parameters to assess alteration of cerebral blood flow and BBB permeability. More recently, Matsushita and colleagues [93] demonstrated, through an MRI-based analysis, a tight relationship between intracerebral hemorrhage and stroke clinical development conferring to MRI investigations the capability to predict neurological dysfunction and animal mortality (Figure 5B). Despite the great advantages provided by MRI, this technique is not extensively used in animal studies since the equipment is really expensive. Alternatively, a more reasonably-priced approach for detecting CE in vivo exploits optical coherence tomography (OCT) [94–96]. Based on the fact that the optical scattering of tissue is influenced by the composition of the tissue itself, it will change accordingly with the increase in water content during cerebral edema. OCT allows for the cross-sectional acquisition of biological tissue with high resolution (micrometer) and tissue penetration of the order of millimeters [94,95]. Rodriguez and collaborators [94] demonstrated the possibility of employing OCT to detect optical changes correlated with cerebral edema in an in vivo water intoxication model (Figure 5C). This study revealed an advancing alteration of the cerebral cortex attenuation coefficient that goes hand in hand with the edema progression. Moreover, they used Doppler OCT imaging to detect a decrease in cerebral blood flow due to blood vessel compression during severe brain swelling [94]. Moreover, different from clinical research, preclinical investigations allow the observation of BBB disruption with high resolution by exploiting fluorescence imaging techniques in vivo. In particular, two-photon fluorescence microscopy (2PFM) combined with fluorescent staining of the vasculature provides a longitudinal evaluation on the blood vessels' permeability within the mouse brain cortex through a cranial window. Moreover, this approach offers sufficient temporal and spatial resolution to track transient changes in BBB permeability at a microvascular level. Proof-of-concept in monitoring BBB disruption using 2PFM has been demonstrated by Raymond et al. [97,98]. In that study, the authors injected fluorescent dyes (e.g., Texas Red, Oregon Green) for the visualization of the microvasculature and transmitted ultrasound from the ventral surface of the brain to induce BBB alterations. These studies characterized the microscopic leakage patterns qualitatively but did not attempt to quantify the rate of agent delivery. Then by extracting and correlating intravascular and extravascular signals from the time-lapse 2PFM images, Nhan and collaborators [87] (Figure 5D) demonstrated a quantitative approach to analyze the 2PFM images after BBB disruption. In detail, they characterized the apparent permeability by comparing the intra- and extravascular fluorescence between two time intervals after the injection of a tracer. Recently, Allegra Mascaro et al. 2019 [82] applied this protocol in order to investigate BBB permeability in a mouse model of photothrombotic stroke in the primary motor cortex. More in detail, they investigated the extravasation of a low molecular weight dye (3KDa Texas red dextran) at two different time points (15 and 30 days after the injury) after stroke. Though 2PFM does not allow whole organ investigation, the great advantage of this approach is the capability to perform longitudinal studies, thus offering the possibility to monitor the integrity of the BBB with high precision even in the chronic phase after stroke.

3.3. Optical Imaging to Investigate Structural and Functional Plasticity in Mouse Models of Stroke

Assessing the extension and progression of the CE and HT may not be sufficient to understand the reasons for the discrepancies in the clinical cases reported above. As described before, the entire NVU is involved in the degradation process triggered by cerebral ischemia. In turn, this cascade of events affects brain organization at all levels, from single synapses to neuronal networks to whole-brain activity. More in-depth understanding of the ischemic progression that leads to neuronal survival or massive degeneration in the penumbral tissue with cellular and subcellular detail is necessary. Preclinical research, though it is still not always able to reproduce the complexity and the variety of human clinical cases, presents the great advantage of dissecting neuronal structure and function over multi-scale. In the last decades, the development of 2PFM [99], coupled with the introduction of transgenic mice expressing genetically encoded fluorescent indicators in cortical neurons [100], has enabled investigators to visualize longitudinal changes in the

