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Review

Non-invasive, non-pharmacological/bio-technological interventions towards neurorestoration upshot after ischemic stroke, in adults—systematic, synthetic, literature review

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1. Abstract

Considering its marked life-threatening and (not seldom: severe and/or permanent) disabling, potential, plus the overall medico-psycho-socio-economic tough burden it represents for the affected persons, their families and the community, the cerebrovascular accident (CVA)—including with the, by far more frequent, ischemic type—is subject to considerable scientific research efforts that aim (if possible) at eliminating the stroke induced lesions, and consist, as well, in ambitious—but still poorly transferable into medical practice—goals such as brain neuroregeneration and/or repair, within related corollary/upshot of neurorestoration. We have conducted, in this respect, a systematic and synthetic literature review, following the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)" concept. Accordingly, we have interrogated five internationally renowned medical data bases: Elsevier, NCBI/PubMed, NCBI/PMC, PEDro, and ISI Web of Knowledge/Science (the last one to check whether the initially identified articles are published in ISI indexed journals), based on a large (details in the body text) number of most appropriate, to our knowledge, key word combinations/"syntaxes"—used contextually—and subsequently fulfilling the related, on five steps, filtering/selection methodology. We have thereby selected 114 fully eligible (of which contributive: 83—see further) papers; at the same time, additionally, we have enhanced our documentation—basically, but not exclusively, for the introductive part of this work (see further)—with bibliographic resources, overall connected to our subject, identified in the literature within a non-standardized search. It appears that the opportunity window for morph-functional recovery after stroke is larger than previously thought, ac-

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tually being considered that brain neurorestoration/repair could occur, and therefore be expected, in later stages than in earlier ones, although, in this context, the number of cases possibly benefitting (for instance after physical and/or cognitive rehabilitation—including with magnetic or direct current transcranial stimulation) is quite small and with more or less conflicting, related outcomes, in the literature. Moreover, applying especially high intense, solicitating, rehabilitation interventions, in early stages post (including ischemic) stroke could even worsen the functional evolution. Accordingly, for clarifications and validation of more unitary points of view, continuing and boosting research efforts in this complex, interdisciplinary domain, is necessary. Until finding (if ever) effective modalities to cure the lesions of the central nervous system (CNS)—including post ischemic stroke—it is reasonable and recommendable—based on rigorous methodologies—the avail of combined ways: physiatric, pharmacologic, possibly also bio-technologic. On a different note, but however connected to our subject: periodic related systematic, synthetic literature reviews reappraisals are warranted and welcome.

2. Introduction

As known, stroke in general—considering its, often: severity, dangerous prognostics, "hyper chronic" [1] evolution, and capacity to generate multiplane and long-term impairment—and specifically ischemic cerebrovascular accident (CVA), including by its prevalent frequency among the stroke types [2–9]—represents a major and still not decisively solved, overall public health problem, worldwide. As a suggestive particularization, in Catalonia "the cumulative incidence of CVD (cerebrovascular disease—o.n.) per 100,000 population was 218 (95% CI, 214–221) in men and 127 (95% CI, 125–128) in women" [10].

From epidemiological and prognostic perspectives "women differ from men in the distribution of risk factors and stroke subtype, stroke severity, and outcome" [11].

Within the stroke—including ischemic—large disability potential main causes, it is to be mentioned, aside different deficits of motor kind, the neuropsychological one: "... neuropsychological deficit may be considered as a common clinical feature in acute lacunar infarction" [12].

A main explanation for this unsatisfactory actual situation refers, on one hand, to the fact that, differing from other structures of the organism, "… the brain is unable to properly regenerate and reconnect the injured areas to the uninjured ..." ones within it [13], and on the other, to the existence, at intimate level, of very complex (not seldom intermingled/dialectically-antagonistic: pro-injury, respectively protective and/or pro-recovery, as well) lesion mechanisms and their final, basically irreversible, results—but all being, on a par, main targets for neurorestoration/neuroregeneration and brain repair. This complicated, ambivalent, bio-/pathological situation occurs because the components "... of EDA (endogenous defense activity—n. n.—i.e., processes, like: neurotrophicity, neuroprotection, neuroplasticity, neurogenesis) share common biological background with the pathophysiological mechanisms of DM" (damage mechanisms—n. n.) [14]. As just an example of how complicated appear to be, overall, neurobiology and neuropathology, including with their often "dialectically": complementary antagonistic relationships in between, as more related knowledge accumulates, in the literature there is emphasized the complex role of microglia and astrocytes, which "... are primary determinants of the environment in peri-infarct tissue and hence strongly influence the potential for neuronal plasticity" [15] relationing, in this context "... with elements of synapses in an activity-dependent manner" [16], including for "... adult learning (activity-triggered synaptic plasticity)"—as neuroplasticity, in principal, "... includes synapse formation, dendritic structure, and neurogenesis" [17], and (more detailed) respectively: "… changes in dendritic branches, axonal sprouts, dendritic spine density, synapse number, and receptor density" [8]—being, thereby, involved also in CNS post-injury recovery (for instance, dialectically: neural plasticity is not exclusively and unconditioned beneficial, as it can be "adaptive" but "maladaptive", i.e., detrimental, too [18]); so, they have an ambivalent subtle contribution: to the development of the secondary lesional events cascades' damage mechanisms (especially—activated microglia—by releasing pro-inflammatory cytokines) but to the brain repair ones (for instance, through anti-inflammatory cytokines and survival neurotrophins—also by activated microglia provided), as well [19, 20], play also a very important role in "... adult neurogenesis and neuroinflammation" [21], but respectively with anti-inflammatory, neuroprotective, tissue repair and pro-neurogenetic actions, too [22]; the same "multifunctional" action profile goes for the astrocytes: "... in the CNS, they can affect neuronal activity, modulate plasticity, and participate in CNS regeneration after brain injury" [23], and their dialectically dynamic capabilities of exist in the acute phase but also afterwards [20].

Some authors even assert that neurogenesis "… in the adult brain …" this would be "… a new dimension of plasticity, with great impact on neuronal remodeling and repair …" [24] and more, that it "… has been known to be an integral component in neural plasticity, brain homeostasis, maintenance, and tissue remodeling" [25]. Neurogenesis is an energy dependent process, which: "... requires adequate amount of ATP supply to facilitate cytoskeletal rearrangement, neuronal sprouting and organelle transport". Because mitochondria are the main energetic producing organelles of a cell, specifically in neurons their functioning is critical for neurogenesis/brain repair [26], that is a (limited) restorative process which's endogenous "key factors", for this purpose and consequent functional improvement, are, including in post ischemic conditions, "Axonal

remodeling and dendritic regulation in the ipsilateral and contralateral cortex …" [8]. To be also emphasized that, in such pathologic conditions, as a natural compensatory neuro-biologic balance attempt to compensate for loose of brain tissue and synapses/inter-neuronal disconnection "… counteracting endogenous regenerative processes are activated, leading to neurogenesis and synaptogenesis" [27], but usually this endogenous/self-reparative reaction does not reach an enough compensatory restorative level. Therefore, exogenously induced/stimulated neurogenesis, together with other neurorestorative interventions (including, at large, of non-invasive, non-pharmacological/bio-technological, kinds —which are the main subject of this article) is part of the rather new and most challenging domain of regenerative medicine, which will hopefully, in the future, contribute to significant curative, translational, outcomes on the consequences of the severe CNS lesions—also those after ischemic stroke—considering the huge pressure exerted by their frequency and harsh clinical features: life-threatening and/or long-term disabling potential.

In a synthetic enumeration of the post stroke path-physiological events ischemic cascade—"... excitotoxicity (glutamate release and receptor activation), calcium influx, ROS scavenging, NO production, inflammatory reactions, and apoptosis ..." [28]—there result, endogenously, brain: neurons (primary and secondary) perish, cellular energetic-metabolic imbalance/failure, blood brain barrier (BBB)—respectively/within neuro-vascular units —disfunction, excitotoxicity, edema, (dis)immune shifts/inflammation, microglia activation, and in subsequent/intermingled dynamics: clearing of the destructed cells' resulting detritus, tissue morph-functional restructuring, "... blood vessel regeneration and neural network rewiring" [3, 20], but as a final stage, too: reactive gliosis and the consequent glial scar, that has also complex bio-pathological roles: beneficial (within the lesioned milieu) ones, such as "… clearance of extracellular glutamate …" , multiplane metabolic homeostatic involvement, ROS depletion ("ROS, which is detrimental to neurons and glia" [29]), "… production of growth factors…" [30], respectively indirect protection/preservation of the non-affected neighbor; it thus contribute to the keep of the remaining tissue's biochemical environment characteristics (as outcome of an astrocytic response), trying to separate the lesioned area from the non-affected ones; this is prone to local brain repair [31, 32], but on the other hand, the glial and fibrotic [30] scar produces the hallmark of the brain injury's irreversible consequences, based on the local-regional "… major rearrangement of the anatomical structure", involving also the BBB (with modifications) recovery, and thus resulting in a biochemical/mechanical (mainly, but not exclusively, constituted by the Chondrotin Sulfate Proteoglycans—CSPGs) impenetrable barrier to the axonal re-growth across the injured zone [30]. So, in brief: "Although, the formation of an early glial scar may prevent progression of the infarct, this may also hamper brain repair by reducing neurogenesis or axonal re-growth" [33], and even worse: "… the glial scar also spreads into regions of the brain where there are often surviving neurons" [34].

Under these very complex and harsh bio-pathological conditions—and their extended: medical/-long term disability, social and economic marked consequences [35]—neurorestoration, respectively neuroregeneration and brain repair, including after ischemic stroke, represent most necessary, ambitious, imperative, revolutionary [35] and intensely desired/awaited scientific advancements, but extremely difficult to be effectively translated into the current medical practice (although with some "… found to be efficacious in animal models of stroke …" [36]); hence, by now, they are not enough confirmed by decisive healing clinical-functional strategies and evidence, in humans [7, 36]. In brief: "... there is a current lack of effective therapies available" [37].

From this overall perspective, functional neuro-recovery may underpin, as above mentioned, aside endogenous mechanisms, on "exogenous" ones, both: combating/mitigating the DM and boosting the EDA [14]—additional related details have been recently presented elsewhere [38], the latter seemingly, at best, by merging—but rigorously structured, within the Evidence Based Medicine (EBM) paradigm—related administration methodologies, within, at least for now, overall more feasible clinical approaches of non-invasive pharmacological/bio-technological and respectively, non-invasive non-pharmacological/bio-technological (such as alphabetically presented—see further) therapeutic-rehabilitative, interventions, in purpose to overall improve the, including post ischemic stroke, patients' functionality and quality of life (QOL).

According to all the above, first is necessary to attempt at cautiously/realistically and thus appropriate, defining the brain neuroregeneration and repair, and consequent (functional) recovery—within neurorestoration—concepts. Obviously, this is neither simple, nor exist perfect, unanimously accepted such definitions.

However, from a larger, biological perspective, regeneration—is considered "… the restoration or new growth by an organism of organs, tissues, etc., that have been lost, removed, or injured" [39], or maybe more specifically and restrictively: "Regeneration means the re-growth of part of the affected or lost organs of the remaining tissue" [40]. To be specified, from a larger perspective, as well, that "Regenerative processes occurring under physiological (maintenance) and pathological (reparative) conditions are a fundamental part of life and vary greatly among different species, individuals, and tissues"; this refers—although still controversial—to the CNS, too, within an inner merge between physiological—acting homeostatic—and pathological (needing for "… reparative regeneration …") states

Table 1. The 120 sets of keywords/combinations of keywords/syntaxes used for the contextual searches in 4 international databases.

Keywords	Elsevier	PubMed	PMC	PEDro	Total
“electromyography biofeedback” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“EMG biofeedback” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“repetitive transcranial magnetic stimulation” + “neuroregeneration” + “ischemic stroke”	0	0	11	0	11
“rTMS” + “neuroregeneration” + “ischemic stroke”	0	0	11	0	11
“transcranial direct current stimulation” + “neuroregeneration” + “ischemic stroke”	0	0	12	0	12
“tDCS” + “neuroregeneration” + “ischemic stroke”	0	0	9	0	9
“virtual reality” + “neuroregeneration” + “ischemic stroke”	0	0	5	0	5
“augmented reality” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“mechatronic exoskeletons” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“robotic exoskeletons” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“mirroring” + “neuroregeneration” + “ischemic stroke”	0	0	3	0	3
“kinesiotherapy” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“multisensory stimulation” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“serious gaming” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“serious games” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“electrical stimulation” + “neuroregeneration” + “ischemic stroke”	0	0	39	0	39
“functional electrical stimulation” + “neuroregeneration” + “ischemic stroke”	0	0	7	0	7
“FES” + “neuroregeneration” + “ischemic stroke”	0	0	2	0	2
“neuromuscular electrical stimulation” + “neuroregeneration” + “ischemic stroke”	0	0	5	0	5
“NMES” + “neuroregeneration” + “ischemic stroke”	0	0	2	0	2
“cognitive training” + “neuroregeneration” + “ischemic stroke”	0	0	3	0	3
“cognitive rehabilitation” + “neuroregeneration” + “ischemic stroke”	0	0	4	0	4
“enriched environment” + “neuroregeneration” + “ischemic stroke”	0	0	33	0	33
“environmental enrichment” + “neuroregeneration” + “ischemic stroke”	0	0	27	0	27
“neurologic music therapy” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“NMT” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“physical exercise” + “neuroregeneration” + “ischemic stroke”	0	0	24	0	24
“constraint-induced movement therapy” + “neuroregeneration” + “ischemic stroke”	0	0	12	0	12
“CIMT” + “neuroregeneration” + “ischemic stroke”	0	0	6	0	6
“task-oriented training” + “neuroregeneration” + “ischemic stroke”	0	0	0	0	0
“electromyography biofeedback” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“EMG biofeedback” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“repetitive transcranial magnetic stimulation” + “neurorestoration” + “ischemic stroke”	0	0	9	0	9
“rTMS” + “neurorestoration” + “ischemic stroke”	0	0	6	0	6
“transcranial direct current stimulation” + “neurorestoration” + “ischemic stroke”	0	2	7	0	9
“tDCS” + “neurorestoration” + “ischemic stroke”	0	2	5	0	7
“virtual reality” + “neurorestoration” + “ischemic stroke”	0	0	3	0	3
“augmented reality” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“mechatronic exoskeletons” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“robotic exoskeletons” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“mirroring” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“kinesiotherapy” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“multisensory stimulation” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“serious gaming” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“serious games” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“electrical stimulation” + “neurorestoration” + “ischemic stroke”	0	0	20	0	20
“functional electrical stimulation” + “neurorestoration” + “ischemic stroke”	0	0	2	0	2
“FES” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“neuromuscular electrical stimulation” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“NMES” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“cognitive training” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“cognitive rehabilitation” + “neurorestoration” + “ischemic stroke”	0	0	2	0	2
“enriched environment” + “neurorestoration” + “ischemic stroke”	0	0	16	0	16
“environmental enrichment” + “neurorestoration” + “ischemic stroke”	0	0	9	0	9
“neurologic music therapy” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“NMT” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“physical exercise” + “neurorestoration” + “ischemic stroke”	0	0	12	0	12
“constraint-induced movement therapy” + “neurorestoration” + “ischemic stroke”	0	0	3	0	3
“CIMT” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0
“task-oriented training” + “neurorestoration” + “ischemic stroke”	0	0	0	0	0

Table 1. Continued.

