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Longitudinal Dynamics of 3-Dimensional Components of Selfhood After Severe Traumatic Brain Injury: A qEEG Case Study

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Abstract:

In this report, we describe the case of a patient who sustained extremely severe traumatic brain damage with diffuse axonal injury in a traffic accident and whose recovery was monitored during six years. Specifically, we were interested in the recovery dynamics of three-dimensional components of selfhood (a three-dimensional construct model for the complex experiential selfhood has been recently proposed based on the empirical findings on the functional-topographical specialization of three operational modules of brain functional network responsible for the self-consciousness processing) derived from the electroencephalographic (EEG) signal. The analysis revealed progressive (though not monotonous) restoration of EEG functional connectivity of three modules of brain functional network responsible for the self-consciousness processing which was also paralleled by the clinically significant functional recovery. We propose that restoration of normal integrity of the operational modules of the self-referential brain network may underlie the positive dynamics of three aspects of selfhood and provide a neuro-biological mechanism for their recovery. The results are discussed in the context of recent experimental studies that support this inference. Studies of ongoing recovery after severe brain injury utilizing knowledge about each separate aspect of complex selfhood will likely help to develop more efficient and targeted rehabilitation programs for patients with brain trauma.

Keywords:

Self-referential network, Default-mode network, DMN, subjective sense of self, first-person perspective, electroencephalogram, EEG, alpha rhythm, operational synchrony, functional connectivity, coma, vegetative state, unresponsive wakefulness syndrome, minimally conscious state.

Introduction

Recently, a three-dimensional construct model for the complex experiential selfhood has been proposed [1,2] based on the current advances in understanding the complex role of self-referential brain network, also referred to as default mode network [3-8] and empirical findings on the functional-topographical specialization of three subnets (or operational modules) of this network during normal states [7,9-13] and during pathological states when self-consciousness is minimal or lost [14,15]. Such operational modules (OMs) can be reliably estimated through operational analysis of the electroencephalogram (EEG) [16,17]. This model is in line with the multi-faceted nature of self-awareness [18-20] and offers a useful “tool” to study separate, though closely related qualities characterizing self-referential processing, which ultimately form a unified sense of self [7].

According to this “triad” model of selfhood [1,2], the *frontal module* of self-referential brain network (Fig. 1) is responsible for the first-person perspective and the sense of agency. We call it the “witnessing observer” or simply the “Self”. The brain structures comprising this module have been shown to be directly involved in the sense of being a self (i.e. being a subject/agent of self-conscious experience [20-22]), where one feels directly present as the centre of an externalized multimodal perceptual reality, thus having the first-person perspective [23-26]. Here the agency is understood as the “sense of ownership” of thoughts, perceptions, and actions relevant to selfhood [23,26-28]. Broadly speaking, agency means the sense that it is ‘I’ who is undergoing an experience in its implicit first-person mode of givenness [29,30]. In such conceptualization, the agent could be a passive observer, who just witnesses events, perceptions, or thoughts in its implicit first-person mode of givenness [1]. The sense of such agent or Self could be voluntary manipulated and could be even enhanced or get sharper as the result of meditation training for example [1,2,31,32]. It also could be lost such as in patients with disorders of consciousness [14,15,33].

The *right posterior module* of the self-referential brain network (Fig. 1) is responsible for the experience of self as a localized embodied entity (through interoceptive and exteroceptive bodily sensory processing), emotion-related thoughts, and autobiographical memories [1,2]. We call it “representational-emotional agency” or simply “Me”. The brain areas comprising this module have been shown to be consistently involved in the embodied aspects of self-related experiences and emotions [34-39]. Such sense of Me could be altered during pathology, as for example in vegetative or minimally conscious states [14], in patients with heautoscopy experiencing out-of-body phenomena [37,40], or in de-personalization syndrome when patients report a loss of body ownership [34]. It could be also modified by will through a long-term meditation training, where meditators achieve experiencing “self-boundarylessness,” or loss of bodily perceptions [2,41-42].

The *left posterior module* of the self-referential brain network (Fig. 1) is involved in experience of thinking about and reflecting upon oneself, including momentary narrative thoughts and inner speech, as well as reinterpretation of short-term memory events related to self [1,2]. We call it “reflective agency” or simply “I”. These described aspects of self-related experiences have been related to the activity of areas involved in the left posterior module [43-48]. The activity of this module and related experiences can also be altered in different pathologies [49] or voluntary modified through a specialized training such as for example meditation [2].

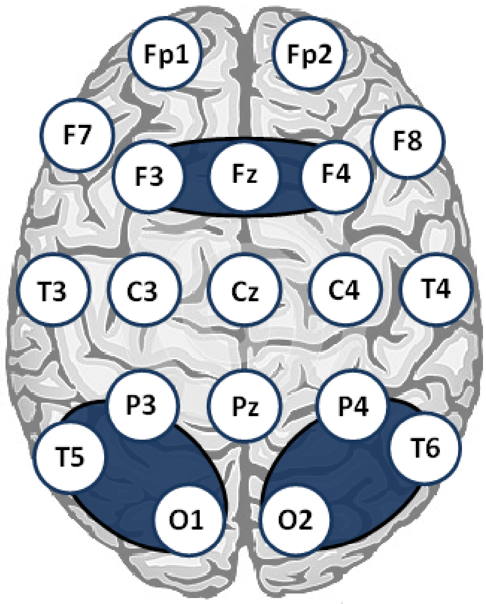

Figure 1. Operational modules (subnets) of the self-referential brain network. The statistically significant ($p < 0.05$) values of operational synchrony among EEG locations (marked by white circles with EEG electrode IDs) are mapped onto a schematic cortex map as the dark blue shapes that indicate OMs. Abbreviations: OM: operational module; EEG: electroencephalogram.

