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Review

Emerging neuroimaging contribution to the diagnosis and management of the ring chromosome 20 syndrome

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ABSTRACT

Ring chromosome 20 [r(20)] syndrome is an underdiagnosed chromosomal anomaly characterized by severe epilepsy, behavioral problems, and mild-to-moderate cognitive deficits. Since the cognitive and behavioral decline follows seizure onset, this syndrome has been proposed as an epileptic encephalopathy (EE). The recent overwhelming development of advanced neuroimaging techniques has opened a new era in the investigation of the brain networks subserving the EEs. In particular, functional neuroimaging tools are well suited to show alterations related to epileptiform discharges at the network level and to build hypotheses about the mechanisms underlying the cognitive disruption observed in these conditions. This paper reviews the brain circuits and their disruption as revealed by functional neuroimaging studies in patients with [r(20)] syndrome. It discusses the clinical consequences of the neuroimaging findings on the management of patients with [r(20)] syndrome, including their impact to an earlier diagnosis of this disorder. Based on the available lines of evidences, [r(20)] syndrome is characterized by interictal and ictal dysfunctions within basal ganglia–prefrontal lobe networks and by long-lasting effects of the peculiar theta–delta rhythm, which represents an EEG marker of the syndrome on integrated brain networks that subserve cognitive functions.

1. Introduction

Ring chromosome 20 [r(20)] syndrome is a rare chromosomal anomaly characterized by severe epilepsy, behavioral problems, and mild-to-moderate cognitive deficits. In most cases, patients' development is normal or mildly delayed, but it is followed by cognitive and behavioral decline after seizure onset [1,2]. Epilepsy, which seems to be a constant finding, arises in childhood or adolescence and becomes refractory to antiepileptic drugs (AEDs) in the majority of the patients [3,4]. Nonconvulsive status epilepticus (NCSE) and brief motor seizures (mainly nocturnal) are among the most common seizure types [3]. Nonconvulsive status epilepticus consists of a prolonged confusional state of varying intensity [2], and it is often associated with EEG changes in the form of long-lasting slow waves with occasional spikes usually predominant over the frontal lobes [4,5]. Other types of seizures include ictal affective behaviors (mainly ictal fear–terror) associated with loss of consciousness, automatisms, or tonic activity [1]. Progressive cognitive delay and behavioral problems are frequently described [6], and the latter occasionally dominates the clinical phenotype [7]. Dysmorphic features are mostly absent or mild, hence making the diagnosis difficult, unless there is a high index of suspicion [2,3,8]. A clue is considered the presence of a typical EEG pattern consisting of long trains of theta–delta waves with sharply contoured or notched appearance, predominant over the frontotemporal regions, and occurring within normal background activity [8].

At the chromosomal level, r(20) chromosome replaces one of the two chromosomes 20 in a percentage of cells, ranging from 1% to 100% of lymphocytes. The relation between the variable mosaicism and the clinical phenotype is still controversial [2,9] although studies have shown that a high degree of mosaicism is associated with earlier age at seizure onset and dysmorphisms [10–12] but not with response to drug treatment [1,3].

Cytogenetic analysis represents the gold standard for the definitive diagnosis, but it is often delayed and not routinely performed [12]. Therefore, [r(20)] syndrome is undoubtedly an underdiagnosed condition, and the real prevalence is not known [13].

To date, the mechanisms that promote ictogenesis and the maintenance of NCSE in this condition are still unknown. The electroclinical pattern strongly suggests the involvement of the frontal lobe networks in the generation of both ictal and interictal activities. Furthermore, since one of the typical clinical features of the syndrome is the presentation with prolonged episodes of NCSE, a dysfunction in "seizure

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control systems" has been proposed, and attention has been pointed to investigate the role of subcortical structures in this syndrome, especially the basal ganglia circuits [14,15].

In recent years, noninvasive imaging techniques, such as simultaneous recording of functional magnetic resonance imaging with electroencephalogram (EEG–fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), electric source imaging (ESI), and magnetic source imaging (MSI), have proved their usefulness in better defining the epileptic networks in both genetic and acquired epilepsies [16,17]. Furthermore, in epileptic encephalopathies (EEs), recent neurophysiologic and functional neuroimaging lines of evidences have tried to build hypotheses about the mechanisms underlying the cognitive disruption observed in these conditions by linking the neuropsychological abilities, the epileptiform discharges, and the brain networks as revealed by the neuroimaging tools [18,19]. With these aims, functional neuroimaging techniques have been applied to study patients with [r(20)] syndrome. Here, we review the main findings derived from functional neuroimaging studies performed in patients with this chromosomal disorder. Especially, we will focus on the contribution of these techniques to improve the knowledge of the following: (i) the mechanisms underlying ictogenesis in [r(20)] syndrome and (ii) the consequences of epileptic activities on brain networks that subserve normal cognition and behavior. Although limited to a relatively low number of studies, given the rarity of [r(20)] patients, this review evaluates the state of the art of this topic in order to stimulate further investigations in patients with this chromosomal disorder.

2. Methods

2.1. Search methods for identification of studies

Searches were run in the following databases from 1990 to 2014: Embase, MEDLINE, PsychINFO, and PubMed. Searches were limited from 1990 to the present day, as studies carried out prior to this would necessarily have included participants without MRI or other functional/metabolic imaging techniques. The search keywords were as follows: "RING20 syndrome", "[r(20)] syndrome", "Ring Chromosome 20 Syndrome" AND "MRI", "imaging", "positron emission tomography" (or PET), "spectroscopy"(or MRS), "single-photon emission computed tomography" (or SPECT), "simultaneous functional MRI and EEG" (or EEG–fMRI), and "magnetic source imaging" (or MSI). For each citation considered, the abstract was read (when available), and articles were excluded if they were outside the scope of the review. The bibliography of each of the retrieved papers was examined to identify relevant references that could have been missed by electronic search. Only peer-reviewed original articles were accepted for inclusion in the review.

