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Review

Social cognition in idiopathic generalized epilepsies and potential neuroanatomical correlates

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ABSTRACT

Social cognition allows us to elaborate mental representations of social relationships and use them appropriately in a social environment. One of its main attributes is the so-called Theory of Mind (ToM), which consists of the ability to attribute beliefs, intentions, emotions, and feelings to self and others. Investigating social cognition may help understand the poor social outcome often experienced by persons with Idiopathic Generalized Epilepsies (IGE), who otherwise present with normal intelligence. In recent years, several studies have addressed social cognition in subjects with focal epilepsies, while literature on social cognition in IGE is scarce, and findings are often conflicting. Some studies on samples of patients with mixed IGE showed difficulties in emotion attribution tasks, which were not replicated in a homogeneous population of patients with Juvenile Myoclonic Epilepsy alone. Impairment of higher order social skills, such as those assessed by Strange Stories Test and Faux Pas Tasks, were consistently found by different studies on mixed IGE, suggesting that this may be a more distinctive IGE-associated trait, irrespective of the specific syndrome subtype. Though an interplay between social cognition and executive functions (EF) was suggested by several authors, and their simultaneous impairment was shown in several epilepsy syndromes including IGE, no formal correlations among the two domains were identified in most studies. People with IGE exhibit subtle brain structural alterations in areas potentially involved in sociocognitive functional networks, including mesial prefrontal and temporoparietal cortices, which may relate to impairment in social cognition. Heterogeneity in patient samples, mostly consisting of groups with mixed IGE, and lack of analyses in specific IGE subsyndromes, represent evident limitations of the current literature. Larger studies, focusing on specific subsyndromes and implementing standardized test batteries, will improve our understanding of sociocognitive processing in IGE. Concomitant high-resolution structural and functional neuroimaging may aid the identification of its neural correlates.

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1. Introduction

Although normal intelligence is considered a hallmark of Idiopathic Generalized Epilepsies (IGE), a poor social outcome has been reported for people with IGE, including higher risk of social isolation, psychiatric comorbidities, lower educational attainment, unemployment, or unstable affective relationships [1,2]. Until recently, it was assumed that poor social outcome was partly due to social stigma related to the diagnosis of epilepsy. However, there is growing evidence that patients with IGE exhibit subtle cognitive impairment, especially involving executive functions (EF) [3,4]. It has been hypothesized that this cognitive profile might negatively affect social functioning [5]. Nevertheless, only recent investigations have formally assessed social cognition in epilepsy [6].

1.1. Social cognition

Social cognition is the ability to elaborate mental representations of social relationships, and to use them appropriately in a social environment [7,8]. It is a complex, high-level cognitive skill that extends to a variety of domains (self-understanding, understanding of others, and interface between self and others) [9]. One of the most relevant components of social

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cognition is represented by the Theory of Mind (ToM), which consists of both a cognitive or "cold aspect", including the ability to attribute beliefs and intentions, and affective or "hot skills", such as the ability to attribute emotions and feelings to self and others. The ToM processing is fundamental to interpret and predict one's own and others' behavior [10,11].

Sustained interactions within frontotemporal network are supposed to underlie both cognitive and affective ToM processing [12]. In fact, ToM impairment was first identified in diseases involving frontal and temporal lobes [13], but also in autism spectrum disorders and schizophrenia [10].

In the last decade, ToM has been assessed in focal epilepsies arising from frontal and/or temporal lobes (see [14] for a comprehensive review). On the contrary, there is limited evidence on ToM assessments in IGE. In this review, we briefly summarize the most relevant clinical features of IGE, and the main findings regarding impaired social cognition, particularly ToM reasoning, in IGE syndromes. Potential neuroanatomical correlates accounting for IGE-associated ToM impairment will also be discussed.

1.2. Idiopathic generalized epilepsy

According to the last International League Against Epilepsy (ILAE) Classification of the Epilepsies, the group of IGE or Genetic Generalized Epilepsies (GGE) includes four epilepsy syndromes: Childhood Absence Epilepsy (CAE), Juvenile Absence Epilepsy (JAE), Juvenile Myoclonic Epilepsy (JME), and Generalized Tonic–Clonic Seizures Alone (IGE-GTCS) [15]. As suggested by the term "idiopathic" and "genetic", the etiology of all these syndromes is presumably genetic, although no specific mutations may be identified. IGE are characterized by generalized seizures (absences seizures, myoclonic seizures, tonic–clonic seizures) with onset during adolescence or early adulthood. The interictal electroencephalogram (EEG) typically shows generalized epileptiform discharges, frequently precipitated by hyperventilation, sleep deprivation, and/or intermittent photic stimulation [16]. Even though they are classified together, there are some relevant differences among IGE syndromes.