Together, such triad of the subnet modules provides a coherent representation of complex selfhood [1,2,7]. As clarified above, the proposed triad of aspects of Self (witnessing observer, representational-emotional agency and reflective agency) cannot be reduced into one another; however they are nonetheless intertwined and all three are intrinsic dimensions of unified Self.

Generally, self-consciousness has been defined as an implicit and explicit awareness of one's own mental and bodily states or actions [50]. Usually healthy individuals do not lose this kind of awareness during wakefulness and also in dreaming [51]. In its absence, when first-person mode of givenness is lost, our experience of ourselves and world around us becomes kaleidoscopic and fragmented [30,52]. We expect this to occur to a varying degree in patients with disorders of consciousness resulting from severe brain injury [53]. Indeed, severe damage to the brain has devastating effects on a person's life, often causing the dissolution of identity and self [54,55]. Capitalizing on the three-dimensional model of complex selfhood proposed above, it can be hypothesized that the recovery of different aspects of complex selfhood in the course of rehabilitation will be paralleled by the restoration of the normal functioning of three modules of brain network responsible for the self-referential processing. **The current case study was aimed to test these predictions**.

In order to do so we have studied a patient whom we followed during six years starting two years after the extremely severe brain injury. During this period, the patient progressed from a minimally conscious state plus (MCS+), which refers to intermittent high-level behavioural responses (i.e. command following and intelligible verbalizations or non-functional communication) [56], to nearly complete functional independence, recovered reliable motor functions, expressive fluent language, and a full self-awareness and consciousness.

Methods

Patient

A 21-year-old (at a time of first evaluation) male with no past history of mental or neurological disorders suffered a severe brain injury in a traffic accident at age 19 years. The patient received advanced life support and was subsequently admitted to the intensive care unit at the University Central Hospital in a comatose state, with a Glasgow Coma Scale (GCS) score of 3. Following a computer tomography (CT) brain scan, the patient underwent two surgical procedures: i) decompressive craniotomy and left subdural hematoma evacuation (day 1) and ii) craniotomy and evacuation of a large epidural haematoma in the occipital region (day 2). A brain magnetic resonance imaging (MRI) performed 8 days after the injury revealed evidence of diffuse axonal injury (DAI), damage to the brainstem/basal forebrain, right mesencephalon and brain peduncle. Damage was also found in bilateral internal capsule, left thalamus, as well as corpus callosum, splenium and left hemisphere frontal-temporal-parietal-occipital cortex. The right side of the frontal midline was also affected. Widespread vascular injury and other traumatic lesions caused cerebral edema, hemorrhages and hypoxic/anoxic injuries (more prevalent on the left side). It was estimated that the patient had a less than 1 percent chance of survival and, if he survived, he would most likely be in a persistent state of unconsciousness. The chances for a full recovery were held to be non-existent.

After 2.5 weeks of hospitalization, the patient recovered cycling of irregular eye opening/closing periods which signified a sleep-wakefulness cycle. Therefore the diagnosis (coma) of the patient was reclassified as a vegetative state (or unresponsive wakefulness syndrome [57]). During the following 5 months the patient stayed at the intensive care unit where he underwent routine neurological examinations and care. After that period he was transferred to the TBI neurorehabilitation centre where he was provided with neurorehabilitation consisting of physiotherapy, functional therapy and vocal therapy. The patient was discharged home having MCS+ [56] after total 11 months hospitalization. At the time of discharge, his GCS score was 14, indicating a good clinical outcome. At home, the patient continued on an intensive rehabilitation program: 1.5 h of orthopedic manual therapy, 3 h of physiotherapy, 3 h of functional therapy, 1.5 h of neuropsychology, 2 h of speech therapy, and 1 h of physiotherapist-assisted dance lessons a week, as well as music therapy, and individualized program of physiologically active substances (vitamins, nutrients, supplements and regulatory peptides). Additionally, the patients was prescribed to use two psychotropic medications – Nootropil (piracetam) and Ebixa (memantine) – that he had used constantly nearly for the whole observation period (six years).

Starting at two years after the injury, when the patient was 21-year-old, he underwent multiple (N = 9) EEG evaluations within six following years. During this period, the patient recovered cognitive, motor, speech, and consciousness functions, and is currently living independently with daily visits of trained assistant.

The study was approved by the organizational Review Board and complies with Good Medical Practice. Informed and overt consent of patient's legal representative (during the five years of observation) and the patient himself (in the last year of observation), in line with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and standards established by the BM-Science Review Board were acquired before each EEG test. Data use was authorized by means of written informed consent of the patient's caregiver/legal representative prior to each electroencephalogram (EEG) scan. The publication of the case report was authorized in writing by the patient himself as well as the patient's caregiver/legal representative. The EEG recordings used in this study were part of a screening procedure during the rehabilitation program and interfered neither with the usual medical practice nor with the everyday rehabilitation therapies received by the patient.