3. Results

Since its first description in 1972 [20–23], nearly 145 patients with [r(20)] syndrome in 67 reports have been described in the literature, most with intractable epilepsy, variable cognitive impairment, and/or behavioral problems. Among these, our electronic literature research revealed 12 studies, for a total of 47 patients, that used advanced morphometric and/or functional neuroimaging techniques to investigate the [r(20)] syndrome (Table 1). Instead of describing the results related to each single methodology independently, we will discuss the neuroimaging findings in relation to the different cerebral structures/networks supposed to be involved in the ictogenesis, seizure maintenance, and cognitive deficits in [r(20)] syndrome based on the electroclinical suggestions. In particular, the following brain structures/networks will be considered: (I) prefrontal cortex; (II) substantia nigra–basal ganglia networks; and (III) cortical networks involved in conscious awareness and attention.

Table 2 reports the main electroclinical and genetic features of the patient included in the present review. The patients' population

Table 1
Neuroimaging studies in [r(20)] patients.

Study	No. of patients	Methods	Main findings (no. of patients)	Correlation between neuroimaging and clinical variables
Inoue et al. [3]	6	SPECT, MEG	*SPECT interictal* (3): F or FT hypoperfusion *SPECT ictal* (2): F hyperperfusion *MEG interictal* (3): F and FT spike dipoles	N/A
da Mota Gomes et al. [24]	1	MRS	*F* and *T MRS*: normal	N/A
Biraben et al. [14]	14	[^{18}F]fluoro-L-DOPA PET, VBM	*PET*: ↓ [^{18}F]fluoro-L-DOPA uptake B Cau and Put *VBM*: normal	No correlation with patients' age, % mosaicism, seizure type.
Tanaka et al. [25]	1	MEG, I^{123}-IMP SPECT	*MEG ictal*: dipole medial F lobe	N/A
Bouilleret et al. [15]	16	[^{18}F]fluoro-L-DOPA PET	*SPECT interictal*: F hypoperfusion *PET*: ↓ [^{18}F]fluoro-L-DOPA uptake B Cau and Put	N/A
Nishiwaki et al. [26]	1	SPECT	*SPECT interictal*: normal	N/A
Jacobs et al. [27]	1	FDG-PET, SPECT	*PET interictal*: diffuse R hypometabolism *SPECT ictal*: R TP hyperperfusion	N/A
Del Sole et al. [28]	5	[^{123}I]ioflupane SPECT [^{123}I]IBZM SPECT	[^{123}I]*ioflupane SPECT*: ↓ DAT expression B Cau and Put	Negative correlation between DATs and seizure frequency and % mosaicism. Positive correlation between D2 receptor density in Put and seizure frequency and % mosaicism.
Elens et al. [9]	6	FDG-PET, SPECT	*FDG-PET interictal* (1): F hypometabolism *SPECT interictal* (3): bilateral FT hypoperfusion	N/A
Meletti et al. [29]	1	EEG–fMRI	*Ictal EEG–fMRI*: ↑ BOLD preF, Op-I, SM, Cau, and SN	N/A
Avanzini et al. [30]	12	ICA analysis and ESI	*Interictal theta–delta rhythm ESI*(12): B SM	No correlation between theta–delta activity density and % mosaicism.
Vaudano et al. [31]	11	EEG–fMRI	*Interictal theta–delta rhythm EEG–fMRI* (7): ↑ BOLD TP junction, O and SM, ↓ BOLD DAN and DMN *Ictal EEG–fMRI* (2): ↑ early BOLD preF *Group analysis EEG–fMRI* (11): ↑ BOLD B TP junction	Positive correlation between the R TP junction BOLD changes and % mosaicism

↑: increase; ↓: decrease; B: bilateral; BOLD: blood oxygen level-dependent; Cau: caudate; DAN: dorsal attentional network; DMN: default mode network; FDG: fluorodeoxyglucose; hSW: high-amplitude frontally predominant spikes and slow waves, sharp waves; I^{123}-IMP: N-isopropyl-p-[I123] iodoamphetamine; [123]IBZM: iodobenzamide; ESI: electrical source imaging; ICA: indipendent component analysis; preF: prefrontal cortex; F: frontal; FT: frontotemporal; MEG: magnetoencephalography; MRS: magnetic resonance spectroscopy; O: occipital cortex; Op-I: opercular–insular cortex; PET: positron emission tomography; Put: putamen; T: temporal; TP: temporoparietal; R: right; SM: sensory-motor cortex; SN: substantia nigra; SPECT: single-photon emission computed tomography; Th:thalamus; N/A: not available; SN: substantia nigra; VBM: voxel-based morphometry.

Table 2
[r(20)] patient clinical features.

