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Review

Orientation and disorientation: Lessons from patients with epilepsy

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ABSTRACT

Orientation in time, space, and person is a fundamental cognitive faculty and the bedrock of neurological and psychiatric mental status examination. Nevertheless, research in orientation and disorientation is neglected in both cognitive science and neuropsychiatry. Specifically, it is still unclear whether disorientations in time, space, and person represent a failure of the same system or merely share a common nomenclature and whether these three domains of orientation depend on different psychological and neural systems. Here, we analyzed descriptions of patients with specific orientation failures associated with circumscribed cortical lesions, with a primary focus on epilepsy. The form of disorientation is analyzed according to its specific domain, the underlying neuropsychiatric disorder, and its anatomical correlate. Disorientations in the different domains are classified as self-referenced (incorrect self-localization) or nonself-referenced (incorrect localization or knowledge of other places, events, and people). Analysis of the cognitive and neural systems disturbed in these patients suggests that disorientation in one or several domains may be related to a failure in a specific brain mechanism localized mostly in the right hemisphere, partially overlapping with the default mode network (mostly the medial and lateral parietal, medial temporal, and lateral prefrontal cortices), which processes essential self-related cognitive faculties such as orientation.

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1. Introduction

Orientation in time, space, and person is fundamental for a behaving self and is, therefore, the bedrock of the neurological and psychiatric mental status examination. In a seminal paper, Berrios [1] defined orientation as "tuning between the subject and the internal representation he forms of the corresponding public reference system". States of disorientation may be the hallmark manifestation of specific neuropsychiatric disorders. Indeed, evaluation of patients' orientation in time and space encompasses a significant portion of many commonly used neuropsychological tests such as the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale — Cognitive (ADAS-Cog), Addenbrooke's Cognitive Examination (ACE), and the Montreal Cognitive Assessment (MoCA) [2–5]. Berrios [1] assigned states of disorientation to three different categories: (1) general "clouding of consciousness"; (2) accompanying some forms of mental disorders such as acute schizophrenia, mood disorders, or fugue states; and (3) "specific orientation failures associated with cerebrocortical syndromes". Two main open questions are posed: (1) Do disorientations in time, space, and person represent a failure of the same system or merely share a common nomenclature, and (2) Does orientation in these three domains depend on different psychological and neural systems. Here, these questions are addressed, referring to specific failures in orientation as they are expressed in cerebrocortical syndromes, with a focus on the special role of epilepsy in disorientation. These syndromes are analyzed through case descriptions and are further classified. We hypothesize that disorientations in the different domains share common fundamental characteristics.

2. Disorientation in epilepsy

Disorientation and confusion are hallmarks of epilepsy and postictal states. Generalized epilepsy and postictal states may lead to a global loss of orientation, which recovers gradually with respect to time, space, and person [6]. Furthermore, disorientation states may persist in the interictal period, leading to chronic disorientation disruptions. Several localized (partial) epilepsy syndromes are manifested as disorientation confined to a specific domain — time, space, person, or other scalable domains in which the patient's behavior is changed periictally. The following subsections provide descriptions of such disorientations and explore the defining characteristics of each form of disorientation.

3. Disorientation in space

Spatial orientation is a complex cognitive function, which may include navigation, head direction, verticality, reaching, spatial-vision, or perspective-taking [7]. Orientation in space may be self-referenced (representation of the spatial environment with respect to one's self-

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location) or nonself-referenced (representation of places with respect to a "cognitive map") [8]. Additionally, spatial orientation may be related to one's self-location either in the immediate environment or with respect to the nonimmediate space [9–12]. Spatial disorientation is diagnosed when the patient is unable to correctly reply to questions regarding his immediate or nonimmediate surroundings or body borders or is unable to identify the location of nonself-related objects or places [1,13].

3.1. Self-referenced disorientation in space

This disorientation type is a disturbance in the correct location of the self either in the immediate or in the nonimmediate environment (e.g., room or city, respectively). The immediate environment can be further separated into the peripersonal space (the body and its hand-reaching proximity) and the immediate extrapersonal space (observable but nonreachable environment). This classification is based on knowledge from cognitive neuroscience regarding the specific mechanism related to these different distances [14–17].

3.1.1. Self-disorientation in the peripersonal space

Self-disorientation in the peripersonal space refers to a group of disorders in which one faces difficulties in localizing oneself into one's body borders. A major class of this group is self-reduplication, which is subdivided into four main distinct forms (Fig. 1).

3.1.1.1. Autoscopy. Fig. 1A: During autoscopy, people experience their "self" or center of awareness within the physical body, seeing a "double" of themselves in extracorporeal space viewed from the perspective of one's own physical body; a patient with epilepsy due to a left temporoparietal lesion has described a repetitive experience in which she saw an image of herself opposite to herself:

> "I have a kind of illusion, a kind of character that penetrates my thoughts. I speak with myself, I can see myself in colors, lots of colors, like psychedelic colors, blue and red, and purple. Everything enters me. Something speaks to me and I hear a voice, my voice. I see myself here, I'm here. I see my face from within myself, opposite to me. It's me, it's me, I speak to myself."

This description exemplifies not only the visual character of autoscopy ("I see myself here … opposite to me") from the patient's own perspective ("within myself") but also the intact self-location ("I'm here"), hyperchromatopsia ("lots of colors"), and a hearing of a presence, which is identified by the patient to be herself.