Childhood absence epilepsy is one of the most common pediatric epilepsy accounting for approximately 12% of newly diagnosed epilepsy in children [17]. It is characterized by multiple daily absence seizures, with onset between 4 and 10 years [16]. Other seizure types are not expected in CAE, except for rare generalized tonic–clonic seizures during adolescence [16]. Seizures are usually self-limiting by the age of 12 years, and long-term prognosis is excellent [16].

Juvenile absence epilepsy represents 8–10% of IGE, and is defined by frequent absence seizures, generalized tonic–clonic seizures, and in 20% of patients, mild myoclonic jerks with onset during adolescence or early adulthood [16]. Seizures are usually precipitated by mental arousal, sleep deprivation, fatigue, and alcohol intake. Prognosis is good since the seizures can be well-controlled in 70–80% of patients [16].

Juvenile myoclonic epilepsy accounts for approximately 20% of all IGE [18]. It is characterized by myoclonic jerks occurring especially during sleep–wake transition, generalized tonic–clonic seizures, and less frequently, absence seizures with onset during adolescence or early adulthood [19,20]. The main precipitants of seizures in JME are sleep deprivation, fatigue, and alcohol intake [16]. Seizures are in general well-controlled with appropriate antiepileptic drug (AED) treatment, but AED withdrawal often results in seizure relapses [16].

Generalized tonic–clonic seizures alone syndrome is characterized by generalized tonic–clonic seizures, occurring on awakening and precipitated by sleep deprivation, fatigue, and alcohol intake, with onset from the second decade [16]. Seizures become more and more frequent with time and the risk of relapse after AED withdrawal is high [16].

Normal brain magnetic resonance imaging (MRI) and normal intelligence are considered essential diagnostic features of all IGE. In recent years, however, advanced neuroimaging studies have revealed a variety of structural and functional network abnormalities in these patients. The latter include gray matter loss affecting overall brain volume as well as the supplementary motor area, cingulate cortex, thalamus, hippocampus, insula, and basal ganglia, along with volumetric increases within medial frontal cortices (see [21] for a recent review). Among IGE subtypes, the strongest evidence is available for JME, for which several authors reported abnormal cortical metrics in mesial frontal areas [22–25], posterior cingulate, lateral temporal, and frontotemporoparietal association cortices [22,24,26], corpus callosum [27], and subcortical structures including thalamus and putamen [23,28].

In addition, recent analyses have identified subtle but widespread cognitive impairment in patients with IGE. As summarized by a recent meta-analysis by Loughman and colleagues [29], subjects with IGE performed worse than healthy controls in all cognitive domains (verbal ability, EF, attention, psychomotor speed, short- and long-term memory), except for visual–spatial abilities. The most investigated subsyndrome is again JME, in which several authors demonstrated a deficit in frontal lobe function, especially EF, verbal fluency, memory, attention, and psychomotor speed [30–35].

1.3. Theory of Mind

Theory of Mind is a complex higher-level skill, involving a variety of inferential abilities [36], and is considered critical for appropriate social conduct [11]. It can be distinguished from more basic social skills, such as facial emotion recognition, because it requires the ability to understand both affective and cognitive mental states [37]. According to the neurocognitive model by Frith and Frith [38], the two skills are strictly interdependent, but studies on patients with brain lesions suggested that they rely on different neuronal networks and could be independently impaired.

The tests administered to assess ToM reasoning are classified in three orders, according to their complexity and the age at which appropriate performance is usually expected. First-order tasks can generally be mastered by four-year-old children, though children younger than four years have already developed competences considered precursors of ToM, including the understanding of symbolic games, comprehension of visual perception, description of one own and others' emotions, or recognition of true beliefs [39–42]. First-order ToM tasks evaluate the ability to attribute a false beliefs to others, and require the understanding that others' mental representations could be different from one's own mental representation (for example: Smarties Task, Sally-Anne Task, and Fishing Task) [36,43,44].

Second-order tasks require the subjects to infer beliefs about beliefs, that is to say, that a person may have an incorrect belief about a third person's belief [43]. These tests could be solved from about six years of age. One of the most used tests is the "John and Mary Task", which is a nonverbal task requiring the description of a situation observed in a comic picture where a character has a false belief about the belief of the other character [45].

Third-order tasks can be solved by children aged nine/ten years and above, and evaluate the ability to infer implicit information and to attribute mental and emotional states to others through the recognition of equivocal social hints (e.g., metaphors, lie, delusion, irony). They involve in general both cognitive and affective ToM skills. The most frequently used third-order tasks are the Reading the Mind in the Eyes Test [46], the Strange Stories Task [47], and the Faux Pas Task [11].