Keywords	Elsevier	PubMed	PMC	PEDro	Total
“electromyography biofeedback” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“EMG biofeedback” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“repetitive transcranial magnetic stimulation” + “brain repair” + “ischemic stroke”	0	0	20	0	20
“rTMS” + “brain repair” + “ischemic stroke”	0	0	18	0	18
“transcranial direct current stimulation” + “brain repair” + “ischemic stroke”	0	0	26	0	26
“tDCS” + “brain repair” + “ischemic stroke”	0	0	23	0	23
“virtual reality” + “brain repair” + “ischemic stroke”	0	0	14	0	14
“augmented reality” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“mechatronic exoskeletons” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“robotic exoskeletons” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“mirroring” + “brain repair” + “ischemic stroke”	0	0	13	0	13
“kinesiotherapy” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“multisensory stimulation” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“serious gaming” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“serious games” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“electrical stimulation” + “brain repair” + “ischemic stroke”	0	0	50	0	50
“functional electrical stimulation” + “brain repair” + “ischemic stroke”	0	0	7	0	7
“FES” + “brain repair” + “ischemic stroke”	0	0	3	0	3
“neuromuscular electrical stimulation” + “brain repair” + “ischemic stroke”	0	0	3	0	3
“NMES” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“cognitive training” + “brain repair” + “ischemic stroke”	0	0	6	0	6
“cognitive rehabilitation” + “brain repair” + “ischemic stroke”	0	0	13	0	13
“enriched environment” + “brain repair” + “ischemic stroke”	0	0	65	0	65
“environmental enrichment” + “brain repair” + “ischemic stroke”	0	0	46	0	46
“neurologic music therapy” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“NMT” + “brain repair” + “ischemic stroke”	0	0	0	0	0
“physical exercise” + “brain repair” + “ischemic stroke”	0	2	45	0	47
“constraint-induced movement therapy” + “brain repair” + “ischemic stroke”	0	0	24	0	24
“CIMT” + “brain repair” + “ischemic stroke”	0	0	10	0	10
“task-oriented training” + “brain repair” + “ischemic stroke”	0	0	7	0	7
“electromyography biofeedback” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“EMG biofeedback” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“repetitive transcranial magnetic stimulation” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“rTMS” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“transcranial direct current stimulation” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“tDCS” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“virtual reality” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“augmented reality” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“mechatronic exoskeletons” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“robotic exoskeletons” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“mirroring” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“kinesiotherapy” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“multisensory stimulation” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“serious gaming” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“serious games” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“electrical stimulation” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“functional electrical stimulation” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“FES” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“neuromuscular electrical stimulation” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“NMES” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“cognitive training” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“cognitive rehabilitation” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“enriched environment” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“environmental enrichment” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“neurologic music therapy” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“NMT” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“physical exercise” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“constraint-induced movement therapy” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“CIMT” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
“task-oriented training” + “neuralrestoration” + “ischemic stroke”	0	0	0	0	0
Total	**0**	**6**	**702**	**0**	**708**

[41]. Thus, it is considered that "Neuroregeneration involves synthesizing new neurons and connections, providing extra resources in the long term to replace those damaged by the injury, and achieving a lasting functional recovery" [42]. Referring to this complex—including taxonomically complicated to be structured —and not yet completely understood, advanced multidisciplinary domain, Modo proposes an interesting and quite exhaustive tabular synthesis of the terms connected to the histological—and consecutive functional—related to the recovery and regeneration concepts [43]; also: "Neurorecovery is the positive outcome that produces clinically relevant results with immediate functional and late structural effects" [14]. At the same time it has to be acknowledged the negative possible (unfortunately not seldom) way of evolution after a CNS, including of the brain: "... when neurons are deeply damaged, functional recovery is impossible" [44]. To be noted that one of the word recovery's synonyms is restoration and in this context, to be evoked the pragmatic vision on this matter of the International Association of Neurorestoratology, which "… recognizes the importance of small functional gains that have significant effects on quality of life" [45]; this is taking into account the enormous difficulty and hurdles still to be overcame in purpose to achieve, in the future, especially in severe impairments of the CNS, respectively the brain, effective and complete heal (although among synonyms of this latter word are: restore [46], regenerate, repair —specifically defined by Cramer: "Neural repair can be defined as restoring the structure or function of the central nervous system (CNS) after injury such as stroke" [47] or specifically, by Carmichael: "The basic or elemental properties of neural repair include axonal sprouting, neurogenesis, gliogenesis, and changes in neuronal excitability in peri-infarct tissue" [48]). A component based taxonomic attempt, considers neurorestoration to consist of two principal kinds of therapeutic-rehabilitative interventions: cell replacement/transplantation (including with the afferent, growing in importance field of tissue engineering)—with not yet translational to clinic significant results —and neuromodulation, with invasive and non-invasive procedures; among the latter category: repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), cerebellar stimulation and respectively, some effects within brain-computer/machine interfaces (BCI/BMI)—larger clinically availed, but likewise, still needing for more related research [49].

On a larger perspective—and this is the reason we have chosen this overall paradigm to approach our work—"Neurorestoratology is the subdiscipline of neuroscience that studies neural regeneration, repair, and replacement of damaged components of the nervous system, neuroplasticity, neuroprotection, and neuro-modulatory mechanisms of recovery" [45]. The (limited) post, including ischemic, stroke, brain—and further: functional—recovery, are based, at intimate level, including/mainly on re-construction processes, that share some pathways with neurodevelopment, without being identical: "Regeneration does not recapitulate development" [48]. On a related note, concerning dynamics of such phenomena—with consistent nuances, not always completely matching, between diverse authors—there are synthesized several main phases, "partially overlapping" [50], of such "functional recovery" [50]: "Three epochs of recovery have been identified including two early phases, the acute phase and the subacute, and a third chronic phase" [51]. Within this dynamics (spontaneous but recommended to be complementary supported and augmented by matched with adequate—especially as framing within the respective stages—therapeutic-rehabilitative interventions), an important step is to overcome the early inhibition/remote dysfunctional consequences (diaschisis) of the post-brain, including ischemic, focal injury [52], and initiation of local broken-down/dead moieties elimination, and of reparative phenomena; then, come endogenous cell/tissue functional plasticity/"Rehabilitation and neural Repair" [53] and reorganization/adaptive shifts of previous specific pathways; eventually, occurs structural (neural, of support, synaptic and vascular) re-building—re-growth/sprouting —with establishing re-(or of new) connections/ "Goal-Specific Training and Repair" [35, 50, 51, 53]. Including in this direction seems to act the "rehabilitation training", as regards synaptogenesis—the basis of neuroplasticity and, in lesioned brain tissue, of connectivity restoring—i.e., by providing cues that, on one hand stimulates the so-called Hebbian, ones' functionality activation, and on the other, prevent related pruning but also synapses' unnecessary extending [43]. Additionally, very important and subtitle, as homeostatic tuning: "Neurons that fail to develop strong synaptic connections will undergo selective apoptosis" [54]. So, as "... connections in mammalian brains may undergo rewiring during learning and experience-dependent plasticity" (but related therapeutic/rehabilitative interventions must be cautiously balanced and controlled in order to avoid excessive—as extent and/or speed—rewiring, which may be withal/besides detrimental) [55], this strengthen one of—if not the—fundamental concept of Rehabilitation, including with NeuroRehabilitation, i.e., relearning [56]. And, since we have already entered the era of human trials on "… human neural stem cell (hNSC) therapy ..." including to combat chronic impairments after stroke, this connects with the need for rehabilitation, which is mandatory, since we do not have, by now, a prompt and complete cure of the CNS—including with the brain—especially severe lesions. Under such conditions appeared also the query concerning the interaction between these two kinds of medical intervention. Obviously, for now, there is no definitive conclusion in this respect (too), but we have found in the literature a need for related cautiousness: "... animal models of nonspecific physical therapies suggest that negative interactions are also possible" [57].

Considering this, neuroregeneration and brain repair, within neurorestoration, including after ischemic stroke, could it be understood, in a different perspective (even dynamic, following possible future progresses in the domain) that: from the above quoted one—corresponding to the nowadays, not spectacular, related reality—to an optimistic/ideal target total cure, with restitutio ad integrum, and consequently, without rehabilitation objectives remained to be aimed?

3. Materials and methods

As it can be determined, considering the domain approached: extremely complex, difficult and encompassing aspects still under debate—including as clinical application—we have achieved in the first part of the article, a brief/synthetic, prerequisite background concerning the definitions and possibilities to objectify processes—(if occurring)—of overall neurorestoration, based on neuroregeneration and brain repair, after ischemic stroke, and for this we have used—mainly but not exclusively—a free identified amount of bibliographic resources.

In order to present the state-of-the-art regarding the main currently availed non-invasive, non-pharmacological/biotechnological related interventions, we have accomplished a systematic and synthetic literature review, based on the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [58]. Accordingly, we have interrogated, employing in this respect, contextually, specific key words combinations/"syntaxes" (see Table 1), five medical international data bases: Elsevier [59], National Center for Biotechnology Information (NCBI)/PubMed [60], NCBI/PubMed Central (PMC) [61], Physiotherapy Evidence Database (PEDro) [62], and—just in order to verify whether the works found according to the respective key words combinations/"syntaxes" by which we have quested for bibliographic resources afferent to this systematic literature review, are published in ISI (Institute for Scientific Information—ex Thomson Reuters—currently administered by Clarivate Analytics) indexed journals—the renowned ISI Web of Knowledge/Science [59, 63, 64] database.

For our PRISMA-type method, adapted flow diagram of bibliographic resources search and filter/ selection, we considered only free full-text available papers, written in English, and appeared between 01.01., 2016-31.12., 2020. After this first step, in the second one, we removed duplicates (same work found in two or more data bases); in the third step we checked for and retained only those works issued in ISI indexed publications. In the fourth step we evaluated indirectly the scientific impact/quality of each of the remaining articles, using an own, customized, quantification weighted algorithm [65]—PEDro classification/scoring-inspired—considering eligible the works that obtained a score of at least 4 ("fair quality = PEDro score 4–5") [66]; in the fifth step we made a direct qualitative analysis of the, by now, 114 selected articles and eliminated those which although seemed eligible according to the above mentioned criteria, eventually, after analyzing their full texts ("full-text articles excluded, with reasons" [58]), we determined they did not contain information with consistent connection to our subject, and consequently we have thus made also a final qualitative and quantitative selection: ultimately we kept and used information elicited from 83 papers (see Fig. 1—showing our completed, adapted PRISMA-type of flow diagram—and respectively, Table 2 (Ref. [3, 5–9, 13, 15, 16, 19–23, 25–29, 33, 34, 41, 43, 44, 47–49, 51, 54, 56, 57, 67–117]—with authors, titles, journals and related links to the finally selected works within our systematic literature review); to be mentioned that despite thoroughly fulfilled the PRISMA-type method of search and selection for this systematic literature review, some works of interest could, however, be missed. On the other hand, we reckon appropriate, freely found, bibliographic resources, added to those acquired/selected according to the above described standardized method, can be—and proved so—helpful to enhance knowledge on the subject approached.

4. Results

We start this section by re-asserting that unfortunately, at present, there is no kind of intervention [115] able to effectively heal (and among synonyms of this latter word are: regenerate, repair, restore [46]) the CNS – respectively brain – lesions, including those of post ischemic stroke.

So, for—at least some—non-invasive, non-pharmacological/biotechnological interventions, is worth to be emphasized that "Traditional rehabilitation therapy including physical therapy, occupational therapy and speech therapy appears to be the only available treatment for stroke survivors in the subacute phase …", and "… advanced physical rehabilitation …" together with medicines [3] and maybe other types of (non-invasive or invasive) dedicated procedures, are practically the actual interventional possibilities to obtain some beneficial outcomes and to continue "functional improvement", in the chronic stage. More detailed but however, in a synthetic enumeration, aside different passive physiotherapy interventions non-invasive, non-pharmacological/biotechnological ones in these later phase/stage mainly consist of: inpatient, alternating with domiciliary, related cares, plus—to be continued, according to the bio-functional, constantly monitored, patient's availability—kinesiotherapy of adequate aims, methods and dosage (including with "task-oriented training", "repetitive task training"), sensory and speech/communication [7], as well as cognitive, rehabilitation procedures. Yet, "... during the chronic stage, physical and cognitive rehabilitation therapies might

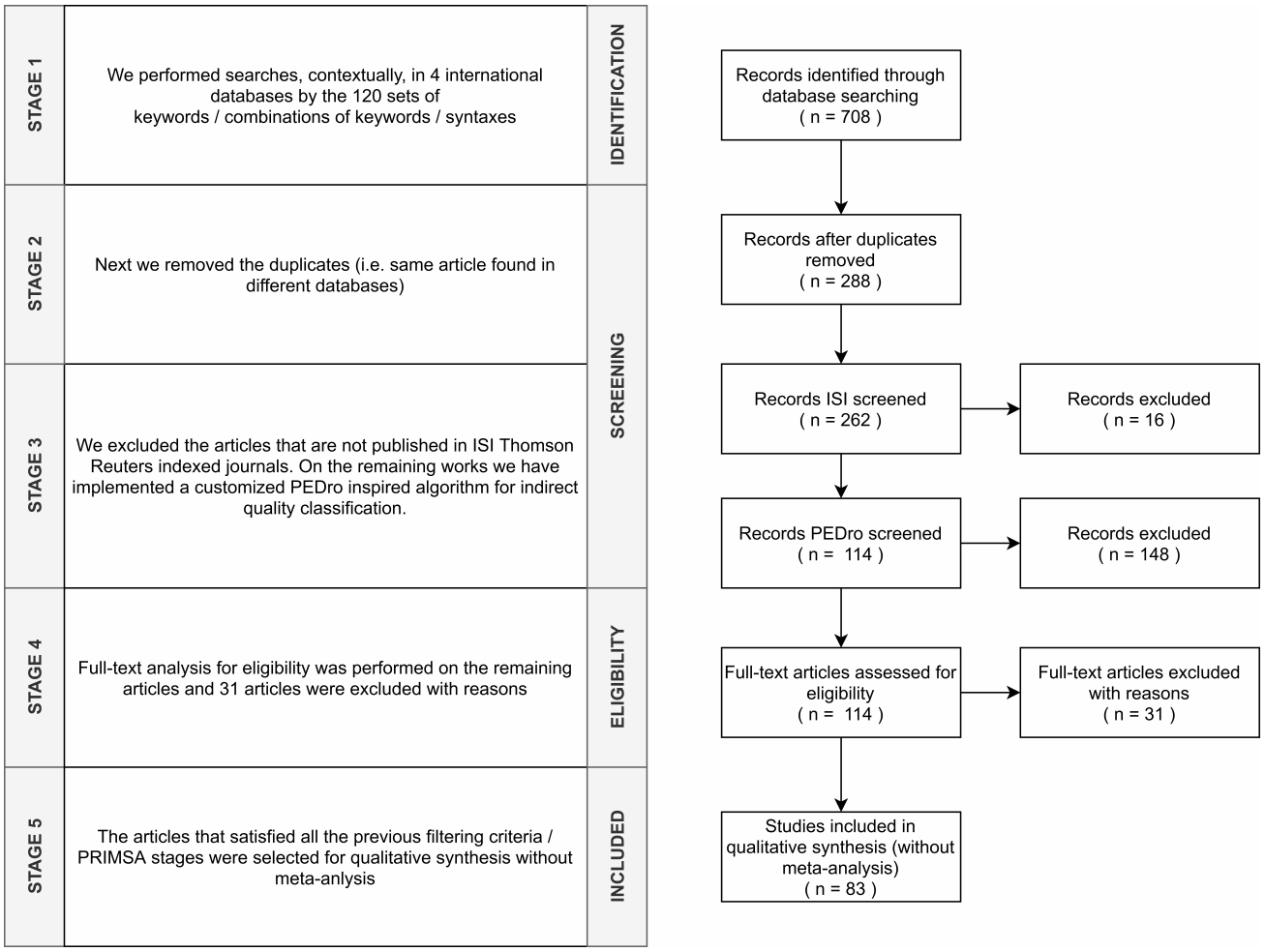

Fig. 1. Our adapted PRISMA-type of flow diagram.

work in a minority of patients, especially in subjects with less extensive damage after the initial insult ..." [118]. Consequently, this (still) unsatisfactory situation regarding the therapeutic-rehabilitative related outcomes obtained is—aside the fully understandable huge expectation for the related cure—a very solid rationale for our actual—including of reappraisal kind—endeavor.

Considering, on one hand, their current considerable amount and quite vast diversity, and on the other, the fact that—at least some of them—are either mixed, overlapping between different categories of such interventions, and/or taxonomically difficult/ debatable on being very precisely arranged in classes, we have chosen to structure the presentation of the main non-invasive, non-pharmacological/biotechnological interventions (detailing the mainly physiatric ones) towards overall neurorestoration, based on neuroregeneration and brain repair after ischemic stroke, by their names, i.e., alphabetically. Taking into account the fairly, always limited editorial space, we shall not detail related methodological aspects, but just remind the "... activity-dependent neuroplasticity principles that should be applied to rehabilitation programs in humans with brain damage ..."—which are enumerated in the literature: "... task specificity, repetition, salience, timing, and intensity ..." [85].