Study	Age/age at epilepsy onset	Seizure type/drug response	Neuropsychology/behavior	% r(20) mosaicism	Dysmorphisms
Inoue et al. [3]	14/8	NCSE; atypical absence; FMSs/drug resistance	IQ = 81, reduced frontal functions	20%	NR
	13/3	NCSE; FMSs/drug resistance	IQ = 59, impulsive behavior	53%	NR
	21/14	NCSE/drug resistance	IQ = 81	25%	NR
	28/7	NCSE; FMSs/drug resistance	IQ = 47, inattentive behavior	40%	NR
	31/7	NCSE/drug resistance	IQ = 95	26%	NR
	25/11	NCSE; GTC; FMSs/drug resistance	IQ = 74	10%	NR
da Mota Gomes et al. [24]	12/21 months	NCSE; MS; GTC; atypical absence/drug resistance	N/A, oligophrenia	90%	Unilateral ocular exotropy
Biraben et al. [14][a]	29/7	NCSE; GTC; ictal fear; FMSs/drug resistance	N/A, mild impairment	25%	NR
	17/5	NCSE/drug resistance	IQ = 108	22%	NR
	18/8	NCSE; GTC; ictal fear; FMSs/drug resistance	N/A, mild impairment	37%	NR
	20/8	NCSE/drug resistance	N/A, severe impairment	11%	NR
	25/6	NCSE; ictal fear; FMSs/drug resistance	IQ = 69	37%	NR
	16/9	NCSE; GTC; ictal fear/drug resistance	N/A, mild impairment	16%	NR
	16/6	NCSE; ictal fear; FMSs/drug resistance	IQ = 92	42.5%	NR
	22/2	NCSE; GTC/drug resistance	IQ = <70	0.5%	NR
	24/8	NCSE; GTC; FMSs/drug resistance	IQ = 73	50%	NR
	14/9	NCSE; FMSs/drug resistance	IQ = 100	31%	NR
	27/7	NCSE; ictal fear; FMSs/drug resistance	IQ = 95	50%	NR
	28/14	NCSE; ictal fear; FMSs/drug resistance	IQ = 68	6%	NR
	20/4	NCSE; ictal fear; GTC; FMSs/drug resistance	IQ = 47	77%	NR
	16/4	NCSE; ictal fear; FMSs/drug resistance	N/A, mild impairment	18%	NR
Tanaka et al. [25]	18/8	FMSs; GTC/drug resistance	IQ = 56	7%	NR
Nishiwaki et al. [26]	36/17	Atypical absence/drug resistance	N/A, cognitive impairment	13%	NR
Jacobs et al. [27]	13/4	NCSE; nocturnal frontal seizures; ictal fear/died	IQ = 71, ADHD	100%	Large and cauliflower-shaped ears
	29/5	NCSE; GTC/drug resistance	N/A, mild impairment	83%	NR
	58/11	NCSE/controlled	Normal	12%	NR
	34/21	NCSE; GTCSE/drug resistance	Normal	13%	NR
	16/10	NCSE/drug resistance	N/A, mild impairment	34%	NR
	21/4	NCSE/drug resistance	N/A, mild impairment	52%	NR
Elens et al. [9]	4/4	Nocturnal frontal seizures/drug resistance	N/A, reckless, obsessive	100%	NR
	8/6	NCSE; FMSs/drug resistance	IQ = 57, aggression	40%	Mild facial, growth failure
	53/6	NCSE/drug resistance	Normal	16%	NR
	66/16	Atypical absence/drug resistance	Normal	18%	NR
	22/13	NCSE/drug resistance	IQ = 79, OCD, aggression	13%	NR
	19/5	NCSE; nocturnal frontal seizures/drug resistance	IQ = 40, aggression, ASD	100%	Mild, growth failure
Avanzini et al. [30][b]	38/21	GTC/controlled	IQ = 130	8%	NR
	17/10	NCSE; FMSs/drug resistance	IQ = 80, behavioral problems	42%	NR
	17/12	NCSE; FMSs; ictal fear/drug resistance	IQ = 73, behavioral problems	7%	NR
	34/17	NCSE; FMSs; ictal fear/drug resistance	IQ = 60, behavioral problems	71%	NR
	63/44	Dyscognitive symptoms; atypical absence/controlled	IQ = 83	9%	NR
	18/9	NCSE; FMSs; ictal fear/drug resistance	IQ = 74, behavioral problems	40%	Sparse teeth
	20/14	NCSE; atypical absence/drug resistance	IQ = 80, behavioral problems	34%	NR
	45/17	NCSE; nocturnal frontal seizures/drug resistance	IQ = 70, behavioral problems	15%	NR
	17/12	NCSE; FMSs/drug resistance	IQ = 90	24%	NR
	14/9	NCSE; FMSs/drug resistance	IQ = 79, behavioral problems	60%	NR
	12/12	NCSE; atypical absence/drug resistance	IQ = 84, behavioral problems	55%	NR
	7/6	No seizure/no treatment	IQ = 111	30%	Frontal bossing, inner, epicanthal folds, low nasal bridge

Age is expressed in years; F = female; M = male; ADHD: hyperactive and aggressive behavior; ASD: autistic spectrum disorder; FMSs: focal motor seizures; GTC: generalized tonic–clonic seizure; GTCSE; generalized tonic–clonic status epilepticus; IQ: intelligence quotient; N/A: not available; NCSE: nonconvulsive status epilepticus; NR: not reported; OCD: obsessive–compulsive disorder.

[a] The patients recruited by Biraben et al. [14] were the patients included in the subsequent work by Bouilleret et al. [15] except for two cases.

[b] The patients studied by Meletti et al. [29] and Vaudano et al. [31] come from the same population investigated in Avanzini et al. [30] for different purposes.

examined by these studies is a representative sample of the disorder, confirming a high incidence of drug-resistant epilepsy, with frequent NCSE, cognitive/behavioral problems, and lack of significant dysmorphic features [3,9]. The neuropsychological examinations revealed a wide spectrum of clinical severity (IQ value range: 40–130) although a high proportion of the patients showed mild mental retardation (14/47) or even normal IQ (12/47). This finding is concordant with the genetic characteristics of the population [2,32]. All patients except three were indeed mosaic. Accordingly, nonmosaic (subtelomeric deletions) patients are the ones with more extensive comorbidities and dysmorphic features [12].

3.1. Seizure generation: the role of the prefrontal cortex

The [r(20)] electroclinical features support the involvement of the frontal lobes in the pathogenesis of epilepsy in this chromosomal disorder. In particular, seizure semiology (often characterized by hypermotor behaviors with affective components), as well as the EEG localization of the interictal and ictal activities, with predominance over the frontal regions point towards a frontal lobe network dysfunction [1,5,8].