structure of dendritic spines in vivo. In particular, many studies have focused on structural and functional plasticity as targets of both acute and chronic ischemia [101–104]. These studies indicated the loss of spines and rapid swelling and beading of dendritic structure within minutes of global ischemia coincident with a wave of ischemic depolarization [103]. Many studies [82,101,102] focused their attention on spines' turnover and dendritic orientation in the peri-infarct cortex. In particular, dendritic structures can be profoundly altered by MCAO [103], whereas reperfusion can lead to recovery of structure similar to pre-stroke levels. In another work, Murphy and collaborators [105] demonstrated that the capability of dendritic arbors to recover within the penumbra was still maintained after 60 min of sustained ischemia (Figure 6A). By exploiting in vivo 2PFM and laser speckle contrast imaging, they correlated dendritic blebbing with the fluctuation of blood flow, showing that the recovery of the dendritic structure following reperfusion is restricted to a relatively small penumbra region. Brown and colleagues [106] took advantage of 2PFM to monitor real-time changes in dendritic and vascular structure in a mouse model of photothrombotic stroke (Figure 6B). In parallel, other studies investigated blood flow before and after multiphoton nano surgery of single blood vessels in living animals [107] (Figure 6C). 2P real-time imaging of blood flow through the blood vessels in the region of the cortex surrounding the vascular lesion permits the characterization of the dynamics of the degenerative event [107]. Since the reorganization of surviving cortical areas is involved in post-stroke recovery, in the last decades, neuroscience pointed their attention to functional in vivo studies too. Harrison and colleagues [108] investigated functional rearrangement between cortical regions in a mouse model of photothrombotic infarct targeted in the motor cortex. In this longitudinal study, they observed, through a combination of sensory-motor stimulations and intrinsic optical signal imaging, which spared regions of the cortex surrounding the stroke core were able to assume functions from stroke affected areas. Thereafter, Lim and collaborators, by taking advantage of voltage sensitive dye and optogenetic cortical stimulation, investigated neural rearrangement of cortical networks in the mouse brain cortex [109]. This relatively noninvasive approach allows recording neuronal activity triggered by optogenetic stimulation with high temporal resolution and large spatial resolution. This work provided evidence of the global depression of cortical activity characterizing the early stages after stroke. Moreover, they observed at a later time point (8 weeks after stroke) that the global depression gradually resolved, though the overall strength of the network remained reduced. Recently, Allegra Mascaro et al. [82] performed a multi-scale study investigating structural and functional plasticity in parallel, in a mouse model of post-stroke rehabilitation. More in detail, they observed in the peri-infarct cortex an increase in spines' surviving fraction and a preferential orientation of dendrites towards the stroke core. Moreover, by investigating cortical activity during the execution of a motor task, they observed a widespread activation in chronic conditions (Figure 6D).

In line with these preclinical studies, a similar system-level measure of functional connectivity in humans through fMRI observed a consistent decrease in brain modularity indicating a reduction in integration within functional areas and segregation between brain systems during a subacute phase after store [110].

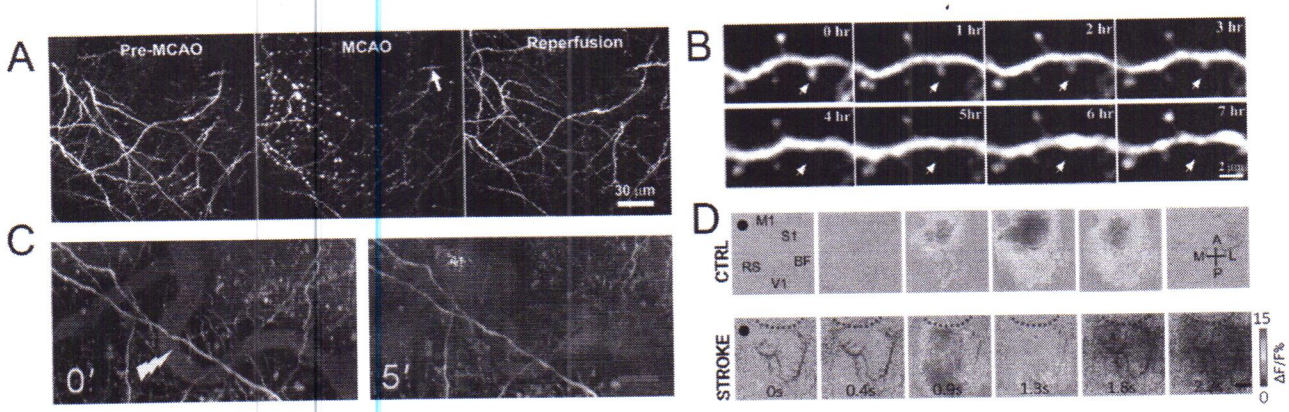

Figure 6. (**A**) Two-photon imaging of local changes in the dendritic structure before, during, and after MCAO. In the left panel, intact dendritic structures were observed; in the middle panel, extensive dendritic blebbing was observed; in the right panel, a significant recovery of dendritic structures after reperfusion was observed. Modified by Li and Murphy 2008, Copyright (2008) Society for Neuroscience. (**B**) Time-lapse imaging of apical dendrites showed the retraction of a dendritic spine. Modified by Brown et al., 2007, Copyright (2007) Society for Neuroscience. (**C**) Time-lapse images of maximum intensity z-projections (from 20 to 60 μm) before (left) and after (right) the laser-induced ischemic hemorrhage. The figures shown in green are the GFP-labeled neurons in a GFP-M mouse, and in red are the vascular networks labeled with Texas-red dextran dye. The tip of the yellow lightning symbol represents the laser irradiation point. The first image was acquired just before the laser irradiation. Scale bar, 20 μm. Modified from Allegra Mascaro et al. 2010. (**D**) Image sequences of cortical activation as assessed by calcium imaging during pulling of the handle by the contralateral forelimb of CTRL (top), STROKE (bottom) Thy1-GCaMP6f mice in the M-Platform. A small area located in the motor-sensory region reproducibly lit up in CTRL mice, while a large area covering most of the cortical surface of the injured hemisphere was activated in STROKE mice 1 month after stroke. A–P, anterior posterior, M-L, medio-lateral, M1, primary motor area, V1, primary visual area, S1, primary sensory area, Rs, Retro splenial area, BF, barrel field. The black dashed lines define the lesion borders. The black dot indicates bregma. Scale bar 1 mm. Modified from Allegra Mascaro et al., 2019.