4.1 Biofeedback

Biofeedback, as therapeutic-rehabilitative method, is a non-invasive [119] "mind-body" [120] "self-regulation" [121] training technique by which patients are instructed and proceed to improve their voluntary control over somatic (motricity performances, muscle tone), autonomic and/or cognitive/psychological, functions (also on pain, epilepsy etc.). Basically, this method converts, through dedicated apparatus (endowed with electrodes, sensors), "... bodily signals indicative of such functions" into light/image (numbers, also possible avatar) and/or acoustic, ones; their magnitude or respectively, correctness towards a given task, objectify—if exists—the progress in the function to be trained [119, 121]. "Surface electromyography (sEMG) is perhaps the most common physiological variable monitored using biofeedback" [120]. (Bio-)/Neurofeedback (NF) [120, 121] "… is a research and clinical technique, characterized by live demonstration of brain activation to the subject …" of co-

Table 2. The articles that satisfied all the previous filtering criteria/PRISMA stages selected for qualitative synthesis without meta-analysis.

Article	Publication year	Citation count	PEDro score	Reference
Reggie H. C. Lee, Michelle H. H. Lee, Celeste Y. C. Wu, Alexandre Couto e Silva, Harlee E. Possoit, Tsung-Han Hsieh, Alireza Minagar, Hung Wen Lin - Cerebral ischemia and neuroregeneration - Neural Regen Res. 2018 Mar; 13(3): 373–385. doi: 10.4103/1673-5374.228711	2018	66	10	[67]
Li-Ru Zhao, Alison Willing - Enhancing endogenous capacity to repair a stroke-damaged brain: An evolving field for stroke research - Prog Neurobiol. Author manuscript; available in PMC 2018 Aug 3. Published in final edited form as: Prog Neurobiol. 2018 Apr-May; 163-164: 5–26. Published online 2018 Feb 21. doi: 10.1016/j.pneurobio.2018.01.004	2018	53	10	[3]
Steven C. Cramer - Treatments to Promote Neural Repair after Stroke - J Stroke. 2018 Jan; 20(1): 57–70. Published online 2018 Jan 31. doi: 10.5853/jos.2017.02796	2018	61	10	[47]
Martina Coscia, Maximilian J Wessel, Ujwal Chaudary, José del R Millán, Silvestro Micera, Adrian Guggisberg, Philippe Vuadens, John Donoghue, Niels Birbaumer, Friedhelm C Hummel - Neurotechnology-aided interventions for upper limb motor rehabilitation in severe chronic stroke - Brain. 2019 Aug; 142(8): 2182–2197. Published online 2019 Jul 1. doi: 10.1093/brain/awz181	2019	41	10	[68]
Ceren Eyileten, Lucia Sharif, Zofia Wicik, Daniel Jakubik, Joanna Jarosz-Popek, Aleksandra Soplinska, Marek Postula, Anna Czlonkowska, Agnieszka Kaplon-Cieslicka, Dagmara Mirowska-Guzel - The Relation of the Brain-Derived Neurotrophic Factor with MicroRNAs in Neurodegenerative Diseases and Ischemic Stroke - Mol Neurobiol. 2021; 58(1): 329–347. Published online 2020 Sep 17. doi: 10.1007/s12035-020-02101-2	2021	11	10	[69]
S. Thomas Carmichael - Emergent properties of neural repair: elemental biology to therapeutic concepts - Ann Neurol. 2016 Jun; 79(6): 895–906. Published online 2016 Apr 21. doi: 10.1002/ana.24653	2016	81	10	[48]
Christine Tschoe, Cheryl D. Bushnell, Pamela W. Duncan, Martha A. Alexander-Miller, Stacey Q. Wolfe - Neuroinflammation after Intracerebral Hemorrhage and Potential Therapeutic Targets - J Stroke. 2020 Jan; 22(1): 29–46. Published online 2020 Jan 31. doi: 10.5853/jos.2019.02236	2020	41	10	[19]
Aurel Popa-Wagner, Dinu Iuliu Dumitrascu, Bogdan Capitanescu, Eugen Bogdan Petcu, Roxana Surugiu, Wen-Hui Fang, Danut-Adrian Dumbrava - Dietary habits, lifestyle factors and neurodegenerative diseases - Neural Regen Res. 2020 Mar; 15(3): 394–400. Published online 2019 Sep 26. doi: 10.4103/1673-5374.266045	2020	20	10	[70]
Vittorio Emanuele Bianchi, Vittorio Locatelli, Laura Rizzi - Neurotrophic and Neuroregenerative Effects of GH/IGF1 - Int J Mol Sci. 2017 Nov; 18(11): 2441. Published online 2017 Nov 17. doi: 10.3390/ijms18112441	2017	64	10	[44]
John D. Sinden, Caroline Hicks, Paul Stroemer, Indira Vishnubhatla, Randolph Corteling - Human Neural Stem Cell Therapy for Chronic Ischemic Stroke: Charting Progress from Laboratory to Patients - Stem Cells Dev. 2017 Jul 1; 26(13): 933–947. Published online 2017 Jul 1. doi: 10.1089/scd.2017.0009	2017	46	10	[57]
Andrew Vogel, Raghavendra Upadhya, Ashok K. Shetty - Neural stem cell derived extracellular vesicles: Attributes and prospects for treating neurodegenerative disorders - EBioMedicine. 2018 Dec; 38: 273–282. Published online 2018 Nov 22. doi: 10.1016/j.ebiom.2018.11.026	2018	37	10	[71]
Nils Lannes, Elisabeth Eppler, Samar Etemad, Peter Yotovski, Luis Filgueira - Microglia at center stage: a comprehensive review about the versatile and unique residential macrophages of the central nervous system - Oncotarget. 2017 Dec 26; 8(69): 114393–114413. Published online 2017 Dec 11. doi: 10.18632/oncotarget.23106	2017	53	10	[21]
Bożena Adamczyk, Monika Adamczyk-Sowa - New Insights into the Role of Oxidative Stress Mechanisms in the Pathophysiology and Treatment of Multiple Sclerosis - Oxid Med Cell Longev. 2016; 2016: 1973834. Published online 2016 Oct 18. doi: 10.1155/2016/1973834	2016	77	10	[29]
Clemens J. Sommer - Ischemic stroke: experimental models and reality - Acta Neuropathol. 2017; 133(2): 245–261. Published online 2017 Jan 7. doi: 10.1007/s00401-017-1667-0	2017	225	10	[72]
Jing Luo, Haiqing Zheng, Liying Zhang, Qingjie Zhang, Lili Li, Zhong Pei, Xiquan Hu - High-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Improves Functional Recovery by Enhancing Neurogenesis and Activating BDNF/TrkB Signaling in Ischemic Rats - Int J Mol Sci. 2017 Feb; 18(2): 455. Published online 2017 Feb 20. doi: 10.3390/ijms18020455	2017	48	10	[73]
Yunxiang Zhou, Anwen Shao, Yihan Yao, Sheng Tu, Yongchuan Deng, Jianmin Zhang - Dual roles of astrocytes in plasticity and reconstruction after traumatic brain injury - Cell Commun Signal. 2020; 18: 62. Published online 2020 Apr 15. doi: 10.1186/s12964-020-00549-2	2020	25	10	[23]
Shenbin Xu, Jianan Lu, Anwen Shao, John H. Zhang, Jianmin Zhang - Glial Cells: Role of the Immune Response in Ischemic Stroke - Front Immunol. 2020; 11: 294. Published online 2020 Feb 26. doi: 10.3389/fimmu.2020.00294	2020	23	10	[20]
Wai Ping Yew, Natalia D. Djukic, Jaya S. P. Jayaseelan, Frederick R. Walker, Karl A. A. Roos, Timothy K. Chataway, Hakan Muyderman, Neil R. Sims - Early treatment with minocycline following stroke in rats improves functional recovery and differentially modifies responses of peri-infarct microglia and astrocytes - J Neuroinflammation. 2019; 16: 6. Published online 2019 Jan 9. doi: 10.1186/s12974-018-1379-y	2019	28	10	[15]

Table 2. Continued.

Article	Publication year	Citation count	PEDro score	Reference
Mark A. Hirsch, Erwin E. H. van Wegen, Mark A. Newman, Patricia C. Heyn - Exercise-induced increase in brain-derived neurotrophic factor in human Parkinson's disease: a systematic review and meta-analysis - Transl Neurodegener. 2018; 7: 7. Published online 2018 Mar 20. doi: 10.1186/s40035-018-0112-1	2018	47	10	[74]
Lauren N. Miterko, Kenneth B. Baker, Jaclyn Beckinghausen, Lynley V. Bradnam, Michelle Y. Cheng, Jessica Cooperrider, Mahlon R. DeLong, Simona V. Gornati, Mark Hallett, Detlef H. Heck, Freek E. Hoebeek, Abbas Z. Kouzani, Sheng-Han Kuo, Elan D. Louis, Andre Machado, Mario Manto, Alana B. McCambridge, Michael A. Nitsche, Nordeyn Oulad Ben Taib, Traian Popa, Masaki Tanaka, Dagmar Timmann, Gary K. Steinberg, Eric H. Wang, Thomas Wichmann, Tao Xie, Roy V. Sillitoe - Consensus Paper: Experimental Neurostimulation of the Cerebellum - Cerebellum. 2019; 18(6): 1064–1097. Published online 2019 Jun 4. doi: 10.1007/s12311-019-01041-5	2019	40	10	[75]
L. J. Volz, A. K. Rehme, J. Michely, C. Nettekoven, S. B. Eickhoff, G. R. Fink, C. Grefkes - Shaping Early Reorganization of Neural Networks Promotes Motor Function after Stroke - Cereb Cortex. 2016 Jun; 26(6): 2882–2894. Published online 2016 Mar 14. doi: 10.1093/cercor/bhw034	2016	62	10	[76]
Swathi Kiran, Cynthia K. Thompson - Neuroplasticity of Language Networks in Aphasia: Advances, Updates, and Future Challenges - Front Neurol. 2019; 10: 295. Published online 2019 Apr 2. doi: 10.3389/fneur.2019.00295	2019	50	10	[51]
Jack J. Q. Zhang, Kenneth N. K. Fong, Nandana Welage, Karen P. Y. Liu - The Activation of the Mirror Neuron System during Action Observation and Action Execution with Mirror Visual Feedback in Stroke: A Systematic Review - Neural Plast. 2018; 2018: 2321045. Published online 2018 Apr 24. doi: 10.1155/2018/2321045	2018	47	10	[77]
Samuel J. Geiseler, Cecilie Morland - The Janus Face of VEGF in Stroke - Int J Mol Sci. 2018 May; 19(5): 1362. Published online 2018 May 4. doi: 10.3390/ijms19051362	2018	56	10	[78]
Nathalie Percie du Sert, Amrita Ahluwalia, Sabina Alam, Marc T. Avey, Monya Baker, William J. Browne, Alejandra Clark, Innes C. Cuthill, Ulrich Dirnagl, Michael Emerson, Paul Garner, Stephen T. Holgate, David W. Howells, Viki Hurst, Natasha A. Karp, Stanley E. Lazic, Katie Lidster, Catriona J. MacCallum, Malcolm Macleod, Esther J. Pearl, Ole H. Petersen, Frances Rawle, Penny Reynolds, Kieron Rooney, Emily S. Sena, Shai D. Silberberg, Thomas Steckler, Hanno Würbel - Reporting animal research: Explanation and elaboration for the ARRIVE guidelines 2.0 - PLoS Biol. 2020 Jul; 18(7): e3000411. Published online 2020 Jul 14. doi: 10.1371/journal.pbio.3000411	2020	60	10	[79]
Martina Svensson, Philip Rosvall, Antonio Boza-Serrano, Emelie Andersson, Jan Lexell, Tomas Deierborg - Forced treadmill exercise can induce stress and increase neuronal damage in a mouse model of global cerebral ischemia - Neurobiol Stress. 2016 Dec; 5: 8–18. Published online 2016 Sep 9. doi: 10.1016/j.ynstr.2016.09.002	2016	60	10	[80]
Luis Federico Bátiz, Maite A. Castro, Patricia V. Burgos, Zahady D. Velásquez, Rosa I. Muñoz, Carlos A. Lafourcade, Paulina Troncoso-Escudero, Ursula Wyneken - Exosomes as Novel Regulators of Adult Neurogenic Niches - Front Cell Neurosci. 2015; 9: 501. Published online 2016 Jan 19. doi: 10.3389/fncel.2015.00501	2016	102	10	[81]
Jan Dąbrowski, Anna Czajka, Justyna Zielińska-Turek, Janusz Jaroszyński, Marzena Furtak-Niczyporuk, Aneta Mela, Łukasz A. Poniatowski, Bartłomiej Drop, Małgorzata Dorobek, Maria Barcikowska-Kotowicz, Andrzej Ziemba - Brain Functional Reserve in the Context of Neuroplasticity after Stroke - Neural Plast. 2019; 2019: 9708905. Published online 2019 Feb 27. doi: 10.1155/2019/9708905	2019	27	10	[5]
Elena Redondo-Castro, Catriona Cunningham, Jonjo Miller, Licia Martuscelli, Sarah Aoulad-Ali, Nancy J. Rothwell, Cay M. Kielty, Stuart M. Allan, Emmanuel Pinteaux - Interleukin-1 primes human mesenchymal stem cells towards an anti-inflammatory and pro-trophic phenotype in vitro - Stem Cell Res Ther. 2017; 8: 79. Published online 2017 Apr 17. doi: 10.1186/s13287-017-0531-4	2017	96	10	[82]
Azad TD, Veeravagu A, Steinberg GK. - Neurorestoration after stroke. - Neurosurg Focus. 2016 May;40(5):E2. doi: 10.3171/2016.2.FOCUS15637.	2016	47	9	[49]
Ya Zheng, Ye-Ran Mao, Ti-Fei Yuan, Dong-Sheng Xu, Li-Ming Cheng - Multimodal treatment for spinal cord injury: a sword of neuroregeneration upon neuromodulation - Neural Regen Res. 2020 Aug; 15(8): 1437–1450. Published online 2020 Jan 28. doi: 10.4103/1673-5374.274332	2020	15	9	[83]
S. M. Mahmudul Hasan, Samantha N. Rancourt, Mark W. Austin, Michelle Ploughman - Defining Optimal Aerobic Exercise Parameters to Affect Complex Motor and Cognitive Outcomes after Stroke: A Systematic Review and Synthesis - Neural Plast. 2016; 2016: 2961573. Published online 2016 Jan 10. doi: 10.1155/2016/2961573	2016	45	9	[56]
Thirunavukkarasu Velusamy, Archana S. Panneerselvam, Meera Purushottam, Muthuswamy Anusuyadevi, Pramod Kumar Pal, Sanjeev Jain, Musthafa Mohamed Essa, Gilles J. Guillemin, Mahesh Kandasamy - Protective Effect of Antioxidants on Neuronal Dysfunction and Plasticity in Huntington's Disease - Oxid Med Cell Longev. 2017; 2017: 3279061. Published online 2017 Jan 12. doi: 10.1155/2017/3279061	2017	35	8	[25]
Yoshiki Hase, Lucinda Craggs, Mai Hase, William Stevenson, Janet Slade, Dianne Lopez, Rubin Mehta, Aiqing Chen, Di Liang, Arthur Oakley, Masafumi Ihara, Karen Horsburgh, Raj N. Kalaria - Effects of environmental enrichment on white matter glial responses in a mouse model of chronic cerebral hypoperfusion - J Neuroinflammation. 2017; 14: 81. Published online 2017 Apr 11. doi: 10.1186/s12974-017-0850-5	2017	34	8	[84]

Table 2. Continued.