The available neuroimaging literature confirms a frontal lobe dysfunction, even with some differences across studies (see Table 1). Interictal SPECT and PET studies indeed have shown, almost homogenously, a decrease in perfusion and metabolism over the bilateral frontal and frontotemporal cortices [3,9,25], while only one report did not document an abnormal perfusion pattern by SPECT [26]. Similarly, one study documented normal frontal and temporal MRI spectroscopy in a single patient with [r(20)] syndrome [24]. As far as ictal studies are concerned, SPECT investigations were reported in only three patients [3,27], demonstrating heterogeneous findings with bilateral frontal hyperperfusion in two cases [3] and diffuse temporoparietal hyperperfusion in one case [27]. However, it must be considered that imaging studies that used PET or SPECT have low spatial and

temporal resolutions and, therefore, are suboptimal to address the neural circuits which underlie the ictal spatiotemporal dynamics subserving seizures.

We recently applied, for the first time, the simultaneous recording of EEG with fMRI (EEG–fMRI) to study the epileptic networks in patients with [r(20)] syndrome [29,31]. Interictal events were investigated, and the hemodynamic patterns that resulted from group-level fMRI data analyses showed the involvement of a complex frontal network encompassing the prefrontal, opercular–insular and the sensory-motor cortex bilaterally. Furthermore, EEG–fMRI recordings have been used to delineate the generators of ictal events (for review, see Chaudhary et al. [33]). This was possible in a few patients in whom no or subtle movements were associated with the onset of the ictal events. The recorded seizures were partitioned into phases based on the