EEG registration and pre-processing

EEGs were recorded 9 times (during the period of six years) using a 21-channel EEG data acquisition system (Mitsar, St. Petersburg, Russian Federation) from 19 electrodes positioned according to the International 10–20 system (i.e. O1, O2, P3, P4, Pz, C3, C4, Cz, T3, T4, T5, T6, Fz, F3, F4, F7, F8, Fp1, Fp2) during waking resting state with closed eyes. Luckily none of these positions were affected by the previously performed craniotomy. The recording parameters were: linked earlobes as a reference electrode; 0.5–30 Hz bandpass; 50 Hz notch filter ON; 250 Hz sampling rate; 6-min closed eyes. The impedance was below 5–10 kΩ. Additionally, an electrooculogram (0.5–70 Hz bandpass) was collected. The following indicates the timeline of the 9 EEG recordings: 1 year and 11 months (1st assessment), 3 years (2nd assessment), 3 years and 6 months (3rd assessment), 4 years (4th assessment), 4 years and 7 months (5th assessment), 5 years and 2 months (6th assessment), 5 years and 7 months (7th assessment), 6 years and 3 months (8th assessment), and 7 years and 10 months (9th assessment) after the accident. Parameters and conditions across all EEG recordings were identical.

All 9 EEG recordings were done in late morning. The patient was asked to relax and engage in no specific mental activity. Immediately after the EEG recording was completed the patient was asked to verify if he followed instructions; only the sessions during which the patient thought he managed to follow instructions were included in this study. The presence of an adequate EEG-signal was determined by visual inspection of the raw signal. Artefacts due to eye movement, eyes opening, significant muscle activity, and movements on EEG channels, as well as drowsy episodes (indexed by slowing of background frequencies by ≥1 Hz, vertex sharp waves and slow eye movements) were corrected or eliminated by (a) using spatial filtration technique based on zeroing the activation curves of individual Independent Component Analysis

(ICA) components corresponding to these artefacts [58,59], as well as (b) excluding epochs with excessive amplitude of EEG (≥ 70 μV) and excessive faster (20-35 Hz, ≥ 35 μV) and slower (0-1 Hz, ≥ 50 μV) frequency activity.

A full artifact-free EEG stream was fragmented into consecutive 1-minute epochs for every registration (in total per EEG recording N = 5-6 min), which were bandpass-filtered (sixth order Butterworth filter) in the alpha (7–13 Hz) frequency band. Phase shifts were eliminated by forward and backward filtering. Even though different EEG frequency bands might have dynamics consistent with the analytical model of consciousness [60], the alpha frequency band was chosen in the current study because: (1) it has been repeatedly demonstrated that the brain network responsible for self-related processes has significant positive correlation with alpha rhythm [61-63] when compared to other EEG bands [64]; (2) alpha oscillations dominate EEG of humans in the absence of external stimuli when internal life (mind-wandering and spontaneous thoughts) is most pronounced [65-70]; (3) it has been shown that operational connectivity within three modules of self-referential network (in the EEG alpha band) is smallest or completely absent in vegetative state, intermediate in minimally conscious state and highest in healthy fully self-conscious state [14]; (4) the three modules of brain network responsible for three dimensions of subjective selfhood can be significantly modulated by systematic intervention technique such as meditation [1,2].

Estimation of self-referential network OMs and their strength

As shown in our previous EEG studies [1,2,7,14] a constellation of nine operationally synchronized cortical areas indexed by three distinct OMs (*frontal* OM: F3-Fz-F4; *left posterior* OM: T5-P3-O1; and *right posterior* OM: T6-P4-O2) could, in large, account for the self-referential brain network (Fig. 1). Similarly, in the current study the following EEG positions (and correspondent cortical areas [71]) were used to estimate the operational synchrony within three OMs: EEG positions F3 and F4 (left and right middle frontal gyri or Brodmann's area 8), EEG position Fz (bilateral medial areas or Brodmann's area 6), EEG positions T5 and T6 (left and right middle temporal gyri or Brodmann's area 21), EEG positions P3 and P4 (left and right precuneus or Brodmann's area 19), and EEG positions O1 and O2 (left and right middle occipital gyri or Brodmann's area 18). The anatomical correlations of EEG electrode positions used were taken from the reference study of Koessler et al. [71], where a clear match between the EEG electrode positions and anatomical areas of the cortex was established and confirmed using an EEG-MRI sensor system and an automated projection algorithm (see also [72] for the correlations between EEG activity in a given electrode position and its correspondent cortical area).