Article	Publication year	Citation count	PEDro score	Reference
Megan Finch-Edmondson, Catherine Morgan, Rod W. Hunt, Iona Novak - Emergent Prophylactic, Reparative and Restorative Brain Interventions for Infants Born Preterm With Cerebral Palsy - Front Physiol. 2019; 10: 15. Published online 2019 Jan 28. doi: 10.3389/fphys.2019.00015	2019	20	8	[85]
Meidan Fang, Lili Zhong, Xin Jin, Ranji Cui, Wei Yang, Shuohui Gao, Jing Lv, Bingjin Li, Tongjun Liu - Effect of Inflammation on the Process of Stroke Rehabilitation and Poststroke Depression - Front Psychiatry. 2019; 10: 184. Published online 2019 Apr 11. doi: 10.3389/fpsyt.2019.00184	2019	22	8	[86]
Aatman M. Shah, Shunsuke Ishizaka, Michelle Y. Cheng, Eric H. Wang, Alex R. Bautista, Sabrina Levy, Daniel Smerin, Guohua Sun, Gary K. Steinberg - Optogenetic neuronal stimulation of the lateral cerebellar nucleus promotes persistent functional recovery after stroke - Sci Rep. 2017; 7: 46612. Published online 2017 Jun 1. doi: 10.1038/srep46612	2017	35	8	[87]
Saba Naqvi, Archna Panghal, S. J. S. Flora - Nanotechnology: A Promising Approach for Delivery of Neuroprotective Drugs - Front Neurosci. 2020; 14: 494. Published online 2020 Jun 9. doi: 10.3389/fnins.2020.00494	2020	14	8	[88]
Linda Ottoboni, Beatrice von Wunster, Gianvito Martino - Therapeutic Plasticity of Neural Stem Cells - Front Neurol. 2020; 11: 148. Published online 2020 Mar 20. doi: 10.3389/fneur.2020.00148	2020	14	8	[41]
Qwang-Yuen Chang, Yi-Wen Lin, Ching-Liang Hsieh - Acupuncture and neuroregeneration in ischemic stroke - Neural Regen Res. 2018 Apr; 13(4): 573–583. doi: 10.4103/1673-5374.230272	2018	23	7	[89]
Jingwei Mu, Abdulhameed Bakreen, Miia Juntunen, Paula Korhonen, Ella Oinonen, Lili Cui, Mikko Myllyniemi, Shanshan Zhao, Susanna Miettinen, Jukka Jolkkonen - Combined Adipose Tissue-Derived Mesenchymal Stem Cell Therapy and Rehabilitation in Experimental Stroke - Front Neurol. 2019; 10: 235. Published online 2019 Mar 26. doi: 10.3389/fneur.2019.00235	2019	18	7	[90]
Parker E. Ludwig, Finosh G. Thankam, Arun A. Patil, Andrea J. Chamczuk, Devendra K. Agrawal - Brain injury and neural stem cells - Neural Regen Res. 2018 Jan; 13(1): 7–18. doi: 10.4103/1673-5374.224361	2018	25	7	[6]
Rafał Szelenberger, Joanna Kostka, Joanna Saluk-Bijak, Elżbieta Miller - Pharmacological Interventions and Rehabilitation Approach for Enhancing Brain Self-repair and Stroke Recovery - Curr Neuropharmacol. 2020 Jan; 18(1): 51–64. Published online 2020 Jan. doi: 10.2174/1570159X17666190726104139	2020	11	6	[91]
Cesar Reis, Vadim Gospodarev, Haley Reis, Michael Wilkinson, Josileide Gaio, Camila Araujo, Sheng Chen, John H. Zhang - Traumatic Brain Injury and Stem Cell: Pathophysiology and Update on Recent Treatment Modalities - Stem Cells Int. 2017; 2017: 6392592. Published online 2017 Aug 9. doi: 10.1155/2017/6392592	2017	25	6	[13]
Juan Du, Fang Yang, Jianping Hu, Jingze Hu, Qiang Xu, Nathan Cong, Qirui Zhang, Ling Liu, Dante Mantini, Zhiqiang Zhang, Guangming Lu, Xinfeng Liu - Effects of high- and low-frequency repetitive transcranial magnetic stimulation on motor recovery in early stroke patients: Evidence from a randomized controlled trial with clinical, neurophysiological and functional imaging assessments - Neuroimage Clin. 2019; 21: 101620. Published online 2018 Dec 3. doi: 10.1016/j.nicl.2018.101620	2019	16	6	[92]
Paula H. Heikkinen, Friedemann Pulvermüller, Jyrki P. Mäkelä, Risto J. Ilmoniemi, Pantelis Lioumis, Teija Kujala, Riitta-Leena Manninen, Antti Ahvenainen, Anu Klippi - Combining rTMS With Intensive Language-Action Therapy in Chronic Aphasia: A Randomized Controlled Trial - Front Neurosci. 2018; 12: 1036. Published online 2019 Feb 4. doi: 10.3389/fnins.2018.01036	2019	16	6	[93]
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Table 2. Continued.

Article	Publication year	Citation count	PEDro score	Reference
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urse being, as well, an auto-checking for the own results on different tasks achievement by the user, and thus prone to improve his/her respective functional performances, together with "training of brain self-regulation"; classically, this is given through EEG, but more recently it may be provided—with higher "… spatial resolution and fidelity …"—by fMRI, i.e., fMRI-NF (but also by fNIRS and/or MEG [121]).

Conceptually and practically, this method, including with its latter mentioned variant, is an example of (re-)learning/neuroplasticity based training, targeting for instance, in post—also ischemic—stroke, rehabilitation, the brain networks and related functionality, with sometimes difficult choice to be made between stimulating "... compensatory networks …", or "… to shape brain networks towards more typical functioning" [121]. On the way of technical progresses—and presumably, their benefits for clinical practice—it is considered, based on animal studies, that associating to such interventions (especially to ones more elaborated) elements of virtual and/or augmented reality—and/or other components of an "environmental enrichment (EE)" (including with "... exercise, socialization, cognitive stimulation" [122])—may augment the beneficiaries' experience, motivation [121], and consequent (re-)learning efficiency; this seems to be (based on "... enhanced hippocampal neurogenesis ...", which would occur when cognitive training entails more complex/challenging specific tasks (for example "... where two similar contexts needed to be distinguished"), resulting in bettered behavioral outcomes [123]. Mirror visual feedback (MVF) is also a form of non-invasive, non-pharmacological/biotechnological intervention towards overall neurorestoration/ neuroregeneration and brain repair after ischemic stroke, that shall be approached further, within the mirror therapy subsection.

4.2 Brain-computer/machine interface (BCI/BMI)

Brain-computer/machine interface (BCI/BMI) therapy is still a rather: new and based on advanced and demanding technology and is mainly addressing post—including ischemic—stroke neurorehabilitation in the chronic stage, when some availability for adaptive neuroplasticity and consequent functional recovery gain, seem to consolidate and persist. By the principle of the way they work, there is (also) an important likeness with NF: such related "… devices allow for real-time feedback of neural activity, which can then be used to train and/or modulate neural activity while performing guided rehabilitative tasks" [124]. Specifically, "signals to trigger an action ..." ("provided by different types of switches …" [65], such as EEG bio-signals afferent to motor voluntary commands—collected in the non-invasive paradigm: "… over the motor cortex") are 'deciphered' and coded into informatic language, which, first, enables the patient to control the shifting of a cursor on a display—for preparatory training: that is "… performed with no external stimuli (i.e., visual feedback only) …"—and subsequently, the respective digital inputs serve to achieve physic functional tasks using "… the addition of triggered FES …" (possibly also with "… tongue stimulation") [124] and/or to compensate the movement capability that has been lost by the, thus, controlled motions of artificial actuators [65, 125–128].

Concerning dose-response, higher levels of most of the parameters involved (mainly: intensity, duration, maybe frequency of BCI/BMI sessions) appear prone to better results, at least regarding force, but supplementary research is needed for delineating more definite related paradigms [124]. Further details on this subject can be found elsewhere [65, 125, 126].

4.3 Cognitive rehabilitation/training

Cognitive rehabilitation/training may be defined, from our subject's point of view, "… as a therapeutic strategy to improve and maintain cognitive skills in patients with stroke", including with Enriched environment (EE)—that can support cognitive rehabilitation by favoring an enhanced patients' interaction with the (enriched) ambient, and thus promoting, through neuroplasticity based (re)-learning and other intimate recovery pathways (see at the subsection dedicated to EE), the (re-)gain of somatic-functional, mental and social, capabilities [129], and no less important: their overall QOL. To be noted that, at intimate level, learning is considered among "positive regulators" of "… the levels of neurogenesis in the adult brain …" [114]; as for the clinical one, neuropsychological impairments of (alphabetically): attention, calculation, memory, praxis, spatial perception, speech, kinds, following (also) ischemic stroke, need and may benefit of rehabilitative approaches (which likewise, basically underpin, as afore emphasized, on re-learning); thus, cognition could be improved by training for both: resuming/consolidating, and respectively, gaining new related skills and/or through the development of compensatory, coping—considering existing neuro-dysfunctionalities, especially when they are severe/irreversible—behavioral strategies [130]. Hence, cognitive rehabilitation constitutes "… an important area of neurological rehabilitation" that tackles, through dedicated training methods, each of the above enumerated disorders. An interesting overlapping, rather extended, indication for cognitive rehabilitation is unilateral spatial neglect (USN)/hemineglect—a recently reported as very frequent consequence among inpatients with "right hemisphere stroke" admitted to rehabilitation, if evaluated through a "sensitive measure, the CBS" (Catherine Bergego Scale o. n.) [131]—too (entailing also/together with physiatric type of interventions—see further—including with "… vestibular stimulation by cold-water infusion into the left outer ear canal …" and/or neck muscle vibration). Thereby, for the cognitive rehabilitation/training are availed (even combined) an array of procedures like: "... training of visual scanning, reading, copying ... figure description ...,

spatiomotor or visuo-motor cueing..." (possibly with "kinetic stimuli" added), "... video ... and visuo-motor feedback", "multisensory representations", "computer training" [132] and/or monitored by feedback practice towards an improved achievement of verbally ordered/instructed "dual tasks", "discrimination reaction time", and distributive attention required by more difficult/challenging circumstances [133]. An, unfortunately still persisting global harsh burden, is the COVID-19 pandemic. The related severe need for adapting rather all the medical activities—and these are, by far, not the only ones: overall, our lives, too—has resulted in specific modalities to achieve, including—(see also in the Discussion section) cognitive rehabilitation at the patients' residences or in nursing homes, remotely. Specifically, digitalization as reliable infrastructural support, prone to a higher level of standardization, including for "cognitive exercises", thus became of growing interest and availability, with lowering, at the same time, the actual epidemiological risk [134, 135].

4.4 Constraint-induced movement therapy (CIMT)

Constraint-induced movement therapy (CIMT) is a quite consistently mentioned in the literature type of non-invasive, non-pharmacological/bio-technological intervention, being considered to bring, including in post-stroke motor disability, aside "robotics", "... Potentially beneficial treatment options for motor recovery of the arm" [136]. Obviously, this is a Kinesio-therapeutic method, but as it encompasses some nuanced underpinning neuro-physiological/pathological items, we have chosen to present it separately. Although since earlier reports on CIMT have been issued [137], subsequently, deeper/sophisticated explanations and related neuro-(path)physiological theories, appeared (for instance: "reactivation" in the damaged zone and "rebalancing" communication between hemispheres—to thus combat maladaptive plasticity [138]) regarding the complicated relationships between different activator and inhibitor stimuli and their influence on brain plasticity—towards motor behavior and consequent methods to train it in impairments, secondary (including) to stroke—there is a rather simple, basic, general conceptual overview on it, claiming that "The common therapeutic factor in all CI Therapy techniques would appear to be inducing concentrated, repetitive practice of use of the more-affected limb" [137]. The related targeted underlying patho-physiologic process refers to the fact that "In patients with chronic stroke, the primary motor cortex of the intact hemisphere (M1(intact hemisphere)) may influence functional recovery, possibly through transcallosal effects exerted over M1 in the lesioned hemisphere (M1(lesioned hemisphere))" [139]. More precisely, there seems to be a quite subtle and complex interference: the non-affected hemisphere exerts, including as regards plasticity, an inhibitory influence on the lesioned one (which if combated—respectively through CIMT—and/or if facilitating the excitability of the affected primary motor cortex, would result in an indirect effect of favoring "… functional recovery"), but—as it has already became of common knowledge: dialectically antagonistically—the respective inhibition is also somehow beneficial, as it might protect against post injury overactive consequences, such as secondary epilepsy [138, 140]. Furthermore, CIMT, likewise task-oriented training (TOT), may stimulate, as well, modifications in brain connectivity, respectively mapping, through modulation, in Hebbian paradigm, of "synaptic plasticity" [141]. Therefore, CIMT appears to be a rater accessible, clinical-therapeutic-rehabilitative type of intervention to modulate brain plasticity, towards mitigating—through the less paretic's arm immobilization—the cortical motor excitability in the non-lesioned hemisphere (classically but not exclusively). Consequently, this "metaplasticity" based mechanism would enhance, competitively between homologue regions of the hemispheres [138] (i.e., "... reducing transcallosal inhibition from this region towards the homologous area in the affected hemisphere" [18]), the voluntary movements in the more paretic limb, and their responsivity to associated/subsequent with/to training motor exercises, of "peripheral somatosensory stimulation (PSS)", (recommended to be added/combined within the post, including ischemic, stroke rehabilitation, as a strategy to valorize the both, central and peripheral, processes underpinning the aimed functional recovery) [18]. Yet, in the literature, there are to be found also conflicting related opinions: the "… long accepted model of detrimental interhemispheric inhibition of the overactive contralesional brain hemisphere on the ipsilesional hemisphere is based on an oversimplification and lack of differential knowledge and is thus called into question" [68]. Concerning dose-response, for such interventions—(and this may go not only for the CIMT, but for the below approached electrical stimulation, and respectively for "... Mobilization and Tactile Stimulation—(MTS)—which includes joint and soft-tissue mobilization and passive or active-assisted movement to enhance voluntary muscle contraction ..." [142], too —there is still need for further research data, in order to draw more reliable conclusions [124]. As for the timing of administration, it appears that initiation of CIMT rather earlier, in the subacute-subchronic phase, i.e., "… within 3–9 months post-stroke …" would provide higher improvement "… in several fine motor tasks …" than if it would start later, in the chronic phase, respectively over 9 months since the acute event [143].

4.5 Electrical stimulation (ES)—Functional electrical stimulation (FES); Neuromuscular electrical stimulation (NMES—favoring "motor re-learning", and/or with prophylactic indication, too [144]); Transcutaneous electrical nerve stimulation (TENS)

Generally, ES is nowadays a category of interventions largely used, including in neurorehabilitation, with neuro-: modulatory, restorative and regenerative,

properties—including as an adjunct to "… facilitate brain plasticity"—[102] that can serve to overall functional recovery, after—including ischemic—stroke, too. Actually, aside "... transcranial direct current stimulation, or transcranial magnetic stimulation after stroke …", ES is considered to improve the recovery processes, underpinned by "Enhancing cortical excitability …" [87].

Very important: "Apparently, non-invasive ES has superiority over invasive ones" [17]. The promising, *in vitro* and *ex vivo* regenerative action capabilities at intimate level of ES—i.e., to support the neuronal stem cells (NSCs)/neural precursor cells (NPCs) migration and differentiation/maturation, thus prone to (including post ischemic stroke) regeneration—need, yet, more translational confirmations [17]: "from benchside to bedside" [145]. Still, as nervous influx is, in fact, an electric current conditioned by specific parameters—mainly but not exclusively: low frequencies and intensities/voltages—physiologically tailored, and the connectivity entailing related "oscillatory patterns" [107] is disturbed, including by ischemic stroke, and also because "brain waves resonate from the generators of electrical current and propagate across brain regions with oscillation frequencies ranging from 0.05 to 500 Hz" [146], ES interventions could favorably influence such circuitry troubles, along with afferent plasticity processes stimulation, towards brain repair, (also) based on the capability to "… promote the drive of neural networks" [107] and thus, overall neurorestoration. Additionally: Low-intensity ES "… of peripheral nerves, inducing paresthesia without substantial motor output …" serves also, including in post ischemic stroke patients, for "somatosensory stimulation (SS)", which in turn, may provide even spectacular motor—of dexterity kind, too—gains [102].

Respectively, FES—considered an involuntary modality of generating (active) movements—showed, including in brain ischemic conditions, also favorable outcomes in relation to cognitive processes, objectified through assays for visualized things/objects spotting [99]. More so, there are animal researches highlighting that FES augments the expression of growth factors that are inductive for NSCs/NPCs multiplication (thus sustaining the replacement of post ischemic lost neurons), putatively contributing, together with "FES-boosted" neuroplasticity, within consequent brain tissue restructuring, to "FES-augmented CNS regeneration" [17]. In the literature—as afore announced—there is mentioned, too, a considered important beneficial effect of the application of transcutaneous electrical nerve stimulation (TENS) over the neck skin/ subjacent muscles, in the rehabilitative treatment of USN/hemineglect [132].

To be noted, however, that although—including with even remote favorable actions, as highlighted above—"Conventional brain stimulation techniques such as electrical stimulation, TMS and tDCS allow direct manipulation of a region's excitability and enhance recovery after stroke", likewise practically any other medical interventions, they can have adverse effects, too [75].

Supplementary data regarding ES (NMES and FES) and the therapeutic-assistive-rehabilitative use of such kind of interventions are presented elsewhere [147].