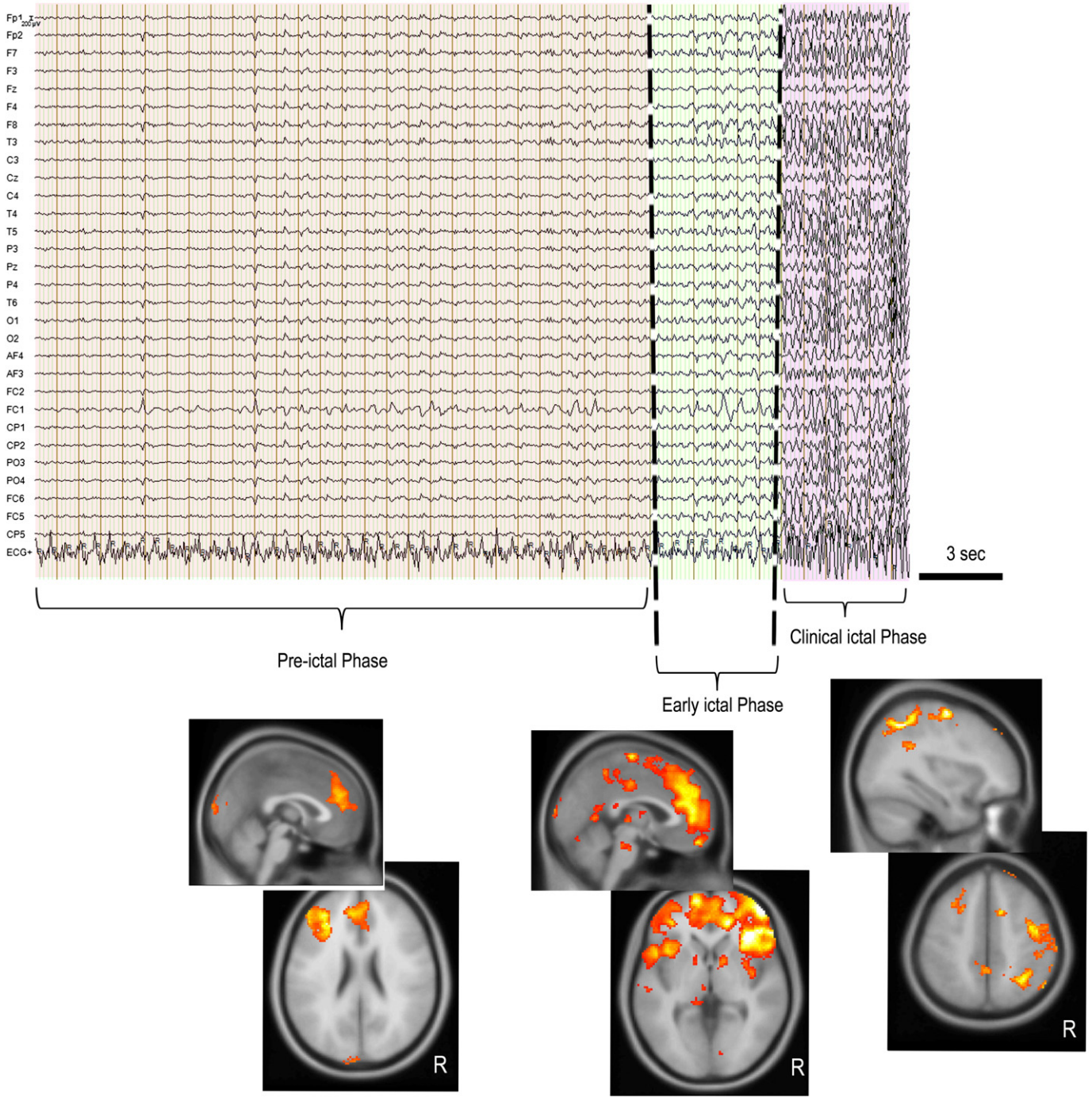

Fig. 1. Seizure-related EEG–fMRI results. Top image — representative page of ictal EEG recorded during the fMRI session. The patient (male, 11 years old) presented one 13-sec length hyperkinetic seizure inside the scanner. More details have been published in Vaudano et al. [31]. According to the definition of ictal phases as reported by Chaudhary et al. [34], the seizure has been divided into three phases: the preictal phase (displayed in pink), the early ictal phase (displayed in green), and the clinical ictal phase (displayed in violet). The EEG trace is shown in monopolar montage after gradient and cardiac artifact subtraction. Bottom image — fMRI maps [F contrast] ($p < 0.05$, corrected for family wise error — FWE) related to each ictal phase are shown onto the normalized T1 structural MRI scan, axial and sagittal slices. Only BOLD signal increases were observed. The preictal phase demonstrated a left prefrontal cortex (global maxima), left opercular–insular cortex, and left supplementary motor area (SMA) positive BOLD response; the early ictal phase showed bilateral prefrontal cortex, opercular–insular cortex, and SMA BOLD increases. Additional smaller clusters were detected at the bilateral basal ganglia and left thalamus. The clinical ictal phase demonstrated BOLD signal changes over the right inferior parietal lobuli and pericentral cortex plus tiny clusters at the posterior cingulate cortex and bilateral premotor cortex. R = right.

spatiotemporal evolution of the EEG signal to distinguish onset from propagation-related BOLD changes [31]. By means of this model, we were able to show a bilateral involvement of the frontal lobes in their dorsal and medial surfaces. Importantly, medial prefrontal cortex hemodynamic changes preceded the first scalp EEG changes (Fig. 1). This result is in agreement with the findings observed in an ictal MEG study that reported the involvement of the medial frontal lobe at seizure onset in one patient with [r(20)] syndrome [25]. When considered overall, PET, SPECT, and fMRI data are consistent with the notion that [r(20)] syndrome is associated with dysfunction of the frontal lobe at network level rather than a localized frontal cortical epileptogenic area. A limitation of these studies is the low number of investigated patients, especially considering ictal data, and the different neuroimaging tools applied, which makes the direct comparison among different studies difficult.

3.2. Dysfunction of the seizure control systems: the role of basal ganglia

Evidence has accumulated suggesting that subcortical systems and basal ganglia (BG) can participate in the control of epileptic seizures [35–37]. Although it is clear that BG cannot generate seizures, ictal activities are known to modify the activity of this system [38]. Furthermore, pharmacological and electrophysiological data from animal models of epilepsy suggest that the basal ganglia might have a remote influence on cortical oscillatory processes related to the control of epileptic seizures [39,40]. Accordingly, a "dopaminergic hypothesis" of seizure suppression impairment has been postulated to explain some characteristics of [r(20)] syndrome. In particular, the electroclinical pattern consisting of prolonged NCSE with bilateral rhythmic spike and waves or slow waves on the EEG [3,8,41] has been linked to possible deficits of the BG systems. The fact that drugs that have a possible effect on dopaminergic system, such as valproic acid and lamotrigine, can be efficaciously used in patients with [r(20)] syndrome [1] also supports a role of BG in this condition.

To test these hypotheses, PET and SPECT studies were conducted in patients with [r(20)] syndrome with radiotracers that explored the dopaminergic activity. In two subsequent studies by the same group [14,15], presynaptic dopaminergic function was investigated by means of 6-^{18}F-L-3,4-fluorodihydroxyphenylalanine (^{18}F-fluoro-L-DOPA). Positron emission tomography data analyses demonstrated a consistent and reliable decrease of ^{18}F-fluoro-L-DOPA uptake in the putamen and caudate of patients with [r(20)] syndrome compared with healthy volunteers. This deficit was homogenous across patients and symmetrical in the BG structures, and it was not correlated with clinical variables, like percentage of mosaicism, age at diagnosis, and seizure semiology. A subsequent SPECT study that evaluated the density of presynaptic dopamine transporters (DATs) and postsynaptic D2 receptors demonstrated a symmetrical decline of DAT expression in both caudate and putamen nuclei [28]. Moreover, Del Sole and colleagues [28] showed a significant negative correlation between BG hypofunction and percentage of mosaic cells as well as seizure frequency. It means that patients with a higher number of lymphocytes bearing r(20) chromosomal aberration and frequent seizures exhibit lower expression of dopamine transporters in the basal ganglia. Taken together, these lines of evidences suggested that the dopaminergic system plays a role in [r(20)] epilepsy. However, two questions remain open: (1) Is the reduced dopaminergic uptake at basal ganglia a cause or a consequence of recurrent seizures? (2) Are the BG dopaminergic deficits specific to [r(20)] epilepsy, or are they also present in different conditions and, more generally, in drug-resistant epilepsy [42–44]? No definite answer to either questions exists. Interestingly, a dopaminergic dysfunction has been observed in nocturnal frontal lobe epilepsy (NFLE) [42], a condition with ictal behaviors that share some similarities with the one observed in [r(20)] epilepsy.

The involvement of BG, including substantia nigra (SN), in [r(20)] seizures has been recently documented by our group by means of ictal EEG–fMRI recordings [29,31]. During ictal discharges, indeed, we observed an increase of hemodynamic demand in the BG circuit, spanning from the caudate nuclei to the SN (Fig. 2). Intriguingly, such involvement was detected after seizure onset, hence supporting the hypothesis according to which BG are unlikely to generate seizures but instead participate in their maintenance and termination.

Altogether, these experimental data support the hypothesis that a BG dysfunction is a key feature of the disorder. Future investigations need to be performed, however, to better understand the nature of BG involvement in [r(20)] syndrome. This objective could be of clinical relevance before considering therapeutic strategies, either pharmacological (dopaminergic) or nonpharmacological (deep brain stimulation), to target the activity of basal ganglia circuits.