To estimate the operational synchrony and its strength within every OM, several stages of data processing were required. The details of these procedures can be found elsewhere [16,17]. Here we provide only a brief overview of the main steps. During the *first step* each local EEG signal was reduced to a temporally organized sequence of nearly stationary (quasi-stationary) segments of varying duration. To uncover these quasi-stationary segments from the complex nonstationary structure of local EEG signals, an adaptive segmentation procedure was used [16,17]. The aim of the segmentation is to divide each local EEG signal into naturally existing quasi-stationary segments by estimating the intrinsic points of 'gluing' – rapid transitional periods (RTPs). An RTP is defined as an abrupt change in the analytical amplitude of the signal above a particular threshold, derived experimentally (and verified in modeling studies) based on statistical procedures [16,17]. The RTP duration is very short compared to quasi-stationary segments, and therefore can be treated as a point or near-point [16,17]. It has been proposed that each stationary (homogeneous) segment in the local EEG signal corresponds to a temporary stable microstate – an operation executed by a neuronal assembly [73]. The temporal coupling (synchronization) of such segments among several local EEG recordings then, reflects the synchronization of operations (i.e. operational synchrony), produced by different neuronal assemblies (located in different cortex regions) into integrated and unified patterns responsible for complex mental operations [73].

Estimation of operational synchrony signifies the *second step* of the analysis. Measurement of operational synchrony estimates the statistical level of RTP temporal coupling between two or more local EEG recordings [16,17]. The measure tends toward zero if there is no synchronization between EEG segments derived from different EEG channels and has positive or negative values where such synchronization exists. Positive values (above upper stochastic threshold) indicate 'active' coupling of EEG segments (synchronization of EEG segments is observed significantly more often than expected by chance as a result of random shuffling during a computer simulation), whereas negative values (below lower stochastic threshold) mark 'active' decoupling of segments (synchronization of EEG segments is observed significantly less than expected by chance as a result of random shuffling during a computer simulation) [16,17]. The strength of EEG operational synchrony is proportional to the actual (absolute) value of the measure: the higher this value, the greater the strength of functional connection.

Using pair-wise analysis, operational synchrony was identified in several (more than two) channels – synchrocomplexes (SC); these define operational modules – OMs. The criterion for defining an OM is a sequence of the same synchrocomplexes (SC) during each 1-min epoch, whereas a SC is a set of EEG channels in which each channel forms a paired combination with valid values of synchrony with all other EEG channels in the same SC; meaning that all pairs of channels in an SC have to have statistically significant synchrony linking them together [16,17].

Clinical evaluations

The patient underwent multiple routine neurological and other clinical examinations during the observational period of six years. We used available medical reports, nurse reports and family notes that have been provided by the family of the patient to extract structured information about the patient's subjective, cognitive, communicative and body/motor functions. To quantify these functions 7 itemized scales (with 0 – absence of function; 10 – full mastery of function) were used by the family and nurses on the regular basis: Communication Ability, Motor Response, Motor Coordination, Language Production, Language Understanding, Long-term Memory, and Short-term Memory. For the purpose of this study, we used the values of these scales from the same months as the every EEG registration session. Those who filled the scales were blind to the fact that the scales will be latter correlated with the EEG parameters. Besides other relevant information we have gathered the values of Functional Independence Measure (FIM) that evaluates the independent performance in self-care, eating and grooming, transfers, locomotion, communication, and social cognition of a patient [74]. The possible total score ranges from 18 (lowest) to 126 (highest) level of independence [75]. The second measure that we have obtained was the Level of Cognitive Functioning (LCF) scale [76]. This measure used to assess cognitive functioning and the expression of clinical consciousness in post-coma patients [77,78]. The LCF has a linearly graded scale ranging from 1 to 8 (1 – patient is unconscious; 8 – patient is self-oriented and conscious of the environment) and is well correlated with resting-state EEG abnormalities in patients with brain damage [77,78]. Clinical EEG classification developed and validated on a large number of neurological and psychiatric patients that estimates the deviation of resting EEG form the norm [79] was also performed by a researcher with extensive clinical EEG experience (~ 26 years). The result of this classification is subsumed in Table 1 and 2.

Table1. General EEG description and its deviation from the standard norm.

Date of EEG test	General EEG description	Deviation from the Standard Norm	
		Degree	%
1y & 11m	Left hemisphere: Disorganized with alpha-theta domination + beta	Considerable	30
	Right hemisphere: Disorganized with alpha-theta domination + beta	Considerable	30
3y	Left hemisphere: Disorganized with alpha-theta domination + beta	Considerable	28
	Right hemisphere: Organized alpha-theta type + beta	Low	12
3y & 6m	Left hemisphere: Relatively organized with alpha-theta domination	Moderate	24.5
	Right hemisphere: Organized alpha-theta type	Low	9
4y	Left hemisphere: Relatively organized with alpha-theta domination	Moderate	15.5
	Right hemisphere: Organized alpha-theta type	Low	9
4y & 7m	Left hemisphere: Relatively organized with alpha-theta domination	Moderate	14.8
	Right hemisphere: Organized alpha-theta type	Low	8.8
5y & 2m	Left hemisphere: Relatively disorganized with alpha-theta domination	Moderate	20.8
	Right hemisphere: Organized alpha-theta type	Low	9
5y & 7m	Left hemisphere: Relatively disorganized with alpha-theta domination	Moderate	15.5
	Right hemisphere: Organized alpha-theta type	Low	6.3
6y & 3m	Left hemisphere: Relatively disorganized with alpha-theta domination	Moderate	11.8
	Right hemisphere: Organized alpha-theta type	Low	6.3
7y & 10m	Left hemisphere: Relatively disorganized with alpha-theta domination	Moderate	21.8
	Right hemisphere: Organized alpha-theta type	Low	5.5

Spearman Rank Order Correlations

Left hemisphere and "Self" OM: $R = 0.1$, $p = 0.71$; Left hemisphere and "Me" OM: $R = 0.2$, $p = 0.68$;
Left hemisphere and "I" OM: $R = 0.05$, $p = 0.88$.

Right hemisphere and "Self" OM: $R = 0.5$, $p = 0.17$; Right hemisphere and "Me" OM: $R = 0.3$, $p = 0.42$;
Right hemisphere and "I" OM: $R = 0.2$, $p = 0.59$.

Table 2. Percent of EEG signal characterised by paroxysmal activity.

Date of EEG test	General EEG description	%
1y & 11m	Sharp waves and groups of sharp waves, Paroxysmal theta, Paroxysmal beta	42.4
3y	Sharp waves and groups of sharp waves, Paroxysmal theta, Paroxysmal beta	29.4
3y & 6m	Paroxysmal theta, Paroxysmal beta	38.4
4y	Paroxysmal theta, Paroxysmal beta	22.8
4y & 7m	Paroxysmal theta, Paroxysmal beta	13.7
5y & 2m	Paroxysmal theta	10.3
5y & 7m	Paroxysmal theta	10.9
6y & 3m	Paroxysmal theta, Paroxysmal alpha	10.8
7y & 10m	Paroxysmal theta	4.7

All paroxysmal activities were present in the left hemisphere.

Spearman Rank Order Correlations

Paroxysmal activity and "Self" OM: $R = 0.6$, $p = 0.11$; Paroxysmal activity and "Me" OM: $R = 0.5$, $p = 0.12$; Paroxysmal activity and "I" OM: $R = 0.6$, $p = 0.11$.

Analysis

For every analysed session ($N = 9$), an average value was calculated for the strength of EEG operational synchrony within each OM for all corresponding 1-minute EEGs. These values of each OM were compared to population normative reference (based on previous study [80]), age normalized and presented as *z*-scores. While this normative reference was not gender matched, we do not think that it could influence the obtained dynamic of results in any meaningful way since this was a common factor across all EEG-sessions. This normative reference included only healthy persons ($N = 87$, – the sample size comparable with the required for the normative database comparisons [81]) without current or past neurologic or mental complains. A *z*-score is the difference between the mean score of a healthy population (normative reference) and the patient's score divided by the standard deviation of the population [82]. Statistically, *z*-scores quantify deviation of an observed value from normative data. It expresses how much higher ($z > 0$: "positive deviation") or lower ($z < 0$: "negative deviation") the OM values of the patient are in comparison with the mean value of the matched normative/healthy data reference, in terms of standard deviation. Deviation from the normative/healthy level was ranged from slight (2 standard deviations; $p < 0.05$), moderate (2.5 standard deviations; $p < 0.01$), high (3 standard deviations; $p < 0.003$) to very high (4 standard deviations; $p < 0.0001$). The normative/healthy range of EEG characteristics (-1 < z < 1) represents certain "ideal" characteristics displayed by a majority of subjects in the group, without current or past neurologic or mental complains, without family history of neurologic and psychiatric diseases, or other illnesses that might be associated with brain dysfunction [79].

To correlate the FIM, LCF, and other itemized scales with EEG OM values, they were also transformed into z-scores. For correlation analysis the Spearman Rank Order Correlation test was used.

Results and Discussion

As a most general outcome of this case study (Fig. 2), one can see a clear recovery in the integrity of all three OMs of the self-referential brain network from the first assessment (1 year and 11 months after the accident) to the ninth assessment (7 years and 10 months after the accident). This was confirmed by the linear regression analysis ($R = 0.67$, $p < 0.05$) that used 3 factors as input ("Self" OM z-score, "Me" OM z-score and "I" OM z-score). More detailed analysis revealed interesting parallels between neurophysiological and clinical/behavioural observations.

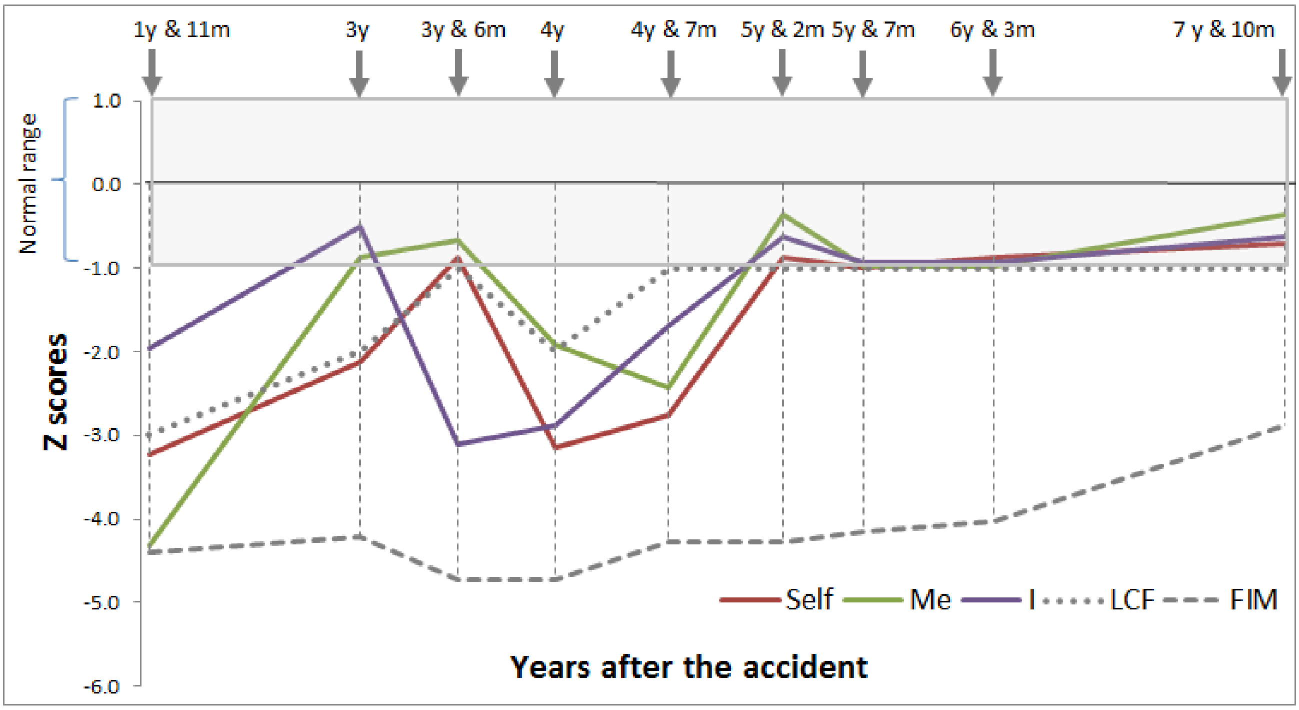

Figure 2. Dynamics of operational synchrony strength within three OMs of the brain self-referential network in the patient during six years of observation. The Y-axis presents z-values of strength of operational synchrony for each OM separately, as well as z-scores for LCF and FIM scales. The X-axis represents years after the accident. Arrows and vertical dotted lines represent the time of assessments. Abbreviations: OM: operational module; LCF: Level of Cognitive Functioning scale; FIM: Functional Independence Measure; y: year; m: month.

At the time of the first evaluation (1 year and 11 months after the accident) EEG analysis revealed (Fig. 2) significant reduction from normal values for the integrity of the self-referential brain network OMs related for “Me” ($z = -4.3$; $p < 0.0001$), “Self” ($z = -3.2$; $p < 0.001$) and “I” ($z = -2.0$; $p < 0.05$). This was paralleled by the findings from the clinical examinations. The “Me” functions that correspond to experience of self as a localized embodied entity (through the interoceptive and exteroceptive bodily sensory processing), emotion-related thoughts, and autobiographical memories [1,2] were significantly diminished or absent at that time. The patient reported that he did not have feeling of ownership of his motor actions as well as his body. His endurance was about 10 minutes and he got behaviourally inhibited very easily. He did not remember autobiographical events and had difficulties to recognise his relatives and friends. The “Self” functions that relate to the first-person perspective and the sense of agency [1,2] was also significantly impaired. The patient exhibited depersonalisation and disorientation together with lack of feeling of being an active agent. He had gross attention to the environment, but was highly distractible and lacked ability to focus attention on a specific task without frequent re-direction back to it. The patient lacked initiation of functional tasks and often showed inappropriate use of objects without external direction. The “I” functions that relate to reflecting upon oneself, including momentary narrative thoughts, inner speech, and short-term memory [1,2] were diminished as well. The patient showed no insight into his condition and did not recognise it as a medical problem. The patient’s short-term memory was significantly impaired (it was ~1 min) and he did not remember the names of most objects and things. His phonemic and semantic fluency were severely impaired, though the patient was able to converse on a social, automatic level for short periods of time.

Taken together, these findings indicate that at that stage the dramatically diminished integrity within three OMs of the self-referential brain network was paralleled by the impairment in the patient’s sense of “Self”, “Me” and “I” resulting in the feeling of lacking the core identity, diminished sense of existing as a self-present, embodied subject of experience who has the first-person perspective and agency. These basic aspects of selfhood are crucially important to guarantee the presence of a primary structure of subjectivity and self-consciousness [23,28,83,84].

Thirteen months later, at the time of the second EEG test, the integrity of two out of three self-referential brain network OMs reached normative values (“Me” OM $z = -0.9$ and “I” OM $z = 0.5$); the third one – “Self” OM – improved ($z = -2.1$, $p < 0.05$) while still exhibiting statistically significant deviation from the normative range (Fig. 2). The clinical and functional reassessment of the patient paralleled these findings. Most notably, the patient regained the sense of ownership of his motor actions and the body as well as to initiate volitional movements. The autobiographical memories before the accident started to pop-up in his mind. All these are the “Me” functions [1,2]. As to the “I” functions, the patient exhibited improved short-term memory, speech intelligibility and conversational speech. He also regained insight of the accident and his own condition. While neurophysiologically these two OMs showed normalisation in their integrity, clinically the related functions, despite been improved, were still far from normal range. This discrepancy could be explained by the gap between neurophysiological recovery that provides the minimal neuronal mechanism that is needed for the consequent functional recovery and the re-learning of correspondent functions during rehabilitation program that involves the multisensory stimulation and environmental enrichment (for a review see [85]). The “Self” functions [1,2] were improved in comparison with the first evaluation: the patient regained the first-person perspective and orientation in person. He also demonstrated an overall increase in baseline arousal accompanied by generalized improvement in attentional focus and response persistence.

At the third EEG test (3 years and 6 months after the accident), there was a change in the dynamics of three OMs: while the “Me” OM continued to “stay” within the normal range ($z = -0.7$) and the “Self” OM also reached the normative range ($z = -0.9$), the “I” OM on the contrary significantly lost ($z = -3.1$, $p < 0.002$) its functional integrity (Fig. 2). At that period, clinically, the patient demonstrated a good level of self-monitoring, self-orientation and intentional behaviour (“Self” functions) and a proper level of motor actions ownership accompanied by improved autobiographical memory (“Me” functions). At the same time the patient’s short-term memory deteriorated (<1 min) and in self-reflection he again started to mix short-term events and belongingness of objects as well as the verbal fluency was lost again (“I” functions). For example, in Boston Naming test, he could name 17 pictures out of 60 (in 28 min) and in Verbal Semantic Presentation – 26 out of 60 (in 45 min).

The next EEG test (4 years after the accident) revealed an abrupt decrease in the integrity of all three OMs of the self-referential brain network despite ongoing intensive rehabilitation (Fig. 2). This was characterised by a marked decrease in volitional control of motor functions (“Me” function), deterioration of short-term memory and orientation in person and in time (“I” functions) as well as the loss of consistent first-person perspective (“Self” function). This unexpected decrease in all three functions and integrity of the self-referential brain network OMs could be explained by the fact that during that period the patient experienced degranulation (sinking skin flap syndrome) of the left-side skull (~10 cm x ~15 cm) and underwent reconstructive surgery to replace it. The degranulation itself [86] and the long surgical operation (~7 h) could be responsible for the observed deterioration [87]. In accordance with these findings, recent studies have reported impairments in the multiple functions during so-called “syndrome of the trephined”/“sinking skin flap syndrome” [88,89] and after the prolonged surgery [90,91].

The following 5 EEG tests revealed progressive improvement in the integrity of all three self-referential brain network OMs (Fig. 2). This was paralleled by marked improvement in the main three aspects of selfhood. A clear improvement was observed at the sixth assessment (5 years and 2 months after the accident) when doctors had reported that, for the first time, many functions showed a clinically significant improvement in comparison to all previous observations. The patient began to exhibit consistent intentional behaviour, his concentration reached normative levels, he felt in control over his body and motor actions, his autobiographic as well as short-term memories nearly normalised and he was able to reflect upon himself and his own condition and integrate past and recent events. It was the first time, when the integrity in all three self-referential brain network OMs reached normative vales (Fig. 2). These changes in the three OMs may explain the dramatic qualitative alteration of the very structure of the patient’s self-awareness at that time. While at the seventh (5 years and 7 months after the accident) and eighth (6 years and 3 months after the accident) assessments the values of integrity of studied self-referential brain network OMs slightly decreased, they did not, however, fall outside the normative range (Fig. 2).

The last EEG observation (7 years and 10 months after the accident) showed continued improvement of all three OMs of the self-referential brain network (Fig. 2). This neurophysiological recovery was accompanied by clinical and behavioural improvement. At that time the patient has had a clear improvement in executive functions, self-monitoring and self-control ("Self" functions). The patient was able to recognize his level of alertness and plan the workload accordingly, his short-term memory as well as speech and language improved significantly ("I" functions). For example in Boston Naming test he could name 40 pictures out of 60 (in 11 min) and in Verbal Semantic Presentation – 43 out of 60 (in 15 min). The patient's intentional control of body and motor actions, as well as recall and integration of past and recent events notably improved ("Me" functions).

Correlation analyses revealed that the averaged value of all three OMs integrity of the self-referential brain network was positively correlated with the FIM measure ($R = 0.57$; $p < 0.05$) and LCF measure ($R = 0.73$; $p < 0.05$) (see also Fig. 2). Furthermore, the OM responsible for "Self" correlated significantly with items "Communication Ability" ($R = 0.7$; $p < 0.05$), "Motor Response" ($R = 0.84$; $p < 0.01$), "Motor Coordination" ($R = 0.85$; $p < 0.05$), and "Long-Term Memory" ($R = 0.89$; $p < 0.001$). The OM responsible for "Me" correlated significantly with items "Communication Ability" ($R = 0.69$; $p < 0.05$), "Motor Response" ($R = 0.85$; $p < 0.001$), "Motor Coordination" ($R = 0.95$; $p < 0.0001$), and "Long-Term Memory" ($R = 0.96$; $p < 0.0001$). The OM responsible for the "I" functions correlated significantly with items "Communication Ability" ($R = 0.80$; $p < 0.01$), "Language Production" ($R = 0.76$; $p < 0.05$), "Language Understanding" ($R = 0.78$; $p < 0.05$), and "Short-Term Memory" ($R = 0.76$; $p < 0.05$). While the strongest correlations of different OMs were in relation to their primary functions (as described in the introduction section), the "Self" OM showed more global correlations. This is in line with our previous studies where the chief role for the "Self" OM among all three OMs has been documented [2,7,14,15]. It has been proposed that this "Self" OM (which is the frontal module of the self-referential brain network) provides a critical quality for the sense of self and agency for the whole spectrum of human behaviours and activities, thus laying the foundation upon which persons "autobiographical", "narrative" and "social" selves (represented by both posterior OMs) are built [15].