4.6 Enriched environment/environmental enrichment (EE)

A general ascertainment, introductory to this paragraph, refers to the fact that "Environment, either deprived or enriched, can affect a wide range of physiological and behavioral responses" [79]. Inherently encompassing simultaneously a bundle of stimuli of various types EE is considered "... a classic paradigm for studying the effects of a complex combination of physical, cognitive, and social stimulation in rodents" [108], allowing for the use and study—often deployed on such animals—of associated interventions of "... physical, cognitive and social …", kinds, including with "… introduction of novel objects …" [113]. Hence, it is reported in the literature that, observed in animal experiments, some neuroregenerative phenomena may occur, also favorized by environmental signals generating "multisensory stimulation" [148], as "... day-to-day activities lead to some functional recovery ...", based, at intimate level, also "... providing an on an increased " "... establishment of functional synapses" [43]; for instance, as regenerative potential: placed in an EE, laboratory animals "... showed enhanced hippocampal neurogenesis" [123]. Additionally, "… neurogenesis in hypothalamus is potentially involved in regulation of energy homeostasis via modulation of eating behavior" [149]; and EE, also at intimate level, can contribute "… to increase endogenous growth factors …", too (the growth factors' neurogenetic—targeting neurons' differentiation and, at the same time, augmentation of the: neuronal soma and nuclear dimensions, dendritic tightness and ramification, and respectively gliogenesis—and synaptogenetic, properties, with overall capabilities to contribute at "brain remodeling", are signaled in the literature, aside their death preventing actions [129, 150]; to be added their generally synergistic, "… anti-inflammation, antioxidative stress, antiapoptosis …" valuable properties [105]).

Furthermore, based on animal experimental models, there are reported capabilities of EE to augment/modulatory influence the action, towards synaptic plasticity potentiation, of some endogenous bio-chemical entities, such as cholinesterase, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), respectively *N*-methyl-$_D$-aspartate (NMDA)-type of receptors, BDNF, nerve growth factor (NGF), neurotrophin-3 (NT-3), PSD-95, synaptophysin [3], and thus to promote neuroplasticity—regarding also the number of synapses [104], and even maybe, to stimulate the neurogenesis and/or of cellular plasticity, kinds, potential of microglia [109] (debitable – o. n.); but therewith, exposure to a

"moderate" EE is prone to combat "... the damage caused by inflammatory microglia …", with added favorable effects on vascular caused cognitive impairments in "… patients with subcortical ischemic stroke …" [16], and respectively, to develop/reveal a high-mobility group box-1 "(HMGB1)/IL-6 signaling pathway in EE-mediated angiogenesis …" [113]. All these result in beneficial outcomes on "sensori-perceptual processing and learning …" [151] / "spatial memory task" [152]—EE being thus, possibly, "... a potent cognitive enhancer …" [153], that consequently "… leads to better learning and memory …" [154]—and overall, including in post ischemic stroke—as afore mentioned, too—in neurogenic, angiogenic and neuroplastic: "… therapeutic effects …" and astroglial activation without glial scarring via secretion of beneficial factors in a normal or injured brain", towards "functional recovery" [108]; this is important because, as known, stroke detrimental outcomes contribute, including with inflammation, to a modified post-injury, hostile to recovery tissue/biochemical local "acidic" [118] micro-surrounding (yet, there must not be considered inflammation just negatively—"Inflammation is known to contribute to neuronal injury, but is also implicated in repair mechanisms in the brain" [82]—, as it can have favorable actions, too: for instance it is "... also involved in the migration of regenerative cells to the site of deficit" [6] and more: "... is an important contributor to neuroregeneration because it stimulates neuroplasticity via trophic factors" [14]). Especially in bio-pathologic circumstances—post ischemic stroke is such a status—and their connected rather restrictive occurrences (because, for instance, of partial or complete motor and/or cognitive deficits and relative consequent isolation), social interaction proves to be beneficial towards functional recovery, with anti-"depressive-like behavior" (at least in animal experimental model models) effects, too [113], including sustained, at macroscopic level, by improvements at intimate one, of brain repair/neuroregenration, kinds. Thereby, in a related animal model, Venna *et al*. [155] report that, in mice with similar dimensions of the infarcted zone "Immediate post-stroke isolation led to a significant increase in infarct size and mortality …". Conversely, the presence of a normal companion proved beneficial towards behavioral improvement when compared to each of the possible alternatives: "…isolated mice or mice paired with a stroke partner. Behavioral improvements paralleled changes in BDNF levels and neurogenesis" [155]. To be specified, in a short parenthesis, that BDNF contributes incluidng to an overal post stroke better functional recovery "... by mediating axonal growth, OPC (oligodendrocyte precursor cells—o.n.) proliferation, oligodendrocyte differentiation, remyelination, and fiber tract connectivity" [33], therefore being, at clinical level, considered to have including prognostic capabilities towards the evolution of the post ischemic stroke patients' functional performances, especially regarding their mobility [69]. In humans, an important rationale to achieve hospital EE, consists of the fact that, inherently, especially in the early stages post—including ischemic—stroke, such patients "… spend a large proportion of time in isolation and physically inactive …"; so they consider "… the rehabilitation setting as being unstimulating and boring" [122]; this strongly differs of the healthy human' environments, which are usually rich enough. Yet, EE is still beneficial for (re-)developing, in such patients, abilities towards personal autonomy (from the International Classification of Functioning, Disability and Health—ICF's—perspective: "activity" and also "participation") and towards further rehabilitation progresses [122]. Basically, the therapeutic-rehabilitative use of EE would be effective—in humans, as well—for ameliorating cognitive impairment, too, with even "… possibly reverse WM (white matter—n. n.) damage" [84]. If consistently further confirmed, this possible capability of the EE approach would be important, as "Without the parallel protection of white matter, true lasting neurorestoration cannot be achieved" [156]. Furthermore, EE is considered able to induce psychologically based stimulation of cerebral structures involved in "…motor relearning", after stroke, too [157]. For instance, hospital EE may encompass the use of "communal areas … to enhance individual and group activities … interactive breakfast … and … interactive lunch time …", in order to combat isolation and favor "social interaction", and to promote, as well, an as pro-active as possible—considering their medical condition—daily life. The patients can also be encouraged to use any personal equipment/facilities and/or satisfy hobbies—(feasible in a hospital ambient and which are not harmful and may enhance their personal motivation for rehabilitation)—such as availing/enjoying: mobile devices for IT/C, computer games, different puzzles, books, journals, music, art, all seeming with encouraging outcomes towards functional recovery. At the same time, EE is now consistently augmented and diversified by medical advanced—non-invasive, non-pharmacological/biotechnological therapeutic-rehabilitative—interventions based on virtual/augmented reality (VR/AR), including with sensor-based computer-aided "serious" [158]/active gaming technologies, thus supplementary augmenting the overall patients' status improvement [159]. Thus, EE is considered—not unanimously (see immediately hereinafter)—to bring a strong added value to a post ischemic stroke rehabilitation program paradigm [113], including as being (also) a "positive regulator" of "… the levels of neurogenesis in the adult brain …" [114]. Yet, for EE, too, there are in the literature also negative reports, regarding, for instance, as a related side-effect, the enlargement of the ischemic brain lesion dimension [3], and more: at intimate level, there are reported, too, opposite effects as regards the (also) mice exposure to an EE (down/up-regulation) over their

"expression profiles" of different kinds of hippocampal MicroRiboNucleicAcids (miRNAs) [54].

4.7 Therapeutic hypothermia (TH)

Therapeutic Hypothermia (TH), as non-invasive, non-pharmacological/biotechnological intervention, can be induced physically, externally through "... ice packs, cooling blankets, or cooling pads …" [160], or "cold air". It is about "… mild to moderate hypothermia (3–5 °C reduction) …" which "is safe" [161], and in the acute phase is neuroprotectively applied to "… rodent stroke models …" [140], as it has anti: "… oxidative stress, inflammatory responses, metabolic disruption, and cell death signals" [161] actions, seeming also to augment "… p53 expression promoting repair after stroke" [162]. In fact, it targets "… multiple pathways at various stages of ischemic stroke", for instance also through favoring elevated concentrations of important neurotrophic factors (BDNF, GDNF—glial cell-derived neurotrophic factor, o. n.: also … a nerve growth factor … associated with neurogenesis after stroke [115], neurotrophin), augmenting angiogenesis, maybe synaptogenesis, too [160], and possibly even by promoting—although controversial [163]—neurogenesis, as: "… newborn immature (BrdU(+)-Tuj-1(+)) and mature (BrdU(+)-Map-2(+)) neurons increased significantly in the hypothermia compared with normothermia …" [164]. However, in humans, classic: physically externally applied TH, raise serious challenges, at least, apparently for less severe cases: "While whole body cooling is a feasible approach in intubated and sedated patients, its application in awake stroke patients is limited by severe side effects: strong shivering rewarms the body and potentially worsens ischemic conditions because of increased O2 consumption" [165], its translational extension needing more pre-clinical research.

4.8 Kinesiotherapy (KT)/physical exercise

Synthetically: "There is substantial evidence …" that such kind of interventions have beneficial effects towards motor control and consequent functionality regain, including with neuroplastic cortical readjustments [166]. More specific: "… the beneficial effects of physical exercise were correlated with the maintenance of pre- and postsynaptic components" [95], including with promoting/enhancing synaptic plasticity, and this may go also for mental exercises and acupuncture (see further a brief comment referring also to this latter type of intervention—with reported beneficial effects upon neurologic impairments consequent to ischemic stroke in rodent experimental models, based on neuroprotective: diminishing of brain edema, and of neurogenesis type: "... proliferation, migration and differentiation of NSCs", actions [167], as well as to on electroacupuncture), respectively [168]. Moreover, together with "... dietary restriction" exercise and EE "... positively modulate neurogenesis ..." [81]. To be mentioned that, although difficult to made complete distinct definitions for each, there still, may, be conceptually, although vaguish, distinguished "physical activity" (considered to be—at intimate level—involved including in controlling the "... fate of neural stem cells", and this goes also for the afore approached EE [169]) of physical "exercise". Specifically, the former "... is defined as any bodily movement produced by skeletal muscles that results in energy expenditure …"—for instance: "… occupational, sports, conditioning, household, or other activities"—being (as well) a "positive regulator" of "… the levels of neurogenesis in the adult brain …" [114]—whereas the latter "... is a subset of physical activity that is planned, structured, and repetitive ..." [170], that (as skilled—analytic/segmentally focused) can have also therapeutic-rehabilitative goals, with case tailored methodological items; it targets the improvement/correction of different—neuro-/loco-motor (including as regards muscle tone and/or trophicity and articular flexibility), coordination, balance/stability, sensory—possible impairments, which are often produced including by ischemic stroke (for instance regarding walking and other basic motor purposeful skills, it entails: "... fitness training, high-intensity therapy, and repetitive-task training. Repetitive-task training might also improve transfer functions. Occupational therapy can improve activities of daily living") [136]. It is notably that overall "... exercise rehabilitation has the same beneficial effects as pharmacological drugs to improve health-related quality of life …" [116], including with "fitness" favorable outcomes being available for post ischemic stroke patients, too [104]; at tissue level, it "... may modify aged microglia", in decremental sense [16]. Moreover, physical exercise has regenerative capabilities too, including of angiogenesis type, because, very important: "Vascularization is key to stroke rehabilitation" [97]; to be added its neuroprotective ("… by enhancing the strength of the cerebrovasculature in the brain") and thus, including possible prophylactic, capabilities, at least in animal models [97]. To this point, in a brief parenthesis, it has to be also emphasized, regarding vascularization, respectively angiogenesis, at intimate level—aside other items already exposed—the NVU evolution (including with the ECM and respectively, with glial cells that "... are also important components of the NVU, which provide structural support for neurons, control neuronal activity through synapse formation, and may participate in the formation of local capillaries"), as part of the related microenvironment—on which strongly depends the success or the fail of a tissue, including post ischemic stroke, repair [100], because NVU, within injuries, thus contributes (also) to an "integrated tissue response"—entailing all kind of brain: cells and ECM components [171]; and as regards "neurovascular coupling" including for the design of future studies on the CVA pathophysiology, to be noted there have been observed differences in between species: data reported "… with generally impaired functional hyperemia in animals but variable findings in stroke pa-

tients" [72]. The therapeutic-rehabilitative physical exercises/kinesiotherapy entail, as well, necessary elements of strengthening—with inevitable non-aerobic ("functional exercises/training"—including possibly "... reaching training and Constraint Induced Movement Therapy—CIMT" [94]), components, and also—proprioceptive neuromuscular facilitation (PNF), Bobath method, —if suitable for a specific case [5] and TOT, guided movements (especially for re-gaining of more complex motor abilities). A diverse portfolio of kinesiological interventions is necessary to be available for the specialized health care providers taking into account, on one hand, the relative fragility of the post stroke survivors (many of them elderly—who's one main pathology feature is multimorbidity) [172]—so it must be always possible to be chosen the appropriate methodology according to the actual patent's "whole picture"—and on the other, because post-stroke sequels are not seldom long-life—and therefore they must be approached as such—therefore being necessary to keep, as tenaciously as possible, continuity, in different evolutive phases of this complex pathologic condition. Considering these, physical exercises should be predominantly of aerobic type: body weight supported training—aland or on treadmill (with body-weight support—if necessary) [47], gait overground, stair climbing, cycling (including stationary), swimming, possibly slow running/jogging [56]. At least in animal experimental models "Treadmill exercise has also been shown to induce neurogenesis, synaptogenesis, and neurotrophin signaling pathways", and also "… angiogenesis in ischemic stroke" [97]. Moreover, in such kind of models, including aerobic exercises (AE) enhanced BDNF concentrations—which is considered important in promoting neuroplasticity and thus, for multiplane consequent functional recovery, including after stroke [173]—with not unanimous opinions in the literature concerning related outcomes of the functional exercises (reaching, training and CIMT) [94]. AE is considered "... part of stroke best practices to improve gait and cardiovascular fitness", and even "... cognition and relearning of complex skills" (mainly based on: general improvement of blood circulation—cerebral, too, stimulation of "neurotrophins" release [56], including with "... synaptic plasticity and ... reorganization of new neuron circuits" [107]). As for the capability to enhance the hippocampal BDNF titre—a molecular basis towards "… motor recovery after brain ischemia …"—in animal experimental models, "… the most effective intervention …" is considered to be "voluntary exercise" [174], but this "… is purported to play a crucial role in neuroplastic effects of rehabilitation interventions of humans with neurodegenerative disease" [74], too; this is including by the stimulation of "... the production of ne^{u}rotrophic factors, which might promote cell growth and enhance neuronal activity" [116]. Thus, overall, in the literature it is considered that "Aerobic physical activity plays a crucial role in promoting cardiovascular fitness, aerobic fitness, quality of life, cognitive performance, walking speed and endurance, balance, mobility, and other health outcomes among post-stroke patients" [103], including with post "left-brain" stroke patients "… who have ^{h}ad … lower baseline score in the 6-min and 10-meter walk tests" [175]. At intimate level, physical activity/exercise exert, aside neuroprotective effects (such as brain inflammation and neuronal apoptosis combat, and BBB/NVU' preservation) regenerative ones: neurogenetic and angiogenetic—at least in "ischemic stroke animals"—augmenting "… vascular endothelial growth factor (VEGF) and insulin-like growth factor (IGF)" actions, too [103]. Both, AE and analytic/segmental specific, functional, exercises prove to be able of favorably driving/enhancing neuroplasticity towards functional recovery, within thus, a sophisticated neurorestorative brain repair process. To be underlined that cognition involvement is mandatory for most of the voluntary motricity items, especially for complex ones. As determined in clinical related trials, these favorable outcomes seem to appear more consistent (none the less, thereby, difficult to be quantified each's contribution) within combined therapeutic-rehabilitative schemata, that encompass also strengthening/endurance and/or more complex—ability task-oriented, considered able to "… induce regenerative capacities … " in the brain after CVA [157]—exercises, and last but not least: cognitive training [56]. Accordingly, in the literature there is noted a "... beneficial influence of physical exercise (e.g., running) on cognitive performance" [176], and respectively, in brief, at least in animal models: "… physical exercise supports neurogenesis" [177], at intimate level, additionally, influencing "… behavior and neuroinflammation through elevation of anti-inflammatory cytokines and reduction in pro-inflammatory cytokines" [116] (although there are also conflicting opinions in this respect—see further). Concerning the relation between physical exercise/activity and cognitive items, synthesizing the results of several clinical studies, Constans *et al*. [99] noted that, in chronic stroke, as for the effects of association between aerobic and "strengthening", training, this bettered "… executive functions, attention and voluntary motor control", respectively that aerobic exercises—especially "… at moderate intensity…"—combined with "resistance" ones, ameliorated "… attention/concentration and visuospatial/executive functioning …" values, as measured on the Montreal Cognitive Assessment (MoCA) scale; additionally, there has been observed that merging aerobic with " … stretching, balance and task-specific …", exercises, and with "… sessions of recreation time …" had favorable outcomes on "… verbal memory and cognitive flexibility", yet without improving "… executive function". To be noted that the respective authors expressed their cautiousness on such conclusions, since the results of the mentioned training-rehabilitative combinations haven't been collated with those of such interventions evaluated each, separately (as we also have pointed out above). As for, the underlying main mechanism of the