4. Conclusions

The limited knowledge on the molecular, cellular, and network level that can be offered by common clinical practice hinders the understanding of the mechanism underlying a specific clinical outcome. Within this review, we discussed the potentials and limits of preclinical research to answer clinical questions raised by the reported exemplary cases. Among others, the two major questions that this review tried to address were: (1) why does MT not improve stroke outcome in all patients, despite full recanalization? (2) how can stroke reperfusion treatments be further improved? Preclinical researchers are thrilled to bring their contribution to stroke care in a way that works alongside stroke clinicians and helps get the right patient to the right treatment (precision medicine), but there is still plenty of work to be done.

The last two decades have witnessed a remarkable increase in the number, breadth, and depth of preclinical research studies on acute ischemic stroke [111], but most of them carry some key mismatches between clinical practice and preclinical models:

- Stroke is most prevalent in elderly men and women, whereas preclinical models mostly test young animals.
- Stroke is more devastating in patients with multiple comorbidities not often captured by preclinical models.

However, exploratory research aimed at investigating potential new therapeutic targets or theoretical understanding of pathophysiological mechanisms does not necessarily need to perform experiments on an extensive range of age and comorbid models. Furthermore, since the incidence of stroke in young adults has increased in the last decades [112,113], preclinical research with young animals represents a fundamental way for understanding the underlying pathophysiological mechanisms in this subgroup of patients. Finally, the capability to investigate, at multiple-scale with different approaches,

the ischemic progression from the onset up to the chronic phase after the insult allows the deep understanding of the post-stroke transformation, disentangled from other factors.

Unlike clinics, where HT and CE are used to define the prognosis of stroke patients, preclinical studies usually characterize the severity of the insult with behavioral tests in vivo or through the evaluation of the lesion volume ex-vivo. Nevertheless, since cerebral hemorrhage and edema are the most frequent clinical complication in the acute phase after an ischemic stroke, we illustrated that preclinical research had developed a multifaceted array of techniques to investigate these pathological processes. Another emerging topic that is catching the attention of preclinical research is the understanding of the role of cortical depolarization waves in the acute phase after stroke. Many studies [114–118], both in animals and humans, suggest that spreading depression-like depolarizations play a crucial role in the tissue damage process. Indeed, in the early stages after focal cortical ischemia, spreading depolarization waves propagate from the rim of the stroke core to the surrounding intact tissue [119,120]. Previous investigations [121] showed that in the injured brain, the succession of spreading depolarizing waves induces a series of intracellular alterations (i.e., collapses ionic gradients, activation of NMDA receptors and gap junctions), triggering a massive calcium influx that in energy-compromised neurons promotes the cell death cascade. Moreover, other studies highlighted the crucial role of the interaction between cortical spreading depression waves and the brain's vasculature since in pathological conditions, they induce severe vasoconstriction and spreading ischemia [122,123]. Balbi and collaborators revealed the propagation of depolarizing waves by inducing a photothrombotic stroke in awake mice without the interference of anesthesia throughout the entire cortex [71]. Moreover, a recent work [124], by simultaneously investigating the neurovascular coupling during and following photothrombosis, identified a determining role of cortical spreading depression waves in the secondary progression of tissue damage during and after acute brain injury, emphasizing their potential therapeutic target. Though up to now the finest cellular and molecular pathophysiological mechanisms of ischemic progression are still largely unknown, future preclinical research should flank the characterization of hemorrhage and edema to neurovascular investigation in order to understand the mechanisms underlying the FR and define better therapeutic paradigms.

To this aim, neuroscientists are making a great effort in order to optimize animal models of stroke with reperfusion to investigate HT and CE in parallel with neuronal functionality and structural plasticity of synaptic contact, better resembling clinic progression observed in humans.

In conclusion, the ongoing technological development of cutting-edge investigation approaches will offer the capability to realize a more specific and detailed investigation of the pathophysiological mechanisms underlying ischemic progression. Undoubtedly, the bi-directional collaborative approach between preclinical and clinical researchers represents a propulsive thrust to improve stroke treatments.

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Informed Consent Statement: All patients' data and imaging included in the study were obtained under informed consent.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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