3.3. Dysfunction of physiological cortical networks

A growing body of literature has investigated the possible interaction between cognitive deficits associated with epileptiform discharges and cognitive brain network activity [45–49]. Epileptiform activities may affect cognition either through transient effects on information processing in the brain (brief-lasting effects) or through more long-lasting effects leading to prolonged inhibition/disruption of cortical areas even distant from, but connected with, the epileptic focus [50,51].

This detrimental effect of epilepsy on cognition is particularly relevant in children carrying [r(20)] syndrome, considering that they are cognitively and behaviorally normal before seizure onset, while some can fall into a severe state characterized by intellective decline, attention deficits, and impaired interpersonal relationship with autistic features after seizure occurrence [1,5,7].

In this context, several authors highlighted the potential role and the pathological meaning of the theta–delta rhythm that characterizes the EEG recording of these patients, independent of seizures and interictal high-amplitude slow spike-and-wave complexes.

The [r(20)] slow-wave rhythm is constituted by long trains of continuous theta–delta waves, with a peak frequency of 5 Hz (range: between 3 Hz and 7 Hz), distributed over the frontotemporal leads and accompanied by normal alpha background (Fig. 3). This EEG pattern is insensitive to opening–closure of the eyes [8] and persists over the wake–sleep transition and even in non-REM sleep and REM sleep [52]. Although described by several previous studies and considered highly characteristic of [r(20)] syndrome [1–4,8], the clinical meaning of this slow-wave activity remains under discussion.

With advanced EEG analysis approaches, we recently studied the morphology, frequency spectrum, and source localization of the slow-wave rhythm in a cohort of patients with [r(20)] syndrome [30]. Our findings demonstrated the presence of this activity in all the patients with [r(20)] syndrome but not in healthy subjects and in patients with generalized epilepsies investigated with the analogue procedure. The high reproducibility of the theta–delta activity in the population with [r(20)] syndrome is clinically relevant, since the observation of this peculiar EEG pattern can improve the diagnostic workup. Furthermore, the EEG source analysis of the [r(20)] rhythm, by means of sLORETA, revealed the involvement of the bilateral sensory-motor network at both single and group-level analyses. These preliminary results were expanded in a subsequent EEG–fMRI study to evaluate which brain region showed BOLD signal changes in relation to the amplitude and frequency of the rhythm [31]. Interestingly, the ring-20 rhythm was negatively correlated to the BOLD signal in cortical regions that represent integrated functional systems of the brain architecture, namely, the associative frontoparietal cortices belonging to the default mode network (DMN) and the dorsal attention network (DAN) [31]. This result indicates that the higher the expression of the rhythm, the greater the decrease of activity within the DMN and the DAN (Fig. 3).

The DMN consists of the precuneus, retrosplenial cortex, and parietal and anterior medial frontal cortices, and it is active in the resting brain with a high degree of functional connectivity [53]. It has been