We herewith provide a brief description of the most frequently used ToM tests in studies assessing IGE, to aid the interpretation of the findings discussed in the following paragraphs. The Reading the Mind in the Eyes Test evaluates the ability to attribute mental state from eye gaze. The examiner shows the subject different photographs of the eye region of the face of actors, and the subject is asked to choose the most appropriate mental state from a list of four options [46]. The Strange Stories Task assesses the ability to interpret nonliteral statements via the use of short stories describing everyday life situation, and addressing joke, lie, white lie, pretense, misunderstanding, double bluff, sarcasm/irony, and persuasion. Each story is accompanied by a comprehension question and a justification question [47]. The Faux Pas Test evaluates the ability to recognize the

presence of a "blunder" in some short stories [11]. The subject has to answer to different questions dealing with the identification of the character making the *faux pas*, the intentionality of *faux pas*, the mental states of the involved characters, and the more basic text comprehension. In the Social Situations Task subjects are requested to read several stories detailing situations in which ordinary and inappropriate behaviors take place and to judge the social appropriateness of each behavior [48]. Finally, the Story-based Empathy Task is a nonverbal test in which the subject has to describe a story presented in a comic strip and to choose the most plausible story ending [49].

2. Theory of mind in idiopathic generalized epilepsy

Currently, literature on social cognition in IGE is limited, and some results appear conflicting.

The first study assessing basic social skills in IGE was conducted by Reynders et al. [50], who reported impairment in fearful facial emotion recognition in 10 adults (mean age 33 years) with mixed IGE compared with that of healthy controls. Gomez-Ibañez et al. [51] described deficit in recognition of disgust and fear in 17 adult patients with IGE (mean age 32.7 years), 10 of whom with IGE-GTCS, 5 with JME, and 5 with absence epilepsy. Realmuto and colleagues [52] reported impaired anger recognition in 18 adults with IGE (mean age 26 years). Difficulties in emotion recognition were not confirmed in a homogeneous sample of 20 adult patients with JME (mean age 26.7 years) by Giorgi and colleagues [30]. Whether this discrepancy relates to a different social cognitive impairment pattern among different IGE syndromes, or rather to a small sample bias, still remains unclear.

Impairment in recognition of negative emotions has been widely described in patients with focal epilepsy including frontal lobe epilepsy (FLE) [53] and mesial temporal lobe epilepsy (MTLE) [50–51, 54–57]. In some of the above studies, [50–52], patients with IGE were compared with temporal lobe epilepsy (TLE), and all authors reported similar levels of impairment in both patient groups.

Studies assessing performance of people with IGE during more complex ToM tasks demonstrated impairment of both affective and cognitive ToM. In a study by Lew et al. [58], a group of 20 children with mixed IGE (5 patients with CAE and 15 with other IGE; mean age 11.6 years) performed worse than healthy controls in the Strange Stories Task, but not in the Reading the Mind in the Eyes test. In another study, impaired eye emotion recognition, assessed with a task similar to the Reading the Mind in the Eyes test, was documented for 47 adolescent patients with IGE (mean age 16.5 years) [59]. Giorgi and colleagues [30] implemented an extensive social cognition test battery (Strange Stories Task, Faux Pas task, Reading the Mind in the eyes, and social situation task) and compared patients with JME with age- and gender-matched healthy controls. Worse performance from patients with JME than controls was observed for the Strange Stories and Faux Pas Tasks, but not for the Reading the Mind in the Eyes and Social Situation Tasks. Stewart et al. [60] also reported impairment for the Strange Stories and Faux Pas Tasks in 22 children with mixed IGE (6 CAE, 5 JAE, 6 JME, 3 EMA, and 2 unclassified; mean age 12.8 years), while Zhang et al. [61] found a deficit in second-order False Beliefs Task and Faux Pas Task in 55 children with mixed IGE (mean age 11.9 years). Only Realmuto et al. [52] did not find impairment in cognitive and affective ToM assessed through the Story-based Empathy Task.

Impairment in affective and cognitive ToM was robustly detected both in FLE [62,63] and TLE [54,55,62–65]. To our knowledge, the only direct comparison between people with IGE and other epilepsy syndromes were reported by Realmuto and colleagues [52], who reported no significant intergroup differences.

2.1. Relationship between social cognition and executive function

Executive functions are a high-level processes supporting flexible behavior, adaptation to novel contexts, and inhibition of stereotyped responses [66]. The EF include "cold" aspects, such as working memory, attentive control abilities, cognitive flexibility, verbal fluency, planning, and problem solving, as well as "hot" aspects, facilitating adaptation of social and emotional conducts [67]. Consequently, several authors emphasized potential associations between social cognition and EF, and it is not clear whether they are distinct and functionally related abilities, or rather representative of a unitary process [68].