beneficial effects of aerobic exercise on cognition, this appears to be—again—the augmentation of neurotrophic—such as BDNF and VEGF—actors' liberation, which "... mediate beneficial neuroplasticity in brain areas involved in cognitive functions" [99]. Regarding the mainly favorable effects of physical exercise on cognition, too, an additional rationale for this—considering, although entailing rater different pathways of action, maybe complementary such kind of intervention with an enriched environment—refers to the fact that, like "... mechanism for endogenous brain repair, rehabilitation exercise training induced neuronal differentiation in the dentate gyrus of the hippocampus". But, such a restorative process was objectified "… only with an enriched environment …"; therefore, "… behavioral experience in a complex environment may be used as a rehabilitation strategy following ischemic insult" [104]. Is worth, as well, being mentioned that to rehabilitative approach motor control regain of the upper extremity in post stroke survivors, there can be used also "RFVE (reinforced feedback in virtual environment)" specifically by "... multidirectional exercises providing augmented feedback provided by virtual reality ..." (precisely: computer, sensor/3D-tracking-based, with "virtual scenarios" projection facilities, technology—with progressively higher complexity given tasks to the patient), in association with classical, analytic, segmental—dedicated to functional improvement—physical exercises (yet, the post ischemic stroke ones have less extended functional re-gains than those post hemorrhagic stroke) [157]. However, a very recent systematic review and meta-analysis concludes such an association "... is an effective method to improve the upper limb motor function and manual dexterity of patients with limb disorders after stroke …" [178]. Very important, from functional perspective, for ambulatory, including post ischemic stroke, survivors, are balance and trunk stability and posture: "Core stability exercises on stable and unstable support surfaces are equally beneficial in ..." approaching these rehabilitative goals [179]. On a relatively different note, despite the quasi unanimous opinion that physical exercise—respectively the physical activity, by its prophylactic capabilities, including with augmenting "cellular stress tolerance"—is in general benefic ("… both limit the brain injury and facilitate behavioral recovery …"), a pre-conditioned state (e.g., very intense/forced treadmill running exercise) preceding a "global cerebral ischemia model" appears to generate, at least in animals, in such a brain sufferance, a "… stress response that correlates with the degree of neuronal damage in hippocampus", worsening it, as compared to "voluntary wheel running"; this is probably because of its association with a "… pro-inflammatory response in the brain …", possibly mainly due to some cytokines' increased response at cerebral level (in connection with elevated systemic concentration of the stress hormone corticosterone); so, the fact that, under such circumstances, a consequent "Neuroinflammatory response can further aggravate the neuronal damage …" [180] has to be considered, too. But, on the other hand (based on the principle of preconditioning: "... mild forms of stress induce tolerance to an otherwise lethal injury")—as, for instance, a "… brief episode or a mild form of hypoxia/ischemia prior to a stroke will reduce the damage produced by the stroke …"—and in animal experimental models such "… type of preconditioning … increase the resistance of the brain to hypoxic/ischemic insult …", this support the opinion—(to be also found in the literature)—according to which, at least this mode of preconditioning can be beneficial [178]; moreover, even patients affected by an "acute nonlacunar ischemic stroke", preceded by a first transient ischemic attack (TIA) have much better, at least early evolution (main preconditioning protective factor possibly involved in the related cell resilience are: influence over the functioning of potassium channels, adenosine A1 receptors and respectively, adenosine-triphosphate mediated also on the protein synthesis as well as "… activation of NMDA receptors, upregulation of antioxidant enzymes and overexpression of immediate early genes..."; furthermore such an improved tissue resistance to ischemia appears to be connected to "…inflammatory cytokines, particularly tumor necrosis factor-α (TNF-α) or interleukin-1ß and interleukin-6…" [181]. From such a perspective, physical exercise appears to be, as well, an excellent preventive intervention against ischemic stroke, just because of its preconditioning capabilities, including with the further stimulation of angiogenesis mediated by the VEGF (and thus contributing to the mitigating of the stroke induced cerebral damage). To be noted too, that in the early phase of ischemic stroke, augmented quantity of released VEGF may be harmful because of BBB aggressing, with consequent leakage and thus, propensity, to brain edema [78]. Yet, in later phases, VEGF might support "… post-ischemic brain repair via promoting neurogenesis and cerebral angiogenesis" [88]. Additionally: "... forced exercise at moderate to high intensity increases brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGF-I), nerve growth factor (NGF), and synaptogenesis in multiple brain regions. Dendritic branching was most responsive to moderate rather than intense training" [182], and "… Improving aerobic fitness prior to stroke may be beneficial by increasing baseline IGF-1 levels" [183]. Accordingly, there are rationales for the need of more research on this matter (too), especially related to dose and timing of administration, as for now there are—but not unanimous—putative, statements such as: "… physical activity is a more important component of EE (enriched environment—n. n.) regarding the effect on astrocytes proliferation and BDNF expression, which may contribute to the improved neurological function of stroke animals" [184], respectively: in post ischemic stroke statuses, physical activity—as component of the (human) lifestyle—may have some anti-detrimental effects, possibly including "… via increased autophagy or increased neurogenesis in

the adult brain" [70]. There is even pointed out, in experiments of ischemic stroke on animals, that "... exercise enhanced neurogenesis, angiogenesis, and synaptogenesis possibly providing redundancy and tolerance to subsequent injury", too, as especially "… aerobic exercise promotes neuroplasticity by upregulating neurotrophins such as brain derived neurotrophic factor (BDNF) …"—although the authors cited below assert there are not enough literature data to support it as a factor to ... repair of the CNS), "… nerve growth factor (NGF), neurotrophin-3 (NT3), and neurotrophin-4 (NT4)" [112]„ and more, it showed anti-neuroinflammation and pro-neuroplasticity, actions, and favorably effects on endurance and gait ability, too ("… because of reciprocal limb movements …") [112], considering also that "… motor training can increase functional recovery by enhancing neuroplasticity in the cortico-spinal tract" [9]. To be also added, in line with the above exemplified queries, that "... highly intense physical activity very early after injury onset can be risky" [143] or even "net harmful" [47]. Some additional related items are presented elsewhere. A special mention refers to Hydro-(/Kinesio-)therapy: in a systematic review and meta-analysis of related randomized controlled trials, Chae *et al*. [185] found that in post stroke patients, "hydrotherapy" resulted in better outcomes regarding postural balance, standing and gait functions, and "... paretic knee extensor strength ..." than with "... land-based conventional therapy ...", and these results occurred significantly, for the postural balance, only in the chronic patients [185]. Connected and convergent with KT, for—(including) post ischemic stroke motor disabilities functional recovery—through enhancing attention, motivation and cooperation of the patients, and refining their capabilities to usefully interact with the physical and—if the case—social-professional milieu, is Occupational Therapy (OT): preferably administered by targeting appropriate "specific measurable-achievable-realistic-time" ("SMART") (see below) concept/ theory/paradigm based aims [5], according to which "… goals should be specific, measurable, difficult, meaningful promote self-efficacy, time-framed and involve strategies for goal achievement" [186]. To be also noted that "the effectiveness of interventions that rely on interhemispheric connections (e.g., bimanual priming or noninvasive stimulation of the nonlesioned hemisphere) may be particularly affected by the structural integrity of the CC (corpus callosum – o. n.) and level of motor impairment …" [96]. Last but not least: for instance, adding to technology/device assisted rehabilitative interventions for walk training, physiotherapeutic ones, would result in improved outcomes regarding independent gait re-gaining, in post (including) ischemic stroke patients; overall, physiotherapy would contribute to enhancing functional recovery, mitigating, at the same time, possible side effects of some necessary motricity exercises [104].

4.9 Mirror therapy

Mirror therapy is a type of non-invasive, non-pharmacological/biotechnological—in fact a physiatric—procedure that relies on "…visual information", through which the affected individuals' focus on the motion of their "nonparetic limbs" is facilitated. Specifically: "Visual illusions make the patients feel as if their two hands are moving simultaneously and symmetrically …"; further, these mirror motor imagery inputs are processed within hemispheres, with their consequent related stimulation, resulting in such "… a neurological mechanism for inducing brain plasticity" [187]. More precisely, in principle: placing a mirror in front of a patient with mono- or hemi-plegia/paresis, so that both upper and/or lower limbs are visible in the reflected image, the plegic/paretic limb(s) appear(s) as being the non-affected one, and vice-versa, thereby creating the illusion, when moving the normal limb(s), that the affected one(s) is/are moving—situation stimulating, through motor mental imagery, functional rehabilitation [91]. The neurophysiologic fundament of this kind of intervention consists in the particular functions of the so-called mirror neurons. The mirror neurons (MNs—also surnamed: "cells that read minds", "the neurons that shaped civilization" [188]) have been discovered almost 30 years ago [188–190], first in the cortex of macaques, and subsequently, there has accumulated including direct electrophysiological proves they exist also in the human brain. A basic feature of these special category of cells is that they can be stimulated by both, the action performed by someone and by only watching such an action effectuated by another ("... they fire during both the execution and the observation of a specific action"). So, very important: "Thus, the motor system may be activated without overt movement" [191]. But also: "… action–execution neurons were seen to be inhibited during observation, possibly preventing imitation and helping self/other discrimination." Specifically, there exist a self-protection mechanism against inappropriate related reactions, too, and this would be achieved by: "anti-mirror neurons", that "… could disambiguate our own actions from those of others" [192]. Mirror therapy interventions, underpinned by the functional capabilities of such neural structures, encompass, as main methods: "… action observation, motor imagery, and imitation …"; so, in this respect, it may constitute a supplementary kind of non-invasive, non-pharmacological/biotechnological intervention, in post ischemic (too) stroke rehabilitation [191], and consequently, it appears to support, including in chronic post ischemic stroke cases, a basic item of rehabilitation: re-learning, by practicing, towards functional re-gain, and consequently, to motricity amelioration [3]; a related action—not unanimously accepted, especially in humans —would target the stimulation of the lesioned cortex "… by enriching the visual and proprioceptive inputs to the MNS …" (mirror neuron system—o. n.) [77]. Regarding mirror therapy/training—for in-

stance using a “mirror box apparatus”—and availing types of motor imagery procedures, such as: “imagined … movements …”, “mental simulations … ” for purposeful tasks, Stevens *et al*. [193] reveal, at the same time, a larger conceptual possible perspective on this physiatric intervention, i.e., as being “… a cognitive strategy for functional recovery from hemiparesis. The intervention targets the cognitive level of action processing while its effects may be realized in overt behavioral performance” [193]. So, within mirror therapy/training, MVF —(that stimulates predominantly the lesioned primary motor cortex), together with action observation (AO—activating larger cortical regions) and action execution (AE–n. n.–with MVF) act “…by revising the interhemispheric imbalance, and MNS recruitment may be one of the potential neural mechanisms in this process”, according to their activation patterns and roles above described, overall prone to motor re-learning (as already emphasized). Specifically, AO training (AOT) “… usually consists of a session of AO followed by a session of imitating the observed action” [77].

4.10 Near-infrared spectroscopy (NIRS)/functional near-infrared spectroscopy (fNIRS)

From the perspective of this paper, being an apparatus component added to some BCI/BMI systems—used including in post ischemic stroke assistive-rehabilitative approaches, specifically as non-invasive, of measurement kind, technology (assessing “… the concentration changes of oxygenated and deoxygenated hemoglobins ([HbO] and [HbR]) in the superficial layers of the human cortex” [194], and not of intervention type, herein shall be only mentioned two important features of effectiveness (common with the EEG): both are rather cheap and respectively, portable [195].

4.11 Neurologic music therapy (NMT)

Neurologic music therapy (NMT) is a borderline “intervention” between its most frequently availed (therefore being very accessible, simple to be “administered” and, usually, not expensive) and perceived dimension: of psychological satisfaction, and the therapeutic-rehabilitative one. Regarding this latter feature, neurophysiologically, “indulging in music” “… is considered as one of the best cognitive exercises”, based on “plasticity”, i.e., through the generation of “… an array of cognitive functions and the product, the music, in turn permits restoration and alters brain functions”. Accordingly, NMT is claimed to be useful in the rehabilitative approach of practically all the major neuro-disabilities, including post ischemic stroke—aside other neurologic/neurosurgical conditions—as it may induce, through “Temporal cues in music and rhythm …” improvement of awareness/“sustenance of attention”, and respectively of cognitive-behavioral, speech, sensorial and/or motor, disorders [196]. There is need, also in this domain, for more basic research, especially to objectify the intimate neurobiological mechanisms that might underpin the beneficial actions of NMT reported in some papers.

4.12 Photobiomodulation

Also named low-level laser (light) therapy (LLLT) [197, 198], photobiomodulation administered non-invasively (transcranial), physically/technically consists in applications—including in ischemic stroke—over the scalp of “… red or near-infrared (NIR) light (600–1100 nm) … either from lasers or from light-emitting diodes (LEDs)” [197]. In animal experimental (basically with the local cranial “periosteum” removed) model of ischemic stroke, there is claimed, in the literature, a large amount of therapeutic effects, such as: reduction of cells death and of the infarcted area, stimulation of cortical neuro-/synapto-genesis—with consequent brain repair and functional recovery—and favorably modulation of the peri-lesion environment (i.e., improving cellular energetics, a beneficial mix of pro-and anti-inflammatory switched profile of the microglia activity—including at its borders, through inhibition of reactive gliosis, because it also “… appeared to induce expression of the growth factor transforming growth factor-beta 1 and suppress the production of peroxynitrite” [199]), and even—as an overall functional improvement—behavioral disorders alleviation; at least some of such effects seem to be applicable in healthy individuals and respectively, in a larger brain lesions spectrum, in humans, too [197, 200].

Regarding the translational to clinic, matter, a major query refers to the deepness the light can penetrate through the scalp (skin, under-skin tissue, bone and periosteum) previous to reach the brain (at least the cortex) [197]. So, the application in humans, specifically in acute ischemic stroke—in which, if non-invasively administered, the brain photobiomodulation must be applied over the intact scalp—transcranial near-infrared light therapy (NILT)—is rather problematic. For instance, the related well-known Neuro-Thera Effectiveness and Safety Trials 1, 2, and 3 (NEST-1, -2, -3), resulted in an unconclusive for a translational hoped perspective: “The NEST-3 trial was halted midpoint when it failed to demonstrate statistical benefit on futility analysis” [199], respectively: “We conclude that transcranial laser therapy does not have a measurable neuroprotective effect in patients with acute ischemic stroke when applied within 24 hours after stroke onset” [201]. Unfortunately, resembling outcomes – in terms of “... infarct reduction or functional recovery …” —are asserted in the literature also concerning the use, in animal experimental models of brain ischemia: there has not been “… observed a beneficial effect of LED photobiomodulation …”, neither applied 24 h after the onset of ischemia, nor after 12 weeks. Consequently, there is need for more related “preclinical studies” [202].

4.13 Prism adaptation [203–205]/prismatic adaptation [206]

It entails patients to exercise—equipped with prism glasses/ spectacles, "… that displace viewed objects rightward—"… pointing movements toward visual targets …" under such interventional circumstances [203]. Although still controversial concerning its mechanisms of action on cerebral systems and beneficial outcomes (especially the power threshold of the prisms used necessary to reach a quite stable corrective/adaptive visual shift, respectively a questionable lasting therapeutic/rehabilitative result—from hours to months—and more: possible existing negative "after effects") [203, 206], "Among various rehabilitation techniques, prism adaptation may be particularly promising" [203]. Yet, including recent/very recent related data in the literature (two—both—meta-analyses regarding the effect/usefulness of prism adaptation interventions in post-stroke USN/hemineglect), are strongly conflicting, i.e., "temporarily" beneficial effects [204] vs. no effects—so, there would not be reasons to "... support the routine use of PA in patients with unilateral neglect after stroke" [205]. This is, we reckon, one more rationale, on one hand for the need to be periodically achieved standardized exhaustive literature review reappraisals, and on the other, for our choice to support the information within this article with so many quotations.