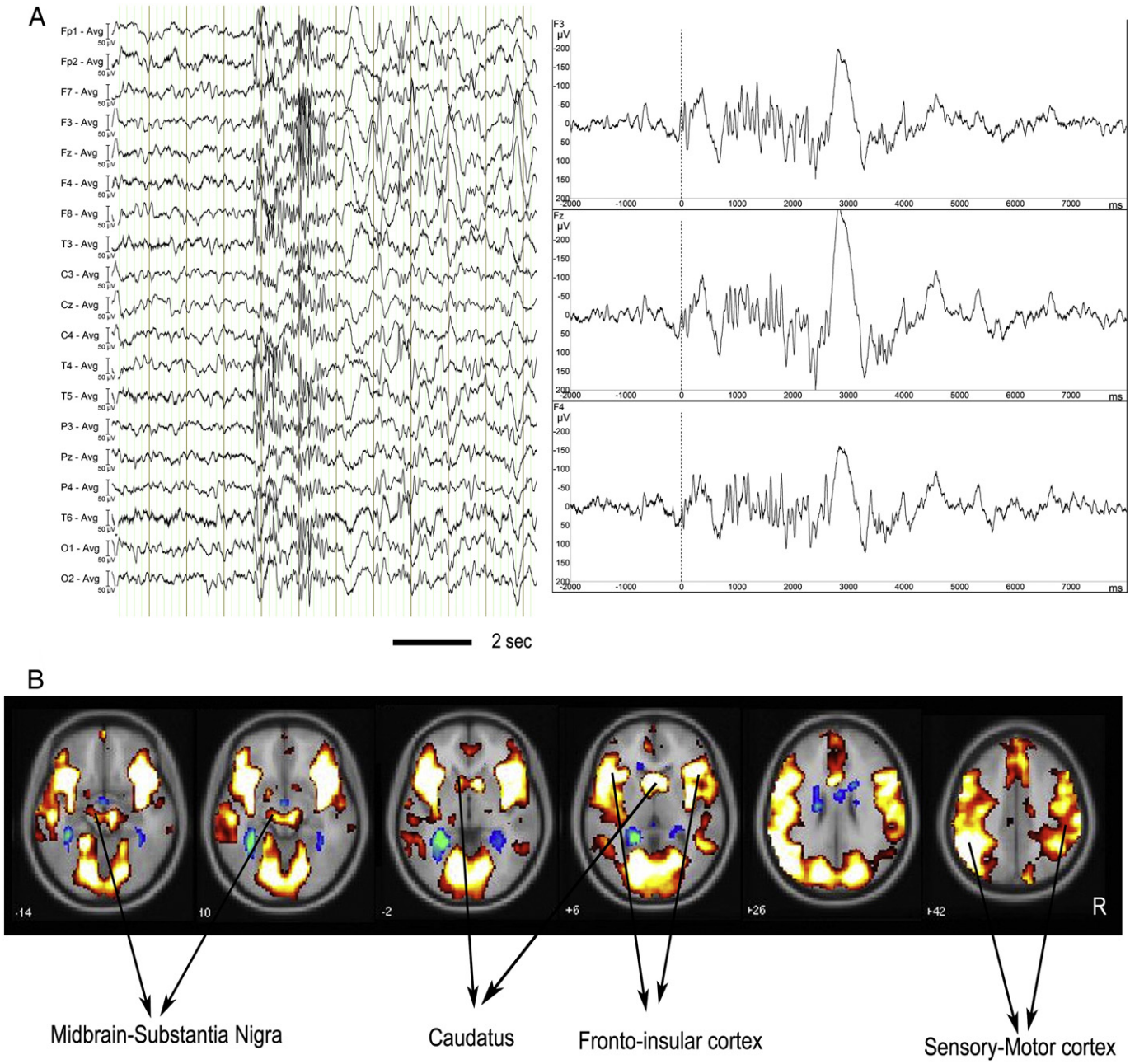

Fig. 2. Ictal substantia nigra and basal ganglia hemodynamic changes. Panel A: left image — representative page of ictal EEG recorded during the fMRI sessions. The EEG is displayed in average montage after gradient and cardiac artifact subtraction. Twenty simple partial seizures were acquired, which were characterized on EEG by high-amplitude slow wave followed by a brief discharge of fast polyspikes predominant over the frontal leads and clinically by minimal motor behavior (eye-opening with eyelid flutter). The postictal EEG showed high-amplitude delta activity diffuse with frontal prevalence. More electroclinical details can be found in Meletti et al. [29] and in Vaudano et al. [31]. Right image — enlarged representation of a representative polyspike discharge on the derivatives F3, Fz, and F4. The amplitude (μV) is displayed on the vertical axis and the duration (ms) on the horizontal axis. The "0" represents the discharge's onset. Panel B: ictal fMRI maps [T contrast] ($p < 0.05$, corrected for family wise error — FWE) are shown onto the normalized T1 structural MRI scan, axial slices. The red-yellow color identifies the BOLD signal increases, and the blue color identifies the BOLD signal decreases. Note the bilateral activation of the brainstem (substantia nigra) and basal ganglia (caudate nucleus). R = right.

suggested that the DMN constitutes a necessary and favorable neurometabolic environment for cognitive functions, representing a physiological baseline for processes of attention and working memory and supporting dynamical integration of cognition and processing [54]. Notably, abnormal activity in the DMN and disturbed connectivity between its components have been observed in several epileptic disorders, including EEs, in relation to interictal and ictal epileptic discharges [55–63]. In particular, the IED-related dysfunction of the DMN has been linked to alterations in conscious awareness, especially in idiopathic generalized epilepsies [64–66]. Similarly, the DAN, which is involved in the endogenous goal-driven attention orienting processes [67], has been demonstrated to be affected in patients with mild cognitive impairment and Alzheimer's disease [68,69], autism spectrum disorders [70], as well as in mesial temporal lobe epilepsies [55]. This means that DMN/DAN alterations are not obviously specific to [r(20)] syndrome. However, if we consider that the theta–delta rhythm is present during wakefulness and sleep, it is possible that this EEG trait reflects enduring alteration of these brain circuits; such dysfunction may in turn influence the task performances and contribute to the pathogenesis of neuropsychiatric disorders. The abnormal activity in the DMN and