Social cognition/ToM and EF may rely on overlapping brain networks and exhibit similar developmental trajectories in normal children, supporting the hypothesis of a functional dependence of the two domains. Most studies assessing social cognition/ToM and EF and patients with neurological and psychiatric disease showed concomitant impairment of both domains [68]. In light of these findings, it was suggested that ToM could be a prerequisite of EF, i.e., that the development of more complex mental state representation may generate a better control of mental states and one's own actions [69], or conversely, that EF could be a prerequisite of ToM owing to the presence of executive components in ToM tasks [70]. Other studies, however, showed impairment of only one domain, suggesting potential independence of EF and ToM [11,13,71,72].

In people with epilepsy, EF have been tested in almost all studies addressing ToM. While some authors found simultaneous impairment of ToM and EF in MTLE [62], others did not [55,64].

In patients with IGE, Jiang et al. [59] showed a correlation between EF and cognitive empathy, which overlaps with affective ToM. A significant correlation between EF and performance in Second-Order False Belief and Faux Pas Tasks was documented for children with mixed IGE [61]. Other authors reported concomitant impairment in social cognition and EF domains in JME [30] and mixed IGE [52,60], but did not detect formal correlations between performance on these two domains.

2.2. Relationship between social cognition and disease-related variables

In adults with IGE, ToM impairment did correlate with disease-related variables, such as age at onset, disease duration, poor seizure control, and ongoing use of AEDs. No significant correlations between ToM tasks and epilepsy features were found in children with mixed IGE [58,59] nor in adult patients with JME [30]. In two recent studies on samples of pediatric patients with mixed IGE, however, performance during ToM tasks was negatively associated with a longer period of untreated seizures [60] or duration of epilepsy [61]. Stewart and colleagues [60] also detected a correlation between higher dosage of valproate and affective ToM impairment. Whether the latter may point to cognitive side effects of AEDs, or rather indicate more severe disease-related features in people treated with higher dose of sodium valproate, still remains undetermined.

2.3. Relationship between social cognition and social functioning

As sociocognitive abilities are fundamental for appropriate social functioning, one could hypothesize that ToM impairment is associated with social difficulties in people with epilepsy. Measures of quality of life and/or social function were only implemented by few studies on social cognition in IGE [52,58,60]. Positive associations between Strange Stories Task [58,60], affective components of Faux Pas Task performance [60], and social competence measures were documented for children with IGE. In addition, a significant positive correlation was described between scores in fear recognition and quality-of-life measures [52].

3. Neuroanatomical substrates of Theory of Mind processing and potential relations to brain abnormalities in IGE

In recent years, several studies have assessed the neural correlates of ToM reasoning, initially using positron emission tomography (PET), and subsequently via task-based functional MRI (fMRI). Initial expert consensus suggested the existence of a "dedicated, domain-specific ToM

system" [43], centered on the amygdala, and relying on dominant frontal lobe language processing as well as mesial frontal, orbitofrontal, and right-hemispheric temporoparietal cortices. The relevance of amygdala for ToM reasoning, however, was challenged by subsequent literature [73]. Recent formal meta-analytical synthesis included task-based fMRI data from over a thousand patients, and grouped different ToM paradigms into conceptually linked domains [74]. Common areas of activation across tasks encompassed bilateral temporoparietal junction, precuneus [74], as well as the medial prefrontal cortex, with smaller areas of convergence in the fusiform and inferior frontal gyrus [74]. Functional subspecialization along an anterior–posterior gradient may occur within the temporoparietal junction. Activation of the anterior temporal lobe was consistently identified only for subset of tasks, supporting previous hypotheses on its role as semantic knowledge hub [75].

Subsequent meta-analytical work also suggested greater recruitment of precuneus, bilateral temporoparietal junction, and right middle temporal gyrus during cognitive ToM, and of anterior temporal lobes, mesial prefrontal, and dorsolateral frontal cortices during affective ToM [76], corroborating previous theories supporting segregated processing of "hot" and "cold" ToM aspects [12]. There may also be a substantial overlap between network subserving implicit ToM processing, which is language-independent, and those for explicit processing, which develops later in life and is heavily dependent upon executive and cognitive control [76,77].