4.14 Repetitive transcranial magnetic stimulation (rTMS)

rTMS holds quite large attention in the literature. It "... is a non-invasive method of stimulating the brain that changes excitability at the site of stimulation as well as at distant anatomically connected sites ...", with remanent effects subsisting, post procedure—possibly because of modifying synaptic connectivity from minutes to hours [207]. TMS, and respectively rTMS, are based on the physical phenomenon of electromagnetic induction [208]: "An electric current passes through the inductive coil and generates a high-intensity magnetic field to stimulate neurons" [209], but not directly: the resulting magnetic field, in its turn, permeates transcranial "… the scalp, skull, and meninges, thus inducing an electrical current …" —again, through electromagnetic induction—that generates responses from the brain neural cells within different zones and structures [106]. From neurophysiological and therapeutic-rehabilitative perspective "The artificially induced action potentials are transmitted via the descending conduction beam and promote axoplasmic transport ..."; especially repetitive such kind of stimulation exerting neurorestorative actions like metabolic resources build-up for/with biotrophic growth promotion and respectively, neuroplastic inputs [83]. Although even isolated/single electric impulses—at adequate (especially of intensity) parameters (but frequency, too, as it influences cortical plasticity: low is suppressive and high is activator)—can, through the above mentioned induction, depolarize and thus excite, straight off, brain neurons, a variant of this method, that is able to prolong stimulation beyond the duration of such an intervention session, consists of applying electro-pulses repetitively. Thereby, consolidating the neural stimulation, rTMS succeeds to induce longer lasting related plasticity driving, i.e., to modulate these preformated specific excitatory cells' activity patterns, hence resulting in neuromodulation. Regarding rTMS (too): low frequency—up to 1 Hz—is suppressive, diminishing neural excitability and thus generating long-term depression (LTD) and high frequency—from 5 Hz upwards—is activator and thus induces long-term potentiation (LTP [106, 107]). It is considered that rTMS may "… 'correct' pathological network configuration …" and "... modulate local plasticity …" in post (respectively ischemic) stroke, —possibly also with "… alleviation of diaschisis …", improving connectivity with far-off motor zones, and—consequent to "… motor network connectivity …" (diminished in such a condition) within "… the lesioned motor system …" (at least partial), restoration—with including (but not exclusively) motor re-gain [76] with other including. Specifically, for an early stage of post ischemic stroke (2 weeks since its onset): high-frequency (HF) rTMS applied over the damaged primary motor cortex or low-frequency (LF) rTMS applied over the corresponding opposite, non-affected, region, have been reported to have encouraging outcomes: "significantly" stimulation of motor "cortical excitability … and motor-evoked fMRI activation …" through "The HF-rTMS", in the lesioned regions, "… significantly correlated with motor function …", respectively related "significantly" inhibition and decreased and motor-evoked fMRI activation, "in contralesional motor areas" [92]. Overall, regarding motor function: "... low-frequency repetitive transcranial magnetic stimulation has a positive effect on grip strength and lower limb function as assessed by FMA (Fugl-Meyer Assessment scale—n. n.)" [210], but—as resulting from a dedicated meta-analysis of which related effects on long-term could not have been "discerned"—"rTMS may have short-term therapeutic effects on the lower limbs of patients with stroke" [211]. At the same time, "A common strategy is to combine cortical excitability-enhancing rTMS with motor training", especially early post stroke [76]. So—as non-invasive, non-pharmacological/biotechnological interventions—rTMS is actually, mainly together with tDCS [107], considered among "Neuromodulation technologies ...", which are "... promising tools for neurorehabilitation …", including post-stroke, also possibly as regards—(although without consensus on this matter) —"… chronic post-stroke aphasia by modulating activity in the distributed bi-hemispheric language network" [93]. There are also discussed in the literature potential favorable, added cognitive effects, since "… low frequency ($\leq$1Hz) rTMS over the unaffected hemisphere in post stroke patients with aphasia was effective

in improving overall language function" [107]. Moreover: "This also implies that behavioral effects evolving after stimulation are based on a remodeling of the whole network rather than being caused by excitability changes of a single motor region" [212]. Additionally, "... low-frequency (1 Hz) rTMS treatment ... to the healthy hemisphere ... " produced, in a few cases of post stroke visuospatial hemineglect "... significant improvement on different tasks (landmark, line bisection, clock drawing) lasting up to 15 days from the intervention" [206]. Thereby, it is considered that TMS—as an electro-magnetically induced non-invasive brain stimulation (NIBS)—can be used, after ischemic stroke, as well, for delivering inhibitory stimulation to the cortical motor areas that control the, less paretic limbs, but also to stimulate the ones connected to the more disabled territories; thus, it would induce "metaplastic" related brain changes—based on "rebalancing" "… the interhemispheric interactions between the two homologous motor cortices …", i.e., the lesioned one and the non-affected contralateral, respectively—with consequent, indirect, gain in functional recovery in those more affected, with their subsequent augmented receptivity to associated task-specific training exercises and "peripheral somatosensory stimulation (PSS)", too—possibly optimized by an associated CIMT of the less paretic arm, that seem to target a negative feed back loop with the opposite, more valid, motor cortex [18]. On the other hand, although the capabilities of TMS appear to stimulate neuroplasticity in animal models, its overall neuroregenerative effects, in humans, require more research [17]. A rather newer rTMS variant [213], considered "… highly efficient …" [214]—including, because of, the shorter time it needs to be applied [215] and as it "... produces more robust changes in cortical excitability (CE) ..." [216]—is theta burst stimulation (TBS); this "… uses bursts of high frequency stimulation (3 pulses at 50 Hz) repeated at intervals of 200 ms (i.e., 5 Hz the theta rhythm in EEG nomenclature)" [217]. For instance, beneficial outcomes are reported with "... cerebellar intermittent theta burst stimulation (iTBS) …" [218], administered over the affected hemisphere's "... lateral cerebellum of patients with ataxia due to chronic posterior circulation ischemic stroke" [49]. TBS is available to be applied in two modalities: intermittent (iTBS), respectively continuous (cTBS) [216]. To be specified that the iTBS "stimulation pattern" consists of "… a 2 s train of TBS is repeated every 10 s for a total of 190 s (600 pulses)" [213]. There can be found, in the literature, assertions regarding beneficial effects of cTBS "... low-intensity stimuli ... into target brain regions …" on motricity and speech [67]—specifically: "... cTBS applied to the skull on the area of the non-lesional hemisphere ..." – i.e., significant improvement of motor function in the paretic upper limb, within post stroke hemiparesis, but associated/"... followed by intensive OT—occupational therapy: n. n.—(comprising 120-min one-to-one training and 120-min self-training) during 15-day hospitalization" [219]. Furthermore, in rat experimental models of ischemic stroke, applied on the lesioned brain site: "… high-frequency rTMS improves functional recovery possibly by enhancing neurogenesis and activating BDNF/TrkB (tropomyosin-related kinase B —o.n.) signaling pathway and (but—n. n.) conventional 20 Hz rTMS is better than iTBS—at enhancing neurogenesis …" [73]. A safety matter must be addressed, too: "... rTMS is known to carry a risk of seizures ... ", and therefore, this type of intervention required—and there have been achieved—related guidelines of its use; as "... it delivers high frequency bursts", TBS might present an even bigger such risk, hence needing for "... more formal safety guidelines ..." [215]. Additionally, there is asserted in the literature that in generally, TMS (i.e., single-pulsed) is considered safe whereas at elevated frequencies and/or intensities, such interventions raise safety concerns. Moreover, a limitation of the clinical effects that can be obtained with (r)TMS refers to the problematic capabilities of these procedures to target exact zones [106]. So, cautiousness and specific guidelines for its practice are necessary [220].

4.15 Robotics—mechatronic/robotic exoskeletons

Such an advanced technology based assistive-rehabilitative kind of therapy is currently one of the most promising directions of progress, including—but not exclusively—for (also ischemic) stroke functionally approach. It "… provides quantifiable, reproducible, interactive, and intensive practice, …", and furthermore "… RT (robot-assisted therapy—o. n.) also provides better research into treatment dosage". Especially concerning motricity amelioration, in post stroke chronic survivors "… Higher-intensity RT …" [221] could represent a methodological choice. Consistent data regarding such medical devices and the therapeutic-assistive-rehabilitative use of connected interventions are presented elsewhere, so here there will not be included further related details.

4.16 Serious gaming/games (SG)

Notions regarding such kind of facilities and interventions will be presented further—connected also to the data previously exposed in the subsection dedicated to Environmental enrichment/Enriched environment (EE)—within the VR/AR and respectively, Visual scanning training (VST), subsections; additional related data can be found, elsewhere [222].

4.17 Speech-language therapy (logopedics, phoniatrics/phoniatry)/intensive language-action therapy (ILAT)

Speech-language therapy is an intervention domain with large applicability in the post, including ischemic, stroke pathology, as not few of the respective patients develop/remain with such type of disability. Thereby, "Intensive language use influences the reorganization and functional restitution of language networks in post-stroke

aphasia …, with important implications for rehabilitation" [93], and overall for the affected individuals' communication/social interaction capability, and consequent QOL.

4.18 Transcranial direct current stimulation (tDCS)—and respectively, Galvanic vestibular stimulation (GVS) ("... a variant of tDCS …")—[206]

tDCS and is a rather accessible procedure: technically relatively easy to be used, with the necessary apparatus rather cheap [208]. Practically, tDCS entails the application, on the scalp, through "sponge electrodes", "… of a low-intensity current (0.5–2.5 mAmp) ..." [75] (usually 1–2 mA [223]), on various positionings: "unihemispherically" (with one "target" and the other "reference"—electrodes), or with the reference electrode placed "... extracephalically, for example on the upper arm", or "bihemispherically" (for instance to action on both cortico-parietal areas) [223]. tDCS can be considered a "… popular brain stimulation method that is used to modulate cortical excitability, producing facilitatory or inhibitory effects upon a variety of behaviors" [223], acting largely within the brain, on: cortex, thalamus, basal ganglia, cerebellum [75].

Overall, tDCS represents a non-invasive, non-pharmacological/bio-technological intervention with therapeutic-rehabilitative potential to be considered, including – through its actions on synaptic plasticity/operating over "… brain networks with high spatial resolution" [223]—after ischemic stroke, with clinical favorable outcomes for alleviating: motor impairments and (also) "unilateral spatial neglect (USN)" [206]/hemineglect [224], in adults, including with re-balancing and consequent amelioration of neural excitability/coordination in between hemispheres and respectively, improved cortico-spinal firing (the same goes for TMS) [3]. Further, in the later post – including ischemic—stroke stages ("subacute and chronic phase"), tDCS applied bilaterally, in humans, may still provide "functional improvements" possibly also because of its capability to, for instance, "… enhance recruitment of endogenous neuroprogenitor cells (but—o. n.) in … rat …". And, again, this goes for high frequency rTMS, too [9]. Generally, the anode is considered excitatory, whereas the cathode would act inhibitory [75, 223]. But as regards polarity, too—aside to other methodological parameters—within the intervention sessions: "... cathodal tDCS elicits regenerative response in stimulated hemisphere …" [17]. So: "... this relationship is more complex than once thought, in that anodal tDCS can actually lead to decreased excitability when the stimulation time is increased, and cathodal tDCS can lead to increased excitability when intensity is augmented" [225]; also for instance, concerning "… firing rate of the vestibular nerve", cathode is augmentative and anode is decremental [206]; so, more comprehensive knowledge on tDCS' intimate mechanisms of action and consequently, on its applying methodology, based on more specific research, is warranted [225]. On a rather different note, but still connected to our subject: "... NIBS techniques …"—encompassing tDCS and rTMS—are interventions for which "… studies have reported the effects of combining these techniques with cell therapy" [141]. To be added to the above mentioned type of interventions—including as regards their capability to augment functional outcomes after ischemic stroke, (and inserting accordingly, the assertion that "These techniques can enhance the effect of practice and facilitate the retention of tasks that mimic daily life activities", too) [208]—the paired associative stimulation (PAS—see below)—with only the enumeration, hereinafter, of some not (yet ?) frequently availed in practice variants of theirs (alphabetically): quadripulse rTMS—a newer and more complex protocol emerging of "… repetitive biphasic-pulse protocols, such as theta-burst stimulation (TBS) …" [226] (maybe also octa-pulse, too), transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) [47, 208].

PAS is a more demanding technique—but having in favor the fact that is "... developed on the basis of LTP/LTD (long-term potentiation/long-term depression—o. n.)-plasticity protocols …", with apparently some good outcomes on motricity, as observed on related motor evoked potentials, in post stroke patients, too [208], with potential to "... optimize training-induced plasticity processes" [227]. Once again, from a synthetic resuming related perspective: tDCS, respectively rTMS "…are aimed at restoring the interhemispheric balance by inhibiting healthy hemisphere or stimulating the lesioned one. These methods noninvasively modulate brain activity, may induce brain plasticity and facilitate stroke recovery" [91].

4.19 Virtual reality (VR)/augmented reality (AR) [206]

Synthetically defined, "Virtual reality based rehabilitation (VRBR) …" is based on the training effects of (multi)sensorial feedbacks resulting from the individuals' interplay with information technology & communication (IT&C) facilities [228]. Two main determinants [228] of VR/AR's efficiency are "… the sense of presence … (defined as the subjective experience of being in one place or environment, even when one is physically situated in another)" [80] and the one of "control over", as a consequence of availing "… interaction with the environment and objects" [228]. VR "… and interactive video gaming …", also for leisure purposes ones—but especially those adapted for or dedicated to medical goals—began to be used in post stroke rehabilitative approaches, too, having, as a rather valuable particularity, the one of being "more motivating" and thus allowing to be spent a longer time within an including therapeutic/training endeavor [229]; and more: at least some of them (not quite few) are feasible in "home environment" [91], as part of the needful infrastructure is rather accessible, including—as afore mentioned—sensor-based computer-aided "serious"/active gaming technologies [158]/"training programs" [91]. Corollary, VRBR

seems to generate even better and faster outcomes—at least as regards "walking speed, balance and mobility"—in post stroke patients, than "standard rehabilitation" [228], and this may also apply "... in improving upper limb function and ADL function ..." [229]. This merges—with favorable action on cognitive capabilities, too [91]—with standard rehabilitation approaches, or "... when used as an adjunct to usual care ...." [229]. Consistent data regarding VR/AR and the therapeutic-rehabilitative use of such kind of interventions are presented elsewhere [222], so here there will not be included further related details in here.

4.20 Visual scanning training (VST)

VST basically consists of the patient's—instructed, including through verbal emphasizing cues, by a therapist—attempt to concentrate on observing zones in the ambient situated on the opposite site to the cerebral damage; this entails activities such as: different objects and respectively body parts watch and recognition, and reading, writing, images reproduction by drawing (when too difficult: using strategies for compensation) [206], including within mental imagery endeavors, but also possibly using "simple board games" [230]. In the literature there are reported—not unanimously—some good results of this technique, probably better to be used in association with tDCS [206], electrical stimulation of the left-hand [224] and/or "contralesional limb activation approach" [230].

4.21 Electroacupuncture (EA)

A type of intervention which taxonomically formal/stricto senso is considered invasive (and hence, we should not address it in this paper) is Electroacupuncture (EA). This is because, as known, EA is applied through inserted —not implanted—needles (and the same goes for acupuncture). Yet, considering on one hand the, in fact, the minim invasive and safe administration profile of these two kinds of procedure, and on the other, their claimed in the literature beneficial effects, including with the pathology domain we approach in this article, we decided to mention, in here, some brief data regarding EA (added to those fore-cited concerning acupuncture). Actually, it is to be discussed whether, practically, such procedures would not be reckoned as rather non-invasive than invasive (It "… has been used in patients with stroke and for post-stroke rehabilitation, as it can improve neurological impairments with no serious adverse events" [111]). Regarding EA effects, in a study on animal model of stroke, it "… improved neuronal function and induced proliferation and differentiation of NSCs through BDNF and VEGF signaling", thus promoting neurogenesis (neurons or astrocytes) as element of brain repair and consequent functional recovery [231].