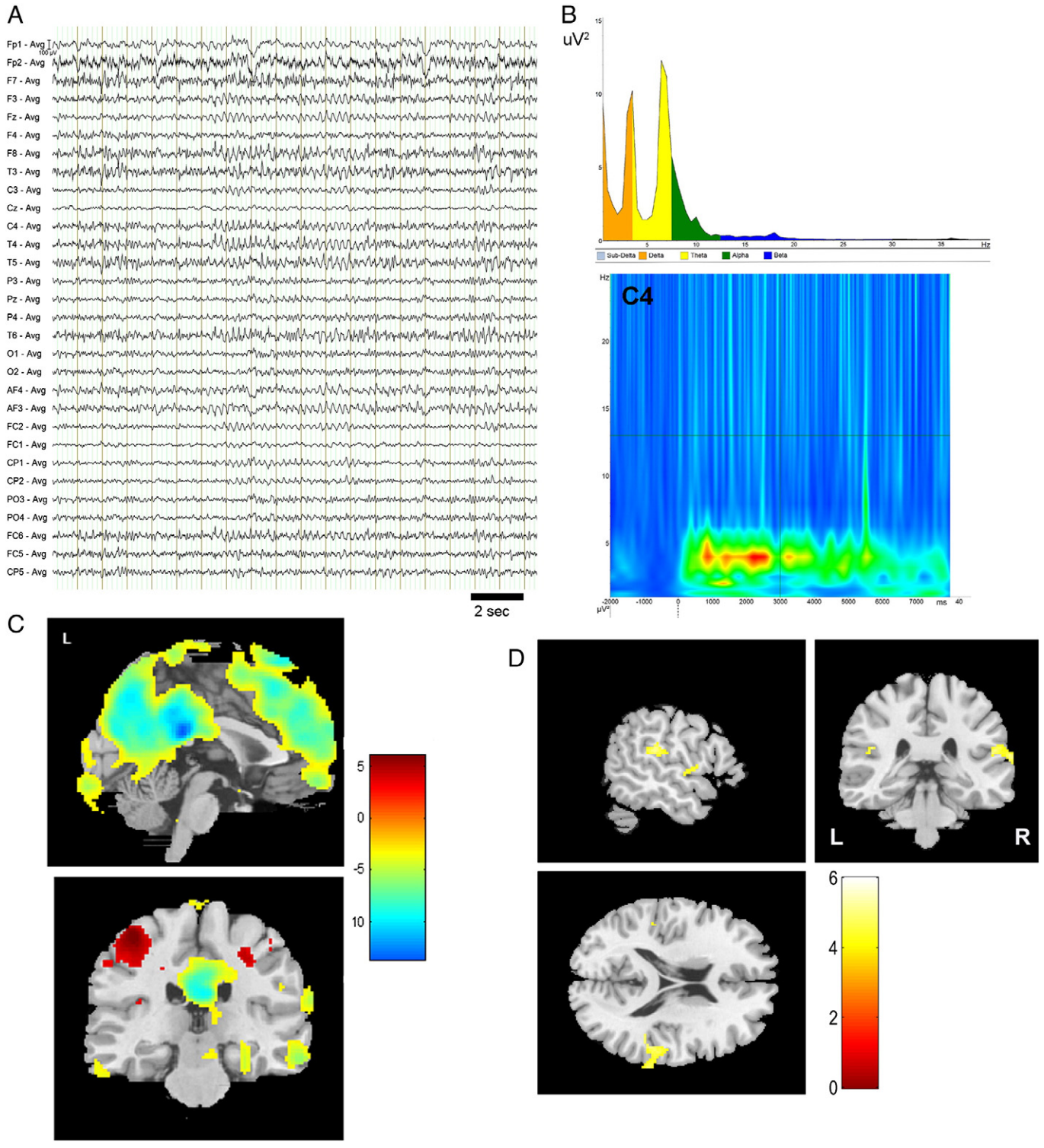

Fig. 3. The theta–delta rhythm in [r(20)] patients. Panel A: representative page of raw EEG recording in one [r(20)] patient. The EEG trace is shown in average montage. Note the long runs of irregular theta (around 4–5 Hz) slow waves with sharp contoured appearance, diffuse over the scalp with better expression on the frontotemporal regions. Panel B: upper image — Fast Fourier Analysis of the slow-wave activity. Each frequency band is represented by different colors. The slow-wave activity peaks in the theta–delta range. Note the bimodal distribution of the spectrum with a clear second peak (around 8 Hz) whose frequency is about double with respect to the first one (around 4 Hz). This behavior is typical of mμ oscillations. Lower image — electrode C4 slow-wave activity time–frequency plot (average of 22 theta bursts). Panel C: theta–delta rhythm-related BOLD pattern in one representative [r(20)] patient: the {T} SPM map ($p < 0.05$ corrected for FWE) is displayed onto the T1-canonical image showing positive correlations with the slow-wave activity (represented in red) at the bilateral primary motor and negative correlations (in green) covering the default mode network and the dorsal attention network. See Avanzini et al. for details [30]. Panel D: activated voxels ($p < 0.001$, uncorrected) representing the brain regions hemodynamically involved at the group level (11 patients) across different EEG abnormalities (ictal events, interictal high-amplitude spikes and slow waves, and slow-wave rhythm). See Vaudano et al. for details [31]. Blood oxygen level-dependent signal increases are detected over the bilateral temporoparietal junction (global maxima at the right temporoparietal junction) and right opercular–insular cortex. No decreases in BOLD signal were detected. L = left; R = right.

in the DAN might represent only one mechanism underlying the cognitive deficits in patients with [r(20)] syndrome. In our EEG–fMRI study [31], indeed, we observed abnormal BOLD changes at the associative right temporoparietal junction and right insular cortex in relation to different EEG activities including the theta–delta rhythm (Fig. 3). The right insular and the temporoparietal cortex have been implicated in important neuropsychological functions. The temporoparietal junction has been involved in a broad range of social cognition tasks, including visual attention and social perception exercises [71–73]. There are also convergent lines of evidence that this region plays a key role in "theory of mind" [74]. In particular, functional neuroimaging data reported increased response of the temporoparietal junction to stimuli that signal the actions and intentions of another individual [75–77]. The right temporoparietal junction is especially involved in understanding the behavior of others as a result of recognizing a physical cause or their mental states [78]. The insular cortices are important parts of neuronal networks of interoception, emotional processing, and social cognition [79,80]. Accordingly, functional abnormalities in these regions might explain the frequent association of [r(20)] syndrome with autistic features that appear after childhood-onset epilepsy [1,3,5,7].

All together, these findings provided evidence that the slow-wave rhythm by itself could contribute to the cognitive and behavioral impairments observed in [r(20)] syndrome. This is in line with the general view about a pathological nature of this slow-wave activity. Future studies should specifically address this hypothesis, correlating neuropsychological–behavioral performances of the patients with [r(20)] syndrome with quantitative EEG measures of the 3- to 5-Hz slow-wave rhythm.

4. Conclusion: clinical implications of neuroimaging findings

Taken together, the neuroimaging studies in patients with [r(20)] syndrome have disclosed the following endpoints: (1) prefrontal lobe circuits are involved in the transition from interictal to ictal state and ictogenesis; (2) an involvement of the nigrostriatal networks is present either during ictal activity or during interictal activity; (3) a disruption of associative brain circuits (DMN and DAN, perisylvian network) is present, possibly being related to the cognitive and behavioral deficits of patients with [r(20)] syndrome. Although these findings need to be confirmed by additional studies, they revealed the importance of using novel imaging techniques for investigating the pathogenetic mechanisms underlying the [r(20)] syndrome, and, undoubtedly, such such studies will receive further impetus in the near future. Multimodal imaging and future developments of neuroimaging tools indeed improve our understanding of the dynamics of the brain noninvasively with high spatial and temporal resolutions. They might reveal subtle functional and structural abnormalities, hence contributing to the diagnosis of [r(20)] syndrome when clinically suspected. Furthermore, neuroimaging tools can reveal possible pathogenic mechanisms that, if confirmed and extended by future research, could drive different therapeutic strategies, either pharmacological or not, with a potential benefit for patients.

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Declaration of interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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