3.1.1.2. Out-of-body experience. Fig. 1B: One feels that the center of awareness is located outside the physical body and somewhat elevated. It is from this elevated extracorporeal location that one experiences seeing one's body and the world, resulting in perceptions organized consistently with this visuospatial perspective. This experience combines three phenomenological elements: the feeling of being outside the body (disembodiment), a change in the visuospatial perspective, and seeing one's own body (autoscopy). A report of a patient with an out-of-body experience [18] illustrates such a disorientation in self-location and perspective-taking with respect to the environment:

> Initially, she felt as being 'above her real body', but that she was rapidly rising higher. … The visual scene always took place outdoors and was described as 'a green meadow or hill'. The sensation of elevation continued and, quickly, she saw everything from so far away that she could not distinguish details anymore stating that she saw "something like a map of some country as you find in geography books". Here, the elevation stopped and she fell back "to earth".

Out-of-body experience may, thus, be conceptualized as disorientation of one's self with respect to his bodily self-location, which further leads to different perspective-taking with respect to the external environment.

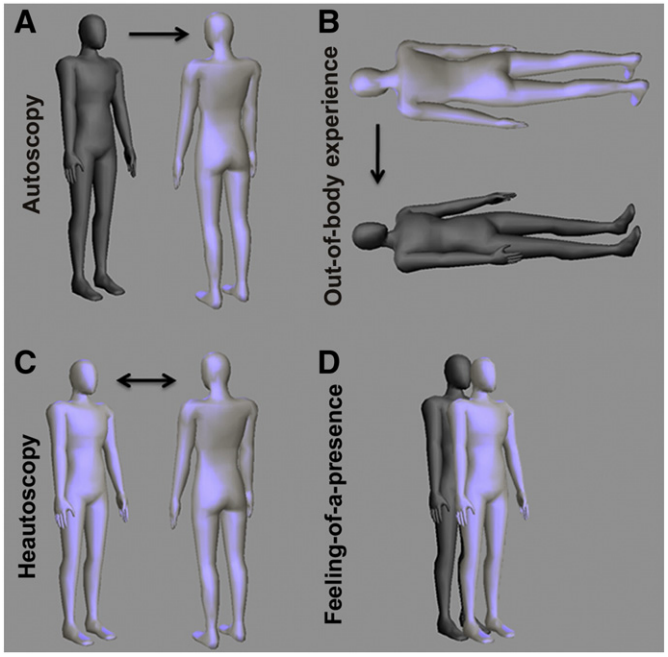

Fig. 1. Autoscopic phenomena. A. Autoscopy: experience of seeing one's body in extracorporeal space (as a "double"). The self is experienced as oriented inside the boundaries of the physical body. The double (right) is seen from the habitual egocentric visuospatial perspective (left). B. Out-of-body experience: during an out-of-body experience, one appears to "see" himself (bottomfigure) and the world from a location above his physical body (extracorporeal location and visuospatial perspective; top figure). The self is oriented outside its physical body. C. Heautoscopy: an intermediate form between autoscopy and out-of-body experience; the experiencer sees his body and the world in an alternating or a simultaneous fashion from an extracorporeal and his bodily visuospatial perspective; it is often difficult for the experiencer to decide whether the self is oriented in the double or in its own body.

3.1.1.3. Heautoscopy. Fig. 1C: An intermediate form between autoscopy and out-of-body experience. During heautoscopy, people also see their double in the extracorporeal space. However, it is difficult for them to decide whether they are "disembodied", that is, whether their sense of "self" is localized within the physical body or within the autoscopic body. Therefore, subjects with heautoscopy may experience the world from two simultaneous or alternating visuospatial perspectives: the habitual physical visuospatial perspective and the extracorporeal perspective [11,12,19]. This is exemplified in a 21-year-old patient of Brugger and colleagues [20] with complex partial seizures due to excised left mesiobasal temporal tumor:

> "When he got up with a feeling of dizziness, he turned around and saw himself still lying in bed … he did not know any more who of the two bodies he really was (or where his self was located) … he experienced his self-location to be alternating between the two bodies … His only intention was described as trying to become one person again".

3.1.1.4. Feeling of a presence. Fig. 1D: The "feeling of a presence" refers to the illusion that somebody is close-by even though no one is around [21,22]. It is defined as the convincing feeling that there is another person close-by, without the patient actually being able to see that person [12]. This phenomenon is demonstrated by the following history of a patient with epilepsy with a right frontoparietal lesion:

> A 73-year-old right handed man has suffered since the age of 50 from fronto-parietal epilepsy, expressed mostly as clonic movements of his left leg. The etiology of his disease was secondary to neurocysticercosis. He then started to complain of a "very strong

impression" of a presence of a person who "accompanies" him while walking, 2-3 times a day, always to his right. Without seeing him he "felt" that a "man in black" is stepping to his side, at the same pace as his. This "person" neither spoke nor made a noise or odor. It seemed to be always the same person. He reported that "while looking on this person I see nothing." MRI demonstrated a right fronto-parietal cystic lesion, compatible with the underlying disease.