To be specified that "EA is the combination of traditional acupuncture and a small electric current to achieve functional recovery by stimulating certain acupoints", through by inserting needles in the respective acupoints [17], and the connected electrical stimulation "... activates several classes of sensory fibers … molecules, including trophic factors, that are produced as a mediator of acupuncture effects …", and based on the actions of such factors, it would stimulate/augment, including, neuraxial neurogenesis [111]. Furthermore, Chang *et al*. [89] assert a quite astonishing vast amount of related beneficial effects of the EA: "… pretreatment or treatment after ischemic stroke by using appropriate electroacupuncture parameters …" would result in exhaustive neurorestorative outcomes, based on: blood brain supply—with BBB integrity support and also modulation of "cerebral ischemic tolerance"—and metabolic oxidative status, improvement, antiexcitotoxic and antiapoptotic effects, and neuroregeneration actions through stimulation of "growth factor production" [89]. Obviously, including for this type of interventions, more of EBM paradigm studies are desirable.

4.22 Hyperbaric oxygen environment (HBOE) [232]/hyperbaric oxygen therapy (HBOT) [233, 234]

HBOT is a borderline type of therapeutical intervention: physical ("... breathing 100% oxygen while under increased atmospheric pressure" [234])—thereby, oxygen (which is transported by the blood flow in a largest proportion reversibly bound to hemoglobin) is also, in a small amount, carried in solution [235]—this part being enhanced "… under hyperbaric conditions" [234]), and also pharmacological, the latter referring to the biochemical actions of the oxygen at intimate level. An important rationale of its proposed therapeutical-rehabilitative use is that "Oxygen concentration is ... decreased during stroke and increased in hyperbaric oxygen environment" [232]. Accordingly, "Since 1 cm3 of nor^{m}al brain tissue contains about 1 km of blood vessels, high oxygen supply is essential for repair of the stunned regions"; such stunned areas might persist: alive but not functional, even for years, keeping thereby a reasonable morph-physiological potential for being, at least partially, rescued. So, this practice, supplementing, under an elevated atmospheric pressure—that augments the dissolvation of O2 in the $_{p}$lasma—the sanguine oxygenation, would bring including to the brain a necessary oxygen amount "... for tissue repair …"; therefore, HBOT is considered to act towards recovery at metabolic level in hypoxic—including through lesions of the local/regional vasculature caused by stroke—cerebral structures and on this intimate basis it would be able to stimulate also neuroplasticity and regenerative/neurorestorative phenomena, and hence being prone to functional recovery even in late – including more than one year—chronic post stroke stage, in adults [233]). Still, a related necessary advocacy for supplementary related clarifications and consequent methodological cautiousness in administering HBO, refers to a study, on animal model, of focal transient ischemia (middle cerebral artery occlusion —MCAO) [236] in which it appeared efficient, respectively neuroprotective (mitigating

the volume of the ischemic lesion and bettering the neurofunctional status) if administered within the first 6 hours—practically within an opportunity window rather twice, or less, the length of that for the recombinant-tissue plasminogen activator—rt-PA—treatment [237]—of post transient MCAO (that is in the very early acute stage of a stroke [53]), whereas if it was introduced after 12 hours or more (yet, still in very early acute stage), the effect was opposite, worsening the "... ischemic injury histologically and clinically" (augmenting the volume of the infarcted zone), and concerning permanent MCAO, HBO provided no improvement (morph-pathologically or clinically), no matter the moment of its initiation [236]. On the other hand, Lee *et al*. [238] assert mixed but mainly beneficial effects of HBOT, administrated early and also prolonged ("repetitive schedules for 3 weeks") post ischemic stroke, in rats: "... orchestrated gliosis and trophic factor production (BDNF, NGF, and GDNF) and decreased harmful effects by neutrophils in the early phase", thus diminishing related "Acute inflammation in the acute phase of cerebral infarction ..." [238]. Considering the above, it seems—again—that HBOT would overall support "… neurological improvement, increased neurogenesis …" [117], also improving neuroplasticity, including "… at chronic late stages" [233]. Moreover, there are reported in the literature (yet, not especially post stroke) also beneficial effects of HBOT on cognitive functions [239]. Yet, it has to be kept in mind, the potential toxicity of oxygen, too: "… vital capacity reduction over a useful range of O2 pressures …" and "… O2 … toxic properties that, at sufficient pressure and duration of exposure, can have ultimately lethal effects on any living cell" [240]; this is—aside other potential side effects, observed in animal experiments (in general rare/very rare—so this procedure is mainly considered safe—but still to be considered): from just claustrophobia to numbness, nausea, ear-barotrauma, headache, seizures (including with consequent, reversible BBB and brain tissue lesions, and accordingly, enhancement of apoptotic markers), "transient cognitive deficits, pulmonary dyspnea, progressive myopia" [117]. So, in this field, too, more research is needed.

5. Discussion and conclusions

The late beneficial therapeutic effects reported above require, as comment, that seemingly, in the recent years, "The restorative window for stroke recovery is much longer than previously thought" [3]. So the best period to act and expect for "brain repair" would occur mainly in a tardily than an incipient post stroke phase [3], and moreover: "... some early behavioral manipulations worsen function" [143], specifically the administration of very strongly demanding rehabilitative procedures; this is considering also the fragility of such patients during the general biologic and neurologic instability—including possibly life-threatening—that characterizes especially the early stage post (including ischemic) stroke [3]. So, practically: "Considering the discussed evidence under translational aspects, intensive physiotherapy or training should be started not earlier as 7 or 14 days poststroke" [241]. On a relatively different, but however, connected note: "Physical and/or cognitive rehabilitation, transcranial magnetic (TMS) or direct-current (tDCS) stimulation may lead to a functional improvement in a reduced number of patients during the chronic phase of disease …", being found, in different bibliographic resources, reported conflicting related outcomes regarding "… the efficacy of these types of approaches …", taking into account—as asserted by the below cited authors—on one hand, matters as regards homogeneity and respectively, small magnitude of the studied groups of patients, and on the other, the diversity of the related methodologies availed in different surveys [101]. On the other hand, within the limited panel—as known and we have also emphasized it, iteratively—of all kind of effective treatment interventions in the pathology we approach, there can—regarding the above mentioned two types of physiatric procedures—be found in the literature, additional to what we have already synthesized previously, that "… cerebral stimulation using transcranial direct-current stimulation and repetitive transcranial magnetic stimulation (neurorehabilitation therapy used to enhance functional recovery after stroke) may augment plasticity, rehabilitation, and neurorestoration" [86]. So, definitely scientific research, including with clinical trials in this interdisciplinary domain must continue and be fostered, in order to reach more consensual, validated related opinions (to be specified this goes for pharmacological therapies—and not only—too) [68]. This is especially as—again—ischemic stroke (and other severe disabling neurologic/neurosurgical conditions) that dramatically and multiplane impact the affected patients (and not only them), are not rare conditions. Hence, for such devastating statuses "After the acute phase, rehabilitation therapy is the only approved treatment for stroke survivors presenting with neurological deficits" [90], because for now, still, "Unfortunately, we do not have therapies to target the subacute and chronic phases of ischemic stroke and efficiently repair the damaged brain promoting a satisfactory degree of functional recovery in most patients" [110], respectively "There are no established safe and effective restorative treatments to facilitate a good functional outcome in stroke patients" [90]. Considering the vast complexity of the CNS biology and pathology, including with the diversity of the post ischemic stroke cases, and the large, quite eclectic, inter-/multidisciplinary portfolio—which doesn't make it neither unitary nor consensual—of currently and/or potentially used related interventions (Coscia *et al*. [68] uses, for generically grouping some most availed and quested type of such interventions: "robotics, muscular electrical stimulation, brain stimulation, and brain computer/machine interfaces"—including with associations in between—involved in the

treatment-rehabilitation, including of post ischemic stroke patients, the naming "neurotechnologies/neurotechnology-aided") [68], this result in an overall insufficiently clarified field, despite its indispensability (this important amount of different/nuanced—even conflicting sometimes—opinions in the domain is, at the same time, the reason we have chosen—as already afore pointed out—to use many quotations from the literature, in order to reflect as accurately and exhaustively as possible, the ongoing current related knowledge). So, all the stakeholders are therefore eagerly/desperately waiting for a—based on effective and widely accepted implementation protocols—healing/brain neurorestoration, regeneration/repair, with consequent complete/"satisfactory" recovery/rehabilitation, but which, as known, hitherto is lacking [110]. Yet, contrary to this strongly motivated wish, likewise practically all other pathology, the post ischemic stroke rehabilitation and rehabilitative cares (including with the activity of the units engaged in this kind of medical complex endeavor—encompassing, for chronic such patients, balneal/spa approaches, too), have been, since last year, and still are, drastically affected/altered. Under such circumstances, "… potential techniques can be used to stimulate neurorestoration and maintain muscle strength with minimal assistance"; in this respect, Wang *et al*. [242] enumerates as accessible for home rehabilitation: TENS (such devices are, by principle, mobile), mirror training and VR/AR. Professionally, adequately indicated—considering co-morbidities (not seldom existing in such patients, especially elderly), the stage and the evolution of such cases—and carefully monitored, there could be effectuated physical rehabilitative exercises, too. So, the main re-structuring of this type of activity addressed the switch—because of epidemiological precautions—as much as possible, towards telerehabilitation (TR), through the IT&C current facilities, and home based rehabilitation training and remote related coaching (also through IT&C capabilities—where accepted and available). To be emphasized that the option for home based rehabilitation is justified not only by the actual pandemic situation but also because—as known and we have afore mentioned—disabilities after (also ischemic) stroke are, not few of them, life-long. Consequently, the many periodic re-admissions in hospitals may be somehow saturating for the affected persons and their kin/voluntary caregivers. On the other hand, sustained pursuing home rehabilitation is, likewise, often demanding, especially because of: mandatory needing for constant professional assistance/support provision, technical and economic, limitative reasons and/or if psychological, further, motivations to constantly continue it, on the long road, are not permanently reinforceable. Yet, despite all hurdles—which are many and tough—in order to progress or at lest keep the functional recovery gains "Currently, a drawn-out series of rehabilitation with a lifetime process of clinical support is the norm for most stroke survivors" [71]. Under all the above and afore presented aspects and rationale to fulfill rehabilitation (also) remotely, hereinafter will be briefly added some related basic considerations regarding telehealth/telemedicine/TR. Hence, TR can be organized in balanced programs containing appropriate physical exercises—according to the patients' general health state and respectively, specific post ischemic stroke disability items targeted to be combated—serious specific games and relaxing/enjoying own chosen ones, as well. At the same time—and this is an important feature of, including, home-based TR—thus can be usefully merged rehabilitation with prophylaxis (encompassing, for instance, "divergent methods to drive patient behavior" and sustained—quotidian recommended—"stroke education"), with good compliance and rather encouraging outcomes [47]. In the literature are reported, in this respect, for post stroke patients, at least regarding motricity and ADLs: "… limited, moderate evidence that telerehabilitation of all approaches has equal effects with conventional rehabilitation …" [243], but also "Inconclusive finding were found on the effect of telerehabilitation for neurological patients …" [244] and respectively, a newer trial (regarding including in post ischemic subacute and chronic stroke patients) asserts: "... TR is not inferior to IC (In-Clinic—o. n.) therapy for improving arm motor function and stroke knowledge …" Yet, TR needs to improve—maybe through a larger time of therapist guided training—as regards "activity-inherent motivation and satisfaction", which is better within and IC paradigm [245]. As to be expected, more research on this subject matter, too, is necessary.

Until a/the complete effective cure of CNS lesions—in post ischemic stroke, too—would, if ever, appear, it is reasonably to consider that more holistically, combining, approaches towards brain neurorestoration/neuroregeneration and repair [3] (including, conceptually, for trying to thus presumably, magnify the otherwise possibly lower effect-size of a single intervention), seem to be an attractive therapeutic-rehabilitative paradigm of choice [90, 241]. Specifically, this could be achieved through the associated use of more and more scientifically based, appropriated administration methodologies of different types of interventions currently available: physiatric (for instance, recently reported: "... combining tDCS and NMES with regular rehabilitation programs ..." would magnify the beneficial effect on upper limb motricity rehabilitation, compared to the outcomes obtained with only classic related programs, in chronic post—including ischemic—stroke [246]), pharmacologic [47, 68, 247], and even (when indicated and feasible/ adequate), of biotechnological/possibly invasive—or just minimally invasive (see the related comments afferent to acupuncture and electroacupuncture)—type (stem cells, maybe in association with suitable advanced biomaterial scaffolds—tissue engineering [101]—respectively, for instance: "... a mix of two or more therapeutic factors consisting of bone marrow stromal cells, exercise and thyroid hormones, endothelial

progenitor cells overexpressing the chemokine CXCL12", or respectively intrajugular administration of bone marrow derived mesenchymal stem cells—BM-MSCs—[98]).

And, in line with the clinical feedbacks on outcomes reported in works achieved according to the above mentioned merging, and pragmatic, regard, within the overall goal to consistently progress towards neurorestoration/neuroregeneration and brain repair—and consequent functional recovery/rehabilitation, with improved QOL for all the people involved—periodic systematic and synthetic literature reviews reappraisals, on such therapeutic-rehabilitative interventions for (including ischemic) stroke, are necessary and useful, as well. And this is despite the fact—as emphasized by us all over this article, about the almost ubiquitarian antagonistic-dialectical paradigm to be observed regarding the concepts and interventional profiles within the subject we have approached—that the more and deeper we know, more related questions arise.

6. Author contributions

All authors had specific but overall equal contributions in achieving this article: Conceptualization, GO and FCF; methodology, GO, AA and CM; software, VC, MO; validation, AS, CP, CDB; formal analysis, FCF, COD; data curation, CM, AS, CP; writing—original draft preparation, GO, FCF, COD, AA; writing—review and editing, VC, MO; visualization, VC, GO and CM; supervision, GO, VC, CDB and CF. All authors have read and agreed to the published version of the manuscript.

7. Ethics approval and consent to participate

This article was approved by the Ethics Commission/Council of the Teaching Emergency Hospital "Bagdasar-Arseni" (No.: 7018/ 26.02., 2021) and of the Teaching Emergency Hospital of the Ilfov County (No.: 1/ 11.02., 2021).

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10. Conflict of interest

The authors declare no conflict of interest.

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Abbreviations: AE, aerobic exercises; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; AR, augmented reality; BBB, blood brain barrier; BCI, brain computer interface; BDNF, brain-derived neurotrophic factor; BMI, brain machine interface; CIMT, constraint-induced movement therapy; CNS, central nervous system; CSPs, Chondrotin Sulfate Proteoglycans; CVA, cerebrovascular accident; DM, damage mechanisms; EA, electroacupuncture; EBM, Evidence Based Medicine; EDA, endogenous defense activity; EE, enriched environment/environmental enrichment ; ES, electrical stimulation; fNIRS, functional near-infrared spectroscopy; FES, functional electrical stimulation; GDNF, glial cell-derived neurotrophic factor; GVS, Galvanic vestibular stimulation; hNSC, human neural stem cell; HBOE, hyperbaric oxygen environment; HBOT, hyperbaric Oxygen Therapy; IGF, insulin-like growth factor; ILAT, Intensive Language-Action Therapy; ISI, Institute for Scientific Information; KT, kinesiotherapy; LED, light-emitting diodes; LLLT, low-level laser (light) therapy; MNs, mirror neurons; MTS, mobilization and tactile stimulation; MVF, mirror visual feedback; NCBI, National Center for Biotechnology Information; NF, neurofeedback; NGF, nerve growth factor; NIBS, non-invasive brain stimulation; NILT, transcranial near-infrared light therapy; NIRS, Near-infrared spectroscopy; NMDA, *N*-methyl-$_D$-aspartate; NMES, neuromuscular electrical stimulation; NMT, Neurologic music therapy; NPCs, neural precursor cells; NSCs, neuronal stem cells (NSCs); OT, Occupational Therapy; PA, prism/prismatic adaptation; PAS, paired associative stimulation; PEDro, Physiotherapy Evidence Database; PNF, proprioceptive neuromuscular facilitation; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSS, peripheral somatosensory stimulation; rTMS, repetitive transcranial magnetic stimulation; RT, robot-assisted therapy; sEMG, surface electromyography; SG, Serious gaming/games; tDCS, transcranial direct current stimulation; TENS, transcutaneous electrical nerve stimulation; TH, therapeutic hypothermia; TMS, transcranial magnetic stimulation; TOT, task-oriented training; TR, telerehabilitation; USN, unilateral spatial neglect; VEGF, vascular endothelial growth factor; VR, virtual reality; VRBR, virtual reality based rehabilitation; VST, visual scanning training; QOL, quality of life.

Keywords: Non-invasive; Non-pharmacological/biotechnological interventions; Neurorestoration; Neuroregeneration; Brain repair; Ischemic stroke; Adults; Systematic; Synthetic; Literature review

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