Whether the above-described regions and networks may specifically relate to ToM reasoning, however, remains unclear. In fact, recent investigations indicated that a distributed network linking medial prefrontal, mesial parietal, and temporoparietal cortices, largely overlapping with the so-called default mode network [78], may represent self-projection and is recruited during multiple cognitive tasks, including ToM but also autobiographical memory, imaging oneself in the future (i.e., prospection), and topographical orientation [79].

It is reasonable to hypothesize that impairment of social cognition in IGE may relate to abnormal structure or function within key regions for ToM processing, in accordance with similar findings in other neurological or psychiatric conditions [80]. Structural abnormalities in areas recognized as ToM hubs, including mesial prefrontal and temporoparietal neocortices, were described in JME, absence epilepsies, and IGE-GTCS [24,81–83]. A recent longitudinal investigation in JME detected aberrant cortical maturational trajectories of high-order temporoparietal neocortices during adolescence [26], providing a neurodevelopmental perspective with potential implications regarding sociocognitive abilities. Resting state functional imaging studies have shown aberrant connectivity of default-mode areas in persons with IGE-GTCS, absence epilepsies, and mixed IGE [84–86], while numerous EEG–fMRI studies related generalized spike–wave discharges and/or absence seizures to patterns of deactivation in default-mode areas [87–90]. Notably, analyses directly testing for correlations between measures of ToM performance and anatomical-functional imaging markers in IGE are lacking, and no studies have thus far assessed people with IGE during fMRI-based ToM tasks. Lack of direct evidence warrants further research to elucidate the imaging correlates of altered sociocognitive behavior in IGE.

4. Conclusions

According to the ILAE definition, normal intelligence should be a prerequisite for a diagnosis of IGE. Nevertheless, it is nowadays well-known that some degree of cognitive impairment is observed in these subjects, particularly affecting frontal lobe functions. There is also growing evidence for impairment of social cognition abilities, with negative implications regarding their social function and quality of life.

In this review, we discussed the current evidence on social cognition impairment in people with IGE. Although results are sometimes conflicting, it is worth noting that people with IGE showed deficits both in basic social skills, such as facial emotion recognition, and in high-level cognitive and affective ToM. Some studies comparing IGE with focal epilepsies, in which social cognition impairment has been more extensively detailed, found no significant group differences.

While findings regarding emotion recognition are conflicting, all studies reported an impairment of higher-level cognitive and affective ToM in IGE, regardless of the task used. The Strange Stories and Faux Pas Task have provided the most consistent results, possibly pointing to a more stable IGE "trait", irrespective of the syndrome subtype. These findings, however, also emphasize the current lack of uniform, validated protocols to assess ToM reasoning, which may hamper comparability of research performed in different centers.

Most studies described in this review include patients with different types of IGE, pooled together without subgroup analyses, with the exception of one study assessing a uniform sample of patients with JME. Because of the relatively small sample sizes, it is currently not possible to compare the different IGE subsyndromes and delineate clear differences in social cognition patterns. This is a very important issue, as IGE syndromes differ regarding clinical and EEG manifestation and, possibly, pathophysiology. Furthermore, the above studies often include subjects of varying age and education, and this factor may significantly affect the outcome of social cognition testing.

Whether social cognition impairment should be considered an intrinsic characteristic of IGE, similar to the mild cognitive impairment, or it should rather be interpreted as a consequence of seizures and AEDs, still remains uncertain. In fact, most studies have so far failed to find a correlation between performance in social cognition and epilepsy-related variables. In this regard, longitudinal studies assessing participants before and after starting AEDs may provide a useful framework.

The relationship between social cognition impairment and social difficulties has not been explored by most studies, even though the few available data confirm a positive association between social cognition tasks performance and quality of life. This aspect has potential clinical implications, as sociocognitive rehabilitation of patients with IGE might improve their social outcome.

The relation between social cognition and EF remains another open issue. In fact, some authors reported a correlation between ToM and EF, while others found concomitant impairment but no formal statistical associations.

Studies specifically assessing the neural correlates of ToM reasoning in patients with IGE are not yet available, and no concomitant neuroimaging analyses were included in any one of the above-described studies. Structural and functional disruptions in areas recognized as ToM hubs have been describe in IGE, and thus it may be hypothesized that impairment of social cognition in IGE may partially relate to these abnormalities.

To advance the current level of knowledge, larger, possibly multicenter, studies are desirable, and should include homogeneous subtypes of patients with IGE, with similar age, gender, and educational status, using a standardized battery of social cognition tests. This will help capture the extent of social cognition alterations in these epilepsy subtypes, while concomitant multimodal neuroimaging analyses will aid the understanding of their pathophysiological substrates.

Disclosure of conflict of interest

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Ethical statement

We confirm that we have read the journal's position on issues involved in ethical publication and that this review is consistent with those guidelines.

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