). Neuroanatomically, these brain areas are highly interesting, because they contain two evolutionarily novel cell types that may play a role in metacognition. One refers to the mirror neuron system (MNS), a neural network that has received great attention in relation to its role in metacognitive abilities. In contrast to research in healthy subjects, studies into abnormalities of the MNS in psychopathological conditions have only recently become available, mainly as regards autism. It has been shown that the μ (mu) rhythm as part of the normal EEG can perhaps open a window into the functional properties of the MNS (54,100,101). Mu rhythms are typically localised over the central region (vertex) and have frequencies similar to the alpha rhythm ranging from 8 to 13 Hz; it is characteristically suppressed when subjects observe actions of others (102, 103). Several studies have pointed to the possibility that the normal mu rhythm suppression during action observation is partially absent in children with autism (53,55,104), indicating a dysfunctional MNS, with negative results in other studies (105,106). In addition, a comparison of fMRI data and mu rhythm suppression in a study by Perry and Bentin (107) provided further evidence in favor of this approach. The same study group could also show that intranasal application of oxytocin influenced mu rhythm suppression and exerted important effects on social cognition, suggesting the functional significance of neuropeptides for the MNS (108). In brief, increased suppression of the mu rhythm after oxytocin administration was detected, while subjects watched the presentation of walking human figures. Kilner and colleagues (109) demonstrated in a MEG study that a specific cortical activation in the 7 to 12 Hz range was modulated depending on the movement and on the position of an observed person presented on video. Both the position (frontal or backward presentation of the person) as well as the hand which was moved (left/right) influenced the extent of the attenuation of the examined cortical activation. Therefore the authors hypothesized that these findings could possibly reflect that socially important information is preferably processed by the MNS. Taken into consideration the low number of studies examining mu rhythm in schizophrenia, this might be a promising field for future studies.

The other key player could be the VEN "system". VENs have been localized in the ACC and in the FI, as well as in the dorsolateral prefrontal cortex of the

human brain. It is currently unknown whether or not VENs form a neural network akin to what is believed for the MNS. Evidence is accumulating, however, that VENs play a role in complex cognition and that these cells make an interesting target for further research in schizophrenia. The latter assertion is based on findings that VEN may be reduced in early-onset schizophrenia (95) and on recent findings that VENs express DISC1 especially on the soma and dendrites (110). DISC1 has been identified as one of the most promising candidate genes involved in schizophrenia. DISC1 seems to reduce secondary and tertiary dendritic branching, which could explain why VENs display relatively little branching. Moreover, DISC1 has undergone recent positive selection during human evolution, however, mainly in regions that differ from those involved in increased vulnerability for schizophrenia (111). Regardless, whether or not these findings reflect a mere coincidence between recent evolutionary changes in DISC1 and VEN density and size, the possible association of the two with regard to cognitive functioning deserve further examination in schizophrenia.

In summary, both the MNS and the VEN seem to be part of a neuronal network that is involved in higher cognitive functions such as self-reflection and reflection about the mental states of others. The question whether or not the two are functionally impaired in schizophrenia is presently under intense investigation. Understanding the neuronal correlates of metacognitive function in schizophrenia seems crucial to help improve treatment strategies for this group of debilitating disorders.

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