A number of observations support the assumption that this "presence" is actually a projection of the patient's own body: the close proximity of the "person", a feeling of psychological affinity, and imitation of the patient's own body movements and position [12,22]. The feeling of a presence is, therefore, a somatosensory form of self-reduplication, appearing mostly as close as possible to the patient. It shares many phenomenological and clinical characteristics with autoscopic phenomena and can be categorized as a self-disorientation in the peripersonal space.

Epilepsy is a major pathology underlying autoscopic phenomena and feeling of a presence [11,12,19,23]. Patients with autoscopy are characterized by posterior brain damage in the occipitoparietal and the occipitotemporal cortex, whereas patients with heautoscopy and out-of-body experiences have more anterior temporoparietal lesions [12], with autoscopy involving primarily left hemispheric lesions and with out-of-body experience involving primarily right hemispheric lesions [11]. Feeling of a presence has been observed in patients with damage to any lobe, although, like autoscopy, it is most often associated with posterior parietal damage with left predominance [12,22].

3.1.2. Egocentric topographical disorientation

Another type of self-referenced disorientation, egocentric topographical disorientation, is manifested as a problem in orientation to the immediate environment [24]. In this form of disorientation, patients cannot represent the location of places or objects with respect to their own self-location because of a disturbance of visuospatial functions (similar to those of spatial neglect). This may be accompanied by an inability to reach or organize objects in the immediate environment with respect to an external reference system. Underlying brain lesions were identified mostly at the right lateral parietal cortex [25].

3.1.3. Self-dislocation in space

Self-referenced disorientation may be manifested as spatial self-dislocation, in which patients may erroneously believe that they are located in another place and may, therefore, incorrectly answer orientation questions. This type of disorientation in the nonimmediate space

Table 1
Classification of disorientation disorders.

Type of disorientation	Clinical features	Neuroanatomy	Reported in epilepsy
Space			
Self-referenced	Lack of knowledge about the current spatial self-location		
Peripersonal space	Disorientation in the body borders and close surroundings		
Autoscopy	Seeing a double in the extracorporeal space, viewed from one's own physical body (as in a mirror)	TPJ (L) occipitotemporal [11]	++
Out-of-body experience	Experiencing one's body and the world from an extracorporeal location	TPJ (R) [11]	++
Heautoscopy	The sense of "self" alternates between the physical body and the autoscopic body	TPJ [11,19]	++
Feeling of a presence	Own-body illusion of another person in near extrapersonal space	Frontoparietal (R) [19,22]	++
Egocentric disorientation	Problems in representing location of objects or places in the immediate environment, with respect to one's own self-location	Parietal (R) [24,25]	−
Self-dislocation in space	Mistakes in answering questions about the current place, secondary to erroneous belief that one is located in another place	TPJ [10]	+
Nonself-referenced	Problems in representation of other locations		
Heading disorientation	Problems in navigation, due to disordered representation of relations in the cognitive map	Retrosplenial cortex (R) [24,27]	+
Disorganization of the cognitive map	Delusion that a place simultaneously exists in two or more locations or is transferred to a different location	Frontal (R) [9]	−
Time			
Self-referenced	Lack of knowledge about the current time, without a matching amnesia		
Age disorientation	Insistence on being younger than one's real age, even with correct knowledge of the current year and year of birth	Inferior parietal cortex	+
Timeline disorganization	Inability to obtain the correct sequence of life events	Orbitofrontal cortex, temporal lobe [28]	+
Timeline reduplication	Reduplicative paramnesia for time (the belief that self-referenced events in time have been duplicated), *Déjà-vu* (feeling that events have already happened)	Temporal [29]	++
Out-of-time experience	Autoscopic phenomena accompanied with a change in the perception of the double's location in time	TPJ [30]	++
Nonself-referenced	Problems in the organization of the self-referenced timeline of events		
Temporal knowledge disorientation	Lack of knowledge regarding the current time (year, month, season)		++
Disorientation in age of others	Belief that other people are younger than their true age		−
Person			
Self-referenced	Disturbance of self-identity		
Dissociative disorientation	One does not know who one is	Temporal (R) [31]	+
Depersonalization	Feeling detached from one's mental processes or body, as if one is an outside observer	TPJ, lateral temporal, lateral parietal, occipital [32]	++
Self-misidentification	Mirror sign — misidentification of oneself in a mirror	Frontal (R) [33]	−
Nonself-referenced	Disturbance of other people's perceived identity		
Misidentification of other people	Misidentification of family and friends		++
Delusional misidentification syndromes			
Capgras syndrome	Familiar persons are believed to be imposters	Occipitotemporal, frontal (R) [34,35]	+
Fregoli syndrome	Belief that a stranger is a familiar person	Frontal (R) [36]	+
Intermetamorphosis	A familiar or unfamiliar person is conceived to morph into a different person		−
Subjective doubles	A person is considered to be mentally and/or physically transformed to the patient		+

TPJ — temporoparietal junction; MTL — medial temporal lobe; PCC — posterior cingulate gyrus; R — right; L — left '++' - frequently reported, '+' - sporadically reported, '-' - not reported.

is common in patients with dementia and Alzheimer's disease and may also appear in postictal states [6,26] (Table 1). In many cases, patients may answer correctly when asked about their current location but may be subjectively disoriented in space, as seen by their behavior, e.g., they try to go to their house which they believe is close-by [9].

3.2. Nonself-referenced disorientation in space

In nonself-referenced disorientation, patients usually retain a correct knowledge of their current self-location but have impairment in the representation of other locations, resulting in the patients' inability to navigate even in the most familiar surroundings [25]. This may result from a disturbance of a "large-scale" cognitive map, leading to duplication or disorganization of the map. This phenomenon is common in dementia, demonstrated in the tendency of some patients with Alzheimer's disease to wander or to get lost [26,37].

3.2.1. Heading disorientation

A common type of nonself-referenced disorientation for space is *heading disorientation* [25], which entails problems in the correct representation of the internal cognitive map and the relations of landmarks inside it, due to right posterior cingulate/retrosplenial lesions [27]. Interestingly, this form of topographical disorientation can occur as a congenital disorder (*developmental topographical disorientation*) often associated with impairment of blood flow in the right retrosplenial cortex [38,39].

Heading disorientation is also found in patients with temporal lobe epilepsy and may be demonstrated by the following case:

> A 72-year-old patient, suffering from past right temporo-parietal stroke, was working in a governmental office, and used to take a bus there daily. One day he did not show up to work, and did not come back home at 16 h00 as he used to do every day. At 22 h00 the patient was found by a bus driver and was referred to the emergency room. He did not know where he is, nor where he was during the day or how to get to his house. Bus company records showed that he travelled by bus back and forth all day long. CT scan identified an old temporo-parietal infarct, and EEG revealed right posterior temporal spikes. A treatment with levetiracetam was initiated, and the patient recovered during the following night. Since then the event did not recur.

The patient suffered from disorientation in place accompanied with amnesia to the occurrences of the day, as is described in other cases of temporal lobe epilepsy and fugue. The disorientation in this patient may be related to disruption of the patient's ability to form a conceptual representation of his environment ("cognitive map") including the objects within it and their spatial relationship [40–42].

3.2.2. Disorganization of the cognitive map

In this type of disorientation, representations of different locations are mixed in the patient's cognitive map. Misrepresentation of another location is found in patients with *reduplicative paramnesia*. These patients usually describe the delusional relocation of their current location to another place [43,44]. This is illustrated in the following description:

> An 80-year-old patient with right frontal hemorrhage was admitted to the department of neurology of Geneva University Hospital. While asked to name the location of the hospital, the patient stated that he is hospitalized in a branch of the Geneva University Hospital located above the city of Montreux, 75 Km to the east of Geneva (no such branch exists). Accordingly, he identified the close-by Salev Mountain to be the French Alps, which are closer to Montreux than to Geneva, and the Jura mountains to be the Swiss Alps.

Similar to this reduplicative paramnesia, other familiar places may be perceived as duplicated in another location (sometimes referred to as Capgras syndrome for place rather than for person) or may be perceived as transferred (and not duplicated) to another location [45]. These phenomena can be described as disorganizations of the cognitive map. They are sometimes related to confabulation and are seen most commonly in patients with right frontal lesions [46,47].

4. Disorientation in time

Several types of temporal disorientation are described in the neurological and psychiatric literature. Here, we refer only to temporal disorientation with respect to one's reference system rather than distortions in the perception of the passage of time or time estimation deficits [48]. Temporal disorientations can also be classified as self-referenced and nonself-referenced.

4.1. Self-referenced disorientation in time

4.1.1. Age disorientation

In age disorientation, patients insist that their age is younger than their real age, even if they are able to accurately cite the current year and their date of birth and compute the difference between the years [6,49]. An example of such a contrast is given in the following case:

> A 62-year-old patient with severe vascular risk factors was referred to the emergency room with abrupt right hand and lower face paralysis, right leg paresis and motor aphasia. Soon after his arrival the patient's situation improved dramatically, presenting only slight right side weakness and no speech disorder. Nevertheless, when asked, the patient insisted that he is 48 years old. The patient correctly noted both the present year and his date of birth and could calculate the difference between the two of them, though slowly. CT scan revealed a left inferior parietal hypo-dense lesion, compatible with sub-acute stroke. This disturbance continued for several hours and then resolved.

Age disorientation may be seen not only in patients with circumscribed brain lesions, as in the previous case (temporoparietal ischemia), but also in those with more diffused disorders such as postictal states, dementia, delirium, and Korsakov psychosis [49].

4.1.2. Timeline disorganization

This form of disorientation results from a severe disruption of the self-referenced timeline, resulting in the inability to identify the correct sequence of events in time [47,50]. This form of isolated temporal disorientation can be found in patients with temporal lobe epilepsy. A patient with temporal epileptic amnesia due to right temporal lobe epilepsy described the following:

> "I don't remember. I was shocked to know that my daughter was with me in the ambulance. In fact, before Saturday I couldn't imagine what is wrong with my hair. It was all goopy. It was like dried, like something was in it. It was only after Saturday that I found out that she has done it to me on Thursday".

The patient describes that she could not refer events to the time in which they took place. Therefore, we refer to this description as timeline disorganization. Timeline disorganization is also frequent in confabulating patients and may partially explain the content of their confabulation [28].

4.1.3. Timeline reduplication

Other timeline disorganization forms may include the belief that self-referenced events in time have been duplicated, referred to as *reduplicative paramnesia for time* [51,52]. Similar phenomena may include déjà-vu/déjà-entendu (where a novel visual/auditory experience feels familiar) and déjà-vécu (a longer and more intense form of the former) [53]. These are described by a patient with right temporal lobe epilepsy:

"While I am doing something, I feel like I have already done this thing, like I was here previously, I have already read this paragraph; I was already in this process, I already heard this sentence; Somebody says something and it is already in my memory, I know he already said it, which goes together with the image of the situation. And I know what is going to happen".

This is a reduplication of the timeline of events, as the patient feels that the events have already happened or will happen.

4.1.4. Out-of-time experience

Temporal disorientation may accompany the spatial disorientation in patients with autoscopic phenomena. In several such patients, we have found the projection of one's self not only to another place but also to another time (*out-of-time*) [30]. For instance, a patient with complex partial seizure due to a left temporoparietal lesion described the experience of heautoscopy, yet mentioned that his heautoscopic image "looked like myself, but ten years younger" [54]. This patient has, therefore, disorientation in both time and space.

Out-of-time experiences are abundant in patients with autoscopic phenomena. A total of 37.3% of the subjects with out-of-body experience described by Green [55] reported a change in their experience of time. This change was mostly described as if time did not exist or passed very quickly:

"While I was out of my body there was no time at all, but once I had regained myself I realized the experience had taken few seconds."; "I omitted to mention the actual time that this experience took. It could have been minutes or hours, there was no sensation of time"; "It all seemed to take a long time but it could be one second or less, because things go with the speed of light".

An out-of-time experience was also described in autoscopy, in which the perceived double was projected not only in space but also in time [56]:

The patient was a 35-year-old woman with epilepsy. At the moment she woke up from a seizure, the patient saw … in front of her somebody who looked exactly like herself 'like she was completely young and charming' who ran away, laughing. She tried to catch her, but failed and fell down.

4.2. Nonself-referenced disorientation in time

4.2.1. Temporal knowledge disorientation

The most common form of temporal disorientation is characterized by lack of knowledge with respect to current time (year, month, day of the month, day of the week, and season). Mistakes in the exact date are common and may appear even in healthy subjects, but mistakes in the year or month are indicative of the presence of an underlying disorder, such as in patients who awaken from a seizure, anesthesia, or electroconvulsive therapy (ECT) and in patients with delirium and dementia [6,57]. In several cases, patients seem to be oriented to the "formal" objective time (hour, date) but may be wrong with respect to subjective measurements like the time which passed from past events. This kind of temporal disorientation is often accompanied by amnesia [50,58], which may be the cause for the temporal dislocation to the last remembered time. However, in many cases, the severity of disorientation is not correlated with the length of retrograde amnesia, and, therefore, the disorientation cannot be explained by amnesia only [6, 58,59]. This kind of temporal disorientation may be related to disorganization of the cognitive map that represents time in these patients.

4.2.2. Disorientation in age of others

Disorientation in age may also involve other people, as illustrated by the above-described patient with reduplicative paramnesia:

The patient was wondering why his mother, who passed away 25 years earlier, was not coming to visit him, insisting that she did so the day before. He mentioned that his parents are living just next to him in Geneva. Furthermore, he was referring to his 75-year-old spouse as a "young lady". When asked, he evaluated her to be around 50 years old. He did remember their exact birth date and knew the correct present date, so he could calculate their age correctly. He did not misidentify people around him, nor did he mistake their age, besides the three abovementioned relatives. The neurological examination showed decreased visual acuity and mild left-sided hemiparesis with no sensory deficit.

5. Disorientation in person

Disorientation in person may refer to the patient's own self, close relatives, or other people. Therefore, similarly to space and time disorientations, person disorientation can be interpreted as self-referenced or nonself-referenced.

5.1. Self-referenced disorientation in person

5.1.1. Dissociative disorientation

This state is characterized by detachment from one's own self or amnesia for personal identity (the patient does not know who he or she is). This phenomenon is found in very severe dementia and is also frequent in dissociative disorders which are characterized by alteration in identity. Despite the fact that epilepsy was not found to be a primary pathophysiological mechanism for developing dissociative symptoms [31], dissociative amnesia (dissociative fugue) may be seen in temporal lobe epilepsy. Dissociation was associated in neuroimaging studies with the medial prefrontal and posterior parietal cortices [60]. The following patient with dissociative amnesia illustrates this kind of personal disorientation [61]:

The patient was a 30-year-old single Hispanic woman, who had lived in Europe for 3 years. Her early history was significant for sexual abuse by her grandfather when she was 8 years old. She held a high-level job and was involved in many social activities. Some months after moving in with her partner, she broke up with him, stating that she 'did not feel satisfied'. She moved to Europe, where she met a new person with whom she moved in 1 year later. Shortly after moving in with her new partner, the patient presented once every several weeks with acute and repetitive, paroxysmal events in which for several days, she felt that she would "lose her own identity" and be displaced in time back to her moment of arrival in Europe. During the acute phase, she had no evidence of episodic memory (personal and non-personal) for the prior 3 years, did not recognize local acquaintances, and did not speak the local language (which she in fact spoke fluently). She also showed a marked change in personal identity to a marked childish personality, dependency and alexithymia, much different from her usual considerate, mature and serious nature. Later, she mentioned that during the events, 'I lost the sense of being myself' and that she would like to 'travel back' to the time 'when I was myself'. The episodes then resolved spontaneously. The patient was first treated with several anti-epileptic drugs yet video-EEG during the events did not show any epileptic activity and drugs were stopped. Following a short cognitive-behavioral therapy (CBT) the patient moved back to her country of origin, where symptoms did not recur anymore.

5.1.2. Depersonalization

Disorientation in personal identity may also be manifested as *depersonalization*, that is, "feeling detached from, and as if one is an outside observer of, one's mental processes or body (e.g., feeling like one is in a dream; sense of unreality of self, perceptual alterations; emotional and/or physical numbing; temporal distortions; sense of unreality of

surroundings)" [62]. Depersonalization was described in patients with epilepsy and in those without epilepsy and is an important component of both heautoscopy and out-of-body experiences [23]. The next case demonstrates this disorder:

> A 34-year-old patient has suffered since the age of 10 from short recurrent events in which he described that "I am not myself anymore, I mean, I know who I am but I just feel like I may be somebody else". These events have recurred several times a year, mostly after sleep deprivation or in stressful situations. At the age of 33, the patient had a nocturnal generalized tonic-clonic seizure. EEG showed right temporal spikes, and MRI was within normal limits. The patient started treatment with carbamazepine. Since then no such events have occurred.

5.1.3. Self-misidentification

A dramatic manifestation of disorientation in personal identity is *self-misidentification*, as observed in the *mirror-sign syndrome*, the misidentification of oneself in a mirror [33,63,64].

5.2. Nonself-referenced disorientation in person

5.2.1. Misidentification of other people

This is a very common type of disorientation in person, in which family members and friends are wrongly identified as different people but without disturbance in self-identity. This phenomenon may be observed in patients with dementia [33] as well as in patients in the postictal state.

5.2.2. Delusional misidentification syndromes

These are more severe types of misidentification of others, as the misidentification is persistent and endures even in the presence of contrasting evidence [36,45,65]. Specific syndromes may include hypofamiliarity in *Capgras syndrome* (familiar persons are taken to be impostors) [66] and hyperfamiliarity in the syndromes of *Fregoli* (a stranger is perceived as a familiar person), *subjective doubles* (another person is considered as a double of oneself), or *intermetamorphosis* (another person is conceived as a different person) [12,45,65].

The Capgras syndrome was apparent in a patient with epilepsy due to an excised right frontal low-grade glioma, who had claimed that each time her husband or daughter came home, they were actually thieves sent by a close-by neighbor to steal her jewelry. As a result of this severe and frequent belief, the patient usually put on most of her jewels when leaving her home in order to avoid the theft during her absence. Another 18-year-old patient with epilepsy with an unspecified seizure disorder describes the subjective doubles syndrome [67]:

> "In here there is a girl as fat and as tall as I am. At night when everyone is asleep, she puts on a wig and a mask and walks from room to room stealing things in order to incriminate me. One night I woke up and saw her with my own eyes. It is unfortunate that due to my confusion I failed to run to the window to shout to the people, 'look here, this is me, and this is my double with a wig and a mask.'"

Delusional misidentification syndromes may be related to damage in the temporal, parietal, and frontal cortices, mostly in the right hemisphere [45,68], and have been shown to occur in patients with epilepsy postictally and interictally [69,70]. They may be interpreted as disturbances in the representation (or "cognitive map") of other people, resulting in its disorganization, duplication, and incorrect location of self and others, similar to the time and place domains.

6. Disorientation outside the time–space–person domains

While disorientation syndromes are classically described as related to time, space, and person, other neuropsychiatric phenomena in which patients change their habitual "self-location", or "project" themselves, on a scalable domain may be conceptualized as disorientation. For instance, patients with hyperreligiosity or ecstatic seizures change their habitual preferences and ideas regarding religion. This phenomenon may be regarded as a type of disorientation in the religious domain, on which people "relocate" themselves to a different set of religious ideas and feelings following a seizure [71,72]. We propose that other phenomena of this nature may be regarded as disorientation. For example, patients with Gourmand syndrome, which is related to right frontal/temporal lesions and temporal lobe epilepsy, change their habitual preference with regard to food and develop a preoccupation with food and fine eating [73,74]. Therefore, these patients may be regarded as disoriented in the taste domain/axis on which they "relocate" their gustatory preferences (from coarser to finer) following the lesion and aberrant activity. In a large cohort of 22,947 patients with epilepsy, Fazel and colleagues [75] found that certain subtypes of epilepsy (including simple partial seizures and temporal lobe epilepsy) are associated with higher rates of violent crime. This criminal behavior may be regarded as a change of orientation in the moral domain. Furthermore, patients with mood disorders may be regarded as having disorientation in the affective domain. Taken together, we suggest that disorientation may be related not only to time, space, and person but also to other more abstract domains in which one may reorient oneself to a different point than the habitual self-reference (Fig. 2). Accordingly, the concept of disorientation may extend to stable interictal personality changes, in which a specific component of behavior is upscaled along a specific dimension. Admittedly, other explanations for these behavioral changes are possible, including socialization processes and other changes unrelated to orientation. Further research, aimed at the identification of orientation-specific brain mechanisms and assessment of their contribution to these disorders, may shed light on the origin of these important clinical syndromes and their relations to the orientation system.

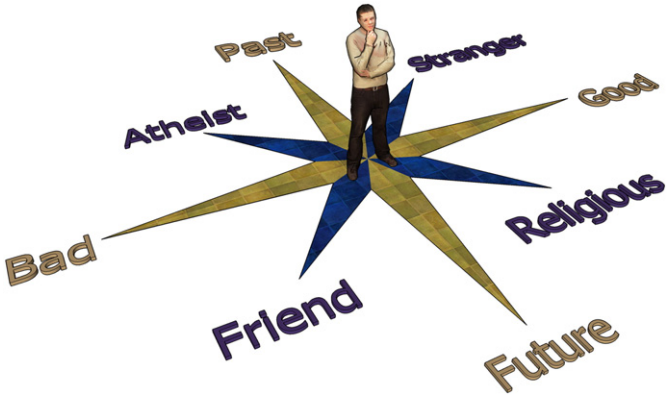

Fig. 2. Potential orientation domains. In addition to the traditional domains of space, time (past to future), and person (e.g., the familiarity aspect: stranger to friend), the orientation system may process domains such as morality (bad to good) or religiosity (atheist to religious).
Figure created with SketchUp Make®, Trimble Navigation, Ltd.

7. Disorientation following generalized seizures

Disorientation has not been systematically investigated in patients with generalized epilepsy. However, such a systematic investigation has been carried out in patients undergoing ECT, which induces generalized seizures [6]. Following ECT-induced seizures, there is commonly a period of disorientation in time, space, and person, which is resolved several hours later [6,76,77]. This disorientation leads to an inability to give correct answers to orientation questions in these domains. Although some level of retrograde amnesia may be observed in these

patients, its length does not correspond to the extent of disorientation, and, thus, disorientation must result here from other mechanisms unrelated to the amnesia [6]. It is, however, important to note that disorientation following ECT may somewhat differ from that elicited by spontaneous epileptic seizures due to the use of general anesthesia and other procedure-specific factors.

An interesting characteristic of the postictal disorientation following ECT is its specific order of recovery across patients: patients recover their orientation firstly in person, secondly in space, and lastly in time [6,76,77]. This sequential recovery is not limited to postictal disorientation and may also be observed in patients recovering from disorientation following traumatic brain injury [58]. Furthermore, in patients with dementia, time orientation is the first to be disturbed, followed by space and finally by person orientation. These findings suggest that person orientation is the most intrinsic and stable of states, followed by space and then time. Intriguingly, differential recovery of orientation in the postictal state is also evident within specific domains, as self-referenced orientation (e.g., age) is recovered prior to nonself-referenced orientation (e.g., calendar time) [6,76]. Overall, these findings support the hypothesis that similar cognitive mechanisms underlie orientation in the different domains and across different clinical conditions.

8. Disorientation and the default mode network

As shown in the previous sections, the affected brain regions involved in disorientation (either epileptic foci or lesion locations) include mostly the temporoparietal, posterior parietal, prefrontal, medial temporal, and medial parietal cortices, with a significant right lateralization. These regions noticeably overlap with the default mode network (DMN) [78,79] (Fig. 3). The DMN is a set of cortical regions which were found to be consistently coactivated during the resting state, including parts of the medial parietal, medial prefrontal, dorsolateral prefrontal, inferior parietal, and medial and lateral temporal cortices [78,81]. This distributed network was initially described as exhibiting deactivation during cognitive tasks and was thought to be involved mainly in passive (or "default") monitoring processes [82,83]. However, recent findings demonstrated that the DMN is highly active during tasks involving self-generated thoughts, theory of mind, navigation, and self-projection in space and time [84–87], leading to the suggestion of a specific role for the DMN in self-referential processing (for a comprehensive review, see [88]). An important component of the DMN is the hippocampus, which has a prominent role in navigation, time perception, and creation of allocentric "cognitive maps" of the immediate environment [89–91]. Damage to the hippocampus (such as in hippocampal sclerosis, a major etiology for temporal lobe epilepsy) is a major cause of various types of disorientation, as described above, and also affects DMN functional integrity [50,92,93]. A major role of the DMN may, therefore, involve creation of "cognitive maps", which represent one's self-location with respect to different landmarks in space, to different people in the society, and to different events in time. The involvement of the DMN in cognitive map creation and self-referential processes suggests that disorientation may be related to a failure in a general orientation mechanism residing in (or overlapping with) the DMN, with right-hemisphere predominance. Disorientation in different domains may potentially arise from disruptions of different submodules of the network (Fig. 3). In the same vein, orientation may extend to mapping of more abstract "landmarks" and to self-location with respect to esthetics, ethics, belief, or mood, relying on cognitive map representations within the DMN.

9. Discussion

In this work, we presented patients with disorientations in time, space, and person. These disorientations can result from localized neurological disorders such as partial seizures and focal brain lesions or following whole-brain disruptions such as generalized epileptic seizures, neurodegenerative disorders, and other general neuropsychiatric states. Furthermore, disorientation states may be transient, as in partial

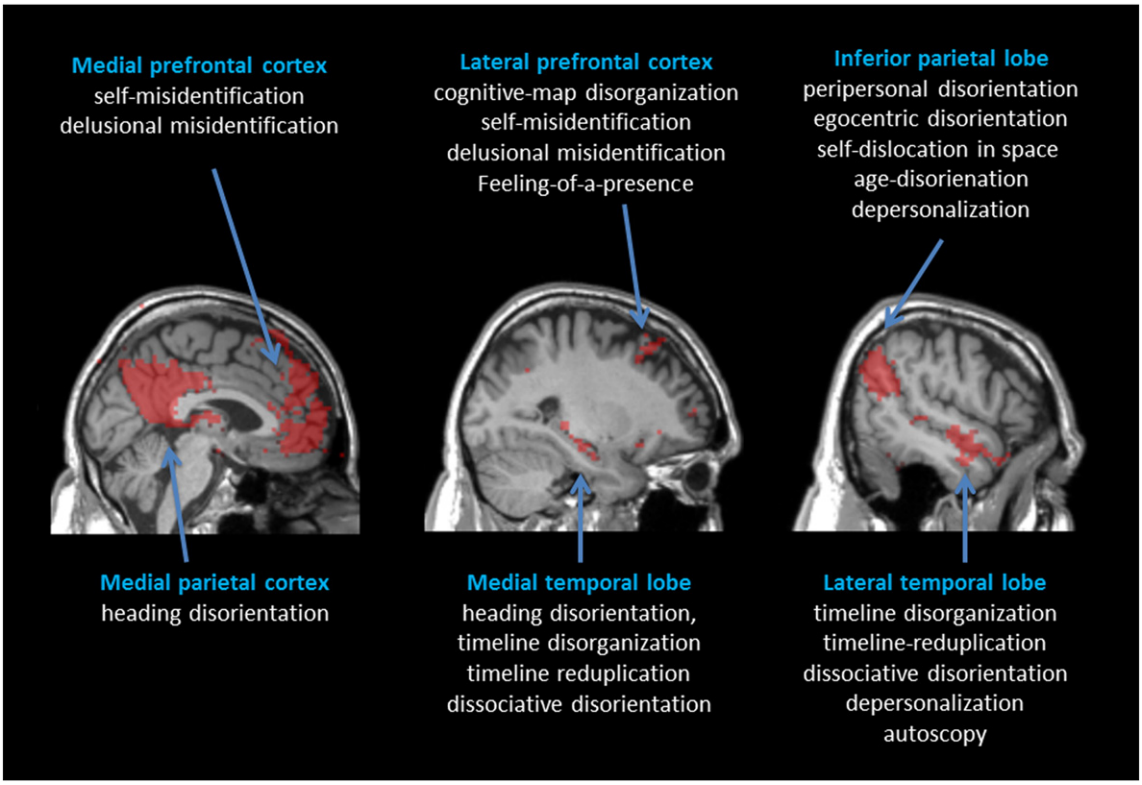

Fig. 3. The default mode network (DMN) and its relation to different disorientation disorders. The DMN was identified from resting-state functional MRI scans of ten healthy subjects using a seed in the posterior cingulate cortex. Preprocessing and analysis were performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK) (for details, see [80]).

epilepsy, in the postictal state, or following anesthesia, or could be manifested as chronic changes in orientation, as seen in patients with dementia or brain lesions or in the context of interictal personality changes in epilepsy [73,94,95]. As shown by the cases described here, disorientation may be confined to specific domains (e.g., in partial epilepsy) or may extend across several domains, depending on the underlying etiology and the disrupted brain regions.

As demonstrated above, in all domains, we may refer to self-referenced orientation, and nonself, environment-referenced orientation. Nonself-referenced orientation may require memorization of landmarks, events, or persons and may operate by a different mechanism. The similarity in the classification of disorientation in the different domains and the common phenomena observed in them (dislocations, disorganizations, and duplications) also support the existence of a common orientation mechanism. When the disorientation state is transient and reversible, orientation in person is mostly regained first, followed by orientation in space and finally in time; self-referenced orientation is mostly regained before the nonself-referenced one. Accordingly, temporal disorientation is lost earlier in patients with dementia, followed by spatial disorientation and finally by personal disorientation. These findings suggest a common orientation mechanism which may operate differently in the different domains.

The commonly used neuropsychological examinations of orientation in time, space, and person – such as the MMSE, MoCA, ADAS-Cog, ACE, or the Blessed Orientation–Memory–Concentration (BOMC) Test – measure mostly objective knowledge and facts. Therefore, these tests examine only *knowledge* regarding these domains and may miss self-referenced disorientation. Furthermore, in the more abstract domains such as morality and religiosity, landmarks are less well defined, and, therefore, disorientation is harder to detect without cautious observation and systematic neuropsychological testing. Therefore, a better design of orientation testing may better capture failures of orientation in the different domains.

Epilepsy is precious for the scientific research of orientation, as disorientation may be confined to specific domains, frequently in a transient manner, often due to a localized lesion/brain activity without accompanying wide-scale brain damage or atrophy. Therefore, epilepsy provides a unique opportunity for investigation of orientation and disorientation. Epilepsy may also benefit from a better evaluation of orientation, for instance, in the framework of presurgical evaluation. Behavioral and neuroimaging research in patients with epilepsy with disorientation may enable a better understanding of this fundamental faculty of human cognition which is largely neglected in current research.

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Disclosure

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