It is important to mention that standard clinical EEG assessment also revealed progression toward normalization of EEG during six years of observation (see Table 1 and 2), though this dynamic did not correlate with the dynamics of operational synchrony in any of the studied OMs (Table 1 and 2). Therefore, a general normalisation of EEG could not explain the observed normalising dynamics in the integrity of OMs.

Conclusions

The currently accumulated empirical evidence suggests that the core or a neural signature of the experiential selfhood is constituted by self-referential processes [5], that are neurophysiologically represented through a specially dedicated and operationally integrated brain network [4,6,8,92]. It organises overall human behaviour from a first-person perspective [7]. This self-referential brain network is heterogeneous – it consists of at least three distant subnets or modules that serve separate but interacting functions or qualities characterizing complex selfhood [1,2]. Previous studies have shown that after severe brain injury the functional integrity of each of these modules is significantly damaged [14,15]. In the present case report, we have studied how the recovery of each of the three OMs within the self-referential brain network was paralleled by the recovery of the appropriate functions in a patient whom we followed during six years starting two years after the extremely severe brain injury when the patient was in the minimally conscious state plus [56] till nearly complete functional independence.

The present case study indicated that the dynamics of functional integrity of the self-referential brain network's OMs related to "Self", "Me" and "I" was tightly paralleled by the findings from the clinical examinations and observations. The theoretical implication of these findings is that functionally differentiable but interacting subnets or modules of the self-referential brain network may indeed relate to different aspects of complex selfhood [1,2], such as first-person agency (or "Self"), representational-emotional agency (or "Me") and reflective agency (or "I"). In the clinical domain, this case study shows that recovery of self-consciousness could happen and may continue to improve over many years after the accident even in patients with devastating brain damage. Among clinicians it is usually assumed that the brain can only recover during the first few days or months after the injury, leading doctors to have rather pragmatic expectations when it comes to managing long-term patients. Although this patient's outcome is clearly an exception to most, the current case report establishes a framework for further efforts to prospectively and longitudinally characterize dynamics in both brain functional integrity of modules of the self-referential brain network and their corresponding functions following severe brain injuries. Studies of ongoing recovery after brain injury utilizing knowledge about each separate aspect of complex selfhood will also likely help to develop more efficient and targeted rehabilitation programs for such patients.

The remarkable recovery of this patient despite initial negative prognosis and intensive rehabilitation asks for the explanation. At the level of speculation, we assume that brain/cognitive reserve might play a role. This patient was extremely talented person before the accident and have had many diverse skills and talents. He had had an extensive dance, music and singing education in a wide variety of styles and achieved recognizable skills in every domain what was reflected in his winning several national-, continental-, and world-level competitions. He also had played several instruments as well composed music and produced his own shows. Furthermore, he was highly skilled in mathematics, languages (Finnish and English as native; French, Swedish, and Italian fluently), and knowledge-based disciplines. The combination of these diverse skills and activities might have contributed to so-called extreme case of brain/cognitive reserve (the brain's capacity for functional resilience against damage, pathology or age; see [93]) that helped this patient to recover.

Caution is warranted in interpreting this case report, as there are several sources of bias. All information related to the functions of the patient was derived from routine "real-life" clinical and rehabilitation assessments, and neither experimental protocols nor standardized scales specifically targeting the studied aspects of selfhood were used. Therefore, future studies should adopt a design that along with neurophysiological assessment will utilize both standardized scales and the first-person reports of patients, as well as being sufficiently powered to detect clinically significant differences in primary outcomes. Another potential source of bias was proposed by an anonymous reviewer: The psychotropic medications (Nootropil and Ebixa) that were used to address some symptoms of the patient could have influenced the findings. According to the published research the main effects of both of these medications are outside of the alpha rhythm, which was a target of the present study [94,95]. Additionally, correlation analysis did not reveal significant correlation between the courses of these medications and the dynamics of operational synchrony in any of the studied OMs (Nootropil and "Self" OM: $R = 0.4$, $p = 0.22$; Nootropil and "Me" OM: $R = 0.2$, $p = 0.71$; Nootropil and "I" OM: $R = 0.5$, $p = 0.18$; Ebixa and "Self" OM: $R = 0.4$, $p = 0.26$; Ebixa and "Me" OM: $R = 0.2$, $p = 0.56$; Ebixa and "I" OM: $R = 0.4$, $p = 0.26$.). Therefore, the regime of psychotropic medications could not explain the obtained results.

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Author Contributions

Both co-authors equally contributed to conception and design of this study. FAnA contributed to acquisition, analysis, and interpretation data/results, while FAlA contributed to acquisition and interpretation. FAnA drafted manuscript and FAlA critically revised manuscript. Both co-authors gave final approval of the manuscript.

Declaration of Conflicting Interests

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