

# 1 Novel Information on Unresponsive Wakefulness Syndrome, Diagnostic Procedures, and Systematic Review

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## ABSTRACT

**Objectives:** This comprehended literature study aimed to search for studies related with the diagnostic procedures of unresponsive wakefulness (UWS), vegetative state (VS), persistent vegetative state (PVS)

**Methods:**

A wide searching of the medical literature of the following database PubMed/MEDLINE, Scopus, and Embase databases was performed to find articles related to the role of [18F]FDG PET imaging in the evaluation of UWS/VSPVS.

From 01st, January 1987 to 30th, October 2025, we searched the medical literature, following the PRISMA guidelines. The authors searched the scientific databases, Scopus, Embassy, Medline, and PubMed Central using the following searches: "Apallic syndrome" OR "severe brain damage" OR "unresponsive wakefulness syndrome" OR "neurobehavioral disturbances" OR "vegetative state", OR "Assessment of consciousness" OR "persistent vegetative state" OR "PET, PET/CT" OR "assessment of consciousness" OR "disorder of consciousness" OR "18F-fluorodeoxyglucose, positron emission tomography" OR "Drug therapy".

**Results:**

Searching literature retrieved 501 articles. 117 duplicated studies and after reviewing the titles and abstracts were removed, 384 publications were selected. After applying the inclusion/exclusion criteria 345 articles were excluded. Six no related publications were separated from the total selection therefore, 33 studies addressing the role of [18F]FDG PET imaging in the evaluation of VS/UWS were selected and retrieved in the full-text version

**Conclusions:**

Our final remarks highly the role of [18F] FDG PET imaging in the assessment of UWS in new efforts, larger prospective studies, variable clinical settings, and multicentre collaborations which needs to clearly evaluate, confirm, or challenge its value, thereby strengthening the reliability of the review.

**Keywords:** *Apallic syndrome, unresponsive wakefulness syndrome, severe brain damage, neurobehavioral disturbances, persistent vegetative state, PET, PET/CT, 18F-fluorodeoxyglucose, positron emission tomography, vegetative state, disorder of consciousness, DOC*

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## INTRODUCTION

**Objectives:** This comprehended literature study aimed to search for studies related with the diagnostic procedures of unresponsive wakefulness (UWS), vegetative state (VS), persistent vegetative state (PVS)

The syndrome of VS is coined in patients who awaken (that is, eye opening) from coma, remaining unresponsive (that is, without response to commands), which is also named as unresponsive wakefulness syndrome (UWS) as had been proposed by Laureys and colleagues [1]. This terminology will be present in the review.

The author Bryan Jennett wrote his book in 2002, entitled

"The vegetative state - medical facts, ethical and legal dilemmas", and chose for the first chapter of his book the caption "A syndrome in search of a name." Almost immediately, the medical terminology of "Vegetative State" (VS) became the most common accepted name for the state of wakefulness without awareness in the English medical literature while the term of Apallic Syndrome (AS) is still in use in Europe which prevalence is around 0.5–2/100.000 population year and the most typical causes are intracranial haemorrhage, cerebral hypoxemia after cardiac arrest, tumours, and end stage of certain progressive neurological diseases which are clinically

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characterized by fully consciousness, normal behaviour and complete unresponsive. The term "vegetative" (meant to refer to the preserved vegetative (autonomous nervous system). Therefore, replacing the names "Apallic Syndrome" (AS) or "Persistent Vegetative State" (PVS) with "UWS" seems more appropriate, based on recent functional fMRI and PET studies that have shed more light on the state of awareness/consciousness [2]. However, for more than three decades, the former terms of AS and VS have been the subject of sustained scientific and moral-legal debates [3-6]. The clinical diagnosis, outcome and drug management of patients with UWS is still a significant challenge. In 2014, Kang et al. reported an innovative, simple score to predict better the prognosis of patients presenting with UWS [7]. An estimated 1,500–5,000 patients with UWS/VS are living in Germany at present [8].

The inability to record neurophysiological information from cortical neurons and thalamic nuclei hampers our understanding of the pathophysiology of UWS/VS and the minimally conscious state (MCS). However, Magrassi and collaborators were able to bilaterally implant electrodes in the thalamus and administer chronic deep-brain stimulation in both pathological conditions. They found that thalamic-cortical network expression was completely different between the two disorders, with neuronal activity approximately half as much in UWS/VS as in MCS, and bursting expression was mildly present in both conditions [9].

On the other hand, it has been reported that in human beings the blocking electrical activity from the medial thalamus (MT) appears before cortical deactivation into non-rapid eye movement sleep (NREMS) [10], despite of intracellular recording investigations (in vivo) in animals suggest that wakeful synaptic dynamics in the cortical neurons happens separately from afferents thalamic fibres

[11] most probable due to an excessive inhibitory input arriving from the globus pallidus internus (GPi) to the MT reducing its excitatory output to the brain cortex neurons [12].

In 2017, Lehnerer and colleagues reported a 36-year-old lady presenting with a subarachnoid haemorrhage (SAH) due to a rupture of a right-sided middle cerebral artery saccular aneurysm, followed by a large ischemic infarct on the middle cerebral artery territory in the right cerebral hemisphere, leading to UWS with remarkable recurrent myoclonia and spastic tetraparesis. The authors performed several investigations, including positron emission tomography with <sup>18</sup>F- fluorodeoxyglucose, and found that brain glucose metabolism was normal. They reported that the patient recovered, making this the first case of recovery from UWS/VS under that therapeutic drug [13].

Recently, Brezic et al. reported a 35-year-old lady presenting a cardiac arrest after an elective caesarean delivery, followed by UWS/VS/PVS, but preceded by posterior reversible encephalopathy syndrome, which suggested a potential link between these conditions [14].

The main aim of this study is to respond the next research question: What are the most accurate and common investigations able to confirm a confidential diagnosis and establish the prognosis in patients presenting UWS/VS/PVS?

## 2. MATERIALS AND METHODS

A wide searching of the medical literature of the following database PubMed/MEDLINE, Scopus, and Embase databases was performed to find articles related to the role of [<sup>18</sup>F]FDG PET imaging in the evaluation of UWS/VS/PVS.

From 01<sup>st</sup>, January 1987 to 30<sup>th</sup>, October 2025, we searched the medical literature, following the PRISMA guidelines. The authors searched the scientific databases, Scopus, Embassy, Medline, and PubMed Central using the following searches: "Apallic syndrome" OR "severe brain damage" OR "unresponsive wakefulness syndrome" OR "neurobehavioral disturbances" OR "vegetative state", OR "Assessment of consciousness" OR "persistent vegetative state" OR "PET, PET/CT" OR "assessment of consciousness" OR "disorder of consciousness" OR "<sup>18</sup>F-fluorodeoxyglucose, positron emission tomography" OR "Drug therapy".

The systematic review performed in this study followed the guidelines recommended by "Preferred Reporting Items for a Systematic Review and Meta-Analysis" (PRISMA 2020 statement), which was used as a guide in this research. The complete PRISMA checklist is available in the [Supplementary Materials](#).

### 2.1. Search strategy

A comprehensive search was conducted across three databases (PubMedCentral/MEDLINE, Scopus, and Embase) to identify published articles addressing the role of [<sup>18</sup>F]FDG PET imaging in the assessment of VS or UWS. The algorithm used for the research was: "(("PET" OR "PET/CT" OR "PET/MRI" OR "positron emission tomography") AND ("vegetative state" OR "unresponsive wakefulness syndrome").

The search had no beginning date limit and was updated until 31 October 2025. Only articles published in English, Spanish and Portuguese were selected. Preclinical studies, conference proceedings, reviews, editorials, and case reports were excluded. If two papers focused on the same cohort to perform research with the same aim, the more updated article was included in the review, while the other was excluded. The references of the retrieved articles were also screened for additional papers to expand the final database.

### 2.2. Study Selection

Two investigators (LdeFIV. and HFS) separately screened the abstracts and titles of the retrieved publications and independently reviewed the full-text versions of the identified articles to determine their eligibility for inclusion. The selection criteria were chosen based on the introductory research question. Medical investigations delivering information on diagnostic procedure to assess UWS/VS/PVS were deemed eligible for inclusion in this

systematic review. Furthermore, publications without a clear protocol of using of PET/MRI/CT/Emerging procedures in UWS/VS/PVS cases, papers with lack of analysis, publications with incomplete data or without mention exact number of patients were not considered for inclusion.

### 2.3. Selection criteria

The following criteria were included:

Articles with detailed pathogenesis and/or drug management. Clinical features of LIS, and demographic information.

### Exclusion criteria were applied:

(1) inaccessibility to full text; (2) articles with unclear pathogenesis; (3) lack of relevant clinicopathological data; (4) non-original studies (i.e., editorials, letters, conference proceedings, book chapters); (5) animal model studies; and (6) non-/Spanish/Portuguese/English studies. The papers that were not thoroughly assessed were removed.

### 2.4. Data extraction and quality assessment

The studies' quality assessment including applicability concerns and risk of bias was categorized as good, poor, fair, or reasonable, in agreement with the National Institutes of Health criteria and the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) evaluation [Whiting P.F., Rutjes A.W., Westwood M.E., Mallett S., Deeks J.J., Reitsma J.B., Leeflang M.M., Sterne J.A.,

Bossuyt P.M. QUADAS-2 Group. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Ann. Intern. Med.* 2011; 155:529–536. doi: 10.7326/0003-4819-155-8-201110180-00009.] Quality assessment was made separately by the two authors, and discrepancies were resolved by scientific discussion and final agreement.

### 2.5. Data Collection, Extraction, and Bias Assessment.

All abstracts and titles with the inclusion criteria were revised by two investigators to collect relevant information

for the review. For each publication selected in the review, data concerning to author's name, age, year of publication, country of information' source, type of the study, radiopharmaceutical employed, total of cases included and most probable aetiology of the UWS/VS/PVS, were collected. The selected data from eligible publications were introduced into an updated Excel software program.

### 2.5. Outcome Measures

Our plan aimed to select the most relevant publications relating to the clinical benefit and real-world effectiveness of different diagnostic procedures for UWS/VS/PVS. This investigation also identified safety outcomes data, including adverse and serious adverse events across the clinical investigations.

### 2.6. Statistical analysis

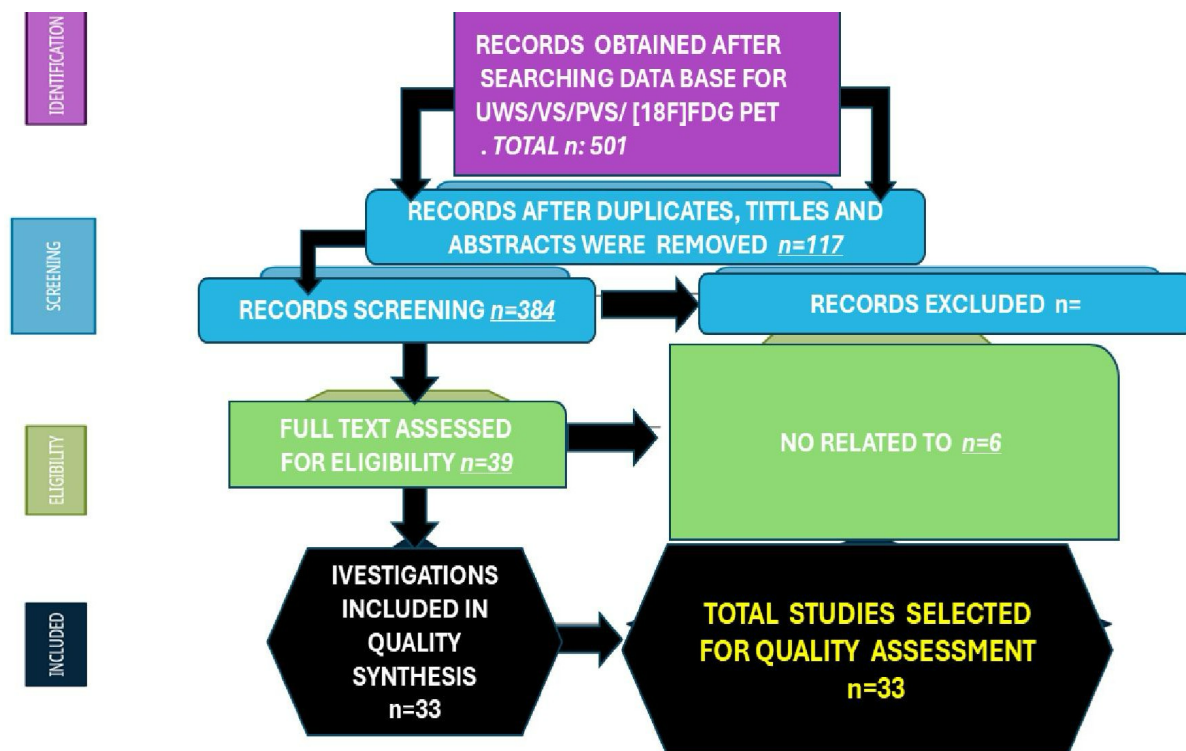
Statistical analyses were performed using XLSTAT (addon for Microsoft Excel, version 2021.4.1, Addinsoft SARL) and RStudio (version 4.3.1, <https://www.rstudio.com/>). Variations in continuous variables were assessed using the Mann–Whitney U-test. We presented descriptive statistics for continuous variables as median (95% confidence interval [95% CI]).

## 3. RESULTS

### 3.1. Literature Search

Searching literature retrieved 501 articles. 117 duplicated studies and after reviewing the titles and abstracts were removed, 384 publications were selected. After applying the inclusion/exclusion criteria 345 articles were excluded. Six no related publications were separated from the total selection as a consequence, 33 studies addressing the role of [<sup>18</sup>F]FDG PET imaging in the evaluation of VS/UWS were selected and retrieved in the full-text version which were cited as follow: [17,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41, 42,43,44,45,46,47,48,49,50,51,52,53,54,

55]. Therefore, 33 studies were included in the review. See **FIGURE 1.**



**FIGURE 1: PRISMA. Flow diagram with included publications.**

To provide an accurate management of this searching, the authors used a QUADAS-2 evaluation to determine low/moderate risk of bias in most domains for all article selected in this review. The diagnosis of UWS/VSPVS was made in overall patients according to current proposed criteria.

Authors considered the elevated technical differences obtained from quite different PET protocols performed in several investigations; Unfortunately, in some articles the proposed protocol were not reported.

Noticeably, in some publications, small and mixed cohorts were processed including different types of DOCs leading to in fewer UWS/VSPVS cases examined with PET.

**COMMENTS AND FINAL REMARKS**

Pupillary light reflex using retinal illumination serves to determine pupillary contraction and the standard size of the pupil within the range between 2 and 5 mm. This year, Sangare et al. adapted this procedure to evaluate alertness through pupillary response in non-communicative patients admitted to the ICU. They found that UWS/VSPVS patients showed a poor brightness effect on pupillary size [15].

Extensive structural brain damage is remarkably different in cases presenting with disorders of consciousness (DOC).

However, injured thalamic nuclei and/or their connections are always present, which is more pronounced in traumatic brain injury patients.

The involvement of the thalamus and its reciprocal connections with the parietal, frontal lobes and the basal

ganglia in keeping the alertness plays a crucial role which has been documented by the increased neural connectivity between the anterior frontal cortex and intralaminar nucleus of the thalamus during recovery of normal level of consciousness confirmed by functional magnetic resonance, EEG and extracellular single unit recordings with microelectrodes [16, 17].

Recently, Bender and other investigators studied the accuracy of diagnostic techniques used to differentiate minimally conscious state (MCS) from UWS/VSPVS and found that the misdiagnosis rate was estimated at 37–43%. On the other hand, they report a pretty easy way to differentiate UWS/VSPVS from brainstem death [18].

The treatment of UWS/VSPVS patients is mainly an interdisciplinary challenge for all people involved, ranging from the attending physicians to the staff of the ICU and other consultants providing chronic care [18]

**BRIEF COMMENTS ON UWS/VSPVS – A CLINICAL DIAGNOSTIC CHALLENGE**

In cases presenting a critical injury in the brain and becoming unconscious, responding to any stimulation, that comatose state may undergo a transition to a state in which the eyes of the patient are intermittently open (wakefulness), but without evidence for an ability to contact the environment, or for awareness (UWS/VSPVS). The components of disorder of consciousness are listed in TABLE 1 See TABLE 1 [18]

TABLE 1: CONSCIOUSNESS			
CONDITION	SLEEP-WAKE CYCLES	AWARENESS	FEATURES OF MOTOR BEHAVIOURAL
COMA	NO	NO	NO PURPOSEFUL BEHAVIOUR
LOCKED-IN SYNDROME	YES	YES	ACCORDING TO THE LESION, RESTRICTED TO VERTICAL EYE MOVEMENTS AND BLICKING
UNRESPONSIVE WAKEFULNESS STATE, VEGETATIVE STATE, PERMANENT VEGETATIVE STATE	NO	NO	NO PURPOSEFUL BEHAVIOUR
MINIMALLY CONSCIOUS STATE	YES	PARTIAL FLUCTUATING	REPRODUCIBLE PURPOSEFUL BEHAVIOURAL INCONSISTENT

When those cases show any reproducible behaviour suggesting conscious perception of the environment, they are no longer considered UWS/Vs. They will be included in the MCS category according to Giacino et al.'s definition [19].

The most confident differential diagnosis of a case's state of consciousness between UWS/Vs and MCS remains a relevant challenge in neurological attention. The average of misdiagnosis in this issue has been estimated at 37%–43%. Therefore, a lot of cases are wrongly diagnosed as UWS/Vs/AS instead of MCS and those patients are suffering a lot because of a lack of personal attention due to non-recognition of their status, followed by wrong assignment of "poor outcomes" leading to early termination of life-sustaining care and its consequences [20].

Bender et al. have established that neither the Glasgow Coma Scale (GCS) nor the Coma Nausea Scale allows an accurate, clear, and confident operationalized differentiation between URS/Vs and MCS [18].

We hypothesized that the best procedure to make the ultra-necessary differentiation among UWS/Vs and MCS is the revised Coma Recovery Scale (CRS-R), because it's based on an ordinary scale assessing those patients from level zero (most profound possible coma) to level 23 (awake and fully capable of contact) allowing to make an accurate, clear and confident differential diagnosis between UWS/Vs and progressive improving MCS to a

still higher level of consciousness ([www.coma.ulg.ac.be/medical/chronic.html](http://www.coma.ulg.ac.be/medical/chronic.html))[21].

**Brief comments on novel procedures for the detection of preserved minimal consciousness.** Because of the high incidence of incorrect clinical differential diagnoses, some authors have increased their efforts to apply new technical procedures to better identify MCS patients, despite the limitations of those tests, due to fundamental methodological difficulties, such as the specificity and sensitivity of most of them. Nevertheless, using the CRS-R as a diagnostic gold standard to distinguish UWS/Vs from MCS and to identify the percentage of cases fulfilling the CRS-R principles for UWS/PVS, the results show a negative fMRI or FDG-PET (fluorodeoxyglucose positron emission tomography) study. Therefore, to ensure that patients are clinically fully conscious, they must be able to obey simple commands, such as "Follow my finger with your eyes." However, some cases might be awake but still unable to obey orders. Then we would be unable to confirm the proper level of consciousness, leading to false-positive/negative responses. Yet, visual fixation alone is always a consequence of preserved MCS, despite the CRS-R operationalization results [18].

Additional comments on the role of [18F]FDG PET Imaging for the Assessment of UWS/Vs An illustration of the [18F]FDG PET Imaging is seen in **FIGURE 2**

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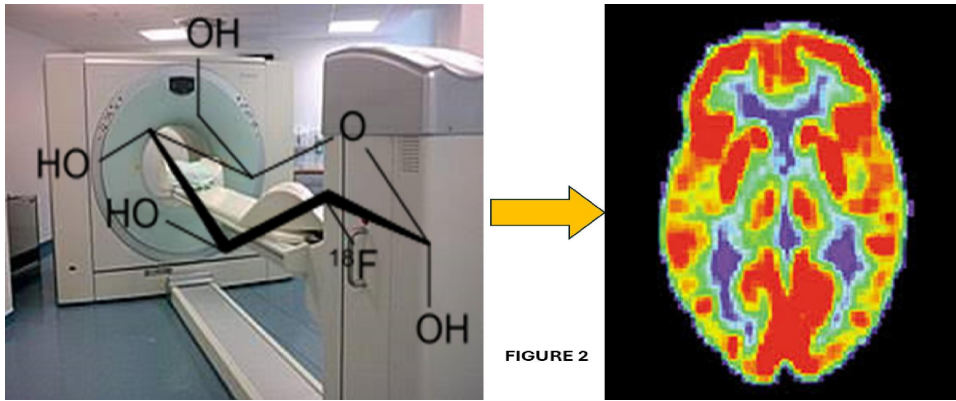


FIGURE 2

**Figure 2:** shows a PET machine using [18F]FDG (a radioactive glucose tracer) to scan the brain and visualize and measure metabolic activity in the brain and the rest of the body. 18F]Fluorodeoxyglucose, or fluorodeoxyglucose F 18, also called fluorodeoxyglucose, is a radiopharmaceutical (radiotracer), used in positron emission tomography, which is a positron-emitting radionuclide. Fluorine-18 is replaced for the normal hydroxyl group at the C-2 position in the glucose molecule.

Recently, Dondi and collaborators evaluated the accuracy of [18F] fluorodeoxyglucose ([18F] FDG) positron emission tomography (PET) imaging in cases with UWS/VS. They found that [18F] FDG PET imaging is quite helpful for accurate differential diagnosis between UWS/VS and other DOC and for predicting their

outcomes [22].

As noted, DOC encompasses several medical conditions, including MCS, coma, VS, UWS, and persistent VS (PVS), when these conditions persist beyond 4 weeks [23]. See **FIGURE 3**.

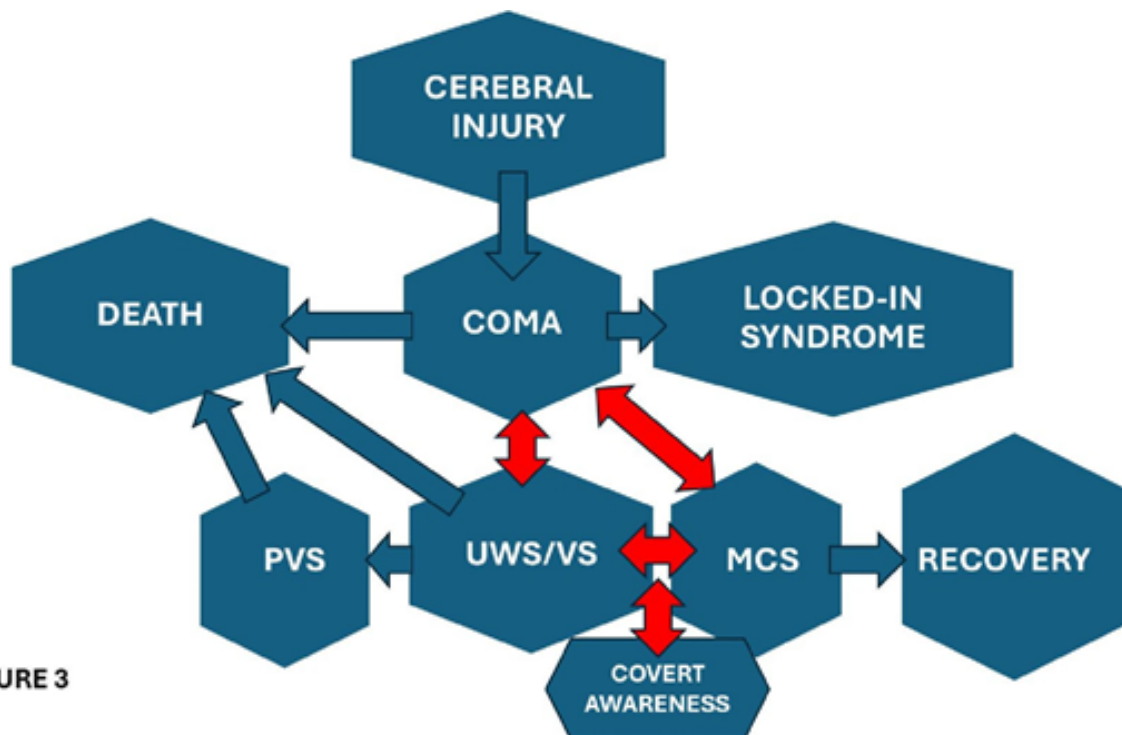


FIGURE 3

As mentioned before, nuclear medicine procedures are implemented to confirm the level of functional cerebral damage in DOC patients. More specifically, [18F] fluorodeoxyglucose ([18F] FDG) positron emission tomography (PET) imaging can assess glycolytic activity in several anatomical structures and evaluate disorders of

the central nervous system, including encephalitis and neurodegenerative processes [23].

The first study reporting assessment of UWS/VS/PVS was conducted by Levy D.E. *et al.* [17] that is summarized in TABLE 2

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Authors	Ref	Year	Country	Study Design	N. Pts.	VS/UWS (%)	Aetiology
Levy D.E. et al.	[17]	1987	USA, Canada	Prospective	10	7 (70)	CPA, trauma, anaesthesia-hypoxia and asphyxia
De Volder A.G. et al.	[24]	1994	Belgium	Prospective	12	7 (58)	CPA
Lommasino C. et al.	[25]	1995	Italy	Prospective	25	10 (40)	Cerebrovascular accident, trauma and CPA
Rudolf J. et al.	[26]	1999	Germany	Prospective	24	24 (100)	CPA, primary hypoxia due to myasthenic crisis, attempted suicide, anaesthesia
Laureys S. et al.	[27]	1999	Belgium	Retrospective	82	4 (5)	intoxication, CPA, trauma
Beuthien-Baumann B. et al.	[28]	2003	Germany	Prospective	23	16 (69)	Trauma, haemorrhage
Kassubek J. et al.	[29]	2003	Germany	Prospective	7	7 (100)	CPA, intoxication
Coleman M.R. et al.	[30]	2005	UK	Prospective	10	6 (60)	Trauma, haemorrhage
Nakayama N. et al.	[31]	2006	Japan	Retrospective	82	17 (21)	Trauma
Bruno M.A. et al.	[32]	2010	Belgium	Prospective	49	10 (20)	Anoxia
Kim Y.W. et al.	[33]	2010	Republic of Korea	Prospective	24	12 (50)	Trauma, hypoxia, cerebrovascular injury
Phillips C.L. et al.	[34]	2011	Belgium	Retrospective	82	13 (16)	Anoxia, CPA, trauma, thrombosis, haemorrhage
Thibaut A. et al.	[35]	2012	Belgium	Prospective	70	24 (34)	CPA, anoxia, trauma, stroke, meningitis, haemorrhage
Kim Y.W. et al.	[36]	2013	Republic of Korea	Prospective	32	17 (53)	CPA
Stender J. et al.	[37]	2014	Denmark, Belgium, Australia, USA, Canada	Retrospective	41	14 (34)	Trauma, CPA, infection, stroke, haemorrhage
Stender J. et al.	[38]	2014	Belgium, Canada, Denmark	Retrospective	12	41 (33)	Trauma, cardiac arrest, stroke, haemorrhage, infection, metabolic disorders
Steinhoff N. et al.	[39]	2015	Austria	Prospective	4	4 (100)	ns
Bodart O. et al.	[40]	2017	Belgium, USA, Italy, Brazil	Retrospective	24	9 (38)	Trauma and non-traumatic injuries
Golkowski D. et al.	[41]	2017	Germany	Prospective	20	14 (70)	Trauma, stroke, anoxia, metabolic
Zhang Y. et al.	[42]	2019	China	Prospective	19	8 (42)	Anoxia, trauma, haemorrhage
Hermann B. et al.	[43]	2020	France, Belgium, USA	Prospective	96	48 (50)	Anoxia, trauma, haemorrhage
Carrière M. et al.	[44]	2020	Belgium, UK	Retrospective	186	64 (34)	Trauma and non-traumatic injuries

Sattin D. et al.	[45]	2020	Italy	Retrospective	54	42 (78)	Trauma, anoxia, ischemia and haemorrhage
Hermann B. et al.	[46]	2021	France, Belgium	Prospective	52	21 (40)	Trauma, anoxia, ischemia and haemorrhage, intoxication, encephalomyelitis
Curatola A. et al.	[47]	2023	Italy	Prospective	3	3 (100)	PCA
Ma H. et al.	[48]	2023	China	Prospective	60	53 (88)	Anoxia, trauma, and stroke
Usami N. et al.	[49]	2023	Japan	Retrospective	50	15 (30)	Trauma
Guo K. et al.	[50]	2024	China	Prospective	57	21 (37)	Trauma, haemorrhage, ischemia, toxic encephalopathy
He Z. et al.	[51]	2024	China	Prospective	15	7 (47)	Trauma, hypoxia, ischemia
Liu D. et al.	[52]	2025	China, UK	Retrospective	56	21 (38)	Trauma, hypoxia-ischemia, haemorrhage
Wu L. et al.	[53]	2025	China	Retrospective	—	19 (67)	Trauma, hypoxia, ischemia
Keyun L. et al.	[54]	2025	China	Retrospective	—	29 (59)	Trauma, hypoxia-ischemia
Kazazian K. et al.	[55]	2025	Canada	Prospective	—	13 (72)	Trauma, hypoxia-ischemia

Since 1994, De Volder et al. have recommended [18F]FDG-PET to assess UWS/VS/PVS. At that time, they found that the average grey matter glucose utilization was lower in post-anoxic patients than in healthy people. That metabolic process was markedly diminished, particularly in UWS/VS patients compared with subjects who regained alertness, and UWS/VS/PVS and alert post-anoxic patients had significantly different metabolic rates, particularly in the parieto-occipital cortex. However, frontal and frontomesial regions were also affected [24].

Later, Tommasino et al. and Rudolf et al. assessed the role of [18F]FDG PET imaging, which found similar findings related to reduced mean glucose metabolism in cases in UWS/VS/PVS except for the brainstem, compared to healthy people, with PVS patients presenting the lowest metabolic rate [25, 26].

Other authors reported a remarkably impaired glucose metabolism in the left inferior frontal gyrus, the left and right middle and superior frontal gyri, the left middle temporal gyrus, the right superior temporal gyrus, the left inferior parietal lobule, the posterior cingulate cortex/precuneus, and the left pre- and postcentral gyri [27].

Other investigators assessed the reduction level of glucose metabolism and perfusion through [99mTc] hexamethylpropylene-amine-oxime ([99mTc]HMPAO) single photon emission computed tomography (SPECT), found an accurate reduction level mainly on the temporal and frontal cortex, and less frequently at the cerebellum, the parietal cortex, and the occipital cortex [28].

Other authors studied the accuracy of homeostatic coupling between brain waves and cerebral metabolism in UWS/VS and MCS, concluding that glucose metabolic

rate was not significantly different between UWS/VS and MCS [29].

Juengling and colleagues also assessed brain glucose metabolism in UWS/VS cases, looking for separate functional and structural cerebral damage through [18F]FDG PET and MRI. PET images showed a large pattern of hypometabolic areas in the frontotemporal cortices, cuneus/precuneus, frontal medial and precentral gyri, transverse temporal gyri, bilateral thalamus (mainly the dorsomedial subnucleus), parietal lobe, and cingulum, like voxel-based morphometry. Other affected regions of the brain (although in minor grade) included the left medial temporal gyrus, right caudate, right operculum, and parts of the cingulum [30].

Other authors who investigated regional cerebral glucose metabolic rate and disorder of alertness in traumatic diffuse brain injury included Nakayama et al., who examined the relationship between the two. Those researchers also documented a remarkable bilateral hypometabolism in the medial fronto-basal region, thalamus, medial prefrontal region, and anterior/posterior regions of the cingulate gyrus in patients presenting UWS/VS/PVS and MCS.

When those investigators compared their findings in UWS/VS/PVS and MCS patients with those of healthy people, they found metabolic reductions in the hypothalamus, cerebral peduncle, thalamus, cingulate gyrus, subcallosal gyrus, inferior frontal gyrus, and medial frontal gyrus [31].

Bruno and collaborators also used [18F]FDG PET to assess metabolic dysfunction in UWS/VS/PVS cases. These authors found that patients without visual fixation

exhibited metabolic dysfunction in an extensive cerebral network, including fronto-temporo-parietal associative cortices and the bilateral thalami.

At the same time, the cerebellum and the brainstem were relatively spared. They concluded that sustained visual fixation does not necessarily reflect alertness or increased cerebral activity [32].

Kim et al. also studied changes in cerebral glucose metabolism in UWS/VS/PVS cases after acquired head injury compared with healthy individuals. The previous cited investigators found a marked decrease in metabolism in the left superior parietal lobule, left precuneus, posterior cingulate cortex, and. In contrast, brain glucose metabolism was increased in the right supramarginal cortex and the cerebellum [33].

Phillips et al. in 2010 and Thibaut et al. two years later studied some cases presenting with UWS/VS/PVS and Locked-in syndrome (LIS) and applied [18F]FDG PET imaging to assess brain glucose metabolism. They found that this procedure had a 100% accuracy in differentiating between LIS and UWS/VS/PVS, and the cases presenting LIS had similar levels of brain glucose metabolism as normal people [34, 35]

Kim et al. also reported severe brain glucose hypometabolism in bilateral precentral gyri, bilateral superior parietal gyri, right superior frontal gyrus, bilateral posterior cingulate gyri, bilateral middle occipital gyri, right angular gyrus, bilateral precuneus, both middle frontal gyri, and right supramarginal gyrus in people affected by UWS/VS/PVS secondary to hypoxic-ischemic brain injuries. At the same time, hypermetabolism was confirmed in the right inferior frontal gyrus, the bilateral insular cortices, the brainstem, and the bilateral cerebella. On the other hand, cases presenting UWS/VS/PVS secondary to respiratory arrest had hypometabolism in the bilateral middle frontal gyri, the right superior frontal gyri, left precuneus, bilateral middle occipital gyri, and bilateral precentral gyri. In contrast, the bilateral insular cortices, bilateral cerebella, midbrain, pons, medulla oblongata, and the right inferior frontal gyrus, showed a remarkable increase in metabolism. They also reported that the Coma Recovery Scale-Revised (CRS-R) score correlated positively with brain glucose metabolism in the bilateral fusiform and superior temporal gyri [36].

Stender et al. conducted a quantitative study that differentiated VS/UWS from MCS. All investigated patients had decreased brain glucose metabolic rates (42%) in motor areas bilaterally and in primary and associative sensory areas (somatosensory, auditory, and visual cortex) compared with healthy people (53%). Additionally, the same investigators reported 82% accuracy in differentiating UWS/VS/PVS from MCS using [18F]FDG PET imaging and functional MRI (fMRI). The CRS-R scale was very good at identifying UWS/VS/PVS, and PET imaging was quite effective at predicting the prognosis in 74% of cases [37, 38].

In a group of patients with UWS/VS/PVS, the effect of

continuous music therapy on several cortical brain regions was assessed through [18F]FDG PET imaging. The results showed hypermetabolism in the hippocampal, cerebellar, and frontal lobes compared with cases receiving discontinuous therapy, who showed lower overall glucose metabolism than the basal level [39].

Using a similar cohort as a previously cited publication, Bodart et al., studied their cases looking for the cross-validating EEG and [18F]FDG PET after transcranial magnetic stimulation (perturbational complexity index [PCI]) procedure and to find diagnostic elements or alertness in patients with DOC and found that MCS cases had an almost normal brain glucose metabolism at the external or internal fronto-parietal network. In contrast, alert cases showed hypometabolism restricted to the midbrain, pons, medulla oblongata, frontal lobe areas, and cerebellum. However, in the cerebellum and brainstem, the metabolic rate was under normal parameters [40].

To confirm the diagnosis of DOC, Golkowski et al. investigated their series using [18F]FDG PET, fMRI connectivity, and EEG band power simultaneously. They found hypermetabolism in the occipital lobes of MCS cases, compared with UWS/VS/PVS, in correspondence with the CRS-R level. In contrast, delta-band power in EEG was associated with a better prognosis [41].

In 1997, Zhang et al. introduced the combination of imaging ([18F]FDG PET) and 1 functional (event-related potentials) to investigate the neurological correlates of several behavioural responses to transcranial direct current stimulation (tDCS) in cases presenting with MCS or UWS/UWS/VS/PVS. They documented that the main differences between the cases mentioned above compared with normal peoples was related to the left Heschl gyrus, left Rolandic operculum, right superior temporal gyrus, left insula, regional uptake at the left caudate, right caudate, left precentral, left mid-temporal gyrus, orbital part of the inferior frontal gyrus, right Heschl gyrus, and the left midfrontal gyrus, and showing a lower cerebral metabolic rate of glucose ratio, compared to MCS and reporting lower uptake compared to normal persons. On the other hand, normal subjects presented lower metabolism than UWS/VS/PVS at the right posterior cingulum, left superior frontal gyrus, left thalamus, left precuneus, left anterior cingulum, right anterior cingulum, and right superior frontal gyrus. They also established that the appropriate behavioural response to tDCS happened when those regions were stimulated [42].

Hermann et al. also proposed combining anatomical imaging and functional investigations, but now only to assess habituation of the auditory startle reflex (hASR) to differentiate VS/PVS from MCS. These investigators reported a correlation between the brain glucose metabolism and hASR, with the metabolic rate higher in cases with extinguishable startle response (ASR-EX) than those people presenting inextinguishable startle response (ASR-IN), while voxel-wise analysis only related to the UWS/VS/PVS cohort had a higher brain metabolism in the premotor area, anterior prefrontal cortex, the posterior

and anterior cingulate, in VS-EX patients than in VS-IN cases [43].

In 2020, Carrière et al. conducted a multimodal investigation to determine whether auditory localization can be interpreted as a new sign of MCS. They found that UWS/VS/PVS cases without auditory localization (NO-LOCA) had diminished [18F]FDG metabolism in a large region of both cerebral hemispheres, mainly the thalamus, in the left premotor cortex, left angular gyrus, right ventral posterior cingulate cortex, left sensorimotor associative regions, and bilateral frontal eye fields. However, those cases with auditory localization (LOCA) showed regional hypometabolism compared with normal people, specifically in the left premotor cortex, right frontal eye fields, right visual secondary and associative areas, right fusiform gyrus, ventral anterior and posterior cingulate cortex, and right angular gyrus. Notwithstanding, no statistical differences were found in the direct comparison between NO-LOCA. MCS, UWS/VS/PVS LOCA, including rated brain glucose hypometabolism mainly in the right primary auditory cortex, right precuneus, bilateral primary motor cortex, right premotor cortex, bilateral visual secondary cortex, right visual associative cortex and right primary somatosensory cortex [44].

In 2020, Davide Sattin from Neurology, Public Health, Disability Unit / Coma Research Centre, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy and his collaborators studied the integrity of neural elements that are part of the visual pathway in cases presenting DOC with reflexive behaviour (visual blink), cortically and cognitively mediated behaviour (visual pursuit). Considering the importance of confirming signs of alertness in cases with DOC to differentiate UWS/VS/PVS from MCS, a new technique has been introduced to demonstrate that visual responses to tailored stimuli are meaningful, relevant evidence of transformation from one state to another, based on the neurophysiological function of the visual pathway components. These authors used sophisticated instruments (fMRI, EEG, 3T Magnetic Resonance, and PET) in more than 50 patients.

They found that the visual pursuit group showed a better fVEP response than the visual blink group, due to a larger area under the N2/P2 component of the fVEP. Taking into consideration the MRI findings, the principal anatomical damage in both groups was observed in the retrochiasmatic areas, particularly in the primary visual calcarine cortex (BA17) and the right optic radiation, and in regions that were statistically less impaired in cases with the capacity to perform a visual pursuit. [18F]FDG PET images proved the real difference between groups at the level of the right primary (B 17) and secondary visual cortex (BA 18/19), which can be included as a new tool for the forthcoming diagnostic protocol [45].

In the following year, Hermann et al., working at the Cerveau Institute, Georges Pompidou hospital and Paris University (France), assessed the accuracy between [18F]FDG PET metabolic index of the best-preserved

hemisphere (MIBH) in cases with DOC diagnosis and the results obtained from EEG-based classification and made a sophisticated analysis of the added value of a multimodal approach combining both procedures. They reported that cases UWS/VS/PVS showed remarkably lower MIBH than the group of cases with MCS, with 84% accuracy, 78% negative predictive value, 85% positive predictive value, 78% specificity, and 85% sensitivity [46].

A group of researchers from the Paediatric Department of the University "A Gemelli", Catholic University and Neurology Institute IRCCS in Rome (Italy) assessed the combination of transcranial direct current stimulation treatments and nerve growth factor (NGF) to improve outcomes in paediatric patients suffering from UWS/VS/PVS preceded by cardiac arrest. They documented an improvement of the children's clinical and neurological conditions after the administration of intranasal human recombinant NGF (hr-NGF), confirmed by [18F]FDG PET, which proved a global reduction in tracer uptake at the cerebellar, subcortical, and cortical levels [47].

Ma and collaborators from Guangzhou, Guangdong, People's Republic of China studied how a group of patients with prolonged DOC after receiving a trigeminal nerve stimulation (TNS) responded to this procedure compared with a healthy group. These investigators found hypermetabolism of brain glucose in the right precuneus, the right parahippocampal cortex, and bilateral middle cingulate cortex after 2 weeks of TNS. Unfortunately, the selection criteria for differentiating the DOC subgroups were not well established. Therefore, confident conclusions were not delivered [48].

At the Chubu Medical Centre for Prolonged Traumatic Brain Injury, Gifu, Japan, Usami et al. assessed brain glucose metabolism using [18F]FDG PET imaging in a series of cases presenting with chronic DOC, compared with UWS/VS/PVS patients. They reported that in cases with DOC, the regional glucose metabolism was increased in the left occipital lobe of the left cerebral hemisphere compared with the UWS/VS/PVS group. At the same time, a remarkable level of hypometabolism was confirmed in both cerebral hemispheres, mainly in the temporal, occipital, and pericallosal regions; the right hemisphere; the corpus callosum; the parietal region; the angular gyrus; the central region; the lenticular nucleus; the thalamus; the hippocampus; and the cerebellar hemisphere. In the left hemisphere, the corpus callosum, parietal region, angular gyrus, central region, temporal region, occipital region, pericallosal region, thalamus, hippocampus, and lenticular nucleus [49].

Last year, a group of researchers composed of Guo et al. from the Department of Nuclear Medicine, Fourth Military Medical University, Xi'an, China, determined the validation of glucose metabolic pattern (GMP) after performing [18F]FDG PET images to differentiate MCS from UWS/VS/PVS compared with normal people. These authors discovered an extended decreased brain glucose

metabolism in the bilateral frontoparietal lobes, including the middle frontal gyrus, inferior parietal lobule and inferior frontal gyrus, coupled with increased cerebral glucose metabolism in the subcortical regions, including the unilateral parahippocampal gyrus, lentiform nucleus, thalamus, anterior cingulate gyrus, bilateral cerebellar hemispheres and mesencephalon. Furthermore, after confronting it with MCS, UWS/Vs/PVS GMP, they found a sustainable hypometabolism in the frontal– parietal cortex, including the postcentral gyrus, paracentral lobule, precuneus, precentral gyrus, frontal lobe, and parietal lobe. At the same time, hypermetabolism was proven in the putamen, lentiform nucleus, and anterior cingulate gyrus. Same authors reported that the GMP expression average correctly predicted 73.7% of outcomes, with 76.2% specificity and 72.2% sensitivity in cases presenting with alertness at follow-up. In comparison, the frontoparietal cortex SUVR correctly predicted 50.9% of outcomes, with only 14.3% specificity and the same sensitivity [50].

Also, last year, He et al. assessed the disease severity and differences between UWS/Vs/PVS and from MCS, looking to establish an identification DOC-related pattern (DOCRP) on [18F]FDG PET imaging and found a bilateral hypometabolic activity in the parieto-temporal lobes, cingulate gyrus, caudate, medial and lateral frontal lobes, with additional hypermetabolic activity in the brainstem and cerebellum. They also achieved good accuracy and performance in distinguishing normal subjects from DOC cases, with clear differentiation between MCS and UWS/Vs/PVS. The reported specificity of 75.0% and sensitivity of 85.7% were also discussed [51].

A few months back, another group of investigators, guided by Liu, organized a research study to assess resting-state brain metabolism in patients with DOC using [18F]FDG PET imaging to determine a quantitative metabolic predictor of their level of alertness. These authors demonstrated that a different global cortical metabolic index between the UWS/Vs/PVS and MCS groups, with high AUCs in the validation and derivation cohorts (0.89), 81% specificity, and 88% sensitivity. Main regional metabolism differences were reported in the left precuneus and left occipital lobe in the UWS/Vs/PVS group. However, hypometabolism was documented in the external cerebellum and the middle frontal gyrus in cases presenting with intraparenchymal brainstem haemorrhage [52].

Recently, Wu et al. investigated network features of the whole brain using resting-state functional near-infrared spectroscopy (fNIRS) in patients with DOC. They also reported new biomarkers useful to distinguish UWS/Vs/PVS from MCS [53].

Nineteen patients were retrospectively studied to develop a machine learning prediction model for confident differential diagnosis among cases presenting with MCS and UWS/Vs/PVS, and to estimate recovery and the relationship with consciousness improvements, using EEG

metrics. They concluded that multiscale entropy values are a valuable predictor of outcome in cases with EEG-confirmed UWS/Vs/PVS [54].

Finally, a team of investigators working in the Western Institute of Neuroscience, Western University, London, Canada N6A 3K7 and the Brain Injury Research Centre, Los Angeles, California, using functional MRI (fMRI), EEG and 18F-FDG-PET in both acute and prolonged DOC cases. These investigators provided a comprehensive review of the accuracy of neuroimaging in DOC, leading to the necessary knowledge to select the best procedure for establishing the final diagnosis and prognosis of the attending case on imaging paradigms used (passive, active, resting state) and the kind of interferences (residual cortical activity) made on those paradigms, like awareness, perception and communication. These authors reported detailed information on how the cited technique should be implemented. They concluded that after two and a half decades of research, it's possible to deliver two remarkable insights. 1.- Around 20% of patients presenting acute/chronic DOC unable to follow commands remain covertly aware, and the diagnostic gold standard is a great challenge. 2.

The previously cited technique allows for predicting the outcome of the DOC cases in the short and long term. Therefore, the inclusion of the advanced techniques to study those cases is mandatory to be able to distinguish between the level of awareness, which is one of the advantages of FDG-PET, as there is no modification of the tracer uptake after administration of sedatives, independently of the tracer uptake phase, to avoid modification of the PET signal. One of the most advantages of fMRI is its capacity to confirm awareness. In contrast, PET only assesses the cortical network's glucose metabolic integrity, which is necessary for awareness, rather than proving that the patient is aware per se [55].

#### **Brief comments on emerging technologies**

An optical equivalent of fMRI in the format of a portable neuroimaging technique known as functional near-infrared spectroscopy (fNIRS), this novel technique has the advantage that it can be used as a bedside test, it's less expensive than the other ones, and it's based on the calculation of changes in Hb concentration (oxygenated and deoxygenated). This procedure infers brain expression through neurovascular coupling by calculating concentration changes in sensorimotor processing, speech-specific auditory processing, volitional command, and resting-state networks, driving cortical expression activity. It also has the capacity to distinguish between acute and chronic DoC conditions, with covert alertness a confident and valuable diagnostic tool due to its portability and ease of use. Other novel combinations of technology include transcranial magnetic stimulation paired with EEG (TMS-EEG), where information from magnetic pulses and electrical brain waves provides an essential diagnostic tool for accurate diagnosis and even for predicting the future prognosis.

**Brief final general comments**

The great importance of [<sup>18</sup>F]FDG PET imaging in assessing altered cerebral glucose metabolism in cases with UWS/VS/PVS has been documented by several investigators, as cited previously, providing valuable insights into residual cerebral tissue activity and assisting in the evaluation of cerebral recovery. They also demonstrated hypometabolism and dysfunctional brain connectivity in UWS/VS/PVS, mainly in the temporal, parietal, and frontal lobes, and the cingulum, compared with normal subjects. However, minimal decreased glucose metabolism was detected in the thalamus, cerebellum, and occipital lobe.

Our final remarks highly the role of [<sup>18</sup>F]FDG PET imaging in the assessment of UWS in new efforts, larger prospective studies, variable clinical settings, and multicentre collaborations which needs to clearly evaluate, confirm, or challenge its value, thereby strengthening the reliability of the review.

**4.1. Limitations**

Obviously, due to the characteristic of the published papers including small and heterogeneous cohorts some arisen limitations affecting our findings are present. Small series

First, most studies are characterized by, and in some of them, only a limited number of patients were in VS/UWS. Small sample sizes (e.g., Curatola et al. [47]) and retrospective design limit the accuracy of the statistical analysis making strong influences on results. Other considerable limitation for a proper and confident results is related to the sustainable variability of imaging protocols including the administration of different tracers (e.g., mixed use of [<sup>11</sup>C]flumazenil · [<sup>18</sup>F]FDG, and [<sup>15</sup>O]H<sub>2</sub>O), the use of different analysis methods (e.g., visual versus quantitative metrics), and devices

(PET/MR, standalone PET, PET/CT,) different resolutions of the scanner machines which mainly affect the validity and confidentiality of the study's results

We found a lack of quantitative evaluation of brain [<sup>18</sup>F]FDG images reported in most of the included articles which also affect the quality of the delivered results

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**Ethics Statement:**

This review does not require Ethical Approval

**Patient Privacy:**

All patient-identifying information has been removed to ensure anonymity.

**Conflicts of Interest:**

Authors of this review report there is not conflicts